2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease

Data Supplements

(Section numbers correspond to the full-text guideline.)

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~ indicates approximately; 1°, primary; 2°, secondary; 2D, 2-dimensional; 3D, 3-dimensional; 4D, 4-dimensional; 6MWT, 6-minute walk test; AAOCA, anomalous aortic origin of the coronary artery; AAOLCA, anomalous aortic origin of the left coronary artery; AAORCA, anomalous aortic origin of the right coronary artery; ACC, American College of Cardiology; ACEI, angiotensin-converting-enzyme inhibitor; ACHD, adult congenital heart disease; AE, adverse events; AF, atrial fibrillation; AHA, American Heart Association; ALCAPA, anomalous left coronary artery arising from the pulmonary artery; ANP, atrial natriuretic peptide; ARB, angiotensin-receptor blocker; AS, aortic stenosis; ASD, atrial septal defect; ASO, arterial switch operation; AT, anaerobic threshold; AVC, atrioventricular canal; AVNRT, atrioventricular nodal reentrant tachycardia; AV, atrioventricular; AVS, aortic valve stenosis; AVSD, atrioventricular septal defect; BAV, bicuspid aortic valve; BB, beta blockers; BDCPA, bidirectional cavopulmonary anastomosis; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; BREATHE-5, Bosentan Randomized Trial of Endothelin Antagonist Therapy-5; CABG, coronary artery bypass grafting; CAC, coronary artery calcium; CAD, coronary artery disease; CAMPHOR, Cambridge Pulmonary Hypertension Outcome Review; CACH, Canadian Adult Congenital Heart; CCT, cardiac computed tomography; CCTGA, congenitally corrected transposition of the great arteries; CHD, congenital heart disease; CI, confidence interval; CKD, chronic kidney disease; CK-MB, creatine kinase-MB; CMR, cardiac magnetic resonance; CoA, coarctation of the aorta; COR, class of recommendation; CPB, cardiopulmonary bypass; CPET, cardiopulmonary exercise stress test; CRT, cardiac resynchronization therapy; CT, computed tomography; CTA, computed tomography angiography; CV, cardiovascular; CVA, cerebrovascular accident; CVD, cardiovascular disease; CXR, chest x-ray; DBP, diastolic blood pressure; DCCV, direct current cardioversion; DCM, dilated cardiomyopathy; DCRV, double-chambered right ventricle; DM, diabetes mellitus; double outlet right ventricle; dp/dt, measurement of the rate of systolic right ventricular pressure increase; d-TGA, dextro-transposition of the great arteries; echo, echocardiography; ECG, electrocardiogram; ED, emergency department; EDA, end diastolic area; EF, ejection fraction; EOL, end-of-life; EP, electrophysiology/electrophysiologic; EPS, electrophysiological studies; ERA, endothelin receptor antagonist; FC, functional class; FDA, Food and Drug Administration; FDR, first-degree relative; GI, gastrointestinal; GUCH, grown up congenital heart; HCT, hematocrit; HD, heart disease; HF, heart failure; HGB, hemoglobin; HLHS, hypoplastic left heart syndrome; HR, hazard ratio; HTN, hypertension; IART, intra-atrial reentrant tachycardia; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICE, intracardiac echocardiography; ICD, implantable cardioverter-defibrillator; ICU, intensive care unit; IE, infective endocarditis; IQ, intelligence quotient; IQR, interquartile range; IV, intravenous; LDL, low-density lipoprotein; LIMA, left internal mammary artery; LMCA, left main coronary artery; LOE, level of evidence; LOS, length of stay; LV, left ventricular; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow obstruction; MACE, major adverse cardiac events; MCV, mean corpuscular volume; MDCTA, multidetector computed tomographic angiography; MI, myocardial infarction; mPAP, mean pulmonary artery pressure; MR, mitral regurgitation; MRA, magnetic resonance angiogram/angiography; MRCA, magnetic resonance coronary angiography; MRI, magnetic resonance imaging; MS, mitral stenosis; MSCT, multi-slice computer tomography; N/A, not applicable; NHLBI, National Heart, Lung, and Blood Institute; NPV, negative predictive value; NS, not significant; NT-BNP, N-terminal-brain natriuretic peptide; NT-proANP, N-terminal pro-atrial natriuretic peptide; NT-proBNP, N-terminal-pro-brain natriuretic peptide; NYHA, New York Heart Association; NSVT, nonsustained ventricular tachycardia; NVE, native valve endocarditis; O_2, oxygen; OR, odds ratio; PA, pulmonary artery; PAD, patent ductus arteriosus; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PAPVC, partial anomalous pulmonary venous connection; PAPVR, partial anomalous pulmonary venous drainage; PASP, pulmonary artery systolic pressure; PCI, percutaneous coronary intervention; PDA, patent ductus arteriosus; PDE-5, phosphodiesterase type-5; PFO, patent foramen ovale; PH, pulmonary hypertension; PLE, protein losing enteropathy; PPVI, percutaneous pulmonary valve implant; PR, pulmonary regurgitation; PS, pulmonary stenosis; PVR, pulmonary vascular resistance; pt, patient; PV, pulmonary valve; PVE, prosthetic valve endocarditis; QOL, quality of life; Qpeff, effective pulmonary blood flow; Qpi, pulmonary blood flow index; Qp:Qs, pulmonary to systemic flow ratio; RACHS-1, Risk Adjusted Classification for Congenital Heart Surgery; RCT, randomized controlled trial; RT3DE real-time 3-dimensional echocardiography; RV, right ventricular; RVEDV, right ventricular end diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end systolic volume; RVOT, right ventricular outflow tract; RVOTO; right ventricular outflow tract obstruction; RV-PA, right ventricular to pulmonary artery; Rx, medical prescription; SBP, systolic blood pressure; SCD, sudden cardiac death; SD, standard deviation; SEM, standard error of the mean; SF-12, Short Form Health Survey; s/p, status post; SND, sinus node dysfunction; SPAP, systolic pulmonary artery pressure; SpO_2, oxygen saturation; STAT, Stending in Aneurysm Treatments Trial; STS, Society of Thoracic Surgeons; SVA, supraventricular arrhythmia; SVC, superior vena cava; SVG, saphenous vein graft; SVT, supraventricular tachycardia; TA, tricuspid annulus; TEE, transesophageal echocardiography; TGA, transposition of the great arteries; TIA, transient ischemic attack;

TOF, tetralogy of Fallot; TOF/PA, tetralogy of Fallot with pulmonary atresia; TPVR, transcatheter pulmonary valve replacement; TR, tricuspid regurgitation; TTE, transthoracic echocardiogram; TV, tricuspid valve; TVR, tricuspid valve replacement; UK, United Kingdom; UL, upper limbs; UNOS, United Network for Organ Sharing; U.S., United States; VA, ventricular arrhythmias; VAD, ventricular assist device; VF, ventricular fibrillation; VHD, valvular heart disease; VO_2, oxygen consumption; VSD, ventricular septal defect; VT, ventricular tachycardia; VTE, venous thromboembolism; WHO, World Health Organization; WPW, Wolf-Parkinson-White; and WU, Wood units.

Data Supplement 1. Anatomic and Physiologic Terms – Section 2.1

Study Name, Author, Year	Study Type/ Design	Study Size	Inclusion/Exclusion Criteria	Classification System	1° Endpoint	Results/p Values	Summary/Conclusions
Afilalo J, et al. 2011 (1) 21939837	Observational, case control, cohort, retrospective	n=3,239 pts; Quebec CHD Database	Inclusion criteria: Pts ≥65 y, 1990–2005, ACHD, Quebec, healthcare interaction	Bethesda 32 (severe, shunt, valvular)	Mortality	● NS	● A rare study that deals with older adults with CHD. ● Administrative database has limitations.
Tutarel O, et al. 2014 (2) 23882067	Observational, cohort, retrospective	n=375 pts	Inclusion criteria: Pts ≥60 y, ACHD January 2000–March 2012	Bethesda 32	Prevalence, demographics, interventions, mortality	● Mortality: standardized mortality ratio simple 0.6 (p=0.06), moderate 1.89 (p=0.002), complex 2.91 (p=0.01); overall 1.82. ● (p<0.05 univariate, not multivariate as HF, FC, ventricular function took over).	● The study shows increase in number of pts ≥60 y for follow-up at ACHD centers. ● Acquired comorbidity in ACHD pts determines outcomes.
Kim YY, et al. 2011 (3) 22010202	Observational, case control, retrospective database	n=3,061 pts	Inclusion criteria: 18–49 y, 2000–2008, ACHD surgery in pediatric hospital, total compared to pediatric surgical pts, ACHD high resource utilization vs. nonhigh resource utilization	RACHS-1	Resource utilization, cost, LOS	● OR: 3–30 for increasing RACHS classification (much tighter RACHS 3 and 4 as compared to 2).	● Administrative database limited. ● The number of adults undergoing congenital heart surgery is increasing. ● High resource utilization admissions associated with higher death rates.
Kim YY, et al. 2011 (4) 21693722	Observational, case control, retrospective	n=3,061 pts Public Health Information System database	Inclusion criteria: 18–49 y, 2000–2008, ACHD surgery in pediatric hospital, total compared to pediatric surgical pts, ACHD mortality vs. nonmorality	RACHS-1	Mortality	● OR: 2–22 (NS RACHS 2, significant for RACHS 3 and 4).	● Pt death after congenital heart surgery is lower in pediatric hospitals with high congenital heart surgery volume.
Opotowsky AR, et al. 2012 (5)	Observational, case control, retrospective	n=622,000 pts	Inclusion criteria: Pts in 1998–2007	Bethesda 32	Combined: death, HF, arrhythmia, CVA,	● Severe: OR combined: 2.0–2.7; HF 3.9–6.0;	● Maternal CHD is linked with higher rates of CV events and death.

21990383			nationwide inpatient sample		embolic events, "unclassified CV events," LOS, costs	arrhythmia 2, LOS 1.9, costs 1.5–2.0.	
Gurvitz MZ, et al. 2013 (6) 23542112	Observational cross-sectional multicenter prospective questionnaire	n=922 pts	Inclusion criteria: Pts ≥18 y, first presentation to ACHD clinic	Bethesda 32	>3 y gap in CV care	● 59%, 42%, 26% gap in care (simple, moderate, complex); p<0.0001.	● The study provides a basis for improving strategies for dealing with the barriers to care.
Mylotte D, et al. 2014 (7) 24589851	Case-control, cohort, and time series analyses	n=71,467 pts from Quebec CHD Registry; nN=2,092 ACHD death cases	Inclusion criteria: Pts with ACHD,18–65 y from 1983–2005	Bethesda 32 (severe vs. other)	Pts in specialized care had lower mortality; mostly driven by the most complex CHD group	● Increased care for severe in specialty ACHD centers (<0.001); increased mortality for severe ACHD (OR: 1.93).	● Study promotes specialized care for the pts.
Zomer AC, et al. 2013 (8) 23602867	Observational, case control, retrospective	n=274 pts from CONCOR registry	Inclusion criteria: Adult pts 1995–2007 with at least 1 HF 1°or 2° ACHD admission	Right heart lesion	Association with HF mortality	● p<0.05; NS.	● It is critical to identify high-risk HF pts.
Rodriguez FH, et al. 2013 (9) 23164196	Observational, case control, retrospective	n=17,193 HF pts of N=84,308 ACHD admissions from nationwide inpatient sample	Inclusion criteria: Adult, 2207, ACHD admission vs.≥1 HF 1° or 2° coding in ACHD admission	Individual diagnoses	Association with HF, death	● Association: VSD outlier OR: 1.54 vs. MI: 1.8 ● Death: VSD outlier OR: 3.2 similar to MI; TOF and TGA suggesting severe Bethesda categorization.	● Mortality risk is increased with the presence of VSDs and certain comorbidities.
Opotowsky AR, et al. 2009 (10) 19628123	Observational, case control, retrospective	n=35,000–72,450 ACHD hospitalizations/y	Inclusion criteria: US, ACHD, ≥18 y admit to acute care hospital	Bethesda 32	Rise in admissions, mortality, comorbidity, LOS, costs	● Rise 0.0001 (complex vs. simple, not seen for unclassified), comorbidities: 0.006 (complex), LOS longer complex (<0.001), costs greater simple (<0.0003) (unclassified shorter and cheaper).	● Number of hospital admissions and costs have risen.
O'Leary JM, et al. 2013 (11) 23471480	Observational, case control, retrospective	n=950,00 adult ACHD and 1,900,000 pediatric CHD pt admissions from nationwide inpatient sample	Inclusion criteria: US pts with ACHD, ≥18 y, admit to acute care hospital	Bethesda 32	Rise in admissions	● From beginning to end of study period, admissions for simple defects changed 112% unclassified 52% and complex 52%. Adult admissions increased from	● Adults account for an increasing proportion of CHD admissions from 1998–2010.

						28.9%–36.5% of CHD admission.	
Marelli AJ, et al. 2014 (12) 24944314	Observational	Quebec CHD Registry	Inclusion criteria: 1983–2000, Quebec, ≥18 y, ACHD health interaction, 107,559	Bethesda 32 (severe vs. other)	Lifetime and point prevalence of CHD.	● In 2010, adults represent 60% (57%, 62%) of all severe CHD vs. 49% (47%, 51%) in 2000; prevalence severe lesions increased 55% (51%, 62%) in adults vs. 19% (17%, 21%) increase in children.	● There is a need for longitudinal data sources in U.S.

Data Supplement 2. Severity of ACHD – Section 2.2

Study Name, Author, Year	Study Type/Design	Study Size	Inclusion/ Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
Koyak Z, et al. 2013 (13) 24071387	Retrospective, multicenter	n=419 pts (mean 38 y ± 14 y)	Inclusion criteria: >18 y who underwent CHD cardiac surgery between Jan 2009–Dec 2011	Prevalence of postop in-hospital arrhythmias and clinical outcomes	● Arrhythmias occurred in 134 pts (32%) and included SVT (n=100), bradycardias (n=47), and VT (n=19). In multivariate analysis age ≥40 y at surgery (p=0.03), NYHA class ≥II (p=0.09), significant subpulmonary AV valve regurgitation (p=0.018), coronary bypass time, (p=0.019), and CK-MB (p=0.021) were associated with in-hospital arrhythmias. Overall, 58 clinical events occurred in 55 pts (13%) and included in the majority of the cases permanent pacemaker implantation (5%), HF (4%), and death (2%). ● In-hospital arrhythmias were independently associated with clinical events; p=0.01.	● Arrhythmias are highly prevalent after congenital heart surgery in adults and are associated with worse clinical outcome. ● Older and symptomatic pts with significant VHD at baseline are at risk of in-hospital arrhythmias.
Bouchardy J, et al. 2009 (14) 19822808	Population-based retrospective	n=5,812 pts with atrial arrhythmias (38,428 pts with CHD)	Inclusion criteria: Adults with CHD between 1983–2005 found in the Quebec administrative database	Prevalence, lifetime risk, mortality, and morbidity associated with atrial arrhythmia in adults with CHD	● Overall, the 20-y risk of developing atrial arrhythmia was 7% in a 20-y subject and 38% in a 50-y subject. >50% of pts with severe CHD reaching 18 y developed atrial arrhythmias by 65 y. In pts with CHD, the HR of any AE in those with atrial arrhythmia compared with those without was 2.50 (95% CI: 2.38–2.62; p=0.0001), with a near 50% increase in mortality (HR: 1.47; 95% CI: 1.37–1.58; p=0.001), more than double the risk of morbidity (stroke or HF) (HR: 2.21; 95% CI: 2.07–2.36; p=0.001), and 3 times the risk of cardiac interventions (HR: 3.00; 95% CI: 2.81–3.20; p=0.001).	● Atrial arrhythmias occurred in 15% of pts with CHD. ● Lifetime incidence increased steadily with age and was associated with a doubling of the risk of AE. ● An increase in resource allocation should be anticipated to deal with this increasing burden.

Koyak Z, et al. 2012 (15) 22991410	Multicenter case control study	n=1,189	Inclusion criteria: Pts >18 y with CHD s/p SCD presumed arrhythmic vs. 2 cases of ACHD pts without SCD	Determine the adult CHD population at risk of SCD and the clinical parameters associated with SCD	● Arrhythmic death occurred in 171 of 1,189 pts. Underlying cardiac lesions were mild, moderate, and severe CHD in 12%, 33%, and 55% of the SCD cases, respectively. Clinical variables associated with SCD were SVT (p=0.004), moderate-to-severe systemic ventricular dysfunction (p=0.034), moderate-to-severe subpulmonary ventricular dysfunction (p=0.030), increased QRS duration (p=0.008), and QT dispersion (p=0.008).	● Clinical parameters found to be associated with SCD in adults with a broad spectrum of CHD, including SRV, are similar to those in ischemic HD. ● Pts with mild cardiac lesions are potentially at risk for SCD.
Yap SC, et al. 2011 (16) 21684512	Retrospective database review	n=378 adult pts with CHD (mean 39 ± 13 y) and atrial arrhythmia who had serial follow-up in a tertiary referral center from 1999–2009.	Inclusion criteria: Adult pts with CHD and atrial arrhythmia who were followed serially from Jan 1999–Dec 2009 in the Toronto Congenital Cardiac Centre for Adults	Identify predictors of mortality in adult with CHD and atrial arrhythmia and to establish a risk score	● During a median follow-up of 5.2 y, there were 40 deaths (11%). Overall mortality rate was 2.0%/pt-y. Common modes of death included HF–related death (35%), SCD (20%), and perioperative death (18%). ● Independent predictors of mortality were poor FC, (p=0.001), single ventricle physiology, (p=0.003), PH (p=0.004), and VHD, (p=0.006). ● A risk score was constructed using these predictors in which pts were assigned 1 point for the presence of each risk factor. Mortality rates in the low-risk (no risk factor), moderate-risk (1 risk factor), and high-risk (>1 risk factor) groups were 0.5%, 1.9%, and 6.5%/pt y, respectively (log-rank p<0.001).	● Specific clinical variables identify pts with CHD at high risk for death. ● Absence of these risk factors is associated with an excellent survival despite the presence of atrial arrhythmias.
Giannakoulas G, et al. 2012 (17) 21196055	Retrospective database review	n=98 pts, mean 31.5 ± 8.9 y, 43.8% male, 31.6% with a total cavopulmonary connection were identified	Inclusion criteria: Pts with previous Fontan operation followed at our institution since 1999 were identified from the electronic database and included in this study	Impact of atrial arrhythmia on adult Fontan pts	● Atrial tachyarrhythmia was present at baseline in 60.2% of pts who were older (33.0 ± 8.3 vs. 29.1 ± 9.4 y; p=0.002), less likely to have a total cavopulmonary connection (13.5% vs. 58.9%; p<0.001), and more symptomatic in terms of NYHA class (51.9% vs. 26.7%; p=0.007) compared to arrhythmia-free pts. ● During a median follow-up of 6.7 y, 18 pts died and 64 pts were hospitalized. Even after adjustment for baseline clinical characteristics, atrial tachyarrhythmia was an independent predictor of death (propensity score adjusted HR: 9.35; 95% CI: 1.10–79.18; p=0.04; c-statistic 0.88) and composite of death or hospitalization (propensity score adjusted HR: 5.00; 95% CI: 2.47–10.09; p<0.0001).	● In adult pts with a Fontan-type operation, the presence of atrial tachyarrhythmias is associated with higher morbidity and mortality at midterm follow-up.
Collins RT, et al. 2013 (18) 24102747	Retrospective database review	n=803 pts with1,333 hospital admissions of	Inclusion criteria: Pts >18 y of with single ventricle admitted	Identify the impact of cardiac arrhythmias on hospitalizations in	● There were 642 admissions in 424 pts with single ventricle CHD and an arrhythmia diagnosis. A single arrhythmia diagnosis was present in 454 admissions (71%).	● In adults with single ventricle CHD, arrhythmias are affected by single ventricle anatomic subtype

		TA, HLHS, or CV from 43 participating hospitals	to 1 of 43 pediatric hospitals between 2004–2011	adults with single ventricle CHD	● Total hospital charges were $80.7 million with mean charge per admission of $127,296 ± 243,094. The mean charge per hospital was $16,653 ± 17,516 and increased across the study period (p<0.01). ● Arrhythmia distributions were impacted by single ventricle anatomic subtype (p<0.001). ● Hospital resource utilization was significantly different among arrhythmia groups (p<0.001).	and impact adversely upon hospital resource utilization.
Diller GP, et al. 2010 (19) 20929979	Retrospective database review	n=321 Fontan pts (57% male, mean age 20.9 ± 8.6 y)	Inclusion criteria: Fontan pts who underwent CPET at 4 major European centers between 1997–2008 were included	To clarify if exercise intolerance is associated with poor outcome in Fontan pts and to identify risk factors for mortality, transplantation, and cardiac-related hospitalization.	● During a median follow-up of 21 mo, 22 pts died and 6 pts underwent cardiac transplantation (8.7%), resulting in an estimated 5 y transplant-free survival of 86%. ● Parameters of CPET were strongly related to increased risk of hospitalization, but with the exception of heart rate reserve-unrelated to risk of death or transplantation. In contrast, pts with clinically relevant arrhythmia had a 6.0–fold increased risk of death or transplantation (p<0.001). Furthermore, pts with atriopulmonary/ventricular Fontan had a 3.7-fold increased risk of death or transplantation compared with total cavopulmonary connection pts (p=0.009). ● The combination of clinically relevant arrhythmia, atriopulmonary/ventricular Fontan, and signs of symptomatic or decompensated HF was associated with a particularly poor outcome (3 y mortality 25%).	● Most parameters of CPET are associated with increased risk of hospitalization but not death or transplantation in contemporary Fontan pts. ● Only decreased heart rate reserve and a history of clinically relevant arrhythmia, atriopulmonary/ventricular Fontan, and/or HF requiring diuretic therapy are associated with poor prognosis, potentially identifying pts requiring medical and/or surgical attention.
Shamszad P, et al. 2014 (20) 23682693	Retrospective review	n=3,800,964 hospitalizations	Inclusion criteria: All index cases of pts <30 y hospitalized with aortic dissection Jan 2004–June 2011	To describe the incidence, characteristics, and outcomes of hospitalized children and young adults with AD	● AD was identified in 124 (<1%), accounting for 110 pts (69% male; p=0.003) at a median age of 12.9 y (IQR 3.9–16.8 y) with a bimodal distribution in infancy and late adolescence. ● Associated diagnoses included CHD (38%), trauma (24%), connective tissue disease (16%), and isolated HTN (8%). ● Common CHD diagnoses included aortic arch (24%) and valve (21%) disease, HLHS (10%), and TGA (10%). ● CHD pts were younger and more likely to undergo inpatient non-AD–related CV procedures compared with other diagnostic groups (p<0.001 for both). Marfan	● AD is rare in children and young adults but most commonly occurs in CHD and connective tissue disease and in males. ● AD is associated with high inpatient mortality.

					and Ehlers-Danlos syndrome were present in 72% and 11% of connective tissue disease pts, respectively. ● Overall in-hospital mortality in pts with aortic dissection was 13% compared with 1% in the database population (OR: 12.0; 95% CI: 6.9–21.1). By diagnostic category, mortality was 22% in HTN, 22% in connective tissue disease, 12% in CHD, and 4% in trauma.	
Roberts CS and Roberts WC 1991 (21) 1993792	Retrospective review	n=186 pts with noniatrogenic aortic dissection were studied at necropsy	Inclusion criteria: Noniatrogenic aortic dissection found at necropsy over 30-y period	The association of congenital aortic valve malformation and aortic dissection	● The aortic valve was tricuspid in 170 (91.4%), bicuspid in 14 (7.5%), and unicuspid in 2 (1.1%). Among the 16 pts with aortic dissection and a congenitally malformed valve, the age at death ranged from 17–82 y (mean 52 y) and 13 (81%) were men.	● A congenitally malformed aortic valve appears to be present at least 5 times more frequently in with aortic dissection, ● In this sample of pts, the entrance tear was consistently in the ascending aorta, which usually had severe loss of elastic fibers in its media.
Schwartz ML, et al. 2004 (22) 15364851	Retrospective review	n=335 pts	Inclusion criteria: Pts were identified who underwent ASO for d-TGA with intact ventricular septum or VSD, including DORV, before 2001 with at least 1 postoperative echo at our institution, at least 1 y after ASO, and no previous ASO (median follow-up of 5.0 y)	We sought to identify predictors of aortic root dissection and aortic root after ASO.	● Probability of freedom from aortic root dissection was 97%, 92%, 82%, and 51%, from at least moderate aortic root was 98%, 97%, 96%, and 93%, and from neo-aortic valve or root surgery was 100%, 100%, 99%, and 95%, at 1, 2, 5, and 10 y, respectively. For pts in whom aortic root dissection developed, progressive dilation was not observed during late follow-up. ● By Kaplan–Meier method, independent predictors of aortic root dissection, with neo-aortic root z-score of ≥3.0, were previous PA band (HR: 2.4; p=0.002) and later time period when ASO was performed (HR: 19.0; p<0.002). Risk factor for at least moderate aortic root was age ≥1 y at ASO (HR: 5.8; p=0.002), which was closely related to VSD repair at ASO (p<0.001) and previous PA band.	● Significant aortic root dissection and aortic root continue to develop over time after ASO, but aortic root dissection does not tend to be progressive during late follow-up. ● Previous PA band was a significant risk factor for aortic root dissection. ● Older age at time of ASO, presence of VSD, and previous PA band were risk factors for AR.
Cohen MS, et al. 2003 (23)	Retrospective review	n=53 pts	Inclusion criteria: Pts with HLHS born	We sought to assess the prevalence and	● During follow-up, the neo-aortic root progressively dilated out of proportion to body size over time, with 52 pts (98%) having a z-score >2 at most recent follow-up.	● After staged reconstruction for HLHS, neoaortic root dilation and

12906985			before January 1995 who had the Fontan operation and had serial echos were included	progression of neo-aortic root dilation and valvar regurgitation after staged reconstruction for HLHS	Neo-aortic root was present in 61% of pts at most recent follow-up, with progression over time in 26 pts (49%).	neo-aortic root progress over time. ● Early volume unloading does not have a beneficial impact on dilation of the neo-aortic root. ● These findings raise concerns about neoAV function into adulthood.
Carlo WF, et al. 2011 (24) 21545468	Retrospective review	n=76 pts with truncus arteriosus	Inclusion criteria: Truncus arteriosus and recent echo	We sought to delineate root dimensions across a population of pts with truncus arteriosus.	● 76 pts whose most recent study was at a median age of 5.4 y (range 0–32.7 y). ● Mean truncal root z-score was 5.1 ± 2.3. All but 3 pts had truncal root z-scores ≥2. Truncal root z-scores remained stable with increasing body surface area and age. ● There were no cases of dissection or rupture. 6 pts underwent truncal root surgery, typically for indications of root dilation with significant truncal valve insufficiency and LV dilation.	● Although repeat surgical intervention was rare and major complications related to root dilation did not occur in our cohort, further studies with longitudinal follow-up into adulthood are needed.
Egan M, et al. 2009 (25) 19357906	Case report	Single-case report of aortic dissection	Inclusion criteria: N/A	Single ventricle Fontan	● 26-y-old man with a history of HLHS, mitral and PV atresia, and malposed great vessels presented with atypical chest pressure. ● Previous palliation included a lateral tunnel modified Fontan. ● The man's physical exam demonstrated aortic insufficiency. TTE showed severe dilation of the aortic root measuring 7.8 cm, severe aortic regurgitation, and moderate global RV systolic dysfunction.	● Those with single ventricle Fontan are at risk for AD.
Van der Linde D, et al. 2013 (26) 23164590	Retrospective review	n=414 pts	Inclusion criteria: All adult pts with congenital valvular AS, who attended the outpt clinic for adult CHD of a participating center, between January 2005 and October	To evaluate the progression rate of AS and aortic dilatation in a large multicenter retrospective cohort of asymptomatic young adults with congenital valvular AS	● A total of 414 pts (age 29 ±10 y, 68% male) were included. Median follow-up duration was 4.1 y (2.5–5.1 y) (1,587 pt-y). ● Aortic dilatation was present in 34% at baseline and 48% at follow-up (p<0.001). The aortic diameter linearly increased over time with a rate of 0.7 ± 0.2 mm/y. Rate of aortic dissection was 0.06% per pt y.	● ADs rarely occur; aortic dilatation is common and steadily progresses over time, warranting serial aortic imaging.

			2011 were identified. Eligible pts were selected from prospective databases: the CONCOR database (the Dutch registry for adult pts with CHD, and the Leuven and Toronto database for adults with CHD. Inclusion criteria were 18–55 y and a baseline peak aortic velocity >2.5 m/s. Pts had to have serial echocardiographic examinations at least 1 y apart			
Lowe BS, et al. 2013 (27) 21777753	Retrospective longitudinal cohort study	n=38,430 adult pts living with CHD in 2005	Inclusion criteria: 2 retrospective cohorts from Quebec's CHD database that included pts age ≥18 y. The study population for the prevalence objective included all adults with CHD alive in 2005, irrespective of a PH diagnosis in the database	The aim of this study was to assess the impact of the diagnosis of PH on mortality, morbidity, and health services utilization in an ACHD population.	● 2,212 (5.8%) had diagnoses of PH (median age 67 y, 59% women). The diagnosis of PH increased the all-cause mortality rate of adults with CHD more than 2-fold compared with pts without PH (HR: 2.69; 95%; CI: 2.41–2.99). ● Morbid complications including HF and arrhythmia occurred with a 3-fold higher risk compared with pts without PH (HR: 3.01; 95% CI: 2.80–3.22). ● The utilization of inpatient and outpatient services was increased, especially cardiac catheterization.	● A diagnosis of PH in adults with CHD is associated with a more than 2-fold higher risk for all-cause mortality and 3-fold higher rates of health services utilization, reflecting high morbidity.

			over the past 23 y			
Verheugt CL, et al. 2010 (28) 20207625	Retrospective database review	n=6,933 pts from CONCOR ACHD database	Inclusion criteria: CONCOR database 2001–2009, adults with CHD >18 y	Dutch CONCOR national registry for adults with CHD to assess mortality and causes of death, and to determine which CV complications predict mortality in adults with CHD.	● Of 6,933 pts, 197 (2.8%) died during a follow-up of 24,865 pt-y. Compared with the general national population, there was excess mortality, particularly in the young. ● Median age at death was 48.8 y. Of all deaths, 77% had a CV origin; 45% were due to chronic HF (26%, age 51.0 y) or SCD (19%, age 39.1 y). Age predicted mortality, as did sex, severity of defect, number of interventions, and number of complications (HR: 1.1–5.9; p=0.05). Several complications predicted all-cause mortality, i.e., IE, SVA, ventricular arrhythmias, conduction disturbances, MI, and PH (HR: 1.4–3.1; p=0.05). These risks were similar in pts ± 40 y. Almost all complications predicted death due to HF (HR: 2.0–5.1; p=0.05); conduction disturbances and PH predicted SCD (HR: 2.0–4.7; p=0.05).	● Mortality is increased in adults with CHD, particularly in the young. ● The vast majority die from CV causes. Mortality risk, particularly by HF, is increased by virtually all complications. ● Complications are equally hazardous in younger as in older pts.
Chen SS, et al. 2014 (29) 24631116	Retrospective database review	n=247 pts (33.0 ± 12.8 y, 60% male)	Inclusion criteria: ACHD pts with CoA who had undergone a CMR imaging	The prevalence of restenosis and dilatation at the repair site and the long-term outcome in pts with repaired CoA	● Restenosis (repair site-diaphragm ratio ≤70%) was present in 31% of pts (and significant in 9% [repair site-diaphragm ratio<50%]), and dilatation (repair site-diaphragm ratio>150%) in 13.0%. A discrete aneurysm at the repair site was observed in 9%. Restenosis was more likely after resection and end-end anastomosis, whereas dilatation after patch repair. ● Systemic HTN was present in 69% of pts. ● Of the hypertensive pts, BP (133 ± 20/73 ± 10 mm Hg) was well controlled in 93% with antihypertensive therapy. Mortality rate over a median length of 5.9 y was low (0.69%/y; 95% CI: 0.33–1.26), but significantly higher than age-matched healthy controls (standardized mortality ratio: 2.86; 95% CI: 1.43–5.72; p<0.001).	● Restenosis or dilatation at the CoA repair site as assessed by CMR is not uncommon. Medium term survival remains good; however, albeit lower than in the general population. ● Life-long follow-up and optimal BP control are likely to secure a good longer-term outlook in these pts.
Dimopoulos K, et al. 2010 (30) 20026774	Retrospective review	n=229 pts (aged 34.5 ± 12.6 y; 35.4% male)	Inclusion criteria: Adult Eisenmenger pts followed at tertiary center over past 10 y	Examined the potential effect of advanced PH therapy on survival with Eisenmenger syndrome	● During a median follow-up of 4.0 y, 52 pts died, only 2 of them while on advanced therapy. Pts on advanced therapy were at a significantly lower risk of death, both unadjusted and after adjustment for baseline clinical differences by propensity score regression adjustment (HR: 0.16; 95% CI: 0.04–0.71; p=0.015) and propensity	● Advanced therapy for pulmonary arterial HTN in a contemporary cohort of adults with Eisenmenger syndrome was associated with a lower risk of death.

					score matching (HR: 0.10; 95% CI: 0.01–0.78; p=0.028).	● Survival benefits should be considered together with improved hemodynamics and FC when decisions are made about advanced therapy in this population.
Drenthen W, et al. 2010 (31) 20584777	Retrospective review	n=1,802 pts	Inclusion criteria: Females in large dataset with CHD completing pregnancy	Outcome of pregnancy in women with CHD	● The most prevalent cardiac complications during pregnancy were arrhythmias (4.7%) and HF (1.6%). ● Factors independently associated with maternal cardiac complications were the presence of cyanotic HD (corrected/uncorrected) (p<0.0001), the use of cardiac medication before pregnancy (p<0.0001), and left heart obstruction (p<0.0001). New characteristics were mechanical valve replacement (p=0.0014), and systemic (p=0.04) or pulmonary AV valve regurgitation related with the underlying (moderately) complex CHD (p=0.03).	● In a tertiary CHD cohort, cardiac, obstetric, and neo-natal complications were frequently encountered, and (new) correlations of maternal baseline data with adverse outcome are reported. ● A new risk score for adverse cardiac complications is proposed, although prospective validation remains necessary.
Cook SC, et al. 2013 (32) 23279961	Prospective case study	n=43 pts with CoA	Inclusion criteria: Adults with CoA who underwent cerebral CTA/MRA.	Prospectively perform CTA of the intracranial vessels in adults with CoA to evaluate the prevalence and identify high-risk features of this complication	● 5 pts (11%) were found to have IA. Pts with intercranial aneurysms were older than those without (45.6 ± 8.17 vs. 30.89 ± 7.89; p=0.0003). ● There were no statistically significant differences detected between measurements of fasting lipid profiles, C-reactive protein, BNP, and homocysteine levels among CoA pts with and without intercranial aneurysms (p= NS).	● Prospective screening of adults with CoA confirmed the increased prevalence of intercranial aneurysms but also identified increased age as the sole risk factor. These data suggested that screening is justified particularly in the 4th and 5th decades of life. ● Further studies are required that focus on the development, natural history, and treatment of IA.
Bottega NA, et al. 2012 (33) 20934761	Retrospective	n=112 pts with d-TGA Mustard	Inclusion criteria: Pts >18 y with d-TGA and a Mustard	Frequency of superior limb stenosis in d-TGA Mustard	● Narrowing of the superior limb of systemic venous baffle was observed in 49/112 pts (70 males) 31 ± 6 y (range 18c49) and was hemodynamically significant in 15/49.	● In this cohort of Mustard pts, narrowing of the systemic venous baffle had a prevalence of 44% and

			procedure with and without a pacemaker/ICD were identified through an institutional database		● Of 29 pts with a pacemaker (23) or ICD (6) and cardiac imaging, 17 had narrowing of the systemic venous baffle, which was hemodynamically significant in 8. ● Nonechocardiographic imaging had a sensitivity of 88% at detecting narrowing of the systemic venous baffle in contrast to pulse-wave Doppler, which yielded a sensitivity of 16% (61% NPV, 88% positive predictive value).	was more likely to be detected by nonechocardiographic imaging. ● Baffle patency should be evaluated before transvenous device implantation.
Gupte PA, et al. 2014 (34) 23834022	Retrospective case control	n=50 autopsied cases of cyanotic CHD	Inclusion criteria: Cyanotic CHD pts who underwent autopsy	This study was undertaken for an objective analysis of histopathological changes of cyanotic nephropathy at autopsy	● The renal changes observed were glomerulomegaly, glomerulosclerosis, periglomerular fibrosis, hyperplastic arteriolosclerosis, and interstitial fibrosis. ● The objectively measured parameters were higher in cases as compared with controls in all age groups, and further these were also found to be higher in pts having decreased pulmonary arterial blood flow than those having normal to increased pulmonary arterial blood flow.	● Pts with critical CHD show significant changes in the kidneys as assessed morphometrically, leading to renal dysfunction, and the age of the pts plays a role in their development.
Ammash N and Warnes CA 1996 (35) 8772770	Retrospective	n=162 pts with cyanotic CHD (mean age 37 y, range 19–70)	Inclusion criteria: Pts with cyanotic CHD between 1988–1995 with cerebrovascular events that occurred at ≥18 y	We sought to determine the frequency of spontaneous cerebrovascular events in adult pts with cyanotic CHD and to evaluate any contributing factors.	● 22 pts (13.6%) had 29 cerebrovascular events (1/100/pt-y). ● There was no significant difference between those with and without a cerebrovascular event in terms of age, smoking history, degree of erythrocytosis, EF, or use of aspirin or warfarin (Coumadin). Pts who had a cerebrovascular event had a significantly increased tendency to develop HTN, AF, microcytosis (mean corpuscular volume <82) and history of phlebotomy ($p<0.05$). Even when pts with HTN or AF were excluded, there was an increased risk of cerebrovascular events associated with microcytosis ($p<0.01$).	● Adults with cyanotic CHD are at risk of having cerebrovascular events. Risk is increased in the presence of HTN, AF, history of phlebotomy, and microcytosis, the latter condition having the strongest significance ($p<0.005$). ● This finding leads us to endorse a more conservative approach toward phlebotomy and a more aggressive approach toward treating microcytosis in adults with cyanotic CHD.

Data Supplement 3. Access to Care and Delivery of Care – Sections 3.2 and 3.3

Study Name, Author, Year	Study Type/ Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
Meijboom F, et al. 2010 (36) 20800805	Review article	N/A	Inclusion criteria: N/A	N/A	N/A	● Too few ACHD centers in Europe to care for the predicted population.
Gurvitz M, et al. 2013 (6) 23542112	Observational cross-sectional multicenter prospective questionnaire	n=922 pts	Inclusion criteria: Pts >18 y, first presentation to ACHD clinic	>3 y gap in CV care	● Disease complexity predictive of gap in care in 59% of simple, 42% of moderate, and 26% of complex pts (p<0.01).	● The study provides a basis for improving strategies for dealing with the barriers to care.
Beauchesne LM, et al. 2012 (37) 21190745	Prospective	15 CACH centers; ~21,000 pts	Inclusion criteria: Outpatient and procedural volumes data	Number of pts in ACHD care, time to nonurgent consult, intervention, surgery	● Only a small proportion of ACHD in care at centers, longer waiting times than targets.	● The ACHD guidelines and process measures are not being complied.
Patel MS and Kogon BE 2010 (38) 20063158	Database review	Clinic directory	Inclusion criteria: Data for number of pts, provider training, and other characteristics	Numbers of pts in centers, procedures performed well below estimates.	N/A	● The data should provide a basis for improved accessibility of services.
Marelli AJ, et al. 2009 (39) 19081390	Data analysis	Population based study	Inclusion criteria: ACHD pts in U.S and Canada	Estimates of population size, number of centers needed per population to allow access to care	N/A	● 1 regional ACHD center for a 2 million adult pt population is required for specialized care of pts with ACHD.
Gurvitz MZ, et al. 2007 (40) 17320746	Retrospective data analysis	Population of California	Inclusion criteria: Pts 12–44 y, with a 1° or 2° ICD-9-CM code for CHD	Increase in admit from ED around transition age. Care divided among ACHD and non-ACHD centers	N/A	● More studies into clinical outcomes, use of services, and healthcare disparities are warranted.
Shirodaria CC, et al. 2005 (41) 16061123	Case report	Output clinic in the UK	Inclusion criteria: N/A	Evaluating a model of care for pts in a local/district clinic. Program successful and no-show rate lower than spec clinic	N/A	● Data useful for planning a CHD center.
Mackie AS, et al. 2014 (42) 24842870	Prospective	n=58 pts	Inclusion criteria: Pts 15–17 y with moderate or complex CHD	N/A	● NS	● Educational intervention was beneficial to CHD knowledge.

Mylotte D, et al. 2014 (7) 24589851	Epidemiologic	n=71,467 pts from Quebec CHD Registry; 2,092 ACHD death cases	Inclusion criteria: Pts with ACHD,18–65 y, between 1983–2005	Pts in specialized care had lower mortality; mostly driven by the most complex CHD group	● Increased care for severe in specialty ACHD centers (p<0.01); increased mortality for severe ACHD (OR: 1.93).	● Study promotes specialized care for the pts.
Sable C, et al. 2011 (43) 21357825	Scientific Statement from AHA	N/A	Inclusion criteria: N/A	N/A	N/A	● Discusses topics and recommendations related to transitioning and transferring pts from pediatric to adult-centered care.
Christman MP, et al. 2013 (44) 23984096	Retrospective	n=175 female pts in single center compared to general population	Inclusion criteria: Pts ≥18 y with ACHD or non-ACHD HD	Preventive screening for Cancer based on American Cancer Society guidelines	● Cancer screening in ACHD pts does not meet recommended overall screening rates	● Improve screening practices by 1°care and CHD providers and better communication for long-term care planning.
Karamlou T, et al. 2008 (45) 18997167	Epidemiologic	National inpt sample 1988–2003	Inclusion criteria: Pts ≥18 y with operation and 1 of 12 CHD diagnoses	In-hospital death rates following surgical procedures	● Congenital heart surgeries in adults performed by pediatric heart surgeons had lower in-hospital death rates.	● Study promotes that congenital heart surgery in adults should be performed by experienced congenital heart surgeons.

Data Supplement 4. Catheter Interventions

Study Name, Author, Year	Document Aim	Study Type (Size, N)	Patient Population	1° Endpoints	Comments
Ruiz CE, et al. 2010 (46) 20850086	N/A –Training recommendations for Structural and Congenital Interventions in adults	N/A	Inclusion criteria: Adults with CHD or structural HD	Describes necessary training competencies for interventional cardiologists performing procedures in adults with CHD and adults with structural HD	● Document is expert consensus from Society of Cardiac Angiography and Intervention but does not have specific outcomes data.
Armsby L, et al. 2014 (47) 24890705	N/A – Training recommendations for Congenital Interventions in Children	N/A	Inclusion criteria: Pediatric cardiac pts	Describes necessary training competencies for pediatric interventional cardiology procedures	● Document is expert consensus from Society of Cardiac Angiography and Intervention but does not have specific outcomes data.

Data Supplement 5. Surgery

Study Name, Author, Year	Study Type/Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/ p Values	Summary/Conclusions
Karamlou T, et al. 2008 (45) 18997167	Systematic review	n=30,250 cases	Inclusion criteria: Children and adults with CHD undergoing surgery for 1 of 12 CHD diagnoses	In hospital death lower for pts operated on by pediatric heart surgeons	N/A	● Study promotes that congenital heart surgery in adults should be performed by experienced congenital heart surgeons
Lamour JM, et al. 2009 (48) 19573734	Systematic review	n=488 pts	Inclusion criteria: Children and adults undergoing transplant for CHD	Survival at 3 mo, 1 y, and 5 y	● Population mean age 12.4 y. Single ventricles (36%), d-transposition (12%), RVOT lesions (10%) were most common diagnoses. 93% were reoperations. Survival at 3 mo worse than pediatric with cardiomyopathy but not adults. 5-y survival 80% with lower survival in Fontan pts (77% and 70% at 1 and 5 y.	● Single ventricles (36%), d-transposition (12%), RVOT lesions (10%) were most common diagnoses. 93% were reoperations. ● Survival at 3 mo worse than pediatric with cardiomyopathy but not adults. 5-y survival 80% with lower survival in Fontan pts (77% and 70% at 1 and 5 y).
Mascio CE, et al. 2011 (49) 21911232	Systematic review from the STS database	n=5,265 pts from 68 centers	Inclusion criteria: Adults undergoing CHD surgery	Mortality	● Mean age 25 y, preoperative risk factors included noncardiac abnormalities, arrhythmias. Mortality overall was 2.1%, common procedures were RVOT procedures (21%) and pacemaker/ arrhythmias. Fontan revision was the highest risk procedure (11% mortality)	● Mean age 25 y, preoperative risk factors included noncardiac abnormalities, arrhythmias. Mortality overall was 2.1%, common procedures were RVOT procedures (21%) and pacemaker/arrhythmias. Fontan revision was the highest risk procedure (11% mortality).
Horer J, et al. 2013 (50) 22491664	Systematic review of European Association for Cardio-Thoracic Surgery Congenital Database	n=542 operations, 773 procedures	Inclusion criteria: CHD pts ≥16 y undergoing surgery at 1 institution from 2005–2008	Morbidity and mortality of surgery	● Mean age 30 y. Early mortality 2.4%, early complications in 53.7%. TVR, mitral valve replacement, elevated	● Mean age 30 y. Early mortality 2.4%, early complications in 53.7%. TVR, mitral valve replacement, elevated lung

					lung resistance, hypothyroidism, and redo sternotomy associated with higher 30-d mortality and complications. Aristotle score may be helpful in risk estimation.	resistance, hypothyroidism, and redo sternotomy associated with higher 30-d mortality and complications. Aristotle score may be helpful in risk estimation.
van Gameren M, et al. 2011 (51) 20846873	Single center cohort	n=963 pts	Inclusion criteria: Adult pts who had congenital cardiac surgery at a single institution between 1990–2007	Morbidity and mortality of surgery	● Applied existing CHD surgical risk scores to ACHD pts. RACHS-1, Basic Aristotle, STS, European Association for Cardio-Thoracic Surgery, and Comprehensive Aristotle Score were calculated, and an age component was also added to each. Best performing risk tool was Comprehensive Aristotle score with an age component.	● Applied existing CHD surgical risk scores to ACHD pts. RACHS-1, Basic Aristotle, STS, European Association for Cardio-Thoracic Surgery, and Comprehensive Aristotle Score were calculated and an age component was also added to each. Best performing risk tool was Comprehensive Aristotle Score with an age component.
Kogon B, et al. 2014 (52) 24252941	Comparison of pediatric risk scoring systems in predicting outcomes in ACHD surgery	n=458 operations	Inclusion criteria: Adults undergoing CHD surgery	Mortality and major events	● Aristotle, STAT, and RACHS-1 are predictive of outcomes in adults undergoing CHD surgery, STAT, and Aristotle were most predictive.	● Aristotle, STAT, and RACHS-1 are predictive of outcomes in pts undergoing CHD surgery; STAT and Aristotle were most predictive.
Gajjar TP, et al. 2011 (53) 21793931	Single-center case series	n=48 pts	Inclusion criteria: Pts with sinus venous ASD who underwent transcaval repair between Jan. 2007—Oct. 2010	Surgical outcome	● All pts came off bypass in sinus rhythm. ● Average pressure gradient across patch: 3 mm/Hg. ● Immediate postop ECGs and echos showed all pts in sinus rhythm with no residual	● Single patch technique is safe and simple for sinus venous ASD and preserves sinoatrial node function after surgery.

					shunt and no pulmonary or systemic venous obstruction, except 1 pt who required SVC augmentation.	

Data Supplement 6. Ionizing Radiation Principles – Section 3.4.2

Study Name, Author, Year	Study Type/ Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
Johnson JN et al. 2014 (54) 24914037	Retrospective review	n=337 pts	Inclusion criteria: Children ≤6 y with specific surgical interventions	Cumulative radiation exposure and lifetime estimation of cancer risk	● Overall, radiation exposure low but most is attributable to catheterization and CT. Select cohorts have higher exposure and higher estimated cancer risk.	● Some cohorts of CHD children will have elevated lifetime estimated cancer risk based on childhood radiation exposure. Attention should be paid to limiting radiation exposure.
Glatz AC, et al. 2014 (55) 24321535	Retrospective data collection	n=4,132 pts	Inclusion criteria: Pts <18 y with CHD surgery from 1/1/00–7/31/09	Cumulative per pt radiation exposure total and annual	● Majority with low exposure; >5% with high exposure (>20 mSv/y). Higher exposures in neonates, those with more complex intracardiac disease.	● Some children with CHD have higher radiation exposure and possibly higher cancer risk in lifetime.
Eisenberg MJ, et al. 2011 (56) 21324846	Retrospective data collection	n=82,861 pts	Inclusion criteria: Pts with acute MI from 4/1/1996–3/31/2006 identified from Canadian administrative data	Radiation exposure, cancer cases and estimated cancer risk from radiation	● 3% increased cancer risk for every 10 mSv exposure.	● Increasing risk of age and sex adjusted cancer rates with increasing radiation exposure.
Yakoumakis E, et al. 2013 (57) 23093098	Prospective data collection and simulation study	n=53 pts	Inclusion criteria: Pts <18 y with ASD, VSD, and PDA undergoing cardiac catheterization	Organ specific simulated radiation exposure and cancer risk	● Increased radiation exposure and death risk for each lesion with ASD > VSD > PDA.	● Strategies to implement reduction in radiation exposure are necessary.
Brenner DJ, et al. 2003 (58) 14610281	Review article	N/A	Inclusion criteria: N/A	N/A	● Radiation doses where evidence suggests increased risk of cancer: acute exposure 10–50 mSv; prolonged or chronic exposure 50–100 mSv.	N/A
Andreassi MG, et al. 2006 (59) 16717079	Prospective data collection	n=32 cases, n=32 controls, n=10 newborns	Inclusion criteria: Cases – CHD with exposure to radiation testing between 1965–2000; Controls – healthy	Chromosomal damage	● Chromosomal damage greater in exposed subjects vs. controls or neonates.	● Evidence of long-lasting chromosomal abnormality may be related to radiation exposure.

			age and sex matched; Neonates – CHD but no procedures			

Data Supplement 7. Echocardiography – Section 3.4.3

Study Name, Author, Year	Study Type/Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
Bartel T, et al. 2005 (60) 15760685	Randomized controlled trial comparing ICE to TEE during transcatheter closure of ASD/PFO	n=80 pts (50 using ICE, 30 using TEE)	Inclusion criteria: Pts undergoing device closure of ASD (12) or PFO (68)	Adequacy of visualization; fluoroscopy and procedure time	● Spatial relationship between device and cardiac structures was accurately demonstrated by ICE. Image resolution provided by ICE was superior to that of TEE, and fluoroscopy time shorter.	● ICE is a safe tool to guide device closure of interatrial communications. For the pt, procedural stress and radiation exposure are negligible.
Boccalandro F et al. 2004 (61) 15224315	Prospective observational study for evaluation of TEE and ICE for sizing of ASD during percutaneous catheter closure, compared to quantitative fluoroscopic analysis	n=42 pts (21 having TEE and 21 having ICE)		Correlation of ASD size with quantitative fluoroscopic measurement	● Correlation between TEE and quantitative fluoroscopy ($r=0.898$; $p<0.001$) and between ICE and quantitative fluoroscopy ($r=0.876$; $p<0.001$), with a significant agreement ($p<0.001$).	● TEE and ICE are excellent methods of interatrial defect sizing when compared with quantitative fluoroscopic measurements.
Cao Q, et al. 2000 (62) 10806019	Prospective observational study to determine feasibility of transcatheter closure of multiple ASDs using 2 Amplatzer devices simultaneously and the role of 2D and 3D TEE	n=22 pts	Inclusion criteria: Pts with more than 1 ASD	Successful closure of multiple ASDs with devices	● 2D TEE was helpful in selection and in guiding correct deployment of the devices. ● 3D TEE provided superior imaging and demonstrated the number, shape, and the surrounding structures of the ASD in 1 single view. Closure successful in 98%.	● 2D and 3D TEE provided useful information for transcatheter closure of multiple ASDs using 2 devices. ● 3D TEE enhanced ability to image and understand the spatial relationship of the ASD anatomy.
Chien JC, et al. 2008 (63) 18772119	Prospective observational study to determine feasibility and accuracy of ICE for sizing ASDs compared with conventional methods	n=270 pts (142 had TEE, 128 had ICE)	Inclusion criteria: Pts going for transcatheter closure of secundum ASD with septal occluders	Comparison of ASD balloon stretched size using sizing plate with size determined by ICE, TEE, TTE and angiography	● ASD diameters measured with the sizing plate were significantly correlated with those measured with ICE ($r=0.963$), TEE ($r=0.912$), angiography ($r=0.88$), and TTE ($r=0.85$). The predicted stretched diameter of the ASDs (i.e., nonstretched diameter measured	● ASD diameters measured with ICE correlated with sizing-plate measurements better than those determined with TEE, angiography, or TTE.

					with ICE null 1.07) + 3.23 mm) agreed well with that measured by using a sizing plate (r=0.974).	
Mullen MJ, et al. 2003 (64) 12535824	Prospective observational study to determine feasibility study of ICE for device closure of ASD	n=24 pts	Inclusion criteria: Pts undergoing device closure of ASD who had ICE and TEE	Success in use of ICE to guide device closure of ASD	● ICE successfully guided closure of 24 out of 25 ASDs (96%) in 23 pts. ● There was close agreement between ICE and TEE in their assessment of device position and the adequacy of septal capture before device release (98%) and in identifying the presence of significant residual shunts. ICE detected all potentially AE	● ICE may be used to guide routine closure of ASDs in adults without the need for TEE and general anesthesia.
Ewert P, et al. 2000 (65) 10694522	Case series: description of technique for transcatheter closure of ASDs under TEE guidance without fluoroscopy	n=22 pts for ASD or PFO closure using TEE and control group of 131 pts who had closure using conventional fluoroscopy		Procedural success	● In the study group, Amplatzer septal occluder was successfully implanted in 19 defects without fluoroscopy with documented complete defect closure in all. ● Similar procedure times to control group.	● Transcatheter closure of interatrial communications with the Amplatzer septal occluder can be safely and successfully performed under echocardiographic guidance without fluoroscopy.
Grewal J, et al. 2010 (66) 19962272	Prospective observational study to compare 3D echo and cardiac MRI in assessment of RV	n=25 pts	Inclusion criteria: ACHD pts with severe PR following TOF repair or pulmonary valvotomy	RVEF, RVEDV, RVESV	● Mean RV EF were 42 ± 8% on 3D ultrasound and 44 ± 7% on MRI (r=0.89; p<0.0001). The mean end-diastolic volumes were 249 ± 66 and 274 ± 82 mL and the mean end-systolic volumes 147 ± 50 and 159 ± 60 mL on 3D ultrasound and MRI, respectively. ● Similarly, there were strong correlations of both end-diastolic volume and end-systolic volume on 3D ultrasound and MRI (r=0.88 and r=0.89, respectively).	● 3D ultrasound was comparable with MRI in determining RV size and function in pts with complex CHD.
Van der Zwaan HB, et al. 2010 (67)	Prospective observational study to compare 3D echo and	n=62 pts	Inclusion criteria: Various sorts of CHD	RVEF, RVEDV, RVESV	● Compared with CMR, RT3DE imaging underestimated RV end-diastolic and end-systolic volumes	● In the majority of unselected pts with complex CHD, RT3DE imaging

20152693	cardiac MRI in assessment of RV				and EF, with highly significant correlations (r=0.93, r=0.91, and r=0.74, respectively; p<0.001). Interobserver variability was reasonable.	provides a fast and reproducible assessment of RV volumes and EF with fair to good accuracy compared with CMR reference data.
Kaku K, et al. 2009 (68) 27278380	Prospective observational study to compare characterization of ASD by 3D echo compared to 2D echo	n=17 pts	Inclusion criteria: Pts with ASD being assessed for device closure	Descriptive report of usefulness of RT3DE	● Real-time 3D TEE allowed delineation of the en-face view of the ASDs. Successful delineation of rim length to the specific cardiac structure was 100% by 3D TEE and 88% by 2D TEE	● Real-time 3D TEE allows measurements of the temporal and spatial changes of ASD size and shape. This methodology provides detailed information on defect dynamics.
Lodato JA, et al. 2009 (69) 19179363	Prospective observational study to compare real time 3D echo vs. ICE during transcatheter closure of ASD	n=13 pts	Inclusion criteria: Pts undergoing transcatheter closure of ASD	Comparison of imaging with 3 modalities	● Real-time 3D imaging was feasible in all pts with similar results but larger balloon dimension measurement.	● RT3D TEE can be used to guide transcatheter ASD closure with the advantages of lower cost than ICE, and ability to visualize en-face views of the ASD.
Mojadidi MK, et al. 2014 (70) 24740212	Meta-analysis of prospective studies comparing TTE with 2nd harmonic imaging and TEE for the diagnosis of intracardiac left-to-right shunt	n=1,995 pts	Inclusion criteria: Prospective studies assessing for intracardiac right-to-left shunts using TTE with second harmonic imaging compared to TEE as the reference; both TTE with second harmonic imaging and TEE were performed with a contrast agent and a maneuver to provoke right-to-left shunting in all studies	Detection of right-to-left shunt	● Weighted mean sensitivity and specificity for TTE with second harmonic imaging were 90.5% (95% CI: 88.1–92.6) and 92.6% (95% CI: 91.0–94.0) respectively. The overall positive likelihood ratio was 13.52 (95% CI: 6.99–26.12) and the overall negative likelihood ratio was 0.13 (95% CI: 0.07–0.24.)	● TTE with second harmonic imaging is a reliable, noninvasive alternative diagnostic modality to TEE which is highly sensitive and specific for detecting right-to-left shunt.
Randolph GR, et al. 2002 (71) 12447184	Case series	n=1,002 pts	Inclusion criteria: Pediatric and adult pts who had TEE during surgery for congenital heart defects	Impact of intraoperative TEE on pt care (major impact was when new information altered the	● TEE had major impact prebypass or postbypass in 13.8% of cases (n=138/1002). Routine use of TEE for all pts with congenital heart defects proved cost-effective.	● Routine use of TEE during most intracardiac repairs of congenital heart defects is justified, particularly for pts undergoing repeat operations.

				planned procedure or led to a revision of the initial repair)		
Rigatelli G, et al. 2012 (72) 16821119	Prospective observational study to measure radiation exposure as a function of use of ICE	n=25 pts (15 with ICE guidance and 10 without)	Inclusion criteria: Pts undergoing transcatheter closure of interatrial communications	Multiple measures of radiation exposure	● In pts who underwent ICE-guided transcatheter closure procedure multiple measures of radiation exposure were significantly lower than in control pts, but the mean procedural time, was significantly higher	● Radiation exposure during ICE-guided transcatheter closure of interatrial communications was lower than radiation exposure of pts in whom the intervention was performed without ICE guidance.
Rigatelli G, et al. 2007 (73) 22010972	Prospective observational study, multicenter	n=56 pts	Inclusion criteria: Referred for catheter based closure of complex secundum ASD	Procedural success	16 pts excluded by preprocedure TEE. ● 40 pts underwent ICE-guided attempt at closure. TEE-planned device and size were modified in 32/40 pts based on ICE. Procedural success 100%; predischarge complete elimination of shunt 90%.	● ICE-guided complex secundum ASD transcatheter closure is safe and effective and appears to have excellent long-term results.

Data Supplement 8. CMR Imaging – Section 3.4.4

Study Name, Author, Year	Study Type/ Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
Arheden H, et al. 1999 (74) 10228528	Comparison of MR velocity mapping and radionuclide angiography done the same. Validation of MR velocity mapping in a phantom and controls	n=24 pts; n=12 controls	Inclusion criteria: 16 adults (20–68 y), 2 adolescents (13 and 17 y), and 6 children (2–12 y). Exclusion criteria: Nonsinus rhythm	Measurement of systemic and pulmonary flow	● In pts, Qp/Qs at radionuclide angiography was 14% ± 3, higher than at MR velocity mapping, and interobserver variability was 4 times higher 0% + 16 vs. 0% ± 4 (n=12)	● MR velocity mapping is accurate and precise for measurements of shunt size over the whole range of possible QP/QS values.
Blalock SE, et al. 2013 (75) 23418153	Prospective observational study of paired MRI examinations interpreted by 2 observers	n=30 pts	Inclusion criteria: Pts with repaired TOF having MRI	Degree of agreement between studies and between observers	N/A	● CMR measures of ventricular size and function have acceptable repeatability across serial examinations in pts with repaired TOF.

						● Measurements of RV mass are subject to higher variability. For most parameters, agreement limits are wider when measurements are performed by multiple operators.
Bonello B, et al. 2012 (76) 23177489	Review	N/A	Inclusion criteria: ACHD studies on repaired TOF, the systemic RV and Ebstein anomaly.	N/A	N/A	● CMR contributes to decision making regarding the types and timings of interventions. ● A dedicated CMR service should be regarded as a necessary facility of a center specializing in the care of ACHD pts.
Boxt, LM, et al. 2004 (77) 15170787	Review of relative utility of contrast enhanced CT and MRI in CHD	N/A	Inclusion criteria: N/A	Adequacy of imaging in CHD comparing 2 imaging modalities	● Intracardiac anatomy well depicted by MRI, and CT provides exquisite images of the great vessels. MR and CT are helpful in demonstrating and quantitating physiologic changes superimposed by acquired CV disease on the underlying congenital malformations. ● Using MRI, spin echo acquisitions provide the image data for evaluation of morphologic changes, and gradient reversal techniques add functional and flow data to complement morphologic changes. ● Contrast-enhanced ECG-gated multidetector and electron beam CT examination provide morphologic information and may be used as a data set for off-line functional quantitation.	● MRI and contrast-enhanced CT are complementary modalities.
Bunce NH, et al. 2003 (78) 12601193	Evaluate a simplified protocol by using free-breathing 3D coronary MRA to determine the	n=26 pts	Inclusion criteria: Suspected of having coronary artery anomalies	Adequacy of imaging of proximal anatomy of anomalous	● In 8 pts with anomalous arteries that coursed between the aortic root and the RVOT, conventional coronary angiography could not be used	● Free-breathing 3D coronary MRA can be used to identify the proximal anatomy of anomalous coronary arteries.

	anatomy of anomalous coronary arteries			coronary arteries using conventional coronary arteriography as a standard	confidently to identify the proximal course	
Crean AM, et al. 2011 (79) 22152255	Comparison of volumetric measurements of RV between CMR and 3D echo	25	Inclusion criteria: ACHD, expected to have a) near normal RV size, or b) expected to have moderate or worse RV enlargement	Comparison of results obtained with CMR and 3D echo or RVEDV, RVESV and RVEF	● Compared to CMR as the reference standard, significant and systematic underestimation of volume by 3D echo, which led to a mean underestimation of RVEDV by -34% (95% CI: -91%–23%). ● The degree of underestimation was more marked for RVESV with a bias of -42% (95% CI: -117%–32%). ● There was also a tendency to overestimate RVEF by 3D echo with a bias of ~13% (95% CI: -52%–27%)	● Meaningful differences in volumetric measurements were observed between the 2 techniques. ● 3D echo is not interchangeable with CMR for volumetric assessment of ACHD pts who have more than mild RV dilatation.
Festa P, et al. 2006 (80) 16547601	To test diagnostic accuracy of magnetic resonance	n=20 pts	Inclusion criteria: Pts with suspected PAPV return	Comparison of MRI results to cardiac catheterization and surgical anatomy	● Among pts who had both magnetic resonance and cardiac catheterization (14 pts) anatomical findings were concordant in 12 of them. In all operated pts, surgical findings were concordant with MRI report. ●There was a good correlation between magnetic resonance and cardiac catheterization QP/QS evaluation (mean value 2.23 and 2.4, respectively)	● MRI provides a comprehensive evaluation of pulmonary venous return and the amount of shunt and can be considered a noninvasive alternative to cardiac catheterization.
Kilner PJ, et al. 2011 (81) 22723533	Review	N/A	Inclusion criteria: N/A	N/A	●TTE is the first-line modality, but rarely adequate for all regions of interest. Choice of further imaging depends on the clinical questions that remain to be addressed, discussed in review	● Adults with relatively complex conditions should ideally be imaged in a specialist ACHD center, where dedicated echocardiographic and CV MRI services are a necessary facility.

Lewis MJ, et al. 2017 (82) 27893192	Retrospective study	ns=27 pts	Inclusion criteria: All adult pts with a Fontan who underwent serial CMRs	Results of CMR evaluation of hepatic disease over mean follow-up of 5.1. years	● CMR detects progressive liver and hepatic vein enlargement. Progressive hepatic congestion is common in adult Fontan pts and may be associated with ventricular dysfunction.	● Extending the MRA field to include hepatic imaging during CMR of adult Fontan pts should be considered as a cost-effective method to detect early liver disease in this population.
van der Linde D, et al. 2013 (83) 23305528	Comparison of TTE and CMR for evaluating aortic size	n=59 pts	Inclusion criteria: Pts with congenital AS and BAV	Size of aorta at multiple levels	● CMR was found to be superior to TTE for imaging of the aorta in pts with congenital AS, especially at the level of the proximal ascending aorta when an aortic aneurysm is present.	● Ideally CMR should be performed at least once in pts with congenital AS to ensure an ascending aortic aneurysm is not missed.
Prasad SK, et al. 2004 (84) 14718402	Comparative study: CMR vs. other modalities in the diagnosis of major aortopulmonary collateral arteries and PAPVC	n=29 pts	Inclusion criteria: Pts with diagnosis of major aortopulmonary collateral arteries or PAPVC, made by other modalities	Correlation between MRA and cardiac catheterization, echo, or surgical inspection	● Excellent correlation ● Additional information was gained for pts with major aortopulmonary collateral arteries on confluence and size of PA, PA stenosis, aneurysmal dilatation of PA and additional anomalous vascular abnormality (n=3). ● Shunt assessment, where present showed patency in all cases. For adults with PAPVD, further information was obtained on drainage origin.	● Contrast-enhanced 3D MRA provides a fast, noninvasive, radiation-free method of accurate and comprehensive diagnosis of major aortopulmonary collateral arteries and PAPVC in adult pts.
Puchalski MD, et al. 2007 (85) 18377513	Comparative study	n=22 pts	Inclusion criteria: Pts with right sided CHD, having had MRI and TTE within 6 mo each other	Comparison of standardized “eyeball” assessment of RV size and function by 4 echocardiographers to assessment by MRI	● Using echo, reliability for accurately identifying a severely dilated RV was "slight" with a prevalence-adjusted bias-adjusted Kappa of 0.25; and for identifying moderately to severely diminished RV systolic function was fair with a prevalence-adjusted bias-adjusted Kappa of 0.43. Inter-rater agreement analysis was poor for both with Kappas of 0.07 (p=0.22) and 0.12 (p=0.09), respectively.	● The usefulness of the echocardiographic "eyeball" method to estimate RV size and systolic function in pts with right HD has limitations when compared with MRI, specifically in regard to the variability between echocardiographers.
Taylor AM, et al.	Comparative study	n=25 pts	Inclusion criteria: Various types of CHD,	Definition of coronary origin	● MRCA results were more likely to agree with the consensus for	● The use of the combination of MRCA with x-ray coronary

2000 (86) 10758049			studied both by conventional coronary angiography and by magnetic resonance coronary angiography	and proximal course by consensus after independent blinded assessment	definition of the proximal course of the coronary arteries	angiography improves the definition of the proximal coronary artery course. ● MRCA provides correct spatial relationships, whereas x-ray angiography provides a view of the entire coronary length and its peripheral run-off.
Grewal J, et al. 2010 (66) 19962272	Comparative study: 3D echo and cardiac MRI in assessment of RV	n=25 pts	Inclusion criteria: ACHD pts with severe PR following TOF repair or pulmonary valvotomy	RVEF, RVEDV, RVESV	● Mean RV ejection fractions were 42 ± 8% on 3D ultrasound and 44 ± 7% on MRI (r=0.89; p<0.0001). The mean end-diastolic volumes were 249 ± 66 and 274 ± 82 mL and the mean end-systolic volumes 147 ± 50 and 159 ± 60 mL on 3D ultrasound and MRI, respectively. Similarly, there were strong correlations of both end-diastolic volume and end-systolic volume on 3D ultrasound and MRI (r=0.88 and r=0.89, respectively)	● 3D ultrasound was comparable with MRI in determining RV size and function in pts with complex CHD.
Van der Zwaan, et al. 2010 (67) 20152693	Comparative study: 3D echo and cardiac MRI in assessment of RV	62	Inclusion criteria: Various sorts of CHD	RVEF, RVEDV, RVESV	● Compared with CMR, RT3DE imaging underestimated RV end-diastolic and end-systolic volumes and EF, with highly significant correlations (r=0.93, r=0.91, and r=0.74, respectively; p<0.001). Interobserver variability was reasonable	● In the majority of unselected pts with complex CHD, RT 3D echo imaging provides a fast and reproducible assessment of RV volumes and EF with fair to good accuracy compared with CMR reference data.
Brenner DJ, et al. 2007 (87) 18046031	Review	N/A	Inclusion criteria: N/A	N/A	N/A	● A review of use of CT, benefits, and level of ionizing radiation to which subjects are exposed, with discussion of strategies to reduce that exposure.

Data Supplement 9. Cardiac Computed Tomography – Section 3.4.5

Study	Study Type/ Design	Study Size	Inclusion/Exclusion Criteria	1°Endpoint	Results/p Values	Summary/Conclusions

Name, Author, Year						
Bazzocchi G, et al. 2011 (88) 21293945	Retrospective evaluation of prevalence of coronary artery variants and congenital coronary anomalies using 64-slice CT	n=3,236 pts	Inclusion criteria: All pts undergoing CT coronary arteriography during a 4-y period	Descriptive report of findings	● Coronary anomalies of origin and course, of termination, and intrinsic anomalies had a prevalence of 5.7%.	● 64-slice CT coronary angiography provides accurate 3D evaluation of the coronary artery tree with correct visualization of coronary anomalies.
Cheng Z, et al. 2010 (89) 20797468	Retrospective review	n=3,625 pts	Inclusion criteria: Pts who underwent dual source CT. Some also underwent conventional coronary angiography	Incidence of coronary artery anomalies	● Incidence of coronary angiography anomalies was 1% (36 pts). Conventional coronary angiography identified the lesion in 10/19 or 53% of pts in whom it was done.	● Dual source CT is a good tool for coronary anomalies, and recognizes anomalies not identified by conventional coronary angiography.
Doganay S, et al. 2011 (90) 21717303	To prospectively evaluate the usefulness of noninvasive cardiac vein imaging using multidetector CT angiography before CRT	n=34 pts	Inclusion criteria: Pts studied in advance of CRT	Identification of anatomic details of coronary venous system to guide lead placement for CRT	N/A	● Multidetector CT can be used to guide interventions for CRT by providing anatomical details of the cardiac venous system rapidly and noninvasively.
Ghoshhajra BB, et al. 2012 (91) 23075048	Case series and review of benefits of second-generation dual source CT in ACHD	N/A (description with 5 illustrated cases)	Inclusion criteria: N/A	Descriptive report of imaging techniques possible with new technology, second-generation dual-source CT	● High-spatial resolution, high-temporal resolution, and the wide z-axis coverage allow novel protocols that markedly reduce scan time, significantly reduce radiation exposure, and expand the physiologic imaging capabilities of cardiac CT.	● Complicated ACHD pts can be imaged by the second-generation dual-source CT scanner with low-radiation doses and excellent image quality.
Torres FS, et al. 2010 (92) 20444667	Retrospective comparative study	n=15 cases of anomalous left coronary artery with intraarterial course found in 6,000 consecutive multidetector CT	Inclusion criteria: LMCA arising from right sinus or from right coronary artery coursing between aorta and main PA	Descriptive classification of anomalous left coronary artery	● 4 subtypes identified, a more granular classification than could be recognized by conventional coronary angiography	● Anatomic spectrum of anomalous left coronary arteries detected by multidetector CT coronary angiography that challenges the traditional classification based on conventional coronary angiography.

		coronary angiograms				
Brenner DJ, et al. 2007 (87) 18046031	Review	N/A	Inclusion criteria: N/A	N/A	N/A	● A review of use of CT, benefits, and level of ionizing radiation to which pts are exposed, with discussion of strategies to reduce that exposure.

Data Supplement 10. Cardiac Catheterization – Section 3.4.6

Study Name, Author, Year	Study Type/ Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values
Moore JW, et al. 2014 (93) 25500227	Report from the Improving Pediatric and Adult Congenital Treatment registry database	n=4,152 catheterization procedures	Inclusion criteria: Registry data from pts enrolled in the Improving Pediatric and Adult Congenital Treatment Registry between Jan 2011–March 2013 who underwent 1 of the following isolated procedures: device closure of ASD; device closure of PDA; pulmonary valvuloplasty; aortic valvuloplasty; CoA angioplasty and stenting; and PA stenting.	● Pt data, procedural data and results, and AEs.	● In 4,152 catheterizations, 1 isolated procedure was reported. ● There were 1,286 single-ASD procedures, 1,375 PDA procedures, 270 "typical" PV procedures, 305 aortic valve procedures, 671 aortic procedures, and 245 PA procedures. ● The reported procedure was performed in >95% of catheterizations. ● Stated outcomes were accomplished in >98% of ASD and PDA procedures, but less commonly in the others, with coarctation angioplasty procedures being the least successful (51%). ● Reported major AE rates ranged from 0% to 3.3%; total AE rates ranged from 5.3%–24.3%.
Learn CP, et al. 2013 (94) 23345073	The C3PO collects data on all catheterizations at 8 pediatric institutions.	2,061 cases (15% of total) were performed on adults and 11,422 cases (85%) were performed on children	Inclusion criteria: Adult (≥18 y) case characteristics and AE were reviewed and compared with those of pediatric (<18 y) cases.	● Cases were classified into procedure risk categories from 1–4 based on highest risk procedure/intervention performed. AE were categorized by level of severity. Using a multivariate model for High severity AE, standardized AE rates	● 2,061 cases (15% of total) were performed on adults and 11,422 cases (85%) were performed on children. Adults less frequently underwent high-risk procedure category cases than children (19% vs. 30%). AE occurred in 10% of adult cases and 13% of pediatric cases (p<0.001). High severity AE occurred in 4% of adult and 5% of pediatric cases (p=0.006). Procedure-type risk category (Category 2, 3, 4 OR=4.8, 6.0, 12.9) and systemic ventricle end diastolic pressure ≥18 mm Hg (OR 3.1) were associated with high severity AE, c-statistic 0.751. There were no statistically significant

				were calculated by dividing the observed rates of high severity AE by the expected rates.	differences in standardized AE rates among institutions.
Sutton NJ, et al. 2013 (95) 23006871	Retrospective single-center review	n=57 catheterizations performed in 53 adult pts; n=59 catheterizations performed in 47 adolescent pts	Inclusion criteria: Adults and adolescents who had catheterization performed by pediatric interventional staff between 2005–2009.	● Description of procedural outcomes and AE	● 57 catheterizations were performed in 53 adults, while 59 were performed in 47 adolescents. The male to female ratio differed significantly between groups; only 15/53 (28%) of adults were male vs. 26/47 (55%) of adolescents (p=0.006). Among adults, 27 had previously corrected CHD, 16 with ASD, and 6 with PFO. This differed significantly from the adolescents, where only 30 had previously corrected CHD, 7 with ASD, and 1 with PFO (p=0.012). Among adults who were catheterized, interventions were performed on 28/53 (53%). All interventions were successful and included ASD/PFO closure, PDA occlusion, coarctation dilation, PA dilations, and 1 SVG aneurysm closure. 19 adults had coronary angiography performed by adult interventionalists in consult with pediatric interventionalists. 2 complications occurred among adults (3.8%) vs. 1 complication (2%; p=1) among adolescents. No femoral vessel complications or catheterization-associated mortality occurred.
Opotowsky AR, et al. 2009 (96) 19376313	Cohort from Nationwide Inpatient Sample	n=2,555 procedures	Inclusion criteria: Pts ≥20 y admitted to an acute care hospital for PFO or ASD closure on hospital day 1 or 2	● Outcomes of interest included LOS, charges, and AEs	● The study included 2,555 (weighted to U.S population: 12,544 ± 1,987) PFO/ASD closure procedures. Mean age was 52.0 ± 0.4 y, and 57.3% ± 1.0% were women. Annual hospital volume averaged 40.8 ± 7.7 procedures (range: 1–114). Overall, 8.2 ± 0.8% of admissions involved an AE. Older pts and those with comorbidities were more likely to sustain AE. Use of ICE was associated with fewer AE. The risk of AE was inversely proportional to annual hospital volume OR: 0.91; 95% CI: 0.86–0.96, per 10 procedures), even after limiting the analysis to hospitals performing ≥10 procedures annually (OR: 0.91; 95% CI: 0.85–0.98). AEs were more frequent at hospitals in the lowest volume quintile as compared with the highest volume quintile (13.3% vs. 5.4%; OR: 2.42; 95% CI: 1.55–3.78).

Gilard M, et al. 2006 (97) 16697319	Single-center cohort analysis	n=55 pts	Inclusion criteria: Pts with severe AS scheduled for preoperative coronary angiography who also underwent 16-slice MSCT 24 h before coronary angiography	● Determine the sensitivity and specificity of MSCT in detecting significant coronary artery stenosis.	● The sensitivity of the MSCT in detecting significant stenosis was 100%, and its specificity 80%. ● The positive and NPVs were respectively 55% and 100%. ● For calcium scores<1,000 (77% of pts), MSCT detected all pts without CAD enabling conventional coronary angiography to be avoided in 35 of 55 cases (80%). ● For calcium scores >1,000, MSCT enabled conventional coronary angiography to be avoided in only 6% of cases, either because significant stenosis was found with a possible indication of revascularization, or because the examination was not interpretable.
Manghat NE, et al. 2006 (98) 16905381	Single-center cohort analysis	n=40 pts	Inclusion criteria: Pts with AS scheduled for preoperative cardiac catheterization underwent 16-slice MSCT evaluation within 1 mo of coronary angiography	● All 13 major coronary artery segments were evaluated for the presence of ≥50% stenosis.	● A total of 412/450 segments from 35 pts were suitable for analysis. ● The overall accuracy of MSCT for detection of segments with ≥50% stenosis was high, with a sensitivity of 81.3%, specificity 95.0%, positive predictive value 57.8%, and NPV 98.4%. ● On a "whole-pt" basis, 100% (19/19) of pts with significant CAD were correctly identified and there were no false-negatives. Excluding pts with CAC >1,000 from the analysis improved the accuracy of MDCTA to: sensitivity 90%, specificity 98.1%, positive predictive value 60%, NPV 99.7%.
Meijboom WB, et al. 2006 (99) 17045904	Single-center prospective cohort analysis	n=70 pts	Inclusion criteria: 145 pts prospectively identified from a consecutive pt population scheduled for valve surgery Exclusion criteria: 35 pts excluded because of irregular rhythm, renal dysfunction or contrast allergy. Other exclusion criteria included: Hospitalization in a community hospital, previous coronary bypass or stenting. Of	● Diagnostic accuracy of 64-slice MDCTA to detect significant CAD.	● Prevalence of significant CAD, defined as having at least 1≥50% stenosis/pt, was 25.7%. ● On a per-pt analysis, the sensitivity, specificity, and positive and NPVs were: 100% (18 of 18; 95% CI: 78–100), 92% (48 of 52; 95% CI: 81–98), 82% (18 of 22; 95% CI: 59–94), and 100% (48 of 48; 95% CI: 91–100), respectively.

			the remaining 97 pts, 27 did not consent. The study population consisted of 70 pts.		
Reant P, et al. 2006 (100) 16679094	Single-center prospective cohort analysis	n=40 pts	Inclusion criteria: Pts with severe acquired valvular HD underwent 16-slice MSCT within 2 d of coronary angiography.	● Evaluate the predictive values of 16-slice MSCT in the detection of significant coronary stenosis	● 458/600 coronary artery segments (77.3%) were considered assessable by MSCT. ● In a per-segment analysis, the sensitivity of MSCT for the detection of significant coronary lesions ≥50% was 77.7%, the specificity was 98%, the positive predictive value was 42.4%, and the NPV was 99%. ● The main cause of false-positive or false-negative results or nonassessable evaluations was severe coronary calcification. In a per-pt analysis, in comparison with quantitative coronary angiography, MSCT correctly classified 33/40 pts (82.5%).
Scheffel H, et al. 2007 (101) 17697832	Single-center cohort analysis	n=50	Inclusion criteria: Pts with chronic aortic regurgitation referred for elective surgery underwent 64-slice MSCT and coronary angiography	● Evaluate the diagnostic accuracy of MSCT for detection of significant coronary artery stenosis	● 50 consecutive pts with chronic aortic root (38 men, mean age 54 ± 14 y) scheduled for valve surgery underwent 64-slice MSCT and coronary angiography. ● Significant stenosis was defined as a luminal diameter decrease >50%. ● Mean Agatston score was 136 ± 278 (range 0–1,207); prevalence of significant CAD in the study population was 26% (13/50 pts). ● 13 of 742 segments (1.8%) in 3 pts were considered nondiagnostic with CT because of motion artifacts (n=9) or calcium (n=4). ● In a pt-based analysis taking nonevaluative segments as falsely positive, sensitivity, specificity, and positive and NPVs of CT were 100%, 95%, 87%, and 100%, respectively. ● Preoperative coronary angiography could have been avoided in 70% of pts (35/50), coronary angiography would have been performed to confirm the CT diagnosis in 26% (13/50), and unnecessary coronary angiography would have been performed in 4% (2/50) on the basis of false-positive CT ratings.
Galas A, et al. 2012 (102) 22992993	Single-center cohort analysis	n=98 pts	Inclusion criteria: Pts with VHD scheduled for elective surgery	● Evaluate the usefulness of MSCT before planned	● Mean pt age was 58.8 (range 30–78) y.

			underwent MSCT in addition to coronary angiography. Exclusion criteria: Criteria included arrhythmias, renal dysfunction, iodine allergy or lack of pt consent.	cardiac valvular surgery	● CAC score was first determined in all pts. Coronary CT angiography was not performed if CAC score was >1,000. ● In the remaining pts, complete CT evaluation was performed with the administration of a contrast agent. Conventional invasive coronary angiography was subsequently performed in pts with at least 1>50% stenosis, artifacts due to calcifications, or motion artifacts. ● In 79 (80.6%) pts, CT angiography excluded the presence of a significant coronary artery stenosis without the need for invasive angiography. Conventional coronary angiography was required in 19 (19.4%) pts, including 13 (13.3%) pts with a >50% stenosis in CT angiography, 2 (2%) pts with calcification artifacts, 1 (1%) pt with motion artifacts, 2 (2%) pts with CAC score >1,000 in whom CT angiography was not performed, and 1 (1%) pt with allergic symptoms during administration of a test dose of the contrast agent. ● Ultimately, significant CAD was diagnosed in 9 (9.2%) pts in whom coronary artery bypass surgery was also performed. ● In addition, vascular anomalies were diagnosed with cardiac CT angiography in 5 (5.1%) pts. ● In 14 pts, CT angiography was also used for previously planned evaluation of a coexisting aortic aneurysm.

Data Supplement 11. Exercise Testing – Section 3.4.7

Study Name, Author, Year	Study Type/ Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
Diller GP, et al. 2005 (103) 16061735	Case series of pts who had cardiopulmonary exercise testing.	n=335 ACHD pts; n=40 noncongenital HF pts n=11 healthy subjects	Inclusion criteria: Consecutive ACHD pts and selected controls undergoing cardiopulmonary testing	Peak O_2 consumption	● Peak VO_2 was reduced in ACHD pts compared with healthy subjects of similar age (21.7 ± 8.5 vs. 45.1 ± 8.6; p<0.001). No significant difference in peak VO_2 was found between ACHD and	● Exercise capacity is depressed in ACHD pts (even in allegedly asymptomatic pts) on a par with chronic HF subjects.

					HF pts of corresponding NYHA class. On multivariable Cox analysis, peak VO_2 predicted hospitalization or death (HR: 0.937; p=0.01) and was related to the frequency and duration of hospitalization (p=0.01 for each).	● Poor exercise capacity identifies ACHD pts at risk for hospitalization or death.
Hager A, et al. 2005 (104) 15772218	Prospective cross-sectional clinical study	n=149 pts	Inclusion criteria: ACHD pts from an ACHD referral center	Peak oxygen uptake	● Peak O_2 uptake correlated significantly with the physical functioning (r=0.521; p<0.0005) and general health scales (r=0.313; p<0.0005) but not with role physical, bodily pain, vitality, social functioning, role-emotional, mental health, and health transition scales.	● Exercise tests and QOL instruments should be used together to get a comprehensive health status of a pt with CHD.
Gungor H, et al. 2014 (105) 23861135	Case series (single-center)	n=23 pts	Inclusion criteria: Pts with Eisenmenger syndrome; awaiting heart-lung transplant	Association between and TTE and 6MWT CPET findings	● Result of 6MWT correlated only with SPAP. ● SPAP did not correlate with any CPET findings.	● 6MWT distance may be more suitable than CPET in the follow-up of pts with Eisenmenger syndrome.
Ross RM, et al. 2010 (106) 20504351	Meta-analysis: linear mixed model analysis of multiple studies in which 6MWT and peak VO_2 from CPET were available	n=1,083 pts	Inclusion criteria: Diverse cardiopulmonary disorders	Development of generalized equation predicting peak VO_2 from 6MWT	● Large standard error of estimate when applied to individual pts.	● General correlation between 6MWT and VO_2 max shown to apply in groups.

Data Supplement 12. Transition Education – Section 3.5

Study Name, Author, Year	Study Type/Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
Wray J, et al. 2013 (107) 23257171	Cohort	n=1,085 pts	Inclusion criteria: TOF with surgery 1964–2009; excluded extra cardiac conduits and overseas pts	Survival, freedom from surgery, loss of follow-up	● 24% followed by general cardiology; 48% of late death in this group; no PVR in this group vs. 28%.	● Loss of specialist follow-up impacts pt management
Gurvitz MZ, et al. 2007 (40) 17320746	Population study	n=9,017 hospitalizations	Inclusion criteria: California hospital discharges	12–44 y, with a 1° or 2° ICD-9-CM code for CHD	● Percentage of pts admitted via ED doubled in early 20s.	● No private insurance and >17 more likely admitted through ED.

Goossens, E, et al. 2014 (108) 23420323	Cross-sectional	n=317 pts	Inclusion criteria: CHD, literate, Dutch speakers, verbal consent Exclusion criteria: Learning disability, no regular follow-up, newly diagnosed ASD or PFO after stroke	Knowledge using Leuven Knowledge Questionnaire for CHD	● Pts in structured education group had mean total knowledge score of 57% vs. 43% in comparison group (p<0.001)	● Structured pt education with advanced practice nurse can be effective in improving level of knowledge in CHD.
Gurvitz M, et al. 2013 (6) 23542112	Multicenter prospective cross-sectional study	n=922 pts from 12 centers	Inclusion criteria: Pts >18 y, CHD on 1st presentation to CHD care between Jan 1, 2009–Dec 31, 2010. Exclusion criteria: No CHD or unable to fill form at 8th grade reading level	Gaps in care >3 y; barriers to care	● 42% reported gap in care; typically at 19.9 y; more common in mild and moderate CHD; Western states more likely to have gap.	● Gaps in care common in late teenage years, during time of transition to ACHD.
Mackie AS, et al. 2014 (42) 24842870	Clinical trial	n=58 pts	Inclusion criteria: 15–17 y with moderate or complex CHD or cardiomyopathy. Allocated to usual care or 1-h nurse-led 1-on-1 teaching	Determine the impact of a transition (1 h nurse led) intervention on improving knowledge and self-management skills	● Mean self-management true advertising quality score was 3.59 (± 0.83) vs. 3.16 (± 1.05), respectively (p=0.048, adjusted for baseline score); the mean self-advocacy true advertising quality score was 4.38 (± 0.56) vs. 4.01 (± 0.95) (p=0.18) and the mean MyHeart score was 75% (± 15) vs. 61% (± 25) (p=0.019).	● The transition intervention resulted in significant improvement in self-management and cardiac knowledge scores. ● An educational intervention should be routine for youth with congenital or acquired HD.
Lotstein DS, et al. 2013 (109) 23530167	Analysis	n=185 pts	Inclusion criteria: Adolescent pts with recently diagnosed type 1 DM	Describe sociodemographic and clinical correlates of poor glycemic control associated with the transfer of care from pediatric to adult providers	● 57% transitioned to adult DM care providers by follow-up visit. ● Odds of poor glycemic control at follow-up were 2.5 times higher for participants transitioned to adult care compared with those who remained in pediatric care.	●Transferring from pediatric to adult care was associated with an increased risk of poor glycemic control during follow-up. ● This suggests that young adults need additional support when moving to adult care.

Data Supplement 13. Exercise and Sports – Section 3.6

Study Name, Author, Year	Study Type	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions

Myers J, et al. 2004 (110) 15629729	Convenience sample of consecutive pts	n=842 pts	Inclusion criteria: Consecutive pts referred to single center for exercise testing for clinical reasons. 1 d/wk, research assistants available to administer survey	All-cause mortality by social security death index	● Using age-adjusted quartiles, exercise capacity was stronger predictor of mortality than activity pattern ($p<0.001$). ● Multivariate analysis showed exercise capacity $p<0.001$, and energy expenditure from adulthood recreational activity $p<0.002$ were the only predictors.	● Fitness and physical activity confer a survival benefit and should be encouraged.
Warburton DE, et al. 2006 (111) 16534088	Review	n=152 pts	Inclusion criteria: Papers addressing 1° or 2° effects of exercise on mortality and chronic disease	N/A	● Analysis reaffirmed "irrefutable" evidence of a positive association between increasing levels of physical activity and lower rates of chronic disease and all-cause mortality.	● Health benefits of exercise are greatest among those who are least active. Promotion of physical activity should begin in childhood.
King AC, et al. 1989 (112) 2767021	RCT	n=120 pts (60 male, 60 female)	Inclusion criteria: Employees of 1 company<25% overweight willing to be randomized. No medical contraindications to exercise	Score on a 14-point scale assessing multiple psychological variables;body weight; CPET performance	● VO_2 max increased 15% in men and 9% in women ($p<0.01$ for both). ● Improvement in 3 psychic measures were significant ($p<0.004$).	● Regular aerobic exercise is associated with improved measures of psychological health, especially in areas of satisfaction with body image, fitness, and weight.
Reybrouck T and Mertens L, 2005 (113) 16210938	Review	38 papers	---	---	● Most ACHD pts are less active than their peers. They can safely participate in moderate activity.	● Cardiologists should encourage GUCH pts to be more active.
Pemberton VL, et al. 2010 (114) 20212294	NHLBI working group report	N/A	Inclusion criteria: N/A	N/A	● Obesity is a significant issue in pts with CHD. ● Associated comorbidities that increase risk of acquired HD are also present.	● A call for research, infrastructure, and resources to study and address the issue of obesity in pts with CHD.
Graham TP, et al. 2005 (115) 15837282	Bethesda 36 consensus conference	N/A	Inclusion criteria: N/A	N/A	● Recommendations for sports participation based on evidence when available.	● Lesion-specific recommendations are provided.
Pellicia A, et al. 2005 (116) 15923204	Consensus conference	N/A	Inclusion criteria: N/A	N/A	● Recommendations for participation by (young) adults in competitive sports.	● Lesion-specific: evaluation techniques, criteria for eligibility, recommendations for specific sports, follow-up guidelines.
Duppen N, et al. 2013 (117) 23746621	Systematic review	31 studies	Inclusion criteria: Studies between 1960–2012 that addressed exercise program and CHD	Positive or negative effects of physical exercise training in pts with CHD	● 23 of 31 studies reported positive effects (improved VO_2 max); no studies reported adverse effects.	● Exercise training in pts with CHD is safe and beneficial. CHD pts should participate in exercise training programs.

Dua JS, et al. 2010 (118) 19217676	Convenience sample, prospective pretest, post-test	n=50 pts in 3 groups by NYHA class	Inclusion criteria: Pts seen at 1 ACHD center; able to walk on treadmill; no surgery within 6 m; no contraindication to exercise	Quality of life; exercise capacity; activity levels	● Quality of life scores improved p=0.004; mean exercise time improved p=0.003; activity level increased p=0.002; no AE or mortality.	● Exercise training programs are safe and feasible for pts with CHD.
Holloway TM, et al. 2011 (119) 21641052	Retrospective review of single-center experience.	n=11 pts (7 of 11 pts completed cardiac rehabilitation)	Inclusion criteria: ACHD pt seen at 1 center; referred to cardiac rehabilitation	Exercise capacity; safety	● Exercise capacity increased p<0.05; no AE.	● A traditionally structured cardiac rehabilitation is effective and safe for pts with CHD.
Cordina RL, et al. 2013 (120) 23846614	Cohort comparison	n=24 pts (16 pts with Fontan; 8 healthy controls)	Inclusion criteria: NYHA FC I, II; Fontan palliation Exclusion criteria: Smoker, clinical HF, recurrent significant arrhythmias	Peak VO_2; lean mass, calf muscle MRI spectroscopy	● VO_2 was 66% predicted; pts had significantly less muscle mass (p<0.0001). ● 4/16 pts were sarcopenic; low muscle mass correlated with lower peak VO_2 (p=0.004); muscle aerobic activity diminished in Fontan pts vs. controls.	● Pts with Fontan palliation have significantly reduced muscle mass that correlates with significantly lower exercise capacity. Pts also have impaired muscle aerobic capacity.
Cordina RL, et al. 2013 (121) 23154055	RCT	n=16 pts	Inclusion criteria: Fontan; NYHA class I or II; exercise program participation; 20 wk of high-intensity resistance training	VO_2; muscle strength; muscle mass; inspiratory dependent venous return	● After training: Increased VO_2; increased muscle strength; increased muscle mass; increased venous return during exercise.	● Resistance training in isolation improves muscle mass and strength with associated improvements in VO_2 and Fontan hemodynamics.
Kempny A, et al. 2012 (122) 22199119	Retrospective review and literature review	n=2,129 pts in single center; 23 papers including 2,286 pts	Inclusion criteria: ACHD pt undergoing CPET	Max VO_2	● ACHD pts showed consistently significantly lower VO_2 than normal. ● Within ACHD diagnoses, peak VO_2 was significantly lower with increasing CHD complexity.	● Provides reference values for peak VO_2 among a variety of ACHD diagnoses.
Diller GP, et al. 2005 (103) 16061735	Cohort comparison	n=335 consecutive ACHD pts; 40 non-ACHD HF pts; 23 healthy controls	Inclusion criteria: ACHD pt performing CPET between Jan 2003–May 2004	Peak VO_2	● VO_2 reduced in ACHD compared to normal. ● VO_2 similar between ACHD and HF of same NYHA class. ● VO_2 declined with increasing CHD complexity. ● Lower VO_2 conferred increased risk of hospitalization or death.	● Even in asymptomatic ACHD pts VO_2 provides risk assessment for hospitalization or death.
Takken T, et al. 2012 (123) 23126001	Consensus report	N/A	Inclusion criteria: N/A	N/A	● Recommendations for physical activity, recreational sport, and exercise training in pediatric CHD pts.	● Physical activity should be promoted, not restricted in CHD pts. Physical activity is generally safe although certain conditions require more caution.

Longmuir PE, et al. 2003 (124)	Chapter	N/A	Inclusion criteria: N/A	N/A	● Strategies for making physical activity achievable for pts with special needs.	● Physical activity can be incorporated into the lifestyle of most people with some modification.
Mitchell JH, et al. 2005 (125) 15837288	Consensus report	N/A	Inclusion criteria: N/A	N/A	● Relative intensity of activities during competitive sports based on VO_2 and isometric maximal voluntary contraction.	● Competition may be less strenuous than training, so that modification of training programs may be needed.
Westhoff-Bleck M, et al. 2013 (126) 24207068	RCT to investigate the effect of aerobic training on exercise capacity and systemic RV function in adults after Mustard procedure	n=48 pts (24 controls vs. 24 in training)	Inclusion criteria: Pts with previous atrial redirection surgery for d-TGA, NYHA class I/II HF, same medications (ACE, BB) for last 6 mo, no physical training at inclusion Exclusion criteria: Known pulmonary vascular disease, significant baffle-obstruction, pregnancy, pacemaker or defibrillator implantation, history of VA, renal/liver insufficiency, claustrophobia, and mental retardation.	Change peak VO_2	● After 24 wk, in trainers peak VO_2 improved (1.8 ± 2.3 mL/kg/min; +7.7%); whereas, it dropped in controls (−1.9 ± 4.2 mL/kg/min; −7.5%) (p=0.001).	● Aerobic exercise is safe and can improve exercise capacity and NYHA class. ● The results cannot be generalized to NYHA III/IV symptoms. The drop-out rate was 20.8%.
Ubeda TA, et al. 2013 (127) 23962775	Retrospective cohort	n=146 pts	Inclusion criteria: ACHD pts ≥21 y that had cycle ergometry exercise testing at Boston Children's Hospital Jan. 2006—July 2011.	Changes in exercise capacity	● Those who participated in frequent exercise tended to have improved p VO_2 (Δp VO_2=+1.63±2.67 mL/kg/min) compared to those who had low or occasional activity frequency (Δp VO_2=+0.06±2.13 mL/kg/min; p=0.003) over a median follow-up of 13.2 mo. ● The difference was independent of baseline clinical characteristics, time between tests, medication changes, and weight change. ● Those who engaged in frequent activity were more likely to have an increase of p VO_2 of ≥1SD between tests as compared with sedentary pts (OR: 7.4; 95% CI: 1.5—35.7).	● ACHD pts who engage in frequent physical activity tend to have improved exercise capacity over time.

Data Supplement 14. Mental Health and Neurodevelopmental Issues – Section 3.7

Study	Study Type	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions

Name, Author, Year						
Amianto F, et al. 2011 (128) 21659976	Systematic review	66 articles	Inclusion criteria: 1989–2009 studies in Medline	Describe neurocognitive and psychopathology outcomes	● IQ of pts < controls but within normal range; not consistent finding associated with younger age at surgery. Other factors include familial education and socioeconomic status. ● Psychopathology is inconsistently associated with CHD; environmental factors may also contribute.	● Limitation is nonquantitative evaluation of literature.
Granberg M, et al. 2008 (129) 18489626	Cohort control	n=28 pts matched in pairs	Inclusion criteria: 14 pts 3–14 y with complex CHD paired to age- and sex-matched healthy controls	Examine differences in children with complex CHD and normal re: performance of activities of daily living and school work	● Pts with CHD had significantly lower mean activities of daily living, school motor and school process performance.	● Significant difference in performance of both ADL and schoolwork task performance between pts with complex CHD vs. healthy controls.
Karsdorp PA, et al. 2007 (130) 17182669	Meta-analysis	11 studies	Inclusion criteria: 1980–2005 studies in Medline and PsycInfo	Effect of CHD on cognitive and psychological function in children and adolescents	● Effect sizes ● Psych: pt > control, overall, internalize, externalize ● Cognitive: pt < control, performance IQ, verbal IQ.	● R=0.67; p=0.005 overall effect ● R=0.77; p=0.001 internalization ● R=0.73; p=0.003 externalization ● R=0.62; p=0.003 performance ● R=0.59; p=0.006 verbal IQ
van der Rijken RE, et al. 2007 (131) 17184562	Cohort study, survey	n=101 pts	Inclusion criteria: Surgical correction of CHD 1992–2000 while pts 6–16 y	Explore long-term physical, educational, emotional outcomes	● 46/101>18 y at time of survey; pts had more use of special education, repeated grades, or used remedial education: pts had lower educational attainment.	p<0.01 special education p<0.01 repeated grades p<0.05 remedial education
Kirshbom PM, et al. 2005 (132) 15867785	Cohort study	n=30 pts	Inclusion criteria: School age, s/p total anomalous pulmonary venous return at single center	Describe neuro-developmental outcomes of survivors of total anomalous pulmonary venous return	● Age at follow-up 6–19 y. ● Full scale IQ within normal limits. ● Performance IQ < control. ● Reading = control. ● Math<control. ● Attention<average.	● p=0.02 performance IQ ● p<0.01 math ● p<0.01 attention
Wernovsky G, et al. 2000 (133) 10952957	Cohort study	n=133 pts	Inclusion criteria: Regional survivors of Fontan palliation at single center	Describe cognitive and academic outcomes after Fontan	● Median age at evaluation n=11 y (3.7–41.0 y). ● Full scale IQ < normal; p<0.006. ● Adjusted for socioeconomic status, lower IQ associated with HLHS, and use of circ arrest.	● Most Fontan pts from 1970s–1980s have cognitive in normal range but lower than general population.
Callus E, et al. 2013 (134) 23750687	Systematic review		Inclusion criteria: Pts with CHD, studies addressing	Psychological function in ACHD	● Variation among studies whether pts psychological functioning is better, worse, or the same as the general population.	● Structured assessment of pts' psychological function may be more reliable and identify more dysfunction.

			psychological functioning, published since 1990 Exclusion criteria: studies on acquired HD, neurodevelopment or multidimensional quality of life		● Disease severity does not correlate with psychological functioning. ● Significant risk of under treatment when assessment is by self-report.	
Kovacs AH, et al. 2005 (135) 18707776	Cross-sectional study	n=280 pts	Inclusion criteria: Adult pts with CHD being seen at 1 of 2 ACHD centers	Describe predictors of symptoms of anxiety, depression	● Self-reported symptoms correlated significantly with loneliness, fear of negative evaluation, and perceived health status. ● Symptoms did not correlate with disease severity. ● Subgroup of interviewed pts revealed 50% with lifetime mood disorder, 39% never treated.	● Symptoms of anxiety and depression are prevalent among ACHD pts but do not correlate with disease severity.
Kovacs AH, et al. 2009 (136) 16086917	Literature review	8 studies	Inclusion criteria: ACHD pts and psychological and/or emotional functioning	Prevalence and predictors of anxiety and depression among ACHD pts	● U.S. studies report ACHD pts have worse emotional functioning reported in both interviews and self-report. European studies do not demonstrate these results.	● Interview data identify more disease than self-report. ● International differences are not well substantiated. ● Symptoms do not correlate well with disease severity.
van Rijen EH, et al. 2003 (137) 12657226	Cohort study	n=362 pts	Inclusion criteria: Single center, CHD surgery between 1968—1980, <15 y at time of surgery, 1 of 5 congenital heart defects	Describe relationship between biographical information and psychological and social function	● Pts were more likely to have been in special education, to have lower academic and occupational achievement. ● Pts scored favorable on measures of self-esteem, hostility, and neuroticism (Cohens D=0.5).	● Long-term impact of CHD is lower academic and occupational achievement; however, psychological and social function may not be significantly impaired.

Data Supplement 15. Endocarditis Prevention – Section 3.8

Study Name, Author, Year	Study Type	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Value	Summary/Conclusions
Chirouze C, et al. 2013 (138) 23517406	Multicenter prospective observational cohort	n=4,974 IE pts (500 with enterococci)	Inclusion criteria: Documented IE	Predictors of enterococcal IE	● Mean age: 65 y. ● 72% male. ● 23% healthcare related. ● 10% Vanco resistant. ● More common than oral or group D streptococcus in North America. ● Mortality: 28.9%.	● Enterococcus is important source of IE with associated high morbidity and mortality.

					● Predictors of congestive HF, cerebral vascular accident, age.	
Thuny F, et al. 2012 (139) 22795288	Single-center observational cohort	n=328 pts	Inclusion criteria: Documented IE	Survival at 1, 3, 5 y post IE	● Relative survival rates: 1 y=92% 3 y=86% 5 y=82%. ● Most excess mortality as well as recurrence and late surgery occurred in the first y.	● IE confers increased risk of mortality, especially in the first y and indicates close monitoring of pts who survive IE.
Verheugt CL, et al. 2011 (140) 21217144	Registry review	n=10,210 pts; 233 IE cases in adulthood	Inclusion criteria: Documented IE	Prediction model of IE at transition from pediatric to adult CHD care	● Predictors included: Sex Multiple defects Main defect. ● Childhood events: IE CVA SVT.	● Model predicted risk of IE up to 60 y and can help guide practice to identify individual pts at increased risk of IE.
Lalani T, et al. 2006 (141) 16767483	International Collaboration on Endocarditis merged database	n=54 coagulase-negative PVE cases; n=58 *S aureus* PVE cases; n=63 strep viridans PVE cases	Inclusion criteria: PVE from coagulase-neg staph vs. *Staphylococcus . aureus* or strep viridans	Characteristics and outcome of pts with PVE from coagulase-negative staphylococcus	● Congestive HF more common (p=0.03). ● Valvular abscess greater (p=0.06; 0.001). ● Mortality from any staph > strep (p=0.002).	● Coagulase-negative staph is an aggressive pathogen in IE with greater morbidity and mortality.
Anderson DJ, et al. 2005 (142) 16244853	International Collaboration on Endocarditis merged database	n=159 pts of enterococcal IE	Inclusion criteria: PVE from enterococcus vs. NVEs from enterococcus	Clinical characteristics and outcomes	● 45/159 cases were PVE. ● PVE had more abscesses (p=0.009), fewer vegetations (p=0.001) and less new regurgitation (p=0.01). ● Mean age: 73 y. ● Similar mortality and surgical rates.	● Enterococcal PVE is more likely than enterococcal NVE to develop abscess.
Chu VH, et al. 2005 (143) 16007540	Cohort to compare time-based and molecular criteria	n=13 pts with repeat IE	Inclusion criteria: Repeat case of IE	Distinguish relapse or reinfection	● 10 of 13 cases molecular agreed with clinical determination.	● Clinical timelines can be useful in determining reinfection vs. relapse of prior infection.
McDonald JR, et al. 2005 (144) 15989910	International Collaboration on Endocarditis merged database	n=1,285 pts; 107 enterococcus	Inclusion criteria: Left-sided NVE	Describe clinical features and outcomes of enterococcal NVE on left sided	● Most common in elderly men. ● Involved aortic valve more often. ● Congestive HF > emboli. ● Lower short-term mortality: OR: 0.49; 95% CI: 0.24–0.97.	● Enterococcal NVE has distinctive features with good prognosis.

Chu VH, et al. 2004 (145) 15546091	International Collaboration on Endocarditis merged database	1,504 NVE; 99 coagulase-negative staphylococcus	Inclusion criteria: Documented IE	Describe clinical features and outcomes of coagulase-negative staphylococcus NVE compared to *S. aureus* and strep viridans	● 85% *Staphylococcus epidermidis*. ● Median age: 68 y. ● 77% male. ● 20% long-term indwelling catheters. ● 40% healthcare related IE. ● Mortality: 19%.	● Coagulase-negative staph is an important cause of NVE with significant risk for morbidity and mortality.
Renzulli A, et al. 2001 (146) 11465227	Retrospective database analysis of consecutive pts	n=271 pts (308 valve replacements for IE)	Inclusion criteria: Pts that underwent valve replacement for IE between 1979–2000	Identify predictors of recurrent IE after surgical valve replacement	● 22.5% recurrent IE. ● Predictors: PVE at index (p=0.0001) Positive valve culture (p=0.0039) Persistent fever at postoperative day 7 (p=0.0001).	● Close attention to antimicrobial treatment and surgical debridement may reduce recurrent IE.
Mansur AJ, et al. 2001 (147) 11136490	Inception cohort study, single center	n=420 pts	Inclusion criteria: Pts discharged from single academic medical center after treatment for IE	Describe: Relapses Recurrence Valve replacement Mortality	● Relapse: 3.3%. ● Recurrence: 12.3%. ● Valve replacement: 19.7%. ● Mortality: 12.3%.	● Long-term survival is reduced for survivors of index IE. ● Predictors of mortality include male sex, increasing age, and recurrent IE.

Data Supplement 16. Concomitant Syndromes – Section 3.9

Study Name, Author, Year	Study Type	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results	Summary/Conclusions
van Engelen K, et al. 2010 (148) 20357389	Cohort	n=479 pts	Inclusion criteria: Adults with TOF and pulmonary atresia/VSD and availability of DNA	Diagnosis of 22Q11	● 20 pts already known to have diagnosis. ● Another 24 diagnosed with 22Q11.	● 9% of pts with TOF and pulmonary atresia/VSD have 22q11 Diagnosis unrecognized in half the pts. ● Diagnostic test should be considered in all adult pts with TOF and pulmonary atresia/VSD.
Piran S, et al. 2011 (149) 21167345	Prospective cohort	n=447 pts	Inclusion criteria: Adults with TOF classified into syndromic if ≥2 features	Compared cardiac and extracardiac features	● More frequent late onset conditions (neuropsych, thyroid, hearing).	● Extracardiac abnormalities warrant regular monitoring.
Fung WL, et al. 2008 (150) 18191243	Prospective cohort	n=103 pts	Inclusion criteria: Adult pts with TOF and conotruncal defects	Clinical and genetic screen	● 31 had 22q11DS. ● Combining 2 clinical features; discriminate ability 82% ● 4 features and discriminant ability >85%.	● Clinicians who consider ≥2 clinical features can help identify 22q11.
Swaby JA, et al. 2001 (151) 21257016	Cohort	n=104 pts with 22q11	Inclusion criteria: >17 y with 22q11	N/A	● Prevalence of severe CHD in the Relatives of probands with 22q11 is 0.36	● Heritable susceptibility for CHD for family members of 22q11, even more than expected with 22q11.

			Exclusion criteria: Pts adopted and with inadequate family history		(p=0.007 compared with general population).	
Liu AP, et al. 2014 (152) 24721633	Prospective study	n=156 pts consecutive pts with conotruncal defects	Inclusion criteria: Pts from ACHD clinic in Hong Kong	Determine prevalence of undiagnosed 22q11 in adult Chinese pts with conotruncal anomalies and phenotypic findings	● 18 pts (11.5%) diagnosed with 22q11. ● Dysmorphic features detected by geneticist in all. ● Only 2/3 considered dysmorphic by cardiologist on initial assessment. ● Significant extra cardiac manifestations (33% neurodevelopmental, 28% thrombocytopenia etc.).	● Underdiagnosis of 22q11 is common. Facial features may not be recognized. ● Testing and genetic referral should be offered to pts with conotruncal defects.
Monteiro FP, et al. 2013 (153) 23440478	Cohort	n=194 pts	Inclusion criteria: Variable features of 22q11 Group 1: clinical with palatal Group 2: clinical without palatal Group 3: cardiac defects associated with 22q11 Group 4: juvenile onset schizophrenia	Delineation of features of 22q11	● 22q11 in 45 pts (23%) ● Group 1: 34.7% ● Group 2: 22.2% ● Group 3: 6/52 (11.5%).	● Propose screening pts with distinct manifestations.
Hinton RB, et al. 2007 (154) 17936159	Cohort	n=38 probands with HLHS	Inclusion criteria: N/A	Determine the size of the genetic effect (heritability) in families identified by a HLHS proband.	● 21 of 38 (55%) families had more than 1 affected individual, and 36% of pts had CV malformation, including 11% with BAV. ● The heritability of HLHS alone and with associated CV malformation were 99% and 74% ($p<0.00001$), respectively. ● The sibling recurrence risk for HLHS was 8%, and for CV malformation was 22%.	● Increased prevalence of BAV in family members.
Robledo Carmona J, et al. 2013 (155) 23684596	Cross-sectional	n=553 pts (348 FDR and 105 controls)	Inclusion criteria:100 families of BAV pts	16 BAV in FDR (15% for families, 4.6 for FDR)	● Aortic dimensions of FDR with TV similar to control.	● BAV recurrence was low (4.6%).
Panayotova R, et al. 2013 (156) 23798202	Prospective cohort	n=47 initial pts	Inclusion criteria: N/A	N/A	● 14% prevalence of aortic valve disease in FDR of pts who had aortic valve surgery.	● High prevalence of BAV in FDR of pts with BAV who have undergone surgery.
McBride KL, et al.	Screened cohort	n=413 FDR of pts with LVOTO.	Inclusion criteria: Nonsyndromic LVOTO	N/A	32/413 (7.7%) had LVOTO (18 BAV, 5 HLHS, 3 CoA, 3 AVS) or other CHD.	● Increased risk of CHD in FDR of pts with LVOTO.

2005 (157) 15690347		351 echoes				
Majdalany DS, et al. 2010 (158) 20136856	Retrospective review	n=50 pts (57 surgeries)	Inclusion criteria: >18 with Down syndrome who underwent cardiac surgery	N/A	● Atrial arrhythmias in 25%. ● 12% had postop pulmonary infection.	● At an experienced center, pts with Down syndrome can undergo cardiac surgery with low risk of mortality and morbidity. ● Atrial arrhythmias and postop infection common.
Crepaz R, et al. 2013 (159) 24047157	Observational	n=7 pts	Inclusion criteria: Adults with trisomy 21 and pulmonary HTN	125 mcg Bosentan Follow up 46–55 mo	● Improved 6MWT and SPO^2. ● Increased pulmonary flow acceleration time.	● Downs syndrome does not affect the response to Bosentan Therapy.
Troost E, et al. 2011 (160) 21744698	Retrospective analysis	n=134 pts	Inclusion criteria: Adults with Eisenmenger syndrome	Survival rate	● Mean survival was 44.9 y ± 2.2; survival of pts with trisomy 21 did not differ from pts without trisomy 21.	● Survival of pts with trisomy 21 did not differ from pts without trisomy 21.
Carlson M, et al. 2012 (161) 23032325	Retrospective	n=20 pts with Turners and dissection	Inclusion criteria: N/A	Ascending aorta size index	● In 9 pts with Type A dissection mean ascending aorta size 2.7 ± 0.6 cm/m^2.	● Adults with Turner syndrome should be considered for aortic operation if aortic size index >2.5 cm/m^2.

Data Supplement 17. Acquired Cardiovascular Disease – Section 3.10

Study Name, Author, Year	Study Type/ Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
(Late) CV Events, Mortality, Acquired Comorbidities in ACHD Pts						
Pillutla P, et al. 2009 (162) 19853711	Retrospective analysis from CDC multiple cause-of-death registry	U.S. population	Inclusion criteria: Pts with CHD and death records, 1979–2005	Trends in mortality from 1979–2005 among individuals with CHD in the U.S.	● Significant decline in mortality in ACHD including VSD, PDA, CoA, and Ebstein anomaly. 71% decline in deaths associated with TGA (p=0.001) and a 40% reduction in deaths associated with TOF (p<0.001). Mortality related to other lesions declined as well. Among adults with cyanotic lesions, the 1° contributing cause of death was arrhythmia followed by HF. For adults with noncyanotic lesions, the major contributing cause before 1990 was arrhythmia; after 1990, MI became the leading contributing cause of death. ● There was an overall decrease in the incidence of arrhythmia as the cause of	● Pts with CHD are living longer. ● Arrhythmia remains the 1°contributing cause of death for those with cyanotic lesions. ● MI is now the leading contributing cause for adults with noncyanotic CHD consistent with late survival and an increasing impact of acquired HD.

					death in all ages, particularly among children.	
Lin YS, et al. 2014 (163) 24655794	Prospective cohort from Taiwan's National Health Insurance Research Database	n=3,267 adult pts with ACHD identified between 2000–2003, median follow-up of 11 y; 6,534 controls	Inclusion criteria: ACHD pts with ASDs, VSDs, PDAs, TOF, and pulmonary stenosis	Incidence of MACE. (MI, HF, PCI, CABG, malignant dysrhythmia, cardiac shock, implantable cardiac defibrillator, and death)	● MACE was 4-fold higher in the ACHD group compared with the controls (after adjustment for age and sex, ACHD pts had an increased risk of HF, malignant dysrhythmia, acute coronary syndrome, and stroke).	● ACHD pts have an increased life-long risk of MACE.
Engelfriet P, et al. 2005 (164) 15996978	European cohort of adults with CHD	n=4,110 pts	Inclusion criteria: ACHD pts who consecutively visited the output clinics of 1 of the participating centers in 1998	Mortality and morbidity (NYHA class) in 5 y	● NYHA FC worsened in 6% (In cyanotic defects and in the Fontan circulation, 21 and 17%). In only 1% of CoA pts, the NYHA class became worse. ● Among ASD pts, the NYHA class improved more often than it worsened. ● Arrhythmias were common.	● Outcomes were worst in cyanotic defects and in the Fontan circulation, but a considerable proportion of the other pts also suffered from cardiac symptoms.
Zomer AC, et al. 2010 (165) 20674998	The CONCOR registry of over 10,000 adults with CHD used to verify the causes of death provided by the WHO guidelines based national mortality registry, by linkage.	n=7,277 pts (196 (2.4%) were recorded deceased vs. 228 deceased pts (3.1%) recorded in the CONCOR registry, during a follow-up of 25,900 pt y.	Inclusion criteria: Registry pts with death records	Cause of death	● Median age at death was 48.9 y. ● Of all deaths in the CONCOR registry, 77% had a CV origin; nearly 50% were due to progressive HF and arrhythmias. The national mortality registry recorded death due to progressive HF and arrhythmias in only 8.5%. Registry recorded death with an 'unspecified' cause in ~30%, primarily containing pts who died due to progressive HF and arrhythmias according to their medical records.	● National mortality registries lack the specificity and completeness needed for accurate research on causes of death in ACHD pts.
Verheugt CL, et al. 2011 (28) 20207625	Retrospective Analysis of death cause in Dutch CONCOR national registry linked to national mortality registry	n=6,933 pts	Inclusion criteria: Pts in CONCOR registry of ACHD and also with death records from mortality registry	Mortality and cause of death	● 197 (2.8%) died during a follow-up of 24 865 pt-y. Median age at death was 48.8 y. ● Of all deaths, 77% had a CV origin; 45% were due to chronic HF. Several complications predicted all-cause mortality beyond the effects of age, sex, and CHD severity, i.e., IE, SVA, VA, conduction disturbances, MI, and pulmonary HTN (HR: 1.4–3.1; p<0.05). These risks were similar in pts > and <40 y. ● Almost all complications predicted death due to HF (HR: 2.0–5.1; p<0.05);	● Compared with the general national population, there was excess mortality, particularly in the young. ● Age predicted mortality, as did sex, severity of defect, number of interventions, and number of complications (HR: 1.1–5.9; p<0.05).

					conduction disturbances and pulmonary HTN predicted SCD (HR: 2.0–4.7; p<0.05).	
Tutarel O, et al. 2014 (2) 23882067	Retrospective cohort study	n=375 pts 64.8 ± 5.9 y	Inclusion criteria: All ACHD pts ≥60 y under active follow-up	All-cause mortality during a median follow-up of 5.5 y	● 55 of the 375 pts died. CAD (HR: 5.04; 95% CI: 1.88–13.51; p=0.0014), symptoms of HF (HR: 2.36; 95% CI: 1.05–5.29; p<0.05), NYHA class (HR: 1.96; 95% CI: 1.18-3.26; p<0.01), and moderate-to-severe reduction in systemic ventricular systolic function (HR: 1.90; 95% CI: 1.20–2.99; p<0.001) were the strongest prognostic factors.	● Acquired morbidities, such as CAD are reasons for mortality in aging ACHD population.
Afilalo J, et al. 2011 (1) 21939837	Population-based cohort study using the Quebec CHD Database	n=3,239 pts	Inclusion criteria: All pts with CHD coming into contact with the Quebec healthcare system between 1983–2005	Types of ACHD lesions in older adults were shunt lesions (60%), valvular lesions (37%), and severe congenital heart lesions (3%)	● The most powerful predictors of mortality in the Cox proportional hazards model were: dementia (HR: 3.24; 95% CI: 1.53–6.85), GI bleed (HR: 2.79; 95% CI: 1.66–4.69), and CKD (HR: 2.50; 95% CI: 1.72–3.65). ● Type of ACHD and ACHD-related complications had a minor impact on mortality.	● The prevalence of geriatric ACHD is substantial, although severe lesions remain uncommon. ● ACHD pts that live long enough acquire general medical comorbidities, which are the pre-eminent determinants of their mortality.
Nieminen HP, et al. 2007 (166) 17888844	Retrospective cohort study of ACHD in Finland	n=6,024 pts who survived their first operation	Inclusion criteria: Deaths of pts operated on for CHD in Finland during 1953–1989 compared to non-CHD-related deaths to those of the general population	Mortality	● 592 (9%) died during the 45-y follow-up period. Majority of pts (397, 67%) died owing to the CHD. Furthermore, non-CHD-related mortality was twice as high (RR: 1.9; 95% CI: 1.5–2.4) as expected. The main mode for CHD-related death was HF (40%). Other modes included perioperative (26%), sudden (22%), and CV (12%) deaths.	● Most pts died owing to CHDs, but non-CHD-related mortality was also high.
Bradley E, et al. 2013 (167) 24082371	Single-center retrospective analysis	n=208 pts	Inclusion criteria: Pts with TOF. Rates and mean values from the AHA 2011 HD and Stroke Statistics Update were used as population estimates for comparison	CV outcomes	● CV disease prevalence was not different in TOF pts from general population (40% vs. 36%; p=0.3). There was significantly more CV disease due to higher prevalence of coronary disease (12% vs. 7%; p<0.05) and HF (16% vs. 2%; p<0.0001).	● Increased prevalence of HF (regardless of PV disease) accounts for the frequency of CV disease in TOF mean aged 20–59 y.

Stuart AG, et al. 2012 (168) 22413988	Review	N/A	Inclusion criteria: N/A	Changing lesion demographics of the adults with CHD	● The ACHD population are now developing problems associated with aging and there is a new population of geriatrics with CHD.	● ACHD pts develop problems related to aging such as acquired CVD.
Risk Factor Modification Assessment and Management (Hyperlipidemia, Obesity, Hypertension, Smoking)						
Pemberton VL, et al. 2010 (114) 20212294	NHLBI Scientific Statement	N/A	Inclusion criteria: Research indicates that a significant portion of children with CHD are also obese or overweight	Prevention of obesity	● Authors discuss the prevalence of obesity, potential etiological factors, possible sequelae, and obesity and CV risk management and treatment in pts with CHD.	● Recommendations for prevention of obesity in CHD.
Kavey RE, et al. 2006 (169) 17130340	AHA Scientific Statement	N/A	Inclusion criteria: CV risk reduction in high-risk pediatric pts	Reduction of CVD incidence and events	● Identifies the importance of premature CVD in the course of certain pediatric diagnoses and addresses the response to risk factor reduction.	● There are no randomized trials documenting the effects of risk reduction on hard clinical outcomes.
James PA, et al. 2014 (170) 24352797	Scientific Statement report from the panel members appointed to the Eighth Joint National Committee (JNC 8)	N/A	Inclusion criteria: N/A	HTN Definition and Treatment Targets	● Writing group discusses the definition and targets for treatment of HTN.	● Recommendations for treatment of HTN for different age and risk groups reviewed.
Rabus MB, et al. 2009 (171) 19267822	Single-center case series	n=988 pts	Inclusion criteria: Pts with rheumatic, congenital, or degenerative AS, who underwent aortic valve replacement at Koşuyolu Heart and Research Hospital between 1985–2005	Effects of hypercholesterolemia and high LDL level on calcific AS or massive aortic valve calcification	● High serum cholesterol level (>200 mg/dL) was related to massive aortic valve calcification in all pts (p=0.003). ● Hypercholesterolemia linked to calcific AS and massive calcification in pts with degenerative etiology (p=0.02 and p=0.01, respectively) and massive calcification in pts with congenital bicuspid aorta (p=0.02). ● Other independent risk factors were high LDL level (>130 mg/dL; p=0.03 and p=0.05) and high serum C-reactive protein level (p=0.04 and p=0.05).	● Hypercholesterolemia is related to increased risk of aortic valve calcification in pts with congenital etiology as well as degenerative etiology. ● Preventive treatment of hypercholesterolemia could play an important role to decrease or inhibit development of aortic valve calcification.

Smith-Parrish M, et al. 2014 (172) 24607241	Single-center cross-sectional study	n=160 pts s/p CoA repair compared to 96 adults with other isolated forms of CHD, including AVS, PV stenosis, or ASD	Inclusion criteria: Pts who underwent CoA repair between 1974–2009.	To determine whether pts with CoA were more likely to develop obesity compared with the general population or others with isolated forms of CHD	● After age 5 y, pts with CoA had significantly greater BMI compared with age-sex matched normal data (p<0.001). The proportion of obesity in pts with CoA significantly increased over time (p<0.001). ● Adults with repaired CoA developed obesity at a greater rate than those with either AVS (p=0.004) or with PV stenosis or ASD (p<0.001).	● There is a greater incidence of obesity that progressively increases with age in pts with repaired CoA, at a greater rate than those with other isolated forms of CHD.
Shustak RJ, et al. 2012 (173) 21892630	Retrospective cross-sectional study	n=795 pts	Inclusion criteria: Pts presenting to an urban center's Pediatric Cardiology Program between Jan 1–Dec 31, 2006.	Prevalence of overweight and obesity in children with HD compared against national data of children without HD	● No significant differences in overweight or obesity rates were detected between HD and non-HD groups. ● Hispanic ethnicity and male sex were the only predictors of obesity.	● Children with HD are as prone to obesity as noncardiac pts.
Pederson TA, et al. 2012 (174) 22459728	Observational cohort study	n=133 adults; s/p repair of COA in childhood/youth. 36 age- and sex-matched healthy pts as controls	Inclusion criteria: s/p repair of COA in childhood/youth	Prevalence of HTN and CV reinterventions	● The prevalence of HTN was high (44% of the cohort, 1/2 despite medication). Reinterventions common (26%) due to aortic valve dysfunction and re-CoA. half of the cohort had a BAV. ● Increased LV mass, systolic and diastolic dysfunction, aortic valve dysfunction, aortopathy, and HTN were common.	● Surgical correction of CoA only repairs the anatomical narrowing, but not the associated vasculo- and valvulopathy.
Zomer AC, et al. 2012 (175) 22444325	Cross-sectional study	n=1,496 pts compared against 6,810 unaffected pts	Inclusion criteria: A random sample from the CONCOR (n=11,047), the Dutch national registry of adult pts with CHD	Smoking, obesity, sport participation, social support, and access to medical care	● Overall, the CHD population smoked less (adjusted OR: 0.5; p<0.05), had more sports participation (adjusted OR: 1.2; p <0.05), and had less obesity (adjusted OR: 0.7; p<0.05) than the reference group.	● There was a substantial social disadvantage in adult pts with CHD. In contrast, adults with CHD had healthier lifestyles compared to the reference group.
Risk Factor Modification Assessment and Management: Promotion of Physical Activity						
Longmuir PE, et al. 2013 (176) 23630128	AHA Scientific Statement	N/A	Inclusion criteria: N/A	Reduction in CVD incidence and events	● This statement recognizes the importance of physically active lifestyles to the health and well-being of children and adults with congenital heart defects.	● Counseling of pts with ACHD should emphasize the importance of daily physical activity and decreasing sedentary behavior as appropriate for the pt's clinical status.
Management of Pts with Coronary Disease in ACHD Pts						

Stulak JM, et al. 2012 (177) 22098921	Retrospective case review	n=122 pts with CAD at the time of correction of CHD	Inclusion criteria: Pts who underwent concomitant CABG at the time of ACHD repair; between February 1972 and August 2009. Most common 1°cardiac diagnoses included secundum ASD in 73 pts (60%), Ebstein anomaly in 14 pts (11%), and partial anomalous pulmonary venous connection in 8 pts (7%).	Outcomes of CABG	● Median age was 64 y (range 40–85 y). ● 30 pts (25%) had preoperative angina, 7 pts (6%) had previous MI, and 6 pts (5%) had previous percutaneous intervention. ● During a median follow-up of 6 y (maximum follow-up, 32 y), actuarial survival was 76% at 5 y and 56% at 10 y. ● In pts with left anterior descending artery disease, survival was higher when a LIMA graft was used (5 y, 86% vs. 66%; 10 y, 66% vs. 36%; p<0.05).	● Concomitant CABG may be required at the time of correction of CHD. Survival is higher when a LIMA graft is used, and late functional outcome is good, with a low incidence of late angina and need for reintervention.
Giannakoulas G, et al. 2009 (178) 19427444	Retrospective chart review of ACHD cohort	n=250 ACHD pts	Inclusion criteria: ACHD pts undergoing selective coronary angiography for reasons other than suspected CAD; mean age 51 ± 15 y; 53% men)	Presence of CAD by coronary angiography	● Significant CAD was found in 9.2% of adult pts with CHD. No pt with cyanosis or <40 y had significant CAD. ● Systolic and diastolic systemic ventricular dimensions were significantly higher in pts with CAD, even after adjustment for age. Systemic arterial HTN and hyperlipidemia were strong predictors of CAD (OR: 4.54; 95% CI: 1.82–12.0; p=0.001; OR: 9.08; 95% CI: 3.56–24.54; p<0.0001, respectively); whereas, no relation to chest pain was found.	● Prevalence of significant CAD in a hospital adult CHD cohort was similar to that in the general population. Supports selective coronary angiography in pts >40 y referred for cardiac surgery. ● Traditional CV risk factors for CAD played a role, 1°prevention of CAD as important as in the general population.
Deva DV, et al. 2014 (179) 24044501	Retrospective cohort, Toronto	n=34 stress perfusion CV magnetic resonance examinations	Inclusion criteria: Cases of perfusion CV magnetic resonance in pts referred from the ACHD service.	Coronary abnormalities	● 11 studies were positive. ● Stress perfusion CV magnetic resonance demonstrated a sensitivity of 82% and specificity of 100%. ● Coronary abnormalities were identified in 71% of cases who had coronary MRA.	● Stress perfusion CV magnetic resonance is a useful and accurate tool for investigation of myocardial ischemia in ACHD population with suspected nonatherosclerotic coronary abnormalities.
Management of Pts with HF in ACHD Pts						
Niazi I, et al. 2014 (180)	Review	N/A	Inclusion criteria: N/A	CRT insertion	● Approach to CRT implant in pts with CHD.	● While CRT device implants have become routine in the

24645638						adult ischemic or nonischemic cardiomyopathy populations, pts with CHD offer special challenges due to unusual anatomic variations.
Stefanescu A, et al. 2014 (181) 24411285	Retrospective analysis	n=153 pts	Inclusion criteria: Adults with TGA, Ebstein anomaly, TOF, DORV, and single ventricle from 2 ACHD centers.	CV death, with a secondary composite outcome of death, transplant, VAD, CV admission, and treatment for arrhythmia. Risk groups based on Seattle Heart Failure Model 5-y predicted survival: high (predicted survival <70%), intermediate (70%–85%), and low risk (>85%).	● 10 pts had the 1° outcome of death, and 46 the combined endpoint. The hazard of death in the Seattle Heart Failure Model high- vs. intermediate-risk group was 7.09 (95% CI: 1.5–33.4; p=0.01; no deaths in the low-risk group) and the hazard of the composite outcome between the high- vs. low-risk group was 6.64 (95% CI: 2.5–7.6; p=0.0001). ● There was greater probability of all-cause mortality (p=0.003) in the high-risk group.	● Seattle Heart Failure Model can help identify subjects with ACHD at risk for adverse outcome and poor cardiopulmonary efficiency.
Mylotte D, et al. 2014 (182) 24275303	Review	N/A	Inclusion criteria: HF in pts with ACHD.	N/A	● A range of transcatheter therapies have recently emerged to expand the therapeutic potential of the more traditional surgical and medical interventions for HF in pts with CHD.	● These complementary interventions aim to treat the growing pt population with ACHD.
Motonaga KS, et al. 2014 (183) 24275296	Review	N/A	Inclusion criteria: Arrhythmias and EP therapies in ACHD pts	N/A	● This review discusses the most common arrhythmias encountered in this population and the therapeutic options available.	● Specific issues unique to this population need to be addressed.
Ohuchi H and Diller GP 2014 (184) 24275294	Review	N/A	Inclusion criteria: N/A	N/A	● Most ACHD pts show high levels of natriuretic peptide when compared with normal controls. Other biomarkers may be elevated in ACHD.	● Role of biomarkers in ACHD is expanding.
Alonso-Gonzalez R, et al. 2013 (185) 23750686	Review	N/A	Inclusion criteria: N/A	N/A	● This review highlights the impact of neurohormonal activation in pts with CHD as well as the usefulness of assessing natriuretic peptide levels in specific clinical situations.	● There is growing evidence that natriuretic peptide levels are elevated in some of the ACHD pts.

Dinardo JA, et al. 2013 (186) 23264549	Review	N/A	Inclusion criteria: HF in ACHD population	N/A	● The ACHD pts currently at greatest risk for HF are those with single-ventricle physiology, those with a 2-ventricle circulation with the right ventricle as the systemic ventricle, and those with repaired TOF and PV insufficiency.	● This article reviews the demographics, diagnosis, FC, and treatment of HF in the ACHD population.
Shaddy RE, et al. 2008 (187) 18248271	Review	N/A	Inclusion criteria: HF in ACHD population	N/A	● Pts at greatest risk of HF are those without a systemic left ventricle, such as Mustard and Senning repairs of TGA, CCTGA, and pts who have had a Fontan procedure. ● Exercise intolerance may predict hospitalization and death in such pts.	● For those pts with systemic left ventricles, may be reasonable to use the HF guidelines developed for pts with acquired HD. For those pts without a systemic left ventricle (e.g., a SRV or single ventricle), no foundation for evidence-based therapy.
Piran S, et al. 2002 (188) 11889012	Prospective cohort	n=188 pts	Inclusion criteria: Consecutive adult pts with single or SRV assessed with gated radionuclide angiography (n=135) or 2D echo (n=188) and followed up clinically	Development of HF, severity of HF	● 82.4% of the pts were in NYHA class I or II, 13.3% were in class III, and 4.3% were in class IV. ● HF occurred in 22.2% of pts with TGA and a Mustard procedure, 32.3% of pts with CCTGA, and 40% of Fontan-palliated pts. ● Symptomatic pts had significantly lower anaerobic thresholds (p<0.0003). ● Systemic ventricular EF in symptomatic vs. asymptomatic pts at rest was 34.8 ± 15.7% vs. 46.7 ± 3.4% (p=0.00001).	● Pts with single or SRV have significant risk for HF accompanied by high mortality. ● Best predictors for mortality were NYHA class, systemic EF, and age at operation. ● Mortality was 47.1% among symptomatic pts and 5% among asymptomatic pts at 15.7 y of postoperative follow-up.
Reardon LC, et al. 2012 (189) 22863176	Retrospective chart review	n=53 pts	Inclusion criteria: ACHD pts who had BNP measurement	The 1° endpoint: death or HF admission	● 15 pts (28%) met the 1° endpoint (death in 7, HF hospitalization in 8). Mean and median baseline BNP in pts meeting the 1° endpoint were 322±346 and 179 pg/mL, compared to 100±157 and 41 pg/mL in those not meeting the 1° endpoint (p=0.0029). ● A Cox proportional hazards model using baseline BNP between the 2 groups yielded a HR of 1.84 (95% CI: 1.19–2.85; p=0.006). The relative risk for baseline BNP level >140 pg/mL was 4.62 (95% CI: 1.80–11.3; p=0.008).	● Elevated BNP levels are predictive of death or HF admission in pts with the ES. A serum BNP level >140 pg/mL is a useful tool in identifying high-risk pts.

Parekh DR 2011 (190) 21685844	Review	N/A	Inclusion criteria: HF treatment in ACHD pts	N/A	● Conventional HF therapy of BB and ACEIs have not demonstrated clear survival benefit in this population.	● Adequately powered and controlled randomized studies are grossly lacking.
Bolger AP, et al. 2002 (191) 12093776	Prospective case series	n=68 pts (53 ACHD pts and 15 healthy controls)	Inclusion criteria: Pts with ACHD who had blood levels of biomarkers	Concentrations of ANP, BNP, endothelin-1, renin, aldosterone, norepinephrine, and epinephrine	● ACHD pts had elevated levels of ANP (56.6 vs. 3.1 pmol/L), BNP (35.8 vs. 5.7 pmol/L), ET-1 (2.5 vs. 0.7 pmol/L; all p<0.0001), renin (147 vs. 16.3 pmol/L), norepinephrine (2.2 vs. 1.6 pmol/L; both p<0.01) and aldosterone (546 vs. 337 pmol/L; p<0.05). ● There was a highly significant stepwise increase in ANP, BNP, ET-1, and norepinephrine according NYHA class and systemic ventricular function.	● Neurohormonal activation in ACHD was associated with presence and severity of chronic HF. ● There was no direct relationship between the 4 anatomic subgroups and any of the neurohormones studied.
Norozi K, et al. 2005 (192) 16236924	Case control study	n=50 adult pts (mean 27.8 ± 1.7 y ± SEM) with TOF after surgical repair (NYHA FC 1.1 ± 0.1) and 100 healthy controls	Inclusion criteria: Adult pts with TOF >20 y after surgical repair Exclusion criteria: Symptomatic HF, acute infection, chronic lung disease, severe mental retardation, and medication (i.e., ACEIs and BB)	Concentrations of NT-proANP, NT-proBNP, endothelin-1, renin, aldosterone, adrenalin, and noradrenalin	● TOF pts had elevated levels of NT-proBNP compared with healthy individuals: NT-proBNP (women: 180 pg/mL vs. 43 pg/mL, and men: 147 pg/mL vs. 32 pg/mL; p<0.0001) and ET-1 (2.5 fmol/L vs. 0.7 fmol/L). ● There was a significant correlation of NT-proBNP to dimension and estimated peak systolic pressure of the RV as well as impairment of VO_2 max.	● RV dysfunction detected by echo and plasma NT-proBNP in asymptomatic or minimally symptomatic TOF pts; correlates well with cardiopulmonary exercise capacity.
Norozi K, et al. 2006 (193) 16635615	Case control study	n=111 (59 pts with surgically corrected TOF and 52 pts with operated left-to-right-shunt defects	Inclusion criteria: Surgically corrected TOF pts	Echocardiographic indices M VO_2, NT-proBNP levels	● Pts with TOF showed significantly greater LV and RV Tei indexes than those with left-to-right-shunt defects (p<0.0001). ● Peak O_2 uptake was significantly reduced in the pts with TOF (p<0.0001) and was correlated inversely with the LV Tei index p<0.0001). NT-proBNP was significantly increased in pts with TOF (150 +/ 141 vs. 57 ± 39 pg/mL; p<0.0001).	● Biventricular dysfunction detected by Tei index. Increased NT-proBNP and impaired peak O_2 uptake are also signs of biventricular dysfunction.
Krieger EV, Valente, AM, et al.	Review	N/A	Inclusion criteria: N/A	N/A	● Not appropriate to extrapolate from the acquired HF literature and apply it to this heterogeneous population of CHD pts.	● Pts with CHD have been excluded from most large trials of HF small retrospective and

2014 (194) 24924621						underpowered studies in the CHD population.

Data Supplement 18. Noncardiac Medical Issues and Noncardiac Surgery – Sections 3.11 and 3.12

Study Name, Author, Year	Study Type/ Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
Wang A, et al. 2007 (195) 17920376	Cohort study	n=198 pts	Inclusion criteria: All ACHD pts with surgery prior to 1992	Hepatitis C antibody testing	● 17 (8.6%) had positive Hepatitis C antibody results, and 8 (4.0%) had positive Hepatitis C ribonucleic acid results.	● Positivity rate was nearly 5-fold higher than general population.
Maxwell BG, et al. 2013 (196) 23907357	Retrospective analysis using administrative database of ACHD cohort and non-ACHD matched comparison cohort	Study cohort n=10,004; matched comparison cohort n=37,581	Inclusion criteria: Pts with ACHD undergoing noncardiac surgery in the Nationwide Inpatient sample database, compared with a matched non-ACHD control cohort	Input mortality. Secondary endpoint: composite endpoint of perioperative morbidity	● Mortality: 407 of 10,004 (4.1%) vs. 1,355 of 37,581 (3.6%); unadjusted OR: 1.13; p=0.031; adjusted OR: 1.29; p<0.001. ● Morbidity: ACHD group 2,145 of 10,004 (21.4%) vs. 6,003 of 37,581 (16.0%); OR: 1.44; p<0.001.	● ACHD pts undergoing noncardiac surgery experienced increased perioperative morbidity and mortality vs. controls.
Maxwell BG, et al. 2014 (197) 24887660	Retrospective cohort analysis of the National Surgical Quality Improvement Program database	Study cohort n=1,191; comparison cohort n=5,127	Inclusion criteria: Pts 18-39 y with prior heart surgery that underwent noncardiac surgery between 2005–2010. Matched cohort had no prior heart surgery	Perioperative outcomes	● Observed rates of death, perioperative cardiac arrest, MI, stroke, respiratory complications, renal failure, sepsis, VTE, perioperative transfusion, and reoperation were significantly higher in the study cohort (p<0.01 for all). ● Mean postoperative LOS was greater in the study cohort (5.8 vs. 3.6 d; p<0.01).	● History of prior cardiac surgery is a marker of substantial perioperative risk; that is not accounted for by the matched variables. Note: not matched on all available variables. ● Multivariable analysis shows prior CV surgery is not an independent marker of risk, but a marker of more extensive comorbid disease.
Christensen RE, et al. 2012 (198) 22717725	Retrospective review	n=40 pts with 73 procedures	Inclusion criteria: HLHS undergoing anesthesia 2002–2008	Perioperative AE	● 11 AE (15%). 13 ICU admissions (18%).	● High rate of AE; perioperative care should be individualized based on the presence of known risk factors such as the stage of palliation, residual

						cardiac disease and severity of planned surgery.
Christensen RE, et al. 2010 (199) 19933174	Retrospective analysis	n=50 procedures (43 pediatric; 7 adult)	Inclusion criteria: Records for pts with surgically corrected d-TGA undergoing general anesthesia for noncardiac surgery between October 2000–April 2008 were reviewed	Perioperative AE	● 4 AE: bradycardia, failed extubation after 2 of the procedures, and postoperative bleeding requiring return to the operating theatre.	● The majority of pts with surgically corrected d-TGA can safely undergo general anesthesia, often as outpts, with no invasive monitoring. ● Perioperative care should be individualized based on the presence of comorbidities, type of repair, residual cardiac disease, severity of planned surgery, and experience of the provider.
Rabbitts JA, et al. 2013 (200) 22998356	Retrospective analysis	n=31 pts (39 procedures)	Inclusion criteria: Fontan pts ≥16 y who underwent general anesthesia for noncardiac surgery at Mayo Clinic	Perioperative complications	● Perioperative complications occurred in 31% of noncardiac surgeries, 1 postoperative death and 13 after ventral hernia repair. ● The 2 pts who had complications that did not resolve (long-term dialysis and death) had LVEF below the mean for the group (22% and 28%).	● It may be more appropriate for Fontan pts to undergo anesthesia for noncardiac surgery in a tertiary institution, particularly pts with a LVEF of <30%. ● Intraoperative arterial BP monitoring and overnight admission are likely appropriate for most cases.
Eagle SS and Daves SM 2011 (201) 21477759	Review	N/A	Inclusion criteria: N/A	Descriptive treatment of management of Fontan pts through noncardiac surgery	N/A	● Summarizes the approach and management issues that arise in Fontan pts undergoing noncardiac surgery.
Ammash NM, et al. 1999 (202) 9935034	Retrospective analysis	n=58 pts with Eisenmenger syndrome	Inclusion criteria: Pts with Eisenmenger syndrome ≥17 y undergoing noncardiac surgery	Perioperative complications and death	● 2 deaths (7%), 1 following spinal fusion and the other following appendectomy. 10 pts were discharged without complications. 1 death occurred 10 d following spinal fusion. This pt had the longest anesthesia (525 min).	● In majority noncardiac surgery accomplished without substantial morbidity, mortality but even with relatively minor surgery, significant complications, including death, can occur.
Warner MA, et al. 1998 (203) 9703297	Retrospective cohort study of 6-y period	n=276 pts undergoing 480 noncardiac procedures	Inclusion criteria: Adult (<50 y) and pediatric CHD pts, surgical or diagnostic	30-d perioperative morbidity and mortality	● Complication rate was 5.8%; only 1 pt died intraoperatively. ● Risk factors associated with complications: cyanosis (p=0.002),	● Perioperative complications risk low. ● Pulmonary HTN, congenital HF, or cyanosis associated with

			procedure with anesthesia		current treatment for HF (p<0.001), poor general health (p<0.001), and younger age at the time of the procedure (p=0.027). ● Respiratory and nervous system procedures were associated with high frequencies of complications. Complications in pts undergoing ambulatory surgical procedures were infrequent (1.7%).	increased perioperative morbidity.
Maxwell BG, et al. 2014 (204) 24869762	Retrospective analysis	n=21 ACHD Claims cases	Inclusion criteria: Cases from the Anesthesia Closed Claims Project database.	Perioperative factors contributing to an AE	● 11 cases (52%) involved cardiac procedures and 10 (48%) noncardiac procedures. Common factors contributing to the AE in noncardiac cases were postoperative monitoring/care (50%), CHD (50%) and preoperative assessment or optimization (40%). The factors contributing to the pt injury were postoperative monitoring/care (50%) and CHD (50%) in noncardiac cases.	● This small study summarizes the role of anesthesiologists in adult pts with CHD. ● Emphasizes that risk is substantially in the postoperative phase rather than during the surgery itself.
Maxwell BG, et al. 2014 (204) 23648140	Survey analysis	n=168 anesthesiologists		Survey responses, including true/false, multiple choice, and Likert scale questions.	● Higher scores in those with cardiac (median IQR: 11 (7–15); p=0.005) and pediatric (median IQR: 12 (6–15); p=0.00) fellowship training, but not in those with critical care, obstetric, regional, or pain management training. ● Only moderate levels of comfort with a range of questions about providing perioperative or obstetric care to ACHD pts, with decreasing levels of comfort reported in pts with more complex lesions.	● Providers may benefit from improved training and protocols for ensuring adequate preparedness for the care of ACHD pts.
Kaemmerer H, et al. 2008 (205) 18312770	Retrospective analysis, multicenter study	n=1,033 admissions of 160 adult pts (16-71 y) with CHD, of which 201 were emergencies	Inclusion criteria: All emergency admissions to 1 of 5 centers for adults with CHD within 1 y	Cause-specific admissions	● 46 pts underwent surgery (CV n=41, general n=5) or EP treatment (n=41). ● 126 of 201 emergencies (63%) required cooperation with another specialized department: surgery (n=46), internal medicine (n=42), neurology (n=12), ophthalmology (n=6), otorhinolaryngology (n=5), gynecology (n=5), psychiatry (n=4),	● Consultants attending adult pts with ACHD need a high degree of specialized experience to manage emergencies properly. Data support the demand for a multidisciplinary approach in specialized centers.

					radiology (n=3), dermatology (n=2), and orthopedics (n=2).	
Niwa K, et al. 2004 (206) 15262035	Survey	Written questionnaire sent to 6 facilities in North America and Europe.	Inclusion criteria: N/A	Admissions, surgeries, facility and provider characteristics	● Hospital admissions ranged from 100–660 pts/unit/y. Of the total number of registered pts, 52%–81% had undergone 1 or more reparative surgeries. Reoperations constituted 25–80% of the 50–170 operations/unit/y. Overall mean surgical mortality was 1.9%/y.	● Comprehensive care by multidisciplinary teams including adult and pediatric cardiologists, cardiac surgeons, specialized nurses, and other cardiac and noncardiac consultants was the unifying feature for all 6 tertiary care facilities.
Mott AR, et al. 2002 (207) 12530496	Retrospective review of single-center experience	n=112 operations (81 cardiac operations in 79 pts and 31 noncardiac operations in 23 pts)	Inclusion criteria: Pts ≥18 y who had undergone cardiothoracic operations at Texas Children's Hospital between July 1995–June 2000	Operative complications and death	● The overall early operative mortality was 6% (6/101). There were 3 late deaths. New-onset cardiac arrhythmias requiring treatment were diagnosed after 5/81 (6%) cardiac operations.	● Agreeable mortality rates can be attained in adult pts undergoing cardiac surgery at pediatric facility.
Maxwell BG, et al. 2014 (208) 25247694	Review of site of surgery (CHD center or not) for pts with CHD from the California Ambulatory Surgery Database 2005–2011	n=10,547 operations in adults; 11,254 in pediatric pts	Inclusion criteria: Pts that had surgery at a CHD center or nonspecialty center	Proportion of adult and pediatric pts with CHD who had surgery at a CHD center, analyzed by distance to the CHD center and the center where the surgery was performed	● Only 2,741 (26.0%) adults with CHD had surgery in a CHD center compared to 6,403 (56.9%) children (p<0.0001). ● Adult CHD pts who had surgery at a nonspecialty center (11.9 ± 15.4 miles away) lived farther from the nearest CHD center (37.9 ± 43.0 miles) than adult CHD pts who had surgery at a CHD center (23.2±28.4 miles; p<0.0001). ● Pediatric CHD pts who had surgery at a nonspecialty center (18.0 ± 20.7 miles away) lived farther from the nearest CHD center (35.7 ± 45.2 miles) than pediatric CHD pts who had surgery at a CHD center (22.4 ± 26.0 miles; p<0.0001).	● Unlike children with CHD, most adults with CHD (74%) do not have outpt surgery at a CHD center. ● For both adults and children with CHD, greater distance from a CHD center is associated with having surgery at a nonspecialty center.
Mylotte D, et al. 2014 (209) 24485223	Meta-analysis	n=718 pts	Inclusion criteria: Adults who underwent ASD closure in Quebec from 1998—2005.	Long-term cost effectiveness	● The 5-y cost of surgical closure was $15,304 ± $4,581 vs. $11,060 ± $5,169 for the transcatheter alternative. ● At 5 y, transcatheter closure was marginally more effective than surgery (4.683 ± 0.379 life-y vs. 4.618 ± 0.638 life-y).	● Transcatheter ASD closure was a cost-effective strategy associated with slightly improved clinical outcomes and reduced costs vs. surgical closure at 5-y follow-up.

					● Probabilistic sensitivity analyses demonstrated that transcatheter ASD closure was a dominant strategy with an 80% probability of cost savings and equal or greater efficacy compared to surgical treatment.	

Data Supplement 19. Pregnancy – Section 3.13.1

Study Name, Author, Year	Study Type/Design	Study Size, N	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
Chan WS, et al. 2000 (210) 10647757	Literature review	n=976 women with 1,234 pregnancies	Inclusion criteria: Pregnant women with prosthetic heart valve on anticoagulation published in English language articles Exclusion criteria: Case reports and if pregnancy was not followed to completion	Maternal and fetal risk of anticoagulation for prosthetic heart valves	● Oral anticoagulation throughout pregnancy associated with warfarin embryopathy in 6.4% of livebirths. The change of oral anticoagulants to heparin at or before 6 wk gestations until 12 wk eliminated risk of warfarin embryopathy. Risk of fetal or neonatal deaths was similar in women treated with oral anticoagulants throughout pregnancy and in those treated with heparin in first trimester. The regimen associated with lowest risk of valve thrombosis was use of oral anticoagulants throughout pregnancy and using heparin between 6 and 12 wk gestation was associated with an increased risk of valve thrombosis (9.2%).	● Anticoagulation in pregnant women with mechanical heart valves is best achieved with oral anticoagulants. ● The associated increased the risk of fetal embryopathy may be reduced by substituting oral anticoagulants with heparin between 6–12 wk gestation.
Pieper PG, et al. 2013 (211) 24192800	Prospective, multicenter cohort	n=209 CHD pts, 70 healthy controls	Inclusion criteria: Female pts with CHD, ≥18 y, pregnancy <20 wk gestation Exclusion criteria: Miscarriages, terminations, and drug use	Uteroplacental Doppler flow parameters	● Uteroplacental Doppler flow parameters were impaired in CHD women at 32 wk in CHD vs. healthy women ● Multivariable analysis: 1) RV function (tricuspid annular plane systolic excursion), 2) high NT-proBNP, 3) systemic, and 4) pulmonary AV valve regurgitation.	● CV function is associated with an abnormal pattern of Uteroplacental Doppler flow.
Roos-Hesselink JW, et al. 2013 (212) 22968232	Registry data 60 hospitals in 28 countries	n=1,321 pts	Inclusion criteria: Pregnant women with CHD (66%), VHD 25%, cardiac myopathy 7%,	Pregnancy outcome in pts with structural or ischemic HD	● 338 pts (26%) were hospitalized, 133 for HF. ● Caesarean section was performed in 41%.	● The vast majority of pts can go safely through pregnancy and delivery as long as adequate prepregnancy

			and ischemic HD in 2%. 2007 and 2011		● Maternal death 1%, fetal mortality 1.7%, and neonatal mortality in 0.6%.	evaluation and specialized high-quality care during pregnancy and delivery are available.
Liu H, et al. 2013 (213) 23245675	Retrospective observational	n=529 pts	Inclusion criteria: Pregnant female pts with CHD who gave birth at the Shanghai Obstetrical Cardiology Intensive Care Center, Shanghai, China, between 1993–2010	Maternal, fetal, and neonatal complications	● Maternal cardiac complications were reported in 33 (6.2%) of the women; fetal and neonatal complications were reported in 145 (27.4%). ● Significant predictive factors for maternal cardiac complications were cardiac events before pregnancy, NYHA FC greater than II, O_2 saturation below 90%, and LV Obstruction (aorta stenosis). ● Factors significantly predictive for fetal and neonatal complications were NYHA FC >2, O_2 saturation <90%, and PAH (systolic pressure ≥50 mm Hg).	● Identification of maternal, fetal, and neonatal complications among women with CHD may guide medical intervention and therefore reduce pregnancy-associated risk for these pts.
Wacker-Gussmann A, et al. 2013 (214) 23179135	Retrospective observational	n=267 pts	Inclusion criteria: Pregnant women with CHD who were seen at the German Heart Centre Berlin.	FC, health, work capability, and physical activity	● The maternal cardiac data revealed that 30% of the pts lost at least 1 FC during pregnancy. Onset arrhythmias (12%). The most prevalent neonatal complication was premature birth (12%).	● 2/3 of the pts tolerated pregnancy without CV complications. Most pts displayed good long-term health, work capability, and physical activity outcomes.
Ohuchi H, et al. 2013 (215) 23059769	Retrospective observational	n=33 pts	Inclusion criteria: Pregnant women with CHD who had undergone CPET 1.8 ± 2.2 y before delivery	Exercise capacity	● Maternal, cardiac, and neonatal events occurred in 8 (24%), 12 (36%), and 14 (42%), respectively. ● All CPET parameters correlated with neonatal birth weight ($p<0.05$–0.001). ● Exercise time, peak heart rate, peak systolic BP, and peak O_2 uptake VO_2 were associated with cardiac events ($p<0.05$–0.01), and exercise time and peak VO_2 were also associated with neonatal events ($p<0.05$). Exercise time, peak heart rate, and peak VO_2 were associated with at least 1 of the 3 events ($p<0.05$–0.01).	● CPET parameters predict pregnancy outcome and peak heart rate ≥150 beats/min and/or peak VO_2 ≥25 mL/kg/min may be reference value(s) for a safer pregnancy outcome in women with CHD.
Opotowsky AR, et al. 2012 (5) 21990383	Database review	n=622,000 pts	Inclusion criteria: 1998–2007 Nationwide Inpatient Sample	Combined: death, HF, arrhythmia, CVA, embolic events,	● Annual deliveries for women with CHD increased 34.9% from 1998–2007 compared with an increase of 21.3% in the general population.	● Maternal CHD is associated with a markedly increased risk of adverse CV events and

				"unclassified CV events," LOS, costs	● Women with CHD were more likely to sustain a CV event (4,042/100,000 vs. 278/100,000 deliveries, univariate OR: 15.1; 95% CI: 13.1–17.4; multivariable OR: 8.4; 95% CI: 7.0–10.0). Arrhythmia, the most common CV event, was more frequent among women with CHD (2637/100,000 vs. 210/100,000, univariate OR: 12.9; 95% CI: 10.9–15.3, multivariable OR: 8.3; 95% CI: 6.7–10.1). ● Death occurred in 150/100,000 pts with CHD compared with 8.2/100,000 pts without CHD (multivariable OR: 6.7; 95% CI: 2.9–15.4). ● Complex CHD was associated with greater odds of having an adverse CV event than simple CHD (8158/100,000 vs. 3166/100,000, multivariable OR: 2.0; 95% CI: 1.4–3.0).	death during admission for delivery.
Jastrow N, et al. 2011 (216) 20659773	Retrospective	n=227 female pts with cardiac disease followed for 312 pregnancies at our tertiary center from 1992–2007.	Inclusion criteria: CHD (81%) or acquired cardiac lesions followed at Ste-Justine Hospital Montreal July 1992–Dec 2007 Exclusion criteria: Miscarriage or pregnancy termination	Cardiac, obstetrical and neonatal complications	● CARPREG risk was low (score=0) in 66.3% and intermediate (score=1) in 33.7% pregnancies. ● Maternal cardiac events complicated 7.4% pregnancies, with pulmonary edema occurring most frequently (3.8%). An intermediate score was associated with a higher rate of cardiac events (19.0% vs. 1.4%; OR: 15.6; 95% CI: 4.5–54.4; p=0.0001). ● AE occurred in 27.5% neonates. ● Preterm deliveries occurred in 16.7% pregnancies, more commonly in pts with intermediate scores (OR: 2.4; 95% CI: 1.2–4.6; p=0.01). ● The sensitivity and NPVs of a low score were respectively 87% and 99% for total cardiac events and both 100% for 1° cardiac events, including pulmonary edema and sustained arrhythmia.	● The CARPREG risk index has a high sensitivity and NPV with regards to cardiac complications in pregnant women with HD.

Ouyang DW, et al. 2010 (217) 19411123	Retrospective cohort	n=65 female pts with CHD with 112 pregnancies	Inclusion criteria: Pts with CHD delivering at Brigham and Women's Hospital between Jan 1998–Dec 2005 Exclusion criteria: Pts with acquired HD, 1° arrhythmia diagnoses without underlying congenital defects, and isolated mitral valve prolapse	Adverse obstetric event	● An adverse obstetric event occurred in 32.6% (n=32) preterm delivery (n=19), postpartum hemorrhage (n=13), and preterm premature rupture of membranes (n=9). Pts who avoided Valsalva had increased rates of postpartum hemorrhage and 3rd/4th degree lacerations.	● 1/3 of pregnancies were associated with an adverse obstetric outcome, but events could not be predicted by baseline hemodynamic characteristics. ● The routine practice of avoiding Valsalva may be associated with high rates of postpartum hemorrhage and 3rd/4th degree lacerations.
Lui GK, et al. 2011 (218) 21220738	Multicenter, retrospective observational	n=83 pts with 89 pregnancies	Inclusion criteria: Women with CHD who were pregnant Jan 1997–Dec 2008. Must have completed CPET within 2 y prior to pregnancy or within the first trimester Exclusion criteria: History of permanent pacemaker	CPET variables included peak O_2 consumption and measures of chronotropic response: peak heart rate, percentage of maximum age predicted heart rate, heart rate reserve (peak heart rate-resting heart rate), and chronotropic index ([heart rate-resting heart rate]/ [220-age-resting heart rate]).	● 1 or more adverse cardiac events occurred in 18%; HF in 14%, and sustained arrhythmia in 7%. Peak heart rate, percentage of maximum age predicted heart rate (OR: 0.93; 95% CIL: 0.88, 0.98; p=0.01), and chronotropic index (OR: 0.65; 95% CI: 0.47, 0.90; p=0.01) were associated with a cardiac event. ● Neonatal events occurred in 20%. Peak heart rate (OR: 0.75; 95% CI: 0.58, 0.98; p=0.04), percentage of maximum age predicted heart rate (OR: 0.94; 95% CI: 0.89, 0.99; p=0.02), heart rate reserve (OR: 0.8; 95% CI: 0.64, 0.99; p=0.04), and chronotropic index (OR: 0.73; 95% CI: 0.54, 0.98; p=0.04) correlated with a neonatal event. ● Peak O_2 consumption was not associated with an adverse pregnancy outcome.	● Abnormal chronotropic response correlates with adverse pregnancy outcomes in women with CHD and should be considered in refining risk stratification schemes.
Balint OH, et al. 2010 (219) 20937754	Retrospective observational	n=318 pts with 405 pregnancies	Inclusion criteria: Consecutive pregnant women with CHD receiving care or referred for consultation between 1995–2007	Late cardiac events included cardiac death/arrest, pulmonary edema, arrhythmia, or stroke	● Late cardiac events occurred after 12% (50/405) of pregnancies. ● The 5-y rate of late cardiac events was higher in women with adverse cardiac events during pregnancy than in those without.	● In women with CHD, prepregnancy maternal characteristics can help to identify women at increased risk for late cardiac events. ● Adverse cardiac events during pregnancy are

			Exclusion criteria: Pregnancies ended before 20 wk gestation; pt death during pregnancy; pts pregnant again within 6 mo delivery		● Women at highest risk for late cardiac events were those with functional limitations/cyanosis, subaortic ventricular dysfunction, subpulmonary ventricular dysfunction and/or significant PR, left heart obstruction and cardiac events before or during pregnancy. In women with 0, 1 or >1 risk predictors the 5-y rate of late cardiac events was 7 ± 2%, 23 ± 5% and 44 ± 10%, respectively.	important and are associated with an increased risk in late cardiac events.
Drenthen W, et al. 2010 (31) 20584777	Retrospective observational	n=1,802 pts with 1,302 pregnancies	Inclusion criteria: Women with CHD 18–58 y enrolled in the nation-wide CONCOR registry Exclusion criteria: Miscarriages and elective abortions	Independent predictors of cardiac, obstetric and neonatal complications	● The most prevalent cardiac complications during pregnancy were arrhythmias (4.7%) and HF (1.6%). ● Factors independently associated with maternal cardiac complications were the presence of cyanotic HD (corrected/uncorrected) ($p<0.0001$), the use of cardiac medication before pregnancy ($p<0.0001$), and left heart obstruction ($p<0.0001$). New characteristics were mechanical valve replacement ($p=0.0014$), and systemic ($p=0.04$) or pulmonary AV valve regurgitation related with the underlying (moderately) complex CHD ($p=0.03$). ● A new risk score for cardiac complications is proposed. ● The most prevalent obstetric complications were hypertensive complications (12.2%). No correlation of maternal characteristics with adverse obstetric outcome was found. The most prevalent neonatal complications were premature birth (12%), small for gestational age (14%), and mortality (4%). Cyanotic HD (corrected/uncorrected) ($p=0.0003$), mechanical valve replacement ($p=0.03$), maternal smoking ($p=0.007$), multiple gestation ($p=0.0014$), and the use	● In this tertiary CHD cohort, cardiac, obstetric, and neonatal complications were frequently encountered and (new) correlations of maternal baseline data with adverse outcome are reported. ● A new risk score for adverse cardiac complications is proposed, although prospective validation remains necessary.

					of cardiac medication (p=0.0009) correlated with adverse neonatal outcome	
Uebing A, et al. 2010 (220) 18835051	Case control	n=93 cases, n=40 controls	Inclusion criteria: Women who underwent clinical and echocardiographic evaluation before and after pregnancy	End diastolic and end systolic and shortening fraction of the morphological LV. Pregnancy was associated with increased subpulmonary ventricular size	● NYHA FC remained unchanged in both groups during follow-up. Pregnancy, however, was associated with a persisting increase in subpulmonary ventricular size in pts with TOF, which was not present in tetralogy controls. Furthermore, diagnosis of TOF was the only predictor of an increase in subpulmonary ventricular size after pregnancy on univariate logistic regression analysis (OR: 8.8; 95% CI: 1.9-41.1; p=0.006).	● No deleterious midterm effects of pregnancy on clinical status and RV and LV function were found. ● Pregnancy was associated with a persisting increase in subpulmonary ventricular size, attributable to pts with repaired TOF.
Khairy P, et al. 2006 (221) 16449731	Retrospective	n=53 pts with 90 pregnancies	Inclusion criteria: Women with CHD delivered between Jan 1998–Sept 2004 Exclusion criteria: Women with acquired HD, 1° arrhythmia diagnoses without underlying congenital defects, and isolated mitral valve prolapse	1° cardiac event consisted of cardiac death, cardiac arrest, stroke, symptomatic sustained Brady arrhythmia or tachyarrhythmia requiring therapy, or pulmonary edema documented by physical examination or radiography	● 1° maternal cardiac events complicated 19.4% of ongoing pregnancies, with pulmonary edema in 16.7% and sustained arrhythmias in 2.8%. Univariate risk factors included prior history of HF (OR: 15.5), NYHA FC 2 (OR: 5.4), and decreased subpulmonary ventricular EF (OR: 7.7). ● Independent predictors were decreased subpulmonary ventricular EF and/or severe PR (OR: 9.0) and smoking history (OR: 27.2). Adverse neonatal outcomes occurred in 27.8% of ongoing pregnancies and included preterm delivery (20.8%), small for gestational age (8.3%), respiratory distress syndrome (8.3%), intraventricular hemorrhage (1.4%), intrauterine fetal demise (2.8%), and neonatal death (1.4%). A subaortic ventricular outflow tract gradient 30 mm Hg independently predicted an adverse neonatal outcome (OR: 7.5). Cardiac risk assessment was improved by including decreased subpulmonary ventricular systolic function and/or severe PR (OR: 10.3) in a previously proposed risk index developed in pregnant women with acquired and CHD.	● Pts with impaired subpulmonary ventricular systolic function and/or severe PR are at increased risk for adverse cardiac outcomes.

Siu S, et al. 2002 (222) 11994252	Preplanned substudy of CARPREG	n=302 pregnancies in women with HD; control group without HD during 572 pregnancies	Inclusion criteria: Pregnant women with structural cardiac lesions or with symptomatic cardiac arrhythmias requiring treatment before pregnancy. Exclusion criteria: Women with isolated mitral valve prolapse (mild MR)	N/A	● The frequency of neonatal complications was higher in the HD group (18% vs. 7%; HD vs. controls). ● The NE complication rate was lowest in pregnancies of women 20–35 y who did not smoke during pregnancy, did not receive anticoagulants, and had no obstetric risk factors: 4% in control pts, 5% in HD pts with no cardiac risk factors for NE complications (left heart obstruction, poor FC, or cyanosis), and 7% in HD pts with 1 such risk factor. In contrast, the event rate in pregnancies of controls age 20 or 35 y that had obstetric risk factors or multiple gestations or who smoked was 11%. In the HD group, women 20-35 y who had obstetric risk factors or multiple gestations, who smoked, or who received anticoagulants experienced an even higher NE complication rate (27% with no cardiac risks for NE events and 33% in the presence of 1 cardiac risk factor). The frequency of CV complications was higher in the HD group (17% vs. 0%; HD vs. controls).	● The risk for NE AE in pregnant women with HD is highest in those with both obstetric and cardiac risk factors for NE complications.
Siu S, et al. 2001 (223) 11479246	Prospective multicenter cohort	n=562 consecutive pregnant pts with HD of 599 pregnancies	Inclusion criteria: Women with HD from 13 Canadian centers Oct 1994–Nov 1999 Exclusion criteria: Pts with isolated mitral valve prolapse (moderate of mild MR); pts referred for termination of pregnancy	1° cardiac events were defined as any of the following: pulmonary edema (documented on chest radiograph or by crackles heard over more than 1/3 of posterior lung fields), sustained symptomatic tachyarrhythmia or bradyarrhythmia requiring treatment,	● Pulmonary edema, arrhythmia, stroke, or cardiac death complicated 13% of pregnancies. Prior cardiac events or arrhythmia, poor FC or cyanosis, left heart obstruction, and LV systolic dysfunction independently predicted maternal cardiac complications. ● Neonatal complications (20% of pregnancies) were associated with poor FC or cyanosis, left heart obstruction, anticoagulation, smoking, and multiple gestations.	● Pregnancy in women with HD is associated with significant cardiac and neonatal complications, despite state of the art obstetric and cardiac care. ● Maternal cardiac risk can be predicted with the use of a risk index.

				stroke, cardiac arrest, or cardiac death.		
Egidy Assenza G, et al. 2013 (224) 23369674	2:1 matched case control: (matching variables were QRS duration, RV EF, indexed RV EDV, time between baseline and follow-up CMR, and age at the baseline CMR)	n=13 rTOF pts who had undergone pregnancy matched to 26 nulliparous TOF controls	Inclusion criteria: Associated complex CHD (such as AV canal defect); syndromic or genetic disease; history of completed pregnancy before the baseline CMR; PV replacement between CMRs	N/A	● The rate of increase of RV EDV in the pregnancy group was higher than the comparison group (4.1 ± 1.1 mL/m^2/y vs. 1.6 ± 0.6 mL/m^2/y; p=0.07). RVEF did not change significantly in either group. ● No definitive interaction between degree of PR and increase of RVEDV was identified.	● Women with repaired TOF who have completed pregnancy appear to experience an accelerated rate of RV remodeling, defined as an increase in end-diastolic volume; however, RV systolic function does not deteriorate.
Kamiya CA, et al. 2012 (225) 22277318	Retrospective observational	n=25 pts with 40 pregnancies	Exclusion criteria: Spontaneous or elective abortions	Cardiac events, obstetric events, offspring events	● There were 23 pts in NYHA class I, and 2 in classes II–III before pregnancy. ● The mean age at delivery was 29.1 y and the mean gestational period was 37.8 wk. 7 pregnancies (17.5%) in 7 pts were complicated with cardiac events, such as a decline in NYHA class and arrhythmia. ● History of ablation and the baseline cardiothoracic ratio on chest radiography were predictors of AE. ● Peak plasma BNP level after the second trimester was higher in pts with cardiac events. ● LV size and contraction did not change from before to after pregnancy, but the right ventricle was enlarged at 6 mo after delivery.	● Many women with repaired TOF had successful pregnancies. However, careful management is required for some pts and BNP level may be a useful marker to identify these pts. ● Pregnancy may affect the long-term prognosis of pts with repaired TOF, as the right heart tended to become enlarged postpartum.
Jain VD, et al. 2011 (226) 21418534	Retrospective observational	n=114 pts with 146 pregnancies	Exclusion criteria: Women with mitral valve prolapse only or noncongenital cardiac disease	Composite of HF, arrhythmia, stroke, cardiac arrest/death during pregnancy or postpartum	● 146 pregnancies in 114 women were included; 15 (10.3%) pregnancies involved a SRV. CARDCOMP complicated 12.3% of these pregnancies. ● Women with a SRV were more likely to develop CARDCOMP even after	● In women with CHD, a SRV is associated with adverse cardiac and pregnancy outcomes.

					adjustment for confounders. PREGCOMP complicated 40.4% of all pregnancies. Women with a SRV were also more likely to develop PREGCOMP compared with women with a systemic left ventricle after controlling for confounders.	
Balci A, et al. 2011 (227) 21315213	Retrospective international multicenter study using 2 CHD registries (CONCOR and Belgium)	n=204 pts with TOF (74 pts had 157 pregnancies)	Inclusion criteria: N/A	Pregnancy outcome in women with corrected TOF	● CV events occurred during 10 (8.1%) pregnancies, mainly (supra) VA. ● Obstetric and offspring events occurred in 73 (58.9%) and 42 (33.9%) pregnancies, respectively, including offspring mortality in 8 (6.4%). The most important predictor was use of cardiac medication before pregnancy (OR for cardiac events: 11.7; 95% CI: 2.2–62.7; OR for offspring events: 8.4; 95% CI: 1.4–48.6). ● In pregnancies with CV events, significantly more small-for-gestational-age children were born (p=0.01).	● CV, obstetric, and offspring events occur frequently during pregnancies in women with TOF. ● Maternal use of CV medication is associated with pregnancy outcome, and maternal CV events during pregnancy are highly associated with offspring events.
Tobler D, et al. 2010 (228) 20643256	Retrospective cohort	n=9 pts with 17 pregnancies	Inclusion criteria: N/A	Pregnancy outcome in women with TGA who had an ASO	● 6 women (67%) had clinically important valve (n=5) and ventricular (n=1) lesions before the index pregnancy. 2 women developed cardiac complications during pregnancy; 1 woman with impaired LV systolic function had NSVT and 1 woman with a mechanical systemic AV valve developed postpartum valve thrombosis. ● There were no maternal deaths.	● Young women with TGA from this early cohort repaired with ASO are reaching childbearing age. ● A significant proportion has residual and/or sequelae that can confer risk for adverse cardiac events in pregnancy. Coordinated care between a CHD specialist and a high-risk obstetrician should be implemented.
Greutmann M, et al. 2010 (229) 20511325	Retrospective cohort	n=47 pts with 76 pregnancies	Exclusion criteria: Miscarriage or terminated abortion	Cardiac complications including death, arrhythmias, HF, and hospitalization for cardiac indication. Right HF was defined as new elevation of the jugular venous pressure >4 cm above	● At conception 20% had RVOTO, 32% had PR and 49% had mixed RVOTO and PR. Moderate-to-severe PR was present in 30 (39%) and RVOTO ≥30 mm Hg in 12 (16%) of pregnancies. ● 7 pregnancies (9%) were complicated by right HF. ● No arrhythmias were documented.	● In pts with CHD and residual RVOT lesions, pregnancy outcomes were successful. Pts with moderate-to-severe PR were at risk for symptomatic right HF only if additional risk factors were present. When treated by a multidisciplinary

				the sternal angle) + symptoms of decreased exercise tolerance ± dyspnea (a common symptom in those with RVOT lesions due to abnormal interventricular interactions) 14 ± pitting peripheral edema	● Predictors for right HF were moderate-to-severe PR in combination with at least 1 additional risk factor (twin pregnancy, branch PA stenosis, RV systolic dysfunction, RV hypertrophy). ● All pts responded to diuretic treatment and had a good pregnancy outcome without fetal complications	team, maternal and fetal outcome was good. ● The general recommendation that PV replacement should be undertaken prior to pregnancy in pts with moderate-to-severe PR and RV dilatation needs to be reconsidered.
Tzemos N, et al. 2009 (230) 19249417	Retrospective cohort	n=51 pts with 70 pregnancies	Exclusion criteria: Pts in whom their only pregnancy was terminated or complicated by miscarriage (fetal demise by 20 wk gestation) as well as pts with hypertrophic cardiomyopathy (n=11) or prosthetic aortic valves (n=24)	Late cardiac events (pulmonary edema, cardiac arrhythmia, cardiac death, cardiac interventions >1 y since baseline evaluation).	● During the follow-up period (6 + 4 y), 43% of women underwent cardiac interventions which comprised all late cardiac events. ● Independent baseline predictors of late cardiac events were 1) moderate or severe AS (HR: 4.5; p=0.045), and 2) NYHA FCII (HR: 4.6; p=0.014). ● When outcomes in 26 women from the postpregnant group were compared to 26 age- and lesion-matched women who have never been pregnant, the postpregnant group had a higher late cardiac event rate than the never-pregnant group (31% vs. 0%; p=0.021).	● Women with moderate or severe AS and symptomatic during pregnancy are at high likelihood of requiring cardiac interventions late after pregnancy. ● Women with congenital AS who have undergone pregnancy have a higher frequency of late cardiac events compared to those who have never been pregnant. ● Late cardiac outcomes after pregnancy should be considered in the counseling of women with AS who are contemplating pregnancy.
Kampman MA, et al. 2014 (231) 24334717	Prospective multicenter cohort	n=213 pregnancies	Exclusion criteria: Miscarriages or pregnancies terminated before 20 wk gestation, women with known drug or alcohol abuse	NT-proBNP	● Adverse CV events occurred in 10.3% of 213 pregnancies. NT-proBNP levels >128 pg/mL at 20 wk gestation, the presence of a mechanical valve, and subpulmonary ventricular dysfunction before conception were independently associated with events OR: 10.6; p=0.039, OR: 12.0; p=0.016, and OR: 4.2; p=0.041, respectively. ● The NPV of NT-proBNP levels <128 pg/mL was 96.9%. NT-proBNP levels >128 pg/mL at 20 wk of gestation had an	● Increased NT-proBNP levels at 20 wk of gestation are an independent risk predictor of CV events during pregnancy in women with CHD.

					additional value in predicting the occurrence of adverse CV events on the top of the other identified predictors (area under the curve 0.90 vs. 0.78; p=0.035)	
Gill HK, et al. 2003 (232) 12957444	Data review	n=6,640 pts	Inclusion criteria: N/A	Fetal CHD	● A recurrence of CHD was seen in 178 (2.7%) of 6,640 pregnancies. ● The referral numbers for sibling, maternal, or paternal CHD cases were 5,151, 1,119, and 370, respectively. ● Exact concordance was seen in 37% of cases (range 0%–80%), and group concordance was seen in 44%. In families where there were ≥2 recurrences, the exact concordance rate was 55%. Exact concordance rates were particularly high for isolated AVSD (4 of 5 [80%]) and laterality defects (7 of 11 [64%])	● Accurate diagnosis of the index case is essential for reliable counseling on patterns of recurrence. ● Minor CHD in the index case does not exclude more severe disease in recurrences.
Drenthen W, et al. 2007 (233) 17572244	Literature review	n=2,491 pregnancies	Exclusion criteria: Reviews and case reports describing ≤1 completed pregnancy were excluded	Identification of independent predictors of cardiac, obstetric and neonatal complications	● This review describes the outcome of 2,491 pregnancies, including 377 miscarriages (15%) and 114 elective abortions (5%). ● Important cardiac complications were seen in 11% of the pregnancies. Obstetric complications do not appear to be more prevalent. ● In complex CHD, premature delivery rates are high, and more children are small for gestational age.	● The offspring mortality was high throughout the spectrum and was related to the relatively high rate of premature delivery and recurrence of CHD.
Cutts BA, et al. 2013 (234) 22840412	Review	N/A	Inclusion criteria: N/A	N/A	N/A	● Clinical trials for new anticoagulant agents to manage pulmonary embolism must be explored.
Holland BJ, et al. 2015 (235) 25904437	Systematic review	N/A, 8 studies	Inclusion criteria: N/A	Survival after planned cardiac surgery	● In pts with comparable anatomy, standard risk, a parental desire to treat and optimal care, newborns with a prenatal diagnosis of critical CHD were significantly less likely to die prior to planned cardiac surgery than were those with a comparable postnatal diagnosis (pooled OR: 0.26; 95%; CI: 0.08—0.84).	● For newborns most likely to benefit from treatment for critical congenital HD, prenatal diagnosis reduced the risk of death prior to planned cardiac surgery relative to pts with a comparable postnatal diagnosis.

Data Supplement 20. Contraception – Section 3.13.2

Study Name, Author, Year	Study Type	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/ p Values	Summary/Conclusions
Pijuan-Domenech A, et al. 2013 (236) 23706389	Retrospective	n=237 pts	Inclusion criteria: Pts referred to ACHD preconception clinic	Progesterone use and safety	● 1 y: 73% of pts who started progesterone remained on meds; gynecological side effects in 25%; no cardiac side effects.	● "Acceptable" gynecological side effects and no thrombogenic side effects (1 y only).
Hinze A, et al. 2013 (237) 22691053	Cross-sectional survey	n=83 pts	Inclusion criteria: Female pts ≥19 with CHD	Receipt of counselling regarding pregnancy and contraception	● 63% did not know if contraception contraindicated.	● Individual counseling regarding pregnancy and contraception must be improved upon.
Kaemerrer M, et al. 2012 (238) 22584383	Clinical assessment and questionnaire	n=536 pts	Inclusion criteria: Female pts ≥18 with CHD	Sources of info about pregnancy and contraception	● Women rated level of information 5 (1–10).	● Current level of information is inadequate.
Vigl M, et al. 2010 (239) 21029831	Clinical assessment and questionnaire	n=536 pts	Inclusion criteria: Female ≥18 y with CHD	Counseling regarding risk of pregnancy and contraception	● 20% using contraindicated contraceptive. ● 28% of high pregnancy risk group not using contraceptive. 43% had not been counselled about contraception and 48% about pregnancy.	● Timely and competent counselling is important for women with CHD.
Kovacs AH, et al. 2008 (240) 18687254	Questionnaire	n=116 pts	Inclusion criteria: Females with CHD (mean age 31 ± 9 y)	Contraception and pregnancy knowledge	● 51% recalled receiving specific info about birth control; 37% had never been informed of pregnancy risk.	● Women with ACHD lack accurate knowledge about pregnancy risk and contraception.
Lidegaard O, et al. 2009 (241) 19679613	National cohort	n=10.4 million women y with 3.3 million women y on oral contraceptive pill	Inclusion criteria: Female pts ≥18 with CHD Danish females 15–49 y between 1995–2005.	Risk of VTE	● 4,13 VTE events ● Absolute risk of 3.01/10000 nonusers 6.29/10,000 users	● Risk of VTE decreased with duration of use and decreasing estrogen dose. ● Progesterone-only pills and hormone releasing intrauterine devices were not associated with increased risk of VTE.
Famuyide AO, et al. 2008 (242) 18380988	Retrospective cohort	n=18 with CHD and n=157 without	Inclusion criteria: Pts with high-risk cardiac conditions in whom pregnancy was	Successful placement of microinsert hysteroscopic sterilization	● There was no significant difference in use of general anesthesia, successful bilateral device placement, postoperative pain score or length of hospitalization.	● For women with cardiac disease in whom pregnancy is contraindicated, microinsert hysteroscopic sterilization can

		cardiac disease	contraindicated vs. pts without cardiac disease			provide minimally invasive and permanent contraception.

Data Supplement 21. Sexual Function – Section 3.13.4

Study Name, Author, Year	Study Type/ Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
Moons P, et al. 2007 (243) 17182130	Matched case control	n=441 pts n=control	Inclusion criteria: ≥18 y, literate, Dutch speaking, able to consent Exclusion criteria: First visit, mental delay, diagnosed with ASD, or PFO	Frequency of sexual problem, the associated distress	● Perceived sexual problems in 10%–20% of pts. ● Pts <controls p=0.03. ● Associated distress pt > controls p=0.032.	● Perceived sexual problems in cases occurred less frequently than in controls, but cases experienced more distress in worrying about sex life than controls. ● Frequency not associated with CHD severity but with NYHA class. ● Sexual functioning in CHD pts not particularly problematic in this group.
Cook SC, et al. 2008 (244) 19064032	Convenience sample survey	n=86 pts	Inclusion criteria: ≥18 y, male, CHD	Sexual dysfunction	● 38% of men reported erectile dysfunction.	● Erectile dysfunction is common in young men with CHD and does not correlate with disease severity. ● 3 times more likely if on BBs.
Vigl M, et al. 2009 (245) 19364753	Consecutive pt surveys including International Index of Erectile Function, SF-12, Allgemeine Depressionsskala	n=332 pts	Inclusion criteria: ≥18 y, male, CHD Exclusion criteria: Mental incapacity	Erectile dysfunction, subjective well-being	● 10% of men had erectile dysfunction. ● Lower SF-12 mental score p<0.001. ● Lower SF-12 physical score p=0.02. ● 10-fold increase in depression p<0.001.	● Men with CHD and <40 y engage in fewer sexual relationships than healthy peers. ● Presence of erectile dysfunction is associated with significant QOL impairments.
Winter MM, et al. 2010 (246) 20920658	Case control survey (169 items)	n=133 pts, (52% male); 73 partners; 3,642 controls	Inclusion criteria: ≥18 y, CHD	Subjective health, relational satisfaction, sexual satisfaction, sexual function	● 71% pts in relationship (vs. 79% population p<0.05).	● Fewer pts in relationship. ● More distress. ● Frequency of erectile dysfunction = 42% (no greater than controls).

Opic P, et al. 2013 (247) 23859255	Longitudinal cohort survey	254 pts (53.5% male)	Inclusion criteria: First open heart surgery at age <15 y between 1968–1980 for diagnosis of ASD, VSD, TOF, TGA	Overall sexual function, disease-specific sexual problems	● Erectile dysfunction in 13.7% pts p=0.002.	● Broad range of sexual concerns in pts, decreased satisfaction, and body image concerns.

Data Supplement 22. Pharmacological Therapy for ACHD – Section 3.17

Study Name, Author, Year	Study Type/Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
Norozi K, et al. 2007 (248) 17572925	Prospective double-blind RCT	n=33 pts	Inclusion criteria: 30.9 ± 9.5 y NYHA class 1 or 2 with BNP >100 pg/mL and a reduced peak uptake of O_2 <25 mL/kg/min Exclusion criteria: Significant bradycardia, average HR <50 bpm, already on BB	Cardiac failure: present if level of BNP significantly >100 pg/mL	● No change in peak VO_2, ventricular size or NYHA class.	● Beta blockade with bisoprolol seems to have no beneficial effect on asymptomatic or mildly symptomatic pts with RV dysfunction secondary to rTOF with residual PR and/or pulmonary stenosis.
Babu-Narayan SV, et al. 2012 (249) 20970202	Prospective double-blind RCT	n=64 pts	Inclusion criteria: Moderate-to-severe PR; CMR Exclusion criteria: Pulmonary stenosis, drug allergy, renal dysfunction	CMR RVEF	● There was no difference in the 1° endpoint RVEF. RV long-axis shortening significantly improved in the ramipril group compared to placebo (RV: 2.3 ± 3.8 vs. 0.02 ± 2.7 mm; p=0.017) as did LV long-axis shortening (1.9 ± 4.5 vs. -0.2 ± 3.7 mm, respectively; p=0.030). ● No clear differences were detected between ramipril and placebo for other measures. In a subgroup of pts with restrictive RV physiology, ramipril resulted in decrease in LV end-systolic volume index and increase in LVEF (2.4 ± 5.0 vs. 2.7 ± 3.6 mL/m^2; p=0.005, 2.5 ± 5.0 vs. -1.3 ± 3.5%; p=0.03). Ramipril did not cause AE and was well tolerated.	● Ramipril is a well-tolerated therapy, improves biventricular function in pts with rTOF and may have a particular role in pts with restrictive RV physiology. Larger, longer-term studies are needed to determine if ACEIs can improve both ventricular remodeling and clinical outcomes.

Lester SJ, et al. 2001 (250) 11728365	RCT with a crossover design and each pt as their own control Losartan	n=7 pts	Inclusion criteria: D-loop TGA after atrial switch Exclusion criteria: >13 y	Bicycle exercise test	● No adverse effects of afterload reduction. ● Decreased BP (0.04), improved EF, (0.04), decreased systemic AV valve regurgitant volume (0.01), and increased exercise time (0.02).	● Improved outcome variables and no adverse effects in this small group.
Hechter SJ, et al. 2001 (251) 11230861	Retrospective data analysis	n=14 pts	Inclusion criteria: D-loop TGA after atrial switch Exclusion criteria: >18 y	CPET before ACEI had been initiated and repeated	● No significant difference in resting variables before and after ACEI. ● MRI: significantly lower resting RVEF and larger right ventricle volumes compared with controls.	● ACEIs: No effect on CPET results. ● No effect on MR studies. ● VO_2 max and exercise duration increased in some.
Dore A, et al. 2005 (252) 16216961	Prospective double-blind crossover trial	n=29 pts	Inclusion criteria: L-loop TGA (8) or D-loop TGA with atrial switch (21) Exclusion criteria: NYHA class III, IV, unable to exercise, pregnancy, rate-fixed pacer, renal dysfunction, history of angioedema	VO_2 max, RVEF, NT-proBNP	● Comparing losartan to placebo showed no differences in VO_2 max (29.9 ± 5.4 vs. 29.4 ± 6.2 mL/kg/·min; p=0.43), exercise duration (632.3 ± 123.0 vs. 629.9 ± 140.7 s; p=0.76), and NT-proBNP levels: 201.2 ± 267.8 vs. 229.7 ± 291.5 pg/mL; p=0.10), despite a trend toward increased angiotensin II levels (15.2 ± 13.8 vs. 8.8 ± 12.5 pg/mL; p=0.08).	● In adults with systemic RVs, losartan did not improve exercise capacity or reduce NT-proBNP levels.
Giardini A, et al. 2007 (253) 21882492	Pilot study	n=8 pts	Inclusion criteria: L-loop TGA (2) or D-loop TGA atrial switch (6) Exclusion criteria: Pacemakers	RVEF, LVEF, by CMR VO_2 max, exercise duration	● RV end-diastolic (119 ±31 vs. 112 ± 28 mL/m^2; p=0.01) and end-systolic volumes decreased (79 ± 17 vs. 65 ± 14 mL/m^2; p=0.006), and RVEF improved (34 ± 6 vs. 42 ± 7%; p=0.004). ● LVEF increased (44 ± 8 vs. 49 ± 9%; p=0.01), suggesting a positive biventricular remodeling. ● Peak O_2 uptake did not change with carvedilol (26.8 ± 5.3 vs. 27.3 ± 5.7 mL O_2/kg/min; p=0.58); whereas, exercise duration increased (13.4 ± 2.6 vs. 17.3 ± 3.1 m; p=0.008).	● Carvedilol administration was safe, and it was associated with positive RV remodeling as well as improved exercise duration.

Doughan AR, et al. 2007 (254) 17317376	Retrospective chart review (carvedilol or metoprolol)	n=60 (31 received BB) pts	Inclusion criteria: D-loop TGA with atrial switch	NYHA class, RV size by ECG	● Only pts with cardiac pacemakers had improvement in functional status after BB compared with pts without cardiac pacemakers ($p<0.05$). No significant changes in RV end-diastolic area, the RVEF, and the degree of systemic TR.	● BB resulted in improvement in NYHA FC in pts with d-TGA and systemic RV dysfunction. ● This improvement was found to be more significant in pts with pacemakers who received higher maintenance doses of BB.
Therrien J, et al. 2008 (255) 18672299	RCT	n=17 pts	Inclusion criteria: D-loop TGA with atrial switch	RVEF, RVEDV	● RVEF did not improve in the ramipril group from baseline to 1 y (43.8 ± 7.1% vs. 40.9 ± 13.3%; p=0.52) and remain unchanged in the placebo group (44.3 ± 6.3 vs. 46.3 ± 9.6%; p= 0.42). RVEDV (184.5 ± 56.4 mL vs. 179.6 ± 66.4 mL; p= 0.64) and RVESV (109.5 ± 19.4 mL vs. 111.8 ± 30.1; p= 0.74) remained unchanged in the ramipril group from baseline to 1 y as well as in the placebo group (228.1 ± 89.2 mL vs. 204.5 ± 50.4 mL; p= 0.42 and 117.5 ± 36.9 mL vs. 117.4 ± 26.2 mL; p= 0.99, respectively).	● 1-y treatment with ramipril does not seem to affect RV function or size in adult pts with SRV after a Mustard or Senning procedure.
Bouallal R, et al. 2010 (256) 20519056	Cohort	n=14 pts	Inclusion criteria: L-loop TGA or D-loop TGA atrial switch	NYHA class QOL RVEF	● Change in NYHA class was significant (p=0.016). QOL improved significantly throughout the study from a median grade 2 with a range from 1–3 to a median grade 1 with a range from 1–2 (p=0.008). ● Systemic RVEF assessed by radionuclide ventriculography improved significantly from a median of 41% (range: 29%–53%) to 49% (range: 29%–62%; p=0.031). However, the change in the EF assessed by MRI was NS	● In pts with cardiac failure due to systemic RV dysfunction, BB improve NYHA class, QOL, and systemic RVEF assessed by radionuclide ventriculography.

					from a median of 29% (range: 12%–47%) to 32% (range: 22%–63%; p=0.063).	
Tutarel O, et al. 2012 (257) 20843567	Retrospective data analysis	n=14 pts	Inclusion criteria: D-loop TGA after atrial switch	Echo, exercise and proBNP at baseline and after 13.3 ± 4 mo enalapril.	● Max O_2 uptake and echo parameters did not change, but proBNP decreased significantly.	● ACEI is safe and reduces proBNP significantly.
Van der Bom T, et al. 2013 (258) 23247302	Prospective double-blind RCT	n=88 pts	Inclusion criteria: L-loop TGA (25) or D-loop TGA atrial switch (53)	1°: RVEF. Secondary: RVEDV, VO_2 max, QOL	● No effect of 3 y valsartan therapy on RVEF, exercise capacity or QOL. ● The RVEDV and mass increased more in the placebo group.	● No significant treatment effect of valsartan on RVEF, exercise capacity or QOL. Small differences seen in RV volume and mass.
Dos L, et al. 2013 (259) 23972966	Double-blind placebo-controlled eplerenone	n=14 pts, 12 controls	Inclusion criteria: Atrial switch pts	Systemic RV mass and EF and neurohormonal and collagen turnover biomarker levels	● Pts had good baseline profile (SRV Mass and EF) Elevated NT-proBNP. C-terminal propeptide of type 1 procollagen and C Terminal telopeptide. ● After 1 y of therapy, a trend towards reduction of C-terminal propeptide of type I procollagen, NT-proBNP.	● Eplerenone pts improved baseline collagen turnover biomarkers, suggesting reduction of myocardial fibrosis.
Kouatli AA, et al. 1997 (260) 9315539	Prospective double-blind crossover trial	n=18 pts	Inclusion criteria: >7 y; Fontan procedure a minimum of 6 mo before this study Exclusion criteria: HF, were dependent on ACEIs, were unable to exercise, had protein-losing enteropathy, had fixed-rate pacemakers, were pregnant, or had a history of angioedema	VO_2 max exercise duration	● No difference was detected in resting heart rate, BP, or cardiac index. ● Diastolic filling patterns were also similar. Exercise duration was not different (6.4 ± 2.6 [enalapril] vs. 6.7 ± 2.6 mo [placebo]). ● The mean percent increase in cardiac index from rest to maximum exercise was slightly but significantly decreased in subjects after 10 wk of enalapril therapy (102 ± 34% [enalapril] vs. 125 ± 34% [placebo]; p<0.02). At maximal exercise, cardiac index (3.5 ± 0.9 [enalapril] vs. 3.8 ± 0.9 L; min^{-1}; m^2 [placebo]), O_2	N/A

					consumption (18.3 ± 9 [enalapril] vs. 20.5 ± 7 mL; min^{-1}; kg^{-1} [placebo]), min ventilation (57.5 ± 17 [enalapril] vs. 55.4 ± 19 L/min [placebo]), and total work (247 ± 181 [enalapril] vs. 261 ± 197 W [placebo]) were not different.	
Giardini A, et al. 2008 (261) 18534975	Prospective double-blind RCT	n=27 pts	Inclusion criteria: >16 y Exclusion criteria: NYHA class IV, liver or renal dysfunction, O_2 saturation <85% at rest, Fontan pathway obstruction, history of exercise-induced severe arrhythmias, pregnancy	VO_2 max Cardiac output, pulmonary blood flow	● The change in peak VO_2, the 1° endpoint, was greater in the sildenafil group (9.4 ± 5.2%) than in the control group (0.3 ± 4.1%' p<0.05). ● Sildenafil increased rest and peak exercise pulmonary blood flow index (p<0.01 and p<0.05 vs. control group, respectively), as well as rest and peak exercise CI (p<0.001 and p<0.05 vs. control group, respectively), without altering rest or peak exercise transcutaneous arterial blood O_2 saturations (p>0.05 vs. control group for both).	● In Fontan pts, oral administration of a single dose of sildenafil improves exercise capacity and hemodynamic response to exercise.
Goldberg DJ, et al. 2011 (262) 21382896	Prospective double-blind crossover trial	n=28 pts	Inclusion criteria: >8 y Exclusion criteria: Liver or renal dysfunction, Fontan pathway obstruction or other residual lesions, ICDs	1°: VO_2 max; Secondary: ventilatory equivalent of elimination rate of CO_2 slope	● At the anaerobic threshold, subjects had significantly decreased ventilatory equivalents of CO_2. There was no change in O_2 consumption during peak exercise, although there was a suggestion of improved O_2 consumption at the anaerobic threshold.	● Sildenafil significantly improved ventilatory efficiency during peak and submaximal exercise.
Rhodes J, et al. 2013 (263) 23545150	Prospective double-blind RCT	n=18 pts	Inclusion criteria: >12 y Exclusion criteria: Reactive airway disease, history of malignant VA; history of syncope during exercise; history of hypersensitivity to iloprost	VO_2 max, O_2 pulse	● O_2 pulse (a surrogate for forward stroke volume) at peak exercise was higher following iloprost (median increase 1.2 mL/beat; p<0.001). ● Peak VO_2 also rose (median increase 1.3 mL/kg/min; p<0.04). 9 pts had peak	● Iloprost improves the peak O_2 pulse and peak VO_2 of pts with Fontan physiology and appears to be particularly beneficial among pts with impaired exercise function.

					VO_2<30 mL/kg/min; each of these pts had higher peak VO_2 following iloprost. Only 3/6 pts with peak VO_2>30 mL/kg/min had higher peak VO_2 following iloprost (p<0.04).	
Galiè N, et al. 2006 (264) 16801459	Multicenter, double-blind, placebo-controlled RCT	n=54 pts	Inclusion criteria: WHO class III	Pulse oximetry: PVR	● Compared with placebo, bosentan reduced PVR index (-472.0 dyne.s.cm (-5); p=0.0383). The mean PAP decreased (-5.5 mm Hg; p=0.0363), and the exercise capacity increased (53.1 m; p=0.0079). ● 4 pts discontinued as a result of AE, 2 (5%) in the Bosentan group and 2 (12%) in the placebo group.	● Eisenmenger syndrome, bosentan was well tolerated and improved exercise capacity and hemodynamics without compromising peripheral O_2 saturation.

Data Supplement 23. Heart Failure and Transplant – Section 3.14.2

Study Name, Author, Year	Study Type/ Design	Study Size	Length of follow-up	1° Endpoint	Results/p Values	Summary/Conclusions
Seddio F, et al. 2013 (265) 22733841	Single-center, retrospective cohort	n=85	Mean 7.8 y posttransplant	Risks factors for survival	● PLE and pretransplant mechanical ventilation were risk factors for mortality, but transplant was also curative.	● Data also presented for pediatric age groups, but not all results differentiated by age.
Boucek D, et al. 2014 (266) 24433616	Multicenter	n=45 pts	5 y with study period 2000–2012	Transplant vs. those not listed for transplant	● 45 pts considered for transplant, 27 listed, 13 not listed because of high risk (cirrhosis, irreversible pulmonary HTN) and 5 not listed because they were "too well." ● Mortality at 5 y no different between those transplanted, those not transplanted; p=0.72 for those too high risk for HTN vs. those too well; p=0.59 for those listed for HTN vs. those too well for listing. 85% of transplanted pts alive at 5 y, all deaths occurred in the first 30 d.	● Overall survival of transplanted ACHD compares favorably to other populations, with all deaths occurring in the first 30 d. ● For those deemed not appropriate for transplant, survival probability was statistically similar, though a larger percentage (38%) of those too high risk for transplant died in the follow-up period than those transplanted (15%).

Patel ND, et al. 2009 (267) 19699904	UNOS data	n=689 pts	Up to 10 y post transplant	Transplant outcomes in ACHD vs. non-ACHD	● Overall higher 30-d mortality in ACHD (16% vs. 6%; p<0.001), but long-term mortality was similar.	● Risks for mortality included Ischemic time, African American race, and PVR >4 WU.
Karamlou T, et al. 2010 (268) 20434179	UNOS data	n=575 pts	N/A, evaluated by era of transplant.	ACHD vs. non-ACHD	● Higher mortality in ACHD (p=0.003) mainly due to early mortality.	● More early hemorrhage in ACHD. Prevalence of transplantation rose in ACHD over time. ● Less induction therapy and steroid maintenance in ACHD. More extracorporeal membrane oxygenation support in ACHD.
Gelow J, et al. 2013 (269) 23921356	UNOS database	n=1,250 pts	N/A	Listing VAD in ACHD vs. non-ACHD by era	● Higher use of VAD over time in non-ACHD pts. Fewer VAD and 1A listing in ACHD.	● More ACHD pts with VAD died prior to transplant than non-ACHD.
Everitt MD, et al. 2011 (270) 21036067	UNOS database	n=314 pts	N/A	Wait list mortality in ACHD vs. non-ACHD	● More CV deaths in ACHD on wait list, fewer devices.	● More likely to be listed with lower status. Overall deaths were not different while on waiting list.
Davies RR, et al. 2011 (271) 21300954	UNOS database	n=1,035 pts	Up to 10 y	Outcome of transplant listing in ACHD vs. non-ACHD	● VAD doesn't improve wait list survival; long-term survival was same (54% at 10 y).	● ACHD pts were younger, smaller BMI, with fewer comorbidities.
Davies RR, et al. 2012 (272) 22500594	Single center	n=155 pts	Up to 15 y	Transplant outcomes after Fontan vs. other CHD	● 90-d mortality greater in Fontan than other ACHD pts (35 vs. 20%; p=0.055).	● Pediatric pts fared worse; PVR index level was contested as an indicator of outcome. ● Renal dysfunction was a risk factor.
Goerler H, et al. 2007 (273) 17900918	Single center	n=46 pts	Mean 5.1 y	Heart-lung and lung transplant in CHD	● 12% 30-d mortality. 10-y survival 53%.	● Similar high upfront mortality, same or better long-term survival.
Harper AR, et al. 2013 (274) 22588032	Single center	n=126 pts	Median 1.2 y	Comparison of transplant vs. nontransplant surgical intervention	● 14 pts who underwent surgery instead; still 1-y mortality 28%.	● Best outcomes in those with normal 2 ventricle anatomy.
Karamlou T, et al. 2012 (275) 22884603	Nationwide inpatient sample database	n=509 pts	N/A	Single ventricle vs. biventricular transplant	● Mortality was 23% in single ventricle (n=143) vs. 8% (p<0.001), which was independent risk factor for mortality (OR: 3.9).	● No differences in newer eras.
Maxwell BG, et al. 2014 (276) 24135956	Scientific Registry of Transplant Recipients	n=83 pts	N/A	Mechanical support pts with CHD vs. those not requiring mechanical support.	● Similar 30-d mortality (11 vs. 14%), but longer LOS and transfusion requirements in those with MCS.	● Mechanical support was less common in CHD than other non-CHD.

Paniagua Martin MJ, et al. 2012 (277) 22463464	Spanish transplant registry	n=55 pts	N/A	Transplant outcome by CHD subtype	● Early mortality was different among types of CHD; worse mortality for single ventricle pts (25%).	● Overall mortality was not different between subgroups.

*Many studies include data on non-ACHD pt groups in addition to the n given here.

Data Supplement 24. Palliative Care – Section 3.15

Study Name, Author, Year	Study Type/ Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
Tobler D, et al. 2012 (278) 21094550	Survey	n=200 pts; n=48 doctors	Inclusion criteria: Pts >18 y with CHD	78% of pts wanted doctor to discuss EOL 62% pts favored early EOL discussion	● 78% of pts wanted doctor to discuss EOL. ● 62% pts favored early EOL discussion.	● Health care providers should discuss EOL issues and preferences with their ACHD pts.
Tobler D, et al. 2012 (279) 21697263	Retrospective cohort	n=48 hospitalized pts	Inclusion criteria: Adults with CHD who died	Review documentation of EOL issues and the circumstances surrounding the deaths	● EOL discussion documented in 5 (10%) pts. EOL discussion will surrogate medical decision maker in 21 cases (41%). Referral to EOL care services in 20 pts (21%).	● Only a minority of pts with advanced HF and ACHD had documented discussion regarding EOL issues. Earlier discussion may avoid unnecessary treatments and improve the quality of the dying process.
Tobler D, et al. 2012 (280) 22459306	Survey	n=200 pts; n=48 doctors	Inclusion criteria: Pts >18 y with CHD	87% pts reported preference for advance directive	● 87% pts reported preference for advance directive.	● CHD providers should educate pts about EOL issues and assist them in documenting EOL wishes.
Greutmann M, et al. 2013 (281) 23279997	Prospective survey	200 pts; 48 doctors	Inclusion criteria: Pts >18 y with CHD	85% pts report discussion facilitated when doctor is trusted	● 85% pts report discussion facilitated when doctor is trusted.	● The close physician-pt relationship enables early discussion of EOL issues.

Data Supplement 25. Cyanosis – Section 3.16

Study Name, Author, Year	Study Type	Study Size	1° Endpoint	Study Intervention	Summary/Conclusions
Dedkov EI, et al. 2006 (282) 16831984	Descriptive	n=5 pts	Microcirculation	● Measured arteriolar length, volume and surface densities. Other pt groups studied for comparison	● Microcirculation adapts to hypoxia.

Duffels MG, et al. 2010 (283) 20526039	Descriptive	n=54 pts	Atherosclerosis	Intima-media thickness in pts and controls	● Microcirculation adapts to hypoxia.
Hirth A, et al. 2008 (284) 18380761	Descriptive	n=29 pts	Migraines	N/A	● High prevalence of headaches in a small population.
Horigome H, et al. 2006 (285) 16415201	Descriptive	n=15 pts	Brain MRI	N/A	● High prevalence of cerebral ischemic events, correlating with lower statistics.
Jensen AS, et al. 2013 (286) 22727966	Descriptive	n=75 pts	Fibrinogen function impaired	● Fibrinogen function related to blood count and clinical events	● Reduced fibrinogen function, related to hematocrit. Has impact on hemostasis.
Jensen AS, et al. 2013 (287) 22578951	Prospective multicenter	n=98 (21 underwent phlebotomy)	Hematocrit and hemostasis	● Thromboelastography after phlebotomy s. baseline in the setting of hemoptysis	● Thromboelastography showed reduced clot formation and strength, relationship with hematocrit. Smaller subset underwent phlebotomy.
Kajimoto H, et al. 2007 (288) 17526995		n=35 pts	Thrombogenicity	● Thrombosis related proteins measured compared to healthy controls	● Higher levels of AT3, lower Protein C suggesting platelet activation and hypercoagulability.
Legault S, et al. 2008 (289) 17643525		n=10 pts	Nocturnal breathing	N/A	● Desaturations, but not obstruction.
Martinez-Quintana E, et al. 2009 (290) 19489941	Descriptive	n=14 pts	Urinalysis	N/A	● Microalbuminuria found.
Pedersen CM, et al. 2009 (291) 19641842	Descriptive	n=13 pts	Flow mediated dilation	● Flow mediated dilatation compared to controls	● Vasodilatation intact, flow mediated dilatation is preserved.
Reiss UM, et al. 2007 (292) 17506064	Observational	n=4 pts	Hydroxyurea	N/A	● Favorable response to hydroxyurea, lower HCT higher MCV to HGB stayed the same.
Tay EL, et al. 2011 (293) 20580108	Observational	n=25 pts	Iron supplementation	● Iron supplementation for 3 mo, measuring response in exercise capacity	● Better walk distance with improved iron stores. ● Peak O_2 consumption was not different.
Trojnarska O, et al. 2010 (294) 19042041	Descriptive	n=53 pts	BNP and exercise	N/A	● Higher BNP, lower exercise than controls.
Tsui I, et al. 2009 (295) 19954382	Descriptive	n=4 pts	Retinal vasculature	N/A	● Tortuous vessels described in cyanotic pts.

Wykretowicz A, et al. 2007 (296) 18377491	Descriptive	n=14 pts	Arterial stiffness	N/A	● Stiffness not significantly different.
Broberg CS, et al. 2014 (297) 24331639	Descriptive	n=32 pts	Lung function	N/A	● Lung function/gas exchange abnormalities described. ● Pts have respiratory alkalosis.
Broberg CS, et al. 2007 (298) 17164484	Descriptive	n=55 pts	PA thrombosis	N/A	● Risk factors for PA thrombosis included poor RV function and LV function, and PA size.
Broberg CS, et al. 2006 (299) 16843187	Descriptive	n=39 pts	Iron deficiency and viscosity	N/A	● Iron deficiency does not increase viscosity.
Broberg CS, et al. 2011 (300) 21295176	Descriptive	n=65 pts	Hemoglobin	N/A	● Optimal hemoglobin defined, and relationship with O_2 sat determined.
Broberg CS, et al. 2007 (298) 17164484	Descriptive	n=53 pts	Air travel	● Pts described all air travel in 10 y, and any AE. Compared to noncyanotic pts	● No major AE, 1 possible TIA. ● Extensive travel reported, generally safe.
Sandoval J, et al. 2012 (301) 22360787	Observational	n=92 pts	Warfarin and survival	● Compared anticoagulated vs. nonanticoagulated pts after mean follow-up of 7 ± 5.4 y	● No difference in survival or bleeding events in anticoagulated pts.

Data Supplement 26. Atrial Septal Defect – Section 4.1.1

Study Name, Author, Year	Study Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results	Summary/Conclusions
Peirone A, et al. 2014 (302) 24677704	Prospective single-arm observational study, multicenter	n=74 pts	Inclusion criteria: Consecutive pts undergoing secundum ASD closure using the Nit-Occlud ASD-R device between 2011–2013	Immediate and short-term outcomes of device closure	● Implantation was successful in 73/74 pts. ● Median age 17 y. ● Excluded pts with ASD diameter >28 mm by stop flow technique. ● Complete occlusion of ASD on 6 mo follow-up ECG in 99%. ● At a mean follow-up of 11 ± 7 mo, no embolization, perforation or erosion. ● No arrhythmias post device closure. ● No embolic events, no wire fracture, no infections noted.	● ASD closure with the Nit-Occlud ASD-R device is feasible, safe and has a high success rate.

Mylotte D, et al. 2014 (209) 24485223	Systematic review; use of a decision-analytic model for assessment of clinical outcome parameters of secundum ASD closure method from the Quebec CHD Database. A cost-effectiveness analysis was performed comparing surgical vs. transcatheter ASD closure	n=718 pts	Inclusion criteria: Adult pts undergoing surgical or transcatheter secundum ASD closure in Quebec	Cost difference between surgical and transcatheter secundum ASD closure	● Between 1998–2005, 718 pts underwent secundum ASD closure, 335 underwent transcatheter closure, and 383 underwent surgical closure. ● The 5-y cost of surgical closure was $15,304 vs. $11,060 (Canadian dollars) for transcatheter closure. ● Probabilistic sensitivity analyses demonstrated that transcatheter ASD closure was associated with an 80% probability of cost savings and equal or greater efficacy compared to surgical treatment.	● Transcatheter secundum ASD closure is associated with reduced costs and slightly improved clinical outcomes compared to surgical closure at 5-y follow-up.
Stroker E, et al. 2013 (303) 23705553	Retrospective single-center review	n=47 pts	Inclusion criteria: Pts >60 y that underwent transcatheter secundum ASD closure	Long-term outcomes	● 47 pts, mean age 69.5 y. ● Median follow-up 3.3 y. ● Post closure, the PAP and RV size decreased but did not normalize. ● LV size, left atrial size, LVEF all increased. ● NYHA class improved after device closure. ● 6 pts died during 3.3 y of follow-up, 16 were hospitalized for cardiac events.	● Transcatheter secundum ASD closure in the elderly improved FC, RV dimensions and PAP
Rhodes JF, et al. 2014 (304) 23674380	Case series; Clinical results of the feasibility, pivotal, continued access, and post approval studies are pooled	n=435 pts	Inclusion criteria: Pts with a secundum ASD treated with a Helex septal occluder device and included in the feasibility, pivotal, continued access or post approval studies. Exclusion criteria: Pts with large secundum ASD (>22 mm stretched diameter).	Intermediate (12 mo) follow-up data	● Of the 435 subjects enrolled, 412 were eligible for follow-up. ● Clinical ASD closure was achieved in 98% of subjects at 12 mo; freedom from major AE at 12 mo was 95%.	● The Gore Helex septal occluder is efficacious and safe for closing secundum ASD measuring ≤22 mm in stretched diameter

Aytemir K, et al. 2013 (305) 23601507	Single-center, retrospective review	n=193 pts	Inclusion criteria: Pts with secundum ASD that underwent transcatheter device closure	intermediate-term follow-up	● Out of a total of 414 pts, 193 underwent secundum ASD closure using a variety of devices, 221 underwent PFO closure. ● Median follow-up was 43 mo for ASD pts. ● Device embolization in 2 pts. ● No residual shunts noted on follow-up transthoracic ECG. ● Device thrombosis in 2 pts.	● Transcatheter ASD closure is associated with good short- and intermediate-term outcomes.
Du ZD, et al. 2002 (306) 12039500	Multicenter, prospective nonrandomized trial	n=614 pts	Inclusion criteria: Pts with secundum ASD at 29 centers were assigned to either surgical or transcatheter device closure using the Amplatzer septal occluder between 1998–2000	Short- and intermediate-term results	● A total of 614 pts enrolled, 442 in the device group and 154 in the surgical group; secundum ASD diameter in the device group was a median of 13.3 mm vs. 14.2 mm for the surgery group. 89% of the device group pts had a single ASD vs. 80.5% in the surgery group. ● Successful device deployment in 95.7%. ● Mean age in device group was 18.1 y vs. 5.9 y in the surgery group. ● 1 device embolization. ● Immediate successful closure (≤ mild residual shunt) in 97.6% of device pts. ● All pts in the surgical group had a successful operation. ● At 12 mo post procedure 98.5% of device pts had ≤ mild residual shunt. ● No device or surgical deaths; major complications occurred in 1.6% of the device group and 5.4% of the surgical group (p=0.03). ● Minor complications in 6.1% of the device group vs. 18.8% of the surgical group (p<0.001). ● Total complications in 7.2% of the device group vs. 24% of the surgical group (p<0.001). ● Mean LOS was 1 d in the device group vs. 3.4 d in the surgery group (p<0.001).	● Transcatheter secundum ASD closure with the Amplatzer septal occluder is a safe and efficacious alternative to surgery.
Kutty S, et al. 2012 (307) 22335856	Single-center retrospective review	n=375 pts	Inclusion criteria: Pts with secundum ASD that underwent surgical or transcatheter closure between 1986–2005	Long-term clinical results	● 375 pts identified, 207 had surgical closure and 168 had device closure. ● >5-y follow-up data available on 300 pts (median follow-up of 11.9 y in 152 surgical and 8.1 y in 148 device closure). ● No significant differences found between the 2 groups with regard to survival, FC, atrial arrhythmia or embolic events. ● 3% died in each group. ● Clinically significant arrhythmia in 9% of pts in each group. ● Multivariate predictors of late arrhythmias included older age at repair (OR: 4.7 for pts >40 y at time of repair) and pre-existing atrial arrhythmia.	● Long-term outcomes are favorable following surgical or device closure of secundum ASD. ● Closure of the ASD before 40 y is associated with a lower risk of late arrhythmias.

Roos-Hesselink JW, et al. 2003 (308) 12573276	Single-center longitudinal follow-up	n=135 pts	Inclusion criteria: Pts with secundum ASD operated on in childhood at Erasmus Medical Center, Netherlands	Long-term clinical results	● 135 consecutive pts with secundum ASD that underwent surgical repair in childhood. ● Pts studied longitudinally with ECG, echo, exercise testing, and Holter monitor at 15 and 26 y post surgery. ● No CV mortality, stroke, HF or pulmonary HTN noted; Symptomatic atrial arrhythmia in 6% after 15 y and an additional 2% at 26 y; pacemaker implantation performed in 5%; ● Exercise capacity is comparable with the normal Dutch population.	● The long-term outcomes of surgical secundum ASD closure in childhood are excellent.
Konstantinides S, et al. 1995 (309) 7623878	Single-center retrospective review	n=179 pts	Inclusion criteria: Pts >40 y with isolated secundum type ASD that had undergone a right heart catheterization and had predominantly left-to-right shunt with a Qp:Qs ≥1.5:1	Long-term clinical results	● 179 consecutive pts with isolated secundum ASD and >40 y; 84 pts (47%) underwent surgical repair, 95 pts (53%) were treated medically. ● Follow-up period was 8.9 ± 5.2 y (range 1–26 y); multivariate analysis demonstrated a significant reduction in all-cause mortality in pts undergoing surgical treatment (RR: 0.31; 95% CI: 0.11–0.85). ● The adjusted 10 y survival rate for surgically treated pts was 95% as compared to 84% for medically treated pts. Surgical treatment prevented deterioration in FC (RR: 0.21; 95% CI: 0.08–0.55). ● No difference in incidence of new atrial arrhythmia or stroke between the 2 groups.	● Surgical repair of isolated secundum ASD with predominant left-to-right shunt in pts ≥40 y is associated with improved survival and less functional deterioration when compared to medical therapy.
Engelfriet P, et al. 2008 (310) 17586067	Analysis of all pts with a diagnosis of secundum ASD in the database of the Euro Heart Survey. Consecutive pts with diagnosis of ASD visiting an outpatient clinic of participating European centers in 1998 were identified and their clinical course documented in	n=882 pts	Inclusion criteria: Pts with a diagnosis of secundum ASD visiting output clinics of participating European centers in 1998	Intermediate- and long-term clinical results	● 882 pts analyzed. ● Mean follow-up 4.2 y. ● At baseline, 377 pts (mean age 39.2 y) had ASD closure, 505 pts (mean age 41 y) had open ASD. ● Pts with open defects were more likely to have pulmonary arterial HTN (35% vs. 13%), RV dysfunction (31% vs. 8%), and severe volume overload (18% vs. 1%). ● Pulmonary arterial HTN prevalence increased with age in pts with unrepaired ASD with moderate or large sized defects; small defects (Qp:Qs<1.5:1) that were not closed did not result in worsening hemodynamics during follow-up. ● Functional limitations were more common in pts with moderate/large open shunts. ● In a multivariable model, the best predictors of functional limitations were pulmonary arterial HTN and RV volume overload. ● No difference in the prevalence of arrhythmias noted.	● Pts with open moderate or large left-to-right atrial level shunts due to secundum ASD (Qp:Qs≥1.5:1) demonstrate worse hemodynamic and functional profiles when compared to those that have undergone ASD closure. ● Pts with small atrial level shunts (Qp:Qs<1.5:1) that have not undergone ASD closure are unlikely to have worsening hemodynamic profiles or FC.

	retrospect from 1998–2004				● During follow-up, 9 pts died and 294 of 505 pts underwent defect closure, 180 pts had surgical closure and 114 underwent transcatheter closure. ● Surgical pts were more likely to have larger shunts, larger defects, worse RV function and pulmonary HTN.	
Kardon RE, et al. 2004 (311) 15246918	Single-center case series	n=74 pts	Inclusion criteria: Pts with secundum ASD undergoing TTE-guided percutaneous closure	Procedural outcomes	● 74 pts were evaluated for TTE-guided ASD closure. ● 56 pts had successful device implantation using TTE guidance. 12 pts were referred for surgical ASD closure on the basis of TTE evaluation. 5 pts with multiple ASDs or poor transthoracic acoustic windows had ASD device closure guided by TEE.	● TTE can be used to guide percutaneous ASD closure, a minority of pts required TEE guidance.
Mazic U, et al. 2001 (312) 11526362	Single-center case series	n=240 pts	Inclusion criteria: Pts with secundum ASD were examined by 2D TTE and TEE with TEE guidance of transcatheter closure with the atrial septal occluder (ASO)	Procedural outcomes	● 16 (6%) pts were found not suitable for transcatheter closure with TTE, 35 (14%) with TEE, and 2 during catheterization. 28 pts (18%) had partial or total deficiency of the posterior, inferoanterior, or inferoposterior rim, 54 (27%) had a centrally positioned ASD, 92 (46%) had insufficient superoanterior rim, and 9 had multiple ASDs, whereas 8 had a septal aneurysm associated with a single defect and 4 a multiperforated aneurysm. ● A total of 170 pts underwent implantation of ASO. The ASO was correctly positioned in 144 at the first attempt. In the remainder TEE revealed unstable position of the left atrial disk (12), opening of both atrial disks in the left atrium (5), deployment of the device through the smaller defect in pts with multiple ASDs (3), and, in 1 pt, the device was too small and had to be replaced by a larger one.	● Morphologic variations of secundum ASD are common. TEE is crucial for the determination of the ASD morphologic features, diameter, and rims, which are crucial for proper pt selection. TEE allows precise guiding and positioning of the ASO, which is essential for safe and effective transcatheter ASD closure.
Teo KS, et al. 2010 (313) 20663157	Single-center comparison of CMR and TEE for evaluation of ASD in pts evaluated for percutaneous ASD closure	n=20 pts	Inclusion criteria: Consecutive pts with ASDs diagnosed on TTE underwent TEE and CMR.	Comparison of diagnostic modalities	● Total CMR scan time was 20 min, and comparable to the TEE examination time. A total of 20 pts (male:female=5:15, mean age 42.8 y ± 15.7) were included in the analyses. ● There was an excellent agreement between CMR and TEE for estimation of maximum defect size (R=0.87). The anterior inferior, anterior superior and posterior inferior margins could be assessed in all pts with CMR. The posterior superior margin could not be assessed in only 1 pt. Furthermore, in 1 pt in whom TEE was unable to be performed, CMR was used to successfully direct percutaneous ASD closure.	● CMR agrees with TEE assessment of ASDs in the work-up for percutaneous closure. Potentially CMR could be used instead of TEE for this purpose.
Zanchetta M, et al. 2004 (314) 15104772	Single-center case series	n=135 pts	Inclusion criteria: Describe the 3-y results of transcatheter ASD closure using the ASO and	Long-term outcomes of transcatheter ASD closure	● Under local anesthesia, 135 consecutive pts with ASDs (male:female=45:90; mean age 42.2 ± 19.2 y; body surface area 1.71 ± 0.7 m^2; mean pulmonary arterial pressure 30.4 +/-	● ICE is an effective and safe alternative to TEE and balloon-sizing maneuver

			intracardiac echocadiography (ICE) as the sole imaging tool both to select the device size and to monitor the procedure.	using ICE guidance	11.5 mm Hg; mean Qp/Qs ratio 2.1 ± 0.6) underwent transcatheter closure using ASO and ICE. ● A 9F-9MHz mechanical transducer was used. 2 orthogonal views on the transverse aortic valve and on the longitudinal 4-chamber planes were obtained for quantitative ICE measurements, from which the diameters of the implanting ASO waist were to be derived. ● In all cases, ICE ASD measurements led to device size selection (mean size 25.0 ± 6.7 mm). Moreover, the ICE allowed the monitoring of device deployment and post deployment evaluation. ● There were no complications related to the procedure or to the use of ICE. During a mean follow-up period of 21.5 ± 12 mo, the cumulative complete occlusion rates were 97.7, 97.0, 97.1, and 98% at 24 h, 3 mo, and 1 and 3 y, respectively.	during transcatheter ASD closure.
Ammash NM, et al. 1997 (315) 9137235	Single-center case series	n=43 pts	Inclusion criteria: Describe the anatomic aspects of PAPVC identified by TEE and the presenting symptoms and signs.	Procedural outcomes	● A total of 66 PAPVCs were detected in 43 pts (1.5/pt); in 2 additional pts, TEE suggested, but did not diagnose, PAPVCs. ● Shortness of breath was the most common presenting symptom (42.2%), followed by heart murmur and SVT ● Right-sided anomalous veins were identified in 35 pts (81.4%), left-sided in 7 (16.3%) and bilateral in 1 (2.3%). There was a single anomalous connecting vein in 23 pts (53.5%), 2 in 18 (41.9%), 3 in 1 (2.3%), and 4 in 1 (2.3%). The connecting site was the SVC in 39 veins (59.1%), right atrial-SVC junction in 6 (9.1%), right atrium in 8 (12.1%), inferior vena cava in 1 (1.5%), and the coronary sinus in 2 (3.0%). 10 anomalous left pulmonary veins were connected by a vertical vein to the innominate vein (15.1%). ● Sinus venous ASD was the most common associated anomaly in 22 pts (49%), followed by ostium secundum ASD in 6 and patent foramen ovale in 4. 15 pts had an intact atrial septum. ● 31 pts (68.8%) underwent surgical repair. PAPVC was confirmed in all pts, including the 2 whose TEE results were suggestive of PAPVC. ● All 49 PAPVCs detected by TEE preoperatively were confirmed at the time of operation.	● TEE is highly diagnostic for PAPVC. Accurate anatomic diagnosis may influence the need for medical and surgical management. ● TEE should be performed in pts with RV volume overload when TTE is inconclusive.
Harmati LB, et al. 2003 (316)	Multicenter retrospective review	n=29 pts	Inclusion criteria: Prevalence and	Procedural findings	● 29 adults with a PAPVC on CCT were retrospectively identified. There were 19 women and 10 men, with a mean age of 53 (range: 19–83) y.	● The prevalence of PAPVC on CCT is 0.2%.

14501365			characteristics of PAPVC on CCT		● 4 cases were identified by review of 1,825 consecutive CCT reports, and 25 cases were culled from chest radiology teaching files at 3 institutions. ● The prevalence of a PAVC connection was 0.2% (4 of 1825 CCT reports). ● 79% (23 of 29 pts) had an anomalous left upper lobe vein connecting to a persistent left vertical vein, only 5% (1 of 23 pts) of whom had a left upper lobe vein in the normal location. ● 17% (5 of 29 pts) had an anomalous right upper lobe vein draining into the SVC, 60% (3 of 5 pts) of whom also had a right upper lobe pulmonary vein in the normal location. 1 pt (3%) had an anomalous right lower lobe vein draining into the suprahepatic inferior vena cava. ● Chest radiographic findings were abnormal left mediastinal contour in 64% (15 of 25 pts), abnormal right mediastinal contour in 8% (2 of 25 pts), and cardiomegaly in 24% (6 of 25 pts). CCT findings were cardiomegaly in 48% (14 of 29 pts), right atrial enlargement in 31% (9 of 29 pts), RV enlargement in 31% (9 of 29 pts), and PA enlargement in 14% (4 of 29 pts). ● Pulmonary or CV symptoms were present in 69% (20 of 29 pts), 55% (11 of 20 pts) of whom had specific alternative diagnoses (excluding congestive HF and pulmonary HTN) to explain the symptoms. Only 1 pat (3%) was diagnosed with a secundum ASD.	● The majority of PAPVC incidentally identified on CCT is anomalous left upper lobe vein.
Nordmeyer S, et al. 2011 (317) 21554824	Single-center case series	n=6 pts	Inclusion criteria: CMR characteristics of PAPVC suspected on TTE	Procedural findings	● In all pts, the diagnosis of PAPVR was confirmed by standard MRI. ● Shunt volumes ranged from 1.4:1–4.7:1. ● Drainage sites were the superior caval vein (n=5) or the vertical vein (n=1). ● Multiple maldraining pulmonary veins were found in 3 pts. ● Pulmonary arteries and veins could be clearly distinguished by selective visualization using 4D velocity-encoded cine MRI. Flow measured individually in maldraining pulmonary veins in 6 pts and across the interatrial communication in 3 pts revealed a percentage of the overall shunt volume of 30%–100% and 58%–70%, respectively.	● Vessel selective 4D cardiac MRI facilitates the accurate diagnosis of PAPVC. By detailed quantification of shunt volumes, additional information for planning of treatment strategies is provided.
Altindag T, et al. 2010 (318) 21113378	Single-center case series	n=47 pts	Inclusion criteria: Transcatheter ASD closure in adults ≥40 y	Procedural and intermediate-term outcomes	● Of the 130 pts who were referred for interventional ASD closure, 47 were 40 y and older and all of them had the device inserted. There were no major complications during the intervention.	● Transcatheter device closure of ASD is a successful and effective treatment, also for pts ≥40 y.

					● Mean follow-up time was 15 ±15 mo. During follow-up, 3 pts needed surgical reintervention because of device embolization (n=2) or dislocation (n=1). ● Of the pts with severe RV dilatation, more than 1/2 (58%) had no or mild dilatation at last follow-up. Reduction of RV dilatation was not related to age. Pulmonary HTN was present in 63% before the procedure and was reduced to 38% at follow-up. ● NYHA FC improved in all age groups, also in pts over 60 y. In 2 of the 3 pts who died during follow-up, no cause of death could be established, but both had responded well to treatment regarding the echocardiographic and clinical findings.	● Pts showed regression of RV enlargement and an improvement in FC.
Attie F, et al. 2001 (319) 11738312	Prospective randomized clinical trial	n=521 pts	Inclusion criteria: Secundum ASDs in pts ≥40 y improves their long-term clinical outcome.	Long-term clinical outcomes	● Recruited 521 pts >40 y old with secundum ASDs referred for treatment; 48 were excluded. ● Pts were randomly assigned to surgical closure (n=232) or medical treatment (n=241). ● The 1° and 2° endpoints were a composite of major CV events (death, pulmonary embolism, major arrhythmic event, embolic cerebrovascular event, recurrent pulmonary infection, FC deterioration or HF) and overall mortality, respectively. ● The analysis was performed on an intention-to-treat basis. The median follow-up period was 7.3 y (range 2–13). The risk of having the 1° endpoint was significantly higher in the medical group, which had a univariate HR of 1.99 (95% CI: 1.23–3.22) and a multivariate HR of 1.85 (95% CI: 1.08–3.17). ● Although the survival analysis did not reveal differences in overall mortality between the surgical and medical treatments (HR: 1.71; 95% CI: 0.76–3.86), the multivariate analysis, adjusted by age at entry, mPAP and cardiac index, demonstrated significant differences between the study groups (HR: 4.09; 95% CI: 1.41–11.89). Surgical closure was superior to medical treatment in improving both the composite of major CV events and overall mortality in pts >40 y old with secundum ASDs. This superiority was related to the mPAP, age at diagnosis and cardiac index.	● Because of the higher risk of morbidity and mortality, the authors recommend that anatomic closure should always be attempted as the initial treatment for ASDs in adults >40 y old with PASP <70 mm Hg and a pulmonary/systemic output ratio ≥1.7. The operation must be performed as soon as possible, even if the symptoms or the hemodynamic impact seems to be minimal.
Brochu MC, et al. 2002 (320) 12356636	Single-center case series	n=37 pts	Inclusion criteria: Transcatheter ASD closure on asymptomatic or minimally symptomatic adults	Procedural and intermediate-term outcomes	● 37 pts (24 females; mean age 49.4 y, range 19–76) with a Qp:Qs of 2.1 (1.2–3.4) had a VO_2 max determination and echocardiographic measurement of RV dimensions before and 6 mo after elective percutaneous closure of ASD. ● At baseline, mean VO_2 max was 23.5 ± 6.4 mL/kg/min and was higher in the 15 NYHA I pts than in the 22 NYHA II pts (27	● Adult ASD pts significantly increase their FC after percutaneous defect closure. This is observed even in pts classified as asymptomatic, in those with lesser shunts,

					± 6.9 vs. 20.8 ± 4.6 mL/kg/min; p=0.0015). VO_2 max increased significantly at 6 mo (23.5 ± 6.4–26.9 ± 6.9 mL/kg/mi; p<0.0001). Improvement was as marked in NYHA I (+22%; p<0.0001) as in NYHA II pts (+12%; p<0.0001), in pts with Qp:Qs 1.2–2.0 (+16%; p<0.0001) as in those with Qp:Qs>2 (+12%; p<0.0001), and in pts ≥40 y of age (+14%; p<0.0001) as in those <40 y (+16%; p<0.0001). Compared with 15 of 37 pts before closure, 35 of 37 pts were in NYHA I at 6 mo. RV dimensions decreased significantly (p<0.0001).	and in older pts. These findings suggest that ASD closure in an adult population should be considered even in the absence of symptoms.
Shah D, et al. 1994 (321) 8142189	Single-center retrospective review	n=82 pts	Inclusion criteria: Pts with ASD followed since 1955 who fulfilled entry criteria and were >45 y	Long-term outcomes of surgical vs. nonsurgical Rx of ASD	● Mean follow-up of 25 y. ● There was no difference in survival or symptoms between the 2 groups and no difference in the incidence of new arrhythmias, stroke, or other embolic phenomena, or cardiac failure. No pt in either group developed progressive pulmonary vascular disease.	● Outcome in adults with ASD was not improved by surgical closure. Because progressive pulmonary vascular disease did not develop in any of these pts its prevention is not a reason for advising closure of ASD in adults.
Varma C, et al. 2004 (322) 14696173	Single-center case series	n=172 pts	Inclusion criteria: Pts with transcatheter closure of small or large secundum ASD	Procedural and short-term outcomes of transcatheter ASD closure	● Outcomes of device closure of large and small secundum ASDs as related to rim anatomy with the Amplatzer atrial septal occluder were compared. ● Rim adequacy (≥5 mm) of the anterior, inferior, posterior, and superior rims was determined using TEE. ● Balloon-stretched defect size defined pts into 2 groups: Group 1, ≤25 mm (n=138); group 2, >25 mm (n=34). ● Rim deficiency (n=62) was more frequent in group 2 compared to Group 1 (50% vs. 33%; p=0.07), especially inferior rim deficiency (35% vs. 2%; p=0.005). ● Device deployment was successful in Group 1 and Group 2 (100% vs. 91%; p=0.007). Unsuccessful deployment was associated with an ASD of >25 mm (p=0.007) and inferior rim deficiency (p=0.001). At first follow-up (54 ± 16 d), RV systolic pressure had improved in both groups (p<0.001).	● Closure of a large ASD associated with a lack of support in the inferior rim may warrant alternative strategies to position the device successfully.
Amin Z, et al. 2004 (323) 15558755	Registry review	n=28 pts	Inclusion criteria: Pts with hemodynamic compromise after ASO placement	Review of registry records to identify risk factors for ASO device erosion.	● In all pts who developed hemodynamic compromise after ASO placement, echos (pre-, intra-, and post procedure), ASD size (nonstretched, stretched), size of the device used, cineangiograms, and operative records were reviewed by a panel selected by AGA Medical Corporation. The findings were compared to the premarket approval data obtained from FDA-	● The risk of device erosion with ASO is low and complications can be decreased by identifying high-risk pts and following them closely. Pts with deficient aortic rim and/or

					approved clinical trials that were conducted in the U.S, before the device was approved. ● A total of 28 cases (14 in U.S) of AE were reported to AGA Medical Corporation. All erosions occurred at the dome of the atria, near the aortic root. Deficient aortic rim was seen in 89% and the defect described as high ASD, suggesting deficient superior rim. The device to unstretched ASD ratio was significantly larger in the AE group when compared to the FDA trial group. The incidence of device erosion in the U.S was 0.1%.	superior rim may be at higher risk for device erosion. Oversized ASO may increase the risk of erosion. The defect should not be overstretched during balloon sizing. Pts with small pericardial effusion at 24-h should have closer follow-up.
Du ZD, et al. 2002 (306) 12039500	Multicenter nonrandomized concurrent study	n=442 pts	Inclusion criteria: This study sought to compare the safety, efficacy and clinical utility of the ASO for closure of secundum ASD with surgical closure.	intermediate-term follow-up post ASD closure	● A total of 442 pts were in the group undergoing device closure, whereas 154 pts were in the surgical group. The median age was 9.8 y for the device group and 4.1 y for the surgical group (p<0.001). In the device group, 395 (89.4%) pts had a single ASD; in the surgical group, 124 (80.5%) (p=0.008) had a single ASD. The size of the 1° ASD was 13.3 ± 5.4 mm for the device group and 14.2 ± 6.3 mm for the surgery group (p=0.099). The procedural attempt success rate was 95.7% for the device group and 100% for the surgical group (p=0.006). ● The early, 1° and 2° efficacy success rates were 94.8%, 98.5%, and 91.6%, respectively, for the device group, and 96.1%, 100%, and 89.0% for the surgical group (all p>0.05). ● The complication rate was 7.2% for the device group and 24.0% for the surgical group (p<0.001). ● The mean length of hospital stay was 1.0 ± 0.3 d for the device group and 3.4 ± 1.2 d for the surgical group (p<0.001). ● Mortality was 0% for both groups.	● The early, 1° and 2° efficacy success rates for surgical vs. device closure of ASD were not statistically different; however, the complication rate was lower and the length of hospital stay was shorter for device closure than for surgical repair. ● Transcatheter closure of secundum ASD using the ASO is a safe and effective alternative to surgical repair.
Lopez K, et al. 2005 (324) 16216021	Single-center series	n=32 pts	Inclusion criteria: Describe the procedural factors and outcome of ASD closure with the 40 mm ASO	Procedural outcomes	● 33 pts (22 female, 11 male) with a large secundum ASD underwent attempted device closure using the 40 mm ASO at a median age of 40 y (range, 14–81 y) and median weight of 65 kg (range, 48–98 kg). The median size of the ASD measured on TEE (27 pts) or ICE (6 pts) was 30.5 mm (range, 24–39 mm) and the median balloon-stretched diameter was 37.7 mm (range, 32–43.7 mm). ● The median Qp:Qs was 3.2:1 (range, 1.4–6.2). ● The attempt was unsuccessful in 5 pts; 2 had device embolization and 1had left atrial wall perforation due to the sheath; all 3 required emergent surgery. ● The attempt was successful in the 28 remaining pts, resulting in complete immediate closure in 14 and a trivial residual shunt	● The 40 mm ASO is safe and effective in most pts with a large ASD up to a diameter of 39 mm. However, the use of this device requires careful attention as the procedure may be unsuccessful or the device may embolize.

					in 14. Fluoroscopy time ranged from 8.6–37.8 min (median: 12.2 min). ● At 24-h follow-up, 2D TTE with color flow Doppler revealed complete closure in 23 pts, and 5 had a trivial residual shunt. There were no complications encountered in pts who received the device. On follow-up, all pts are doing well.	
Bradley EA, et al. 2013 (325) 23993122	Single-center case series	n=12 pts	Inclusion criteria: ASD pts with PAH may undergo treatment with pulmonary vasodilators and undergo delayed ASD closure	intermediate-term outcomes of PAH treatment and ASD closure	● Invasive hemodynamic and clinical parameters from 12 pts with an open ASD and PAH PVR, 8.8 ± 1.2 WU; mPAP, 55 ± 6 mm Hg; Qp:Qs 1.1 ± 0.1; and 6MWT of 1,046 ± 116 feet) were analyzed. Responders (n=5) underwent successful ASD closure at 1.3 ± 0.3 y after initiation of medical therapy and were characterized by >30% reduction in PVR (7.2 ± 1.5–4.6 ± 0.9 WU) vs. <20% in nonresponders (n=7; 9.9 ± 1.7–8.2 ± 1.5 WU; p<0.03), increased 6MWT (1,087 ± 174 vs. 1,405 ± 109 feet; p=0.05), and higher Qp:Qs after therapy (1.9 ± 0.2 vs. 1.1 ± 0.2; p<0.02). BMI was a significant clinical predictor of response (23.3 ± 1.9 vs. 30.0 ± 2.1 kg/m^2; p<0.05) and the change in arterial saturation with exercise correlated inversely with change in PVR (r=-0.739; p<0.01).	● Medical therapy led to a significant improvement in hemodynamic and clinical parameters in a subset of pts with an open ASD and PAH, who were able to safely undergo delayed ASD closure.
Cho YH, et al. 2012 (326) 22543336	Single-center case series	n=16 pts	Inclusion criteria: Pts with fenestrated surgical patch in ASD pt with severe pulmonary HTN	intermediate- and long-term outcomes	● All pts had a secundum type ASD and severe pulmonary HTN. Pts ranged in age from 6–57 y (mean ± SD, 34.9 ± 13.5 y). The follow-up period was 9 –59 mo (mean, 34.5 ± 13.1 mo). ● The ranges of preoperative systemic systolic and PA systolic pressure were 63–119 mm Hg (mean, 83.8 ± 13.9 mm Hg) and 37–77 mm Hg (mean, 51.1 ± 10.1 mm Hg). The ranges of preoperative values for the ratio of the pulmonary flow to the systemic flow and for pulmonary arterial resistance were 1.1–2.7 (mean, 1.95 ± 0.5) and 3.9–16.7 WU (mean, 9.8 ± 2.9 WU), respectively. ● There was no early or late mortality. Tricuspid annuloplasty was performed in 14 pts (87.5%). The peak TR gradient and the ratio of the systolic PAP to the systemic arterial pressure were decreased in all pts. ● The NYHA class and the grade of TR were improved in 13 pts (81.2%) and 15 pts (93.7%), respectively.	● ASD closure in pts with severe pulmonary HTN can be performed safely if there is a fenestration. Tricuspid annuloplasty and a Cox Maze procedure may improve the clinical result.
Shim M, et al. 2013 (327) 23614094	Single-center case series	n=46 pts	Inclusion criteria: Pts undergoing the Maze procedure in conjunction with ASD closure	Long-term follow-up	● 46 pts underwent the Maze procedure as a concomitant operation with ASD closure. ● The mean follow-up duration was 3.2 ± 2.5 y. ● ECG was performed 1 mo, 3 mo, 6 mo, and 1 y after surgery, and checked annually after that.	● Concomitant treatment with the Maze procedure and ASD closure is safe and effective for restoring the sinus rhythm.

					● AF persisted in 4 pts after surgery. 1 y after surgery, among 38 pts, 55.3% remained in sinus rhythm without antiarrhythmic drugs. However, when including the pts who took antiarrhythmic drugs, 92.1% were in sinus rhythm. ● Freedom from AF recurrence at 3 mo, 6 mo, 1 y, 2 y, 3 y, and 5 y after surgery were 97.4 ± 2.6, 94.4 ± 3.8, 91.2 ± 4.9, 87.8 ± 5.8, 79.5 ± 7.6, and 68.2 ± 12.4, respectively. There was no early mortality after operation.	
Giamberti A, et al. 2006 (328) 16996928	Case series	n=15 pts	Inclusion criteria: Pts >40 y with ASD and atrial arrhythmia who had elective surgical closure and intraoperative irrigated radiofrequency ablation (IRF) ablation	Procedural and intermediate outcomes	● All pts had supraventricular arrhythmia: 8 had permanent AF; whereas, 7 had previous episodes of atrial flutter or intra-atrial reentry tachycardia. ● The biatrial approach (Cox-Maze III procedure) was used in 7 pts and a right-sided Maze procedure (ablation lines on the right atrium only) was carried out in the remaining 8 pts. ● All pts survived the procedure. 14 pts left the operating room in sinus rhythm and 1 had a pacemaker implanted. ● There were no complications resulting from the irrigated radiofrequency ablation. No deaths during an average follow-up period of 24 mo. ● 13 pts were still in sinus rhythm, 1 had pacemaker rhythm, and only 1 (1 of 15; 6.5%) suffered a recurrence of AF 3 mo after the procedure.	● Addition of intraoperative irrigated radiofrequency ablation during surgical closure of an ASD in adult ASD pts with arrhythmias is beneficial in maintaining sinus rhythm. ● The irrigated radiofrequency ablation is easy to perform, safe, and effective.
Kouchoukos NT, et al. 1978 (329) 619518	Review	N/A	Inclusion criteria: Pts with large VSD prior to surgical closure	Mortality	● Mortality related to age at operations (older did worse) and to preoperative PVR.	● Prepulmonary vasodilator era. Careful consideration of mortality and late effects prior to considering closure of large VSD.
Shohtsu A, et al. 1976 (330) 950729	Retrospective cohort	n=64 pts	Inclusion criteria: Pts with large VSD, PH; also small number with PDA and ASD	Mortality	● Optimal timing of closure is at 1-3y for VSD with PH; PDA and ASD not clear.	● Closure of large septal defects with PH should be considered for closure only at young ages to improve mortality.
Gajjar TP, et al. 2011 (53) 21793931	Single-center case series	n=48	Inclusion criteria: Pts with sinus venous ASD who underwent transcaval repair between Jan. 2007—Oct. 2010	Surgical outcome	● All pts came off bypass in sinus rhythm. ● Average pressure gradient across patch: 3 mm/Hg. ● Immediate postop ECGs and echos showed all pts in sinus rhythm with no residual shunt and no pulmonary or systemic venous obstruction, except 1 pt who required SVC augmentation.	● Single patch technique is safe and simple for sinus venous ASD and preserves sinoatrial node function after surgery.

Data Supplement 27. Anomalous Pulmonary Venous Connections – Section 4.1.2

Study Name	Study Type/ Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
Festa, P, et al. 2006 (80) 16547601	Single-center retrospective study	n=20 pts	Inclusion criteria: Pts with suspected PAPVC that underwent MRI	To test the diagnostic accuracy of MRI in PAPVR	● 20 consecutive pts (10 male, mean age: 27 ± 20 y) with suspected PAPVC underwent a magnetic resonance study comprehensive of Gadolinium-enhanced 3D MRA and phase-velocity-contrast in order to evaluate pulmonary and systemic venous anatomy and Qp:Qs. ● In 14 pts, a cardiac catheterization was also performed. Anatomy findings and Qp:Qs result of both exams were compared. ● 16 pts underwent surgical correction. In the other 4 pts with Qp:Qs<1.5, surgical correction was not performed. ● Among pts who had both magnetic resonance and cardiac catheterization (14 pts) anatomical findings were concordant in 12 of them. In all operated pts, surgical findings were concordant with MRI report. ● There was a good correlation between magnetic resonance and cardiac catheterization Qp:Qs evaluation (mean value 2.23 and 2.4, respectively).	● In pts with suspected anomalous pulmonary venous connection, magnetic resonance provides a comprehensive evaluation of pulmonary venous connections and the Qp:Qs.
Nordemeyer S, et al. 2011 (317) 21554824	Single-center prospective imaging study	n=6 pts	Inclusion criteria: Pts with suspected PAPVC by echo referred for 4D MRI	Functional and anatomic analysis by 4D MRI	● 6 pts with PAPVC suspected on echo underwent MRI/MRA. ● Functional analysis included shunt calculations from flow measurements. The authors used 4D velocity-encoded cine MRI for visualization of anomalous pulmonary veins and quantification of flow via the anomalous veins and interatrial communications, if present. ● In all pts, the diagnosis of PAPVC was confirmed by MRI. Shunt volumes ranged from 1.4:1–4.7:1. Drainage sites were the superior caval vein (n=5) or the vertical vein (n=1). ● Multiple anomalous pulmonary veins were found in 3 pts. Pulmonary arteries and veins could be clearly distinguished by selective visualization using 4D velocity-encoded cine MRI. Flow measured individually in anomalous pulmonary veins in 6 pts and across the	● Selective visualization of individual vessels and their flow characteristics by 4D velocity-encoded cine MRI is feasible and improves the accurate diagnosis of PAPVC. By detailed quantification of shunt volumes, additional information for planning of treatment strategies is provided.

					interatrial communication in 3 pts revealed a percentage of the overall shunt volume of 30%–100% and 58%–70%, respectively.	
Dyme JL, et al. 2006 (331) 16784931	Retrospective case review from 2 institutions	n=6 pts	Inclusion criteria: Pts with isolated PAPVC from 2002–2005 identified by searching the MRI databases of 2 institutions. Subjects with >1 anomalous vein or ASD or other associated lesions were excluded	Assessment of the magnitude of left-to-right shunt and RV dilation in patients with single anomalous PAPVR	● In the 6 subjects identified, the median pulmonary-to-systemic flow ratio was 1.55 (range 1.3–1.6). The mean RVEDV indexed to body surface area in the subjects was significantly larger than in a normal reference cohort (108 ± 16 vs. 78 ± 18 cm^3/m^2; p=0.0009) and >the upper limit of normal in all 6 subjects. ● Older age did not correlate with increased magnitude of shunting (r=0.3; p=0.5), but increased age did correlate with RVEDV indexed to body surface area (r=0.96; p=0.01).	● Isolated partial anomalous pulmonary venous connection with only 1 vein connecting anomalously results in a modest left-to-right shunt and mild RV dilation.
Majdalany DS, et al. 2010 (332) 21106012	Retrospective single-center study	n=43 pts	Inclusion criteria: Pts with isolated PAPVC >18 y attending Mayo ACHD clinic from 1998–2008	Review of clinical characteristics and outcomes	● 43 pts 20–73 y were included. ● 15 pts had no surgery, 11 of whom had a single anomalous pulmonary vein. ● Surgical repair was performed in 28 pts: 27 had RV volume overload, 21 had more than 1 anomalous pulmonary vein, and 1 had stenosed pulmonary veins. ● RV systolic pressure was elevated (>35 mm Hg) in 12 pts. ● 11 pts had anomalous left pulmonary veins: 10 had the pulmonary vein anastomosed to the left atrial appendage and 1 pt had anastomosis to the left lower pulmonary vein. 1 pt had bilateral anomalous pulmonary veins anastomosed directly to the left atrium. ● 16 pts had anomalous right pulmonary veins: 15 had a baffle through a surgically-created ASD, while 1 had the anomalous pulmonary vein anastomosed to the left atrium. ● There was no early mortality. There were 10 postoperative complications including 2 baffle leaks, 2 baffle stenosis. ● During mean echo follow-up of 2.7 y, 19 pts (68%) had reduced RV size and 5 had improved RV function. 7 pts with increased pulmonary pressure had a decrease postoperatively.	● Partial anomalous pulmonary veins can cause symptoms, RV volume overload, and pulmonary HTN, particularly when more than 1 pulmonary vein is anomalous. ● Surgical repair can be accomplished with low morbidity and mortality, with improvement in the RV size and pulmonary pressures.
Jemielity M, et al. 1998 (333)	Retrospective single-center study	n=25 pts	Inclusion criteria: Consecutive pts between 1981–1995	Surgical and intermediate-term outcomes post	● Mean age at surgery was 37.8 ± 13.0 (range: 16–62 y).	● Patch repair of PAPVC with sinus venous ASD in adults with use of

9697063			that underwent surgical repair of PAPVC with ASD.	PAPVC and ASD repair	● All pts underwent the procedure of covering both defect and vein with pericardial patch to direct blood flow from anomalous pulmonary veins through the ASD into the left atrium. ● Mean follow-up was 7.8 ± 4.0 y (range: 2–16 y). No pts were lost to follow-up. ● There were no early deaths. 1 pt died 11 mo after surgery from progressive HF. ● At follow-up, 10 (42.7%) pts were clinically asymptomatic.1 pt had clinical signs of SVC obstruction. ● ECG showed no abnormalities in 7 (29.2%) pts. ● Chest radiography revealed normal pulmonary vascularity in 22 (91.7%) pts and no residual shunts were found in the SVC.	autologous pericardium is a safe and effective procedure.
Brink J et al. 2015 (334) 25288102	Retrospective single-center study	n=21 pts	Inclusion criteria: Pts with scimitar syndrome that underwent corrective surgery between 1974–2001	Surgical and long-term outcomes	● The mean age of surgery was 5.4 y (2.5 mo–6.7 y). ● 16 (76.2%) pts were symptomatic at presentation. 15 (71.4%) pts presented with the infantile form and 6 (28.6%) with the adult form of scimitar syndrome. ● Operative techniques included baffle repair in 15 (71.4%) pts, reimplantation in 5 (23.8%) pts and pneumonectomy in 1 (4.8%) pt. ● 6 (28.6%) pts were operated in infancy at a mean of 4 mo (2.5–9.6 mo). ● There was 1 (4.8%) hospital death and 3 (15%) late deaths. The risk factors for mortality included preoperative pulmonary HTN (p=0.006) and surgery during infancy (p=0.003). ● The incidence of postoperative pulmonary vein stenosis was 23.8% (n=5). 3 (14.3%) pts underwent reoperation for pulmonary vein stenosis. ● Neither baffle (p=0.6) nor reimplantation (p=0.55) surgical techniques influenced the rate of stenosis. ● The follow-up was complete in 15 (88%) survivors at a mean of 13.7 y (1.3–38.5 y). ● All surviving pts were asymptomatic and had a NYHA FC Class I.	● Surgical mortality is highest in pts operated on before 1 y of age and those with pulmonary HTN. ● Baffle/vein stenosis occurs in 23.8% of pts. ● Most survivors are asymptomatic at long-term follow-up.
Sachweh JS, et al. 2006 (335) 16368366	Retrospective single-center study	n=75 pts	Inclusion criteria: Adult pts that underwent surgical closure of secundum	Assess the prevalence and histologic degree of hypertensive	● Lung biopsies of 75 pts, mean age 44 ± 14 y (18–71 y), with secundum ASD or sinus venous defect including 10 pts with PAPVC were analyzed. Lung biopsy was	● Histologic changes consistent with hypertensive pulmonary vascular disease are

			or sinus venous ASD along with lung biopsy between 1981–1999. Pts with ostium primum ASD, congenital mitral valve disease, or other CHD were excluded	pulmonary vascular disease	performed at the time of defect closure and was classified according to Heath and Edwards. ● Structural changes of the pulmonary vasculature were found in 59% of pts; grade 3 and higher changes were present in 19%. ● There were no statistically significant relations between histologic findings and preoperative clinical and hemodynamic data, intraoperative findings, and operative outcome. ● The prevalence of moderate (32–50 mm Hg) and severe (>50 mm Hg) systolic pulmonary HTN was 27% and 17%, respectively. ● Increased systolic pulmonary arterial pressure was associated with increased PVR (p<0.000) and pts' age (p=0.001). Pts with a lower FC had a higher prevalence of pulmonary HTN (p=0.011).	present in 59% of pts with secundum or sinus venous ASD, advanced changes are present in 19%. Interestingly, preoperative hemodynamic data did not predict the degree of histologic changes in lung biopsy specimens.
Dusenbery SM, et al. 2013 (336) 23622914	Single-center cohort	n=80 pts	Inclusion criteria: Pts with scimitar syndrome evaluated between 1964—2011	Postoperative pulmonary vein stenosis or death	● Median follow-up: 4.5 y. ● Pts >1 y had higher incidence of symptoms, aortopulmonary collaterals, CHD, extracardiac anomalies, and pulmonary HTN. ● Of 36 pts with scimitar vein surgery, 18 had postoperative pulmonary vein obstruction that occurred with similar frequency after baffle or reimplantation procedures, early or late in the study period, and tended to be more common in infants (p=0.10). ● Overall, 19 (24%) of 80 died. Multivariate risk factors for death included systolic pulmonary pressure >0.5 systemic level (p=0.007) and left pulmonary vein stenosis (p=0.009). ● PASP <0.5 systemic level (p=0.01) and absence of CHD excluding ASD (p=0.01) were predictive factors in 28 pts who survived and did not have scimitar vein surgery; these pts had no or mild RV dilation and a ratio of pulmonary-to-systemic flow <1.6 either at baseline, after coiling aortopulmonary collaterals or nonscimitar vein intervention.	● Postoperative pulmonary vein obstruction is common after scimitar vein surgery regardless of redirection technique. Pulmonary HTN and left pulmonary vein stenosis are risk factors for death; whereas, pts without significant pulmonary HTN or associated CHD did well without scimitar vein surgery.
Haramati LB, et al. 2003 (316) 14501365	Retrospective cohort	n=29 pts	Inclusion criteria: Pts with CT evidence of PAPVC	Describe the features of anomalous	● 79% (23 of 29 pts) had an anomalous left upper lobe vein connecting to a persistent left vertical vein, ● 17% (5 of 29 pts) had an anomalous right upper lobe vein draining into the superior vena cava, 60% (3 of 5	● CTA identifies the course and types of anomalous pulmonary veins.

				pulmonary veins as seen by CT	pts) of whom also had a right upper lobe pulmonary vein in the normal location. One pt (3%) had an anomalous right lower lobe vein draining into the suprahepatic inferior vena cava. ● Chest radiographic findings were abnormal left mediastinal contour in 64% (15 of 25 pts), abnormal right mediastinal contour in 8% (2 of 25 pts), and cardiomegaly in 24% (6 of 25 pts). ● Computed tomography findings were cardiomegaly in 48% (14 of 29 pts), right atrial enlargement in 31% (9 of 29 pts), right ventricular enlargement in 31% (9 of 29 pts), and pulmonary artery enlargement in 14% (4 of 29 pts). ● Pulmonary or cardiovascular symptoms were present in 69% (20 of 29 pts), 55% (11 of 20 pts) of whom had specific alternative diagnoses (excluding congestive heart failure and pulmonary hypertension) to explain the symptoms. Only 1 pt (3%) was diagnosed with a secundum atrial septal defect.	● Right-sided chamber enlargement is common.

Data Supplement 28. Ventricular Septal Defect – Section 4.1.3

Study Name, Author, Year	Study Size	Study Design	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
Corone P, et al. 1977 (337) 858186	n=790 pts	Single-center cohort	Inclusion criteria: Pts with VSD cared for at a single institution	Long-term clinical outcomes of pts with untreated VSD	● The mean observation interval is 6 y, and the average age at the latest data is 19.5 y; this study covers 4,717 pt y. ● For the entire population, the incidence rate or aortic regurgitation is 6.3% (4.3 for 1,000 pt y). ● The bacterial IE rate is 3.7% (2.4 for 1000 pt y). ● 25 pts died, 15 of them between the ages of 1–39 y. ● Of the 499 cases with several clinical examinations, 71% remained stable. ● In 21%, changes suggesting some level of closure developed; in 7%, infundibular stenosis began to evolve and in 1% pulmonary vascular disease began to appear or became accentuated	● Natural history of unrepaired VSD.

Yoshimura N, et al. 2010 (338) 21031514	n=23 pts	Single-center cohort	Inclusion criteria: Pts with suspected coronary cusp prolapse in pts with VSD	Concordance between echo and MRI in diagnosis	● 19 pts with right coronary cusp prolapse. ● Mean age 9 y. ● 17 pts with outlet defects, 6 with membranous defects.	● MRI correlated with echo for outlet VSD but less so for other types.
D'Alto M, et al. 2013 (339) 23850317	n=22 pts	Single-center open-label cohort	Inclusion criteria: Presence of PAH after closure of ASD, VSD, PDA, AVSD, with pre- and postclosure hemodynamics	Demographics, hemodynamics (catheterization) pre- and post-defect closure	● Mean age at closure 25.3 ± 20.1 y (3 mo–56.7 y) Mean age at PAH diagnosis 37.0 ± 20.8 y (5–61.2 y). ● At preclosure catheterization 18/22 subjects had PVR ≥5 U, 21/22 had PVR index ≥6 U × m^2, 21/22 Rp/Rs ≥0.33.	● Preclosure PVR (≥5 U), PVR index (≥6 U × m^2) and Rp/Rs ≥0.33 appeared to correlate with PAH late after shunt closure.
Janjua AM, et al. 2011 (340) 21453613	n=40 pts	Cohort	Inclusion criteria: Pts with VSD and elevated PVR treated with surgical double patch repair	Mortality	● Mean age 7 y. ● PVR 9.6 WU, double patch technique allowing "fenestrated" closure of VSD. Modified ultrafiltration and sildenafil used for all pts.	● Only 1 death (2.5%) with patch that essentially allows continued, but less, right-to-left shunt in pts with elevated PVR.
Talwar S, et al. 2014 (341) 24332111	n=13 pts	Single-center cohort	Inclusion criteria: Pts with VSD and elevated PVR undergoing unidirectional patch repair	Mortality/morbidity	● Mean follow-up 34.7 ± 18.6 mo. ● VSD with PAH >8 WU, mean preoperative systemic saturation 94.1% ± 3.4%, mean age of 20 pts, 13 agreed to postoperative catheterization and were included. ● Mean age 8.5 y. ● At follow-up catheterization, mean saturation 98%, PVR 5.8 WU, no severe PAH, all NYHA Class I, no deaths.	● "Fenestrated" closure of VSD in severe PAH improves symptoms/hemodynamics without significant mortality.
Kouchoukos NT, et al. 1978 (329) 619518	Review	N/A	Inclusion criteria: Pts with large VSD prior to surgical closure	Mortality	● Mortality related to age at operations (older did worse) and to preoperative PVR.	● Prepulmonary vasodilator era. Careful consideration of mortality and late effects prior to considering closure of large VSD.
Shohtsu A, et al. 1976 (330) 950729	Retrospective	n=64 pts	Inclusion criteria: Pts with large VSD, PH; also small number with PDA and ASD	Mortality	● Optimal timing of closure is 1-3 y for VSD with PH; PDA and ASD not clear.	● Closure of large septal defects with PH should be considered only at young ages to improve mortality.
Nishimura RA, et al. 2014 (342) 24603191	ACC/AHA guideline	N/A	Inclusion criteria: N/A	N/A	N/A	N/A

Data Supplement 29. Atrioventricular Septal Defect – Section 4.1.4

Study Name, Author, Year	Study Type/ Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
Hoohenkirk GJ, et al. 2009 (343) 19660422	Retrospective review	n=21 pts; follow-up out to 25 y	Inclusion criteria: Surgical repair of AVSD with dual orifice left AV valve. Surgeries done from 1975–2006	Outcomes compared to 291 typical AVSD	● 3 late deaths, 12 reoperation in 7 pts, most for regurgitation. ● No association with mortality but was a risk factor for reoperation.	● AVSD with double orifice left AV valve can be repaired safely but is a risk for reoperation.
Majdalany DS, et al. 2010 (158) 20136856	Retrospective review	n=50 pts and 57 operations (17 partial AVSD): 15 had childhood surgery, 9 were AVSD or partial AVSD or TOF/AVSD	Inclusion criteria: Down syndrome with CHD and cardiac surgery ≥18 y	Survival 2 y: ventilator d/LOS /arrhythmias/ pulmonary infection	● 1 in hospital death; 8 late deaths (average 15 y later); vent support 2.4 d; hospital stay 10.6 d; 6 pulmonary infection.	● Surgery can be considered in adults with Down syndrome with fairly good outcomes.
Liberman L, et al. 2008 (344) 17768649	Retrospective database review	n=15 pts with new need for pacemaker 1998–2006 after discharge from hospital with normal conduction	Inclusion criteria: New pacemaker and history of CHD surgery and discharged from hospital with normal conduction	CHD diagnosis, y from surgery to pacer; symptoms presentation	● 15 cases: 9 VSD, 4 AVSD, 2 other ● Last ECG was average 5 y after surgery; average time between surgery/pacemaker 6.8 y (2 mo to 19 y; 7 pts were more than 6 y post operation).	● Unending need to monitor for complete heart block.
Agarwal V, et al. 2009 (345) 19258062	Retrospective record review	n=51 pts	Inclusion criteria: ≥18 y with primum ASD repair	Mitral valve function (mean follow-up 36 mo); mean age at surgery 27 y	● Pre: 80% NYHA class I/II; 88% cleft; 35% moderate MR; 4% severe; 27% moderate PH, 8% severe. ● Post: 1.9% in hospital death; 94% NYHA class I; 21% moderate MR/8% severe preoperation.	● Surgical repair of primum ASD in adults can be performed successfully. Continued monitoring for residual or progressive MR especially in females or pts with pulmonary HTN.
Malhotra SP, et al.	Retrospective review	n= 31 pt for left AV valve reoperation	Inclusion criteria: All young children	Survival, freedom from reintervention	● 10-y survival: 88%. ● Freedom reintervention 10 y: 67%.	● Left AV valve repair can be performed with good short- and mid-term results but had high need for further reoperation.

2008 (346) 18573414		(AVSD, primum)			● 23 repair/8 replace; patch more durable repair than 1° cleft.	
Bianchi G, et al. 2011 (347) 21398648	Meta-analysis	8 articles. Repair vs. replacement of left AV valve	Inclusion criteria: All adults	Survival and additional interventions	● 109 papers initially identified; 8 used for meta-analysis. Most were small series of pts. ● In general, repair is first choice as replacements with more complications. ● May differ in pts with complex left AV valve and LV outflow anatomy.	● Repair is generally first choice for reoperation on left AV valve when other abnormalities are not present. ● Replacement had higher rate of complete heart block and need for pacemaker.
Hoohenkerk GJ, et al. 2012 (348) 22265201	Retrospective review	n=45 pts	Inclusion criteria: Children and adults reoperated after initial repair of AVSD	Survival; risk factors for reintervention	● 88% survival at 15 y after reoperation; 31 repair, 14 replace; 10 pts with repair needed additional reoperation.	● Left AV valve repair can be completed successfully but there is a reasonable chance of requiring another operation.
Stulak JM, et al. 2010 (349) 23804729	Retrospective review	n=146 pts (partial and complete AVSD)	Inclusion criteria: Children and adults reoperated after initial repair of AVSD	Survival, reoperation	● Mostly left AV valve regurgitation and sub-AS. ● Freedom from reoperation at 10 y from initial repair was 48% for complete and 84% for partial.	● Reoperation is common after childhood AVSD repair and can involve left AV valve or LV outflow.
Digilio MC, et al. 2013 (350) 22781091	Retrospective	n=101 pts	Inclusion criteria: Congenital heart defect and molecularly confirmed RASopathy	Gene testing	● 8% of RASopathy with AVSD or partial AVSD; most PTPN11 (Noonan).	● Consideration of genetic testing.
Bando K, et al. 1995 (351) 7475207	Retrospective	n=203 pts	Inclusion criteria: Infants and children	Mortality and left AV valve repair failure	● Decreasing operative mortality over time, risk factors for major reoperation included preoperative severe left AV valve regurgitation or severe left AV valve regurgitation postoperatively.	● Infant repair of AVSD now with low mortality and good outcome. Cleft closure is typically safe, and most pts do not have significant left AV valve regurgitation.
Kouchoukos NT, et al. 1978 (329) 619518	Review	N/A	Inclusion criteria: Pts with large VSD prior to surgical closure	Mortality	● Mortality related to age at operations (older did worse) and to preoperative PVR.	● Prepulmonary vasodilator era. Careful consideration of mortality and late effects prior to considering closure of large VSD.
Shohtsu A, et al. 1976 (330) 950729	Retrospective	n=64 pts	Inclusion criteria: Pts with large VSD, PH; also small number with PDA and ASD	Mortality	● Optimal timing of closure is 1-3 y for VSD with PH; PDA and ASD not clear.	● Closure of large septal defects with PH should be considered for closure only at young ages to improve mortality.

Data Supplement 30. Patent Ductus Arteriosus – Section 4.1.5

Study	Study Type/ Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions

Name, Author, Year						
El-Said HG, et al. 2013 (352) 24284214	Retrospective, multicenter	n=496 pts	Inclusion criteria: All ages, PDA, devices and coils	Successful closure	● ~60% <3 y; only 4% adults.	● High success, low event rate, more events in younger children.
Chen LY, et al. 2013 (353) 24088423	Observational, single center	n=150 pts (108 transvenous)	Inclusion criteria: Only PDA, >6 mo, no pulmonary HTN	Successful closure (secondary complications)	● Similar closure rates (98% vs.100%), more complications, longer LOS, higher cost with surgical approach.	● Equally successful, choose transvenous when able.
Chen H, et al. 2012 (354) 22037885	Single center	n=294 (196 video-assisted thoracoscopic surgery, 98 transcatheter)	Inclusion criteria: Isolated PDA	Closure, complications, cost	● Video-assisted thoracic surgery: 100% closure, 1.5% complication, LOS=6 d, ~40% cost vs. transvenous: 98% success (+ 4 residual leak late), 10% complications, LOS=4 d.	● Video-assisted thoracic surgery better closure rate, fewer complications (1.5% vs. 10%), lower cost; video-assisted thoracic surgery was longer LOS and procedure time (very diff numbers than El-Said study 2013).
Brunetti MA, et al. 2011 (355) 20690153	Retrospective review of prospective multicenter data registry	n=359 pts	Inclusion criteria: Isolated PDA, predominantly children	Successful closure, complications, cost, radiation	● 357 successful closure.	● Gianturco coils, the arterial defect occluders were successful, low complication profiles, predominate devices.
Fortescue EB, et al. 2010 (356) 20653702	Review article	N/A	Inclusion criteria: Isolated PDA	Literature review of comparison and complications of closure of the very small/small PDA	● Closure of small or silent PDA can be done safely but not zero risk. For small not hemodynamically significant PDA, closure to prevent the rare episode of endarteritis may not outweigh the risk.	● Unlike large PDA, the small or silent PDA creates controversy surrounding closure. Risk and benefit of closure or continued observation must be considered carefully for each individual pt.
Gamboa R, et al. 2010 (357) 20515630	Cross-sectional, retrospective	n=23 pts	Inclusion criteria: Isolated PDA, adults only	Successful closure and complications	● Closure in 85%–100% depending on device used; 1 minor complication (inguinal hematoma)	● Isolated PDA can be successfully closed in adults.
Zabal C, et al. 2010 (358) 20357390	Single center	168 (mostly children)	Inclusion criteria: Isolated PDA with elevated PAP	Closure, complications, PASP	● Device placed in 98%, trivial or no leak in 75%, 6 complications.	● Success in most; reduced PASP (selected group).
Jeong YH, et al. 2007 (359) 17719286	Single center, retrospective	n=45 pts	Inclusion criteria: Isolated PDA in adults, some surgical/some device closure	LV size and function after closure; immediately and >6 mo	● All had decreased LVEF and LV end diastolic dimension immediately; those with preprocedure decreased EF more likely to have below normal LVEF even at 6 mo.	● Most pts will have immediate decrease in LVEF immediately after closure. In most this will recover to normal range but not necessarily to baseline. Those with preprocedure decreased LVEF more likely to not recover LVEF.

Yan C, et al. 2007 (360) 16954130	Single center, observational	n=29 pts	Inclusion criteria: Adults, isolated PDA with severe PAH	Closure, PASP, O_2 saturation	● 20 pts had closure, all of those had decreased PASP and improvement in saturations; also had increased LV/LA/PA size on follow-up; in other 9, closure not tried as were worse with trial of closure.	● Closure can be done safely in the short term for pts with PDA and reactive PAH.
Kouchoukos NT, et al. 1978 (329) 619518	Review	N/A	Inclusion criteria: Pts with large VSD prior to surgical closure	Mortality	● Mortality related to age at operations (older did worse) and to preoperative PVR.	● Prepulmonary vasodilator era. Careful consideration of mortality and late effects prior to considering closure of large VSD.
Shohtsu A, et al. 1976 (330) 950729	Retrospective	n=64 pts	Inclusion criteria: Pts with large VSD, PH; also small number with PDA and ASD	Mortality	● Optimal timing of closure is 1-3 y of age for VSD with PH; PDA and ASD not clear.	● Closure of large septal defects with PH should be considered for closure only at young ages to improve mortality.

Data Supplement 31. Cor Triatriatum – Section 4.2.1

Study Name, Author, Year	Study Type/ Design	Study Size	Follow-up time	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
Ozyuksel A, et al. 2014 (361) 25312520	Observational	n=15 pts	5.2 y	Inclusion criteria: Children with cor triatriatum	Clinical events	● 2 late deaths, 14 reoperations.	● Common association with ASD/PAPVR.
Saxena P, et al. 2014 (362) 24630764	Observational	n=25 pts	12.8 y	Inclusion criteria: Cor triatriatum, ages 0–73 y	Clinical events	● No residual obstruction in follow-up.	● 84% with ASD/VSD/PAPVR. Mean gradient was 8 mm Hg (range 8–40 mm Hg) at time of surgery.
Yaroglu Karanzi S, et al. 2012 (363) 22078218	Observational	n=65 pts	5.4 y	Inclusion criteria: Cor triatriatum	Clinical events	● 8 with pulmonary vein stenosis.	● 75% with ASD/VSD/PAPVR.

Data Supplement 32. Congenital Mitral Stenosis – Section 4.2.2

Study Name, Author, Year	Study Type/ Design	Study Size	Follow-up time	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions

Marino BS, et al. 2009 (364) 19185158	Observational	n=86 pts	6.4 y	Inclusion criteria: Children ages 0–6 y undergoing surgery	Clinical events, MS/MR	● Progression to MS and MR was seen.	● Outcome associated with associated anomalies; "true" parachute with MS, mortality associated with coexisting congenital defects.
Schaverien MV, et al. 2004 (365) 15117833	Observational	n=86 pts	Up to 10 y	Inclusion criteria: Children ages 0–5 y	Need for valvotomy	● Needed in 75 pts.	● No progressive MS.
Brauner RA, et al. 1997 (366) 9307464	Observational	n=19 pts	8 y	Inclusion criteria: Shone's with MS	Death/reoperation	● 2 late deaths, 14 reoperations.	● Not progressive MS or MR. Operations for other issues.
Ozuksel A, et al. 2014 (361) 25312520	Observational	n=15 pts	5.2 y	Inclusion criteria: Children with cor triatriatum	Clinical events	● 2 late deaths, 14 reoperations.	● Common association with ASD/PAPVR.
Saxena P, et al. 2014 (362) 24630764	Observational	n=25 pts	12.8 y	Inclusion criteria: Cor triatriatum, ages 0–73 y	Clinical events	● No residual obstruction in follow-up.	● 84% with ASD/VSD/PAPVR. Mean gradient was 8 mm Hg (range 8–40 mm Hg) at time of surgery.
Yaroglu Karanzi S, et al. 2012 (363) 22078218	Observational	n=65 pts	5.4 y	Inclusion criteria: Cor triatriatum	Clinical events	● 8 with pulmonary vein stenosis.	● 75% with ASD/VSD/PAPVR.
Alphonso N, et al. 2005 (367) 16242436	Observational	n=28 pts	8 y	Inclusion criteria: Cor triatriatum, ages 0–20 y	Clinical events	● 1 late death.	● No reoperations for stenosis.

Data Supplement 33. Subaortic Stenosis – Section 4.2.3

Study Name, Author, Year	Study Size	Study Design	Inclusion/Exclusion Criteria	1° Endpoint	Results	Conclusions
Oliver JM, et al. 2001 (368) 11527642	n=134 adult pts	Single-center retrospective case series	Inclusion criteria: 2,057 consecutive ACHD pts evaluated for presence of discrete subAS	Evaluate prevalence and clinical characteristics of discrete subAS	● 134 adults (mean age 31 ± 17 y): the prevalence was 6.5% for all adults with CHD 44% had other associated CHD. - 29/134 underwent surgery as adults, mean age 56 y compared to 27 y for those that had not undergone surgery. ● A significant relationship between LVOT obstruction and pt age (r=0.61; p<0.0001) was found: 21 ± 16 mm Hg in pts<25 y old, 51 ± 47 mm Hg for those between 25–50 y, and 78 ± 36 mm Hg for those >50 y.	● Discrete subAS is progressive with age. ● Pts operated on in adulthood are likely to be older than those that have not undergone operative intervention. ● Pts with resting peak echo gradient ≥50 mm Hg are likely to have progressive subAS. ● AR is common but typically not severe.

					● LVOT obstruction increased from 39.2 ± 28 to 46.8 ± 34 mm Hg (p=0.01) during a mean follow-up of 4.8 ± 1.8 y in 25 pts. ● In the overall group, 4 of 8 pts with gradients >50 mm Hg significantly increased the severity of obstruction, whereas only 3 of 18 pts with initial gradients under 50 mm Hg showed significant, albeit mild, progression of the subaortic gradients. ● The slope of the change in LVOT obstruction was 2.25 ± 4.7 mm Hg/y of follow-up. ● AR was detected by Doppler in 109 pts (81%), but it was hemodynamically significant in<20%. Increase in aortic root over time was NS	
McMahon CJ, et al. 2004 (369) 15325929	n=220 child pts	Retrospective single-center case series	Inclusion criteria: Evidence of discrete subAS by echo	Evaluate aortic valve dysfunction in discrete subAS	● 220 pts with subAS (109 with previous surgery 111 had no surgery). ● Age at diagnosis, sex, and duration of follow-up (median 7.2 y, range 1–20.4 y) did not differ significantly between medical and surgical pts. ● Independent risk factors for moderate to severe aortic root (n=30) were older age at diagnosis (OR for age ≥17 y: 5.13; p=0.024), previous balloon or surgical aortic valvuloplasty (OR: 19.6; p<0.001), and a longer follow-up period (OR for 1-y increase: 1.15; p=0.032). ● Excluding pts with previous surgical or balloon aortic valvuloplasty, a higher maximal Doppler gradient was an independent risk factor for moderate to severe aortic root (OR for peak gradient ≥50 mm Hg: 10.8; p=0.001). ● Independent predictors of low-risk pts (none or trivial aortic root and peak gradient ≤30 mm Hg) included thin and mobile aortic valve leaflets and an associated VSD.	● Aortic valve regurgitation is progressive in subAS. ● A resting peak Doppler gradient of ≥50 mm Hg is a risk factor for moderate/severe AR. ● Moderate/severe aortic root is additionally associated with older age and prior aortic valve intervention. ● A resting peak Doppler gradient of ≤30 mm Hg is associated with trivial AR.
Brauner R, et al. 1997 (370) 9385915	n=75 pts	Retrospective single-center case series	Inclusion criteria: Consecutive pts that underwent surgical subAS resection	Evaluate long-term clinical outcomes and associated factors in pts that have undergone surgical subAS resection	● Follow-up was 6.7 y. ● SubAS was discrete in 68 pts (91%) and of a tunnel type in 7, with associated VSD in 28 (37%). ● All underwent transaortic resection, no deaths occurred. ● 18 recurrences of subAS in 15 pts (20%). 13 pts (17%) underwent 17 reoperations. ● Residual end-operative LVOT gradient >10 mm Hg and tunnel lesions were predictors of recurrence. ● 2 recurrences were noted in pts with a preoperative peak LVOT gradient ≤40 mm Hg (n=40), whereas higher gradients	● Peak-to-peak catheter LVOT gradient ≥40 mm Hg is associated with worse long-term outcomes following surgical resection, including a higher recurrence rate and worse AR. ● Tunnel type subAS is more likely to recur postoperatively.

					(n=35) were associated with a greater than 7-fold recurrence rate. ● The aortic valve required concomitant repair in 17 cases in the high gradient group (48.6%) but in only 8 in the low gradient group (20%; p=0.018). ● Despite relief of the obstruction, progressive aortic regurgitation was noted at follow-up after 14 procedures in the high gradient group (40%) but after only 5 procedures in the low gradient group.	
Parry AJ, et al. 1999 (371) 10386409	n=37 pts	Retrospective single-center case series	Inclusion criteria: Pts that have undergone discrete surgical subAS resection	Evaluate whether an aggressive surgical approach could reduce both the severity of aortic root and rate of recurrence of discrete subAS	● 37 pts aged 0.5–35 y (median 7.5) underwent resection of a discrete subaortic membrane. ● 10 underwent reoperation for recurrent obstruction and 8 followed previous VSD closure. ● The preoperative peak Doppler gradient in pts with mild or moderate preoperative aortic root (73.9 ± 27.7 mm Hg) was greater than in pts with none/trace preoperative aortic root (57.3 ± 32.0 mm Hg). ● Postoperative assessment was performed early (1 wk) and at mid-term (27.0 mo; range 2–59 mo). ● There was significant improvement in aortic root from mild/moderate to none/trivial (p=0.019) immediately postoperatively and LVOT gradient from 66.9 ± 30.4 to 15.1 ± 12.2 mm Hg ($p \ll 0.0001$). ● By stepwise logistic regression preoperative gradient correlated significantly with postoperative mild/moderate aortic root (p=0.015) and LVOT gradient (p=0.0036). ● Preoperative mild/moderate aortic root also correlated with postoperative mild/moderate aortic root (p=0.034). ● At mid-term follow-up, there was no increase in aortic root or LVOT gradient (14.8 ± 12.8 mm Hg). ● Early postoperative aortic root was the strongest predictor of late mild/moderate aortic root (p=0.02). Early postoperative gradient was a weaker predictor (p=0.04). ● Preoperative and early postoperative gradient were significant predictors of late gradient.	● A higher preoperative subAS gradient is associated with more AR. ● Degree of aortic root improves following surgical resection. ● A higher preoperative subAS gradient is associated with a higher likelihood of recurrence post surgery.

Suarez de Lezo J, et al. 2011 (372) 15868319	n=76 pts	Retrospective single-center case series	Inclusion criteria: Pts with discrete subAS that underwent balloon angioplasty	Immediate, intermediate- and long-term clinical outcomes	● 76 pts with isolated thin discrete subAS underwent percutaneous transluminal balloon tearing of the membrane and were followed up for a mean period of 16.6 y. ● Mean age at treatment was 19 ± 16 y. Immediately after treatment, the subvalvular gradient decreased from 70–18 mm Hg. ● No significant postprocedural aortic root noted. ● 11 pts developed recurrent subAS. ● 12 (16%) pts were redilated at a mean of 5 y post procedure. ● 4 pts (5%) underwent surgery at a mean of 3 y after their first treatment. ● 58 pts (77%) remained alive and free of redilation or surgery at follow-up. ● Larger annulus diameter and thinner membranes were independent factors associated with better long-term results.	● Transcatheter balloon dilation is a reasonable option for the treatment of discrete membranous subAS with good immediate and long-term outcome.
Geva A, et al. 2007 (373) 17919571	n=111 pts	Retrospective single-center series	Inclusion criteria: Pts with discrete subAS that underwent surgical intervention and had ≥36 mo follow-up or reoperation	The 1° outcome was repeat surgical resection after successful 1° resection (residual peak Doppler gradient <40 mm Hg)	● 16 pts (14%) required reoperation. Median time to reoperation was 6.9 y (range 1.7–11.2 y). ● Younger age at first surgery, smaller aortic velocity annulus diameter, shorter distance between the obstruction and the aortic velocity, and higher preoperation peak gradient (peak Doppler gradient ≥60 mm Hg) were associated with reoperation. ● Peeling of the obstructive fibrous tissue from the aortic velocity or mitral valve and myomectomy during the initial surgery were associated with future reoperation.	● Pts with preoperative LVOT peak Doppler gradient ≥60 mm Hg are more likely to require reoperation following successful initial resection. ● Other factors predicting need for reoperation include earlier age at initial operation, smaller aortic annulus diameter, and proximity of the obstructive membrane to the aortic valve.
Diller GP, et al. 2005 (103) 16061735	n=335 pts	Retrospective single-center review of cardiopulmonary exercise data	Inclusion criteria: 335 ACHD pts, 63 controls that underwent cardiopulmonary exercise testing	Assessment of cardiopulmonary exercise capacity and degree of impairment in ACHD pts	● Peak VO_2 was reduced in ACHD pts compared with healthy subjects of similar age (21.7 ± 8.5 vs. 45.1 ± 8.6; p<0.001). ● No significant difference in peak v was found between ACHD and HF pts of corresponding NYHA class (p=NS for each NYHA class). Within ACHD subgroups, peak VO_2 gradually declined from aortic coarctation (28.7 ± 10.4) to Eisenmenger (11.5 ± 3.6) pts (p<0.001). Multivariable correlates of peak VO_2 were peak heart rate (r=0.33), forced expiratory volume (r=0.33), pulmonary HTN (r=-0.26), sex (r=-0.23), and BMI (r=-0.19). ● After a median follow-up of 10 mo, 62 pts (18.5%) were hospitalized or had died.	● Exercise capacity is depressed in ACHD pts (even in asymptomatic pts) on a par with chronic HF subjects. ● Lack of heart rate response to exercise, pulmonary arterial HTN, and impaired pulmonary function are important correlates of exercise capacity, as is underlying cardiac anatomy. ● Poor exercise capacity identifies ACHD pts at risk for hospitalization or death.

					● On multivariable Cox analysis, peak VO_2 predicted hospitalization or death (HR: 0.937; p=0.01) and was related to the frequency and duration of hospitalization (p=0.01 for each).	
Trinchero R, et al. 1988 (374) 3234666	n=55 pts	Retrospective single-center review	Inclusion criteria: Diagnosis of fixed subAS	Operated and unoperated outcomes in fixed subAS	● 55 pts, 37 men and 18 women, 8– 71 y (median age 23 y) with a diagnosis of fixed sub-AS were seen between January 1966 and December 1983. ● Their subvalvular gradient varied between 0–135 mm Hg. Aortic regurgitation was present in 44 pts. 38 pts were operated on. ● 16 pts had some additional cardiac disease, either congenital, or acquired. ● There were 2 early and 2 late deaths. ● 15 pts were studied again after surgery: the average peak-to-peak gradient has decreased from 88 ± 28 to 19 ± 16 mm Hg and is 0 in 5. No pt needed a reoperation. ● Of the 17 nonoperated pts, 13 had a gradient of <50 mm Hg; they were all in Class I–II after 1–5 y. The gradient had increased to 70 mm Hg in 1 of the 4 recatheterized cases. 4 pts had died, 2 suddenly, 2 of HF. They all had a gradient ≥55 mm Hg.	● In asymptomatic with sub-AS, an operation can be deferred if the pressure gradient is less than 50 mm Hg, and there are no associated lesions. ● Identification of pts running the risk of SCD remains elusive.

Dall'Agata A, et al. 1999 (375) 10190410	n=28 pts	Single-center prospective cohort	Inclusion criteria: Pts with LVOT and RVOTO undergoing 2D and 3D echo evaluation	Evaluate the feasibility and accuracy of 3D echo in analysis of RVOT and LVOT obstruction	● 3D echo was performed in 28 pts, 4 mo–36 y, with outflow tract pathology. Type of lesion and relation to valves were assessed. Length and degree of obstruction were measured. 3D data sets were adequate for reconstruction in 25 of 28 pts; 47 reconstructions were made. ● In 13 pts with LVOT obstruction, 3D echo was used to study subvalvular details in 8, valvular in 13, and supravalvular in 1. 4 of these 13 pts had complex subaortic obstruction. ● In 12 pts with RVOT lesions, 3D echo was used to study subvalvular details in 11, valvular in 12, and supravalvular in 2. 3D reconstructions were suitable for analysis in 100% of subvalvular LVOT, 77% valvular LVOT, 100% supravalvular LVOT, 100% subvalvular RVOT, 50% valvular RVOT, and 50% supravalvular RVOT. ● 20 pts underwent operation, and surgical findings served as morphologic control for 34 3D reconstructions (LVOT 17, RVOT 17). ● Operative findings revealed accuracy at subvalvular LVOT of 100%, valvular LVOT 90%, supravalvular LVOT 100%, subvalvular RVOT 100%, valvular RVOT 100%, and supravalvular RVOT 100%. ● Quantitative measurements could adequately be performed.	● 3D echo is feasible and accurate for analyzing both outflow tracts of the heart and allows a good definition of extension and severity of lesions.
Diller GP, et al. 2006 (376) 16979014	n=727 pts	Single-center retrospective cohort	Inclusion criteria: Consecutive ACHD pts undergoing cardiopulmonary exercise testing	Assess prognostic value of heart rate response to exercise in ACHD pts	● 727 consecutive ACHD pts (mean age [± SD] 33 ± 13 y) with varying diagnoses and without pacemaker under cardiopulmonary exercise testing. ● Peak VO_2, resting heart rate, and the increase in heart rate from resting level to peak exercise ("heart rate reserve") were measured. Quantified the decrease in heart rate ("heart rate recovery") after cessation of exercise. ● During a median follow-up of 28 mo, 38 pts died. ● Lower values of heart rate reserve, peak heart rate, heart rate recovery, and peak VO_2 ($p<0.01$ for each) were associated with increased mortality in univariate analysis. ● Heart rate reserve predicted mortality independently of antiarrhythmic therapy, FC, and peak VO_2. ● Stratifying pts by diagnostic groups revealed that a lower heart rate reserve was also associated with a greater risk of death in pts with complex anatomy, Fontan circulation, and TOF ($p<0.05$ for each).	● An abnormal heart rate response to exercise identifies ACHD pts with a higher risk of mortality in the midterm.

Data Supplement 34. Congenital Valvular Aortic Stenosis – Sections 4.2.4

Study Name, Author, Year	Study Type/ Design	Study Size	Follow-up time	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
Mookadam F, et al. 2010 (377) 20329493	Series of published cases	n=231 pts	N/A	Inclusion criteria: Unicuspid valves	N/A	● Most associated with AS.	● Often not diagnosed until surgery or autopsy.
Gleason TG, et al. 2014 (378) 24930615	Observational	n=32 pts	2.9 y	Inclusion criteria: BAV with aortic root/valve repair	Clinical events	● No reoperations.	● Minimal AR in follow-up.
Kari FA, et al. 2013 (379) 23260433	Observational	n=75 pts	2.9 y	Inclusion criteria: BAV with aortic root/valve repair	Clinical events	● Freedom from reoperation 90% at 6 y.	● Reasonable mid-term results from repair.
Alsoufi B, et al. 2005 (380) 16359055	Observational	n=71 pts	N/A	Inclusion criteria: BAV with aortic valve repair	Clinical events	● Moderate aortic root in >50%, reoperation in 18%.	● Dilation of the aortic root leads to aortic insufficiency.
Davierwala PM, et al. 2003 (381) 14658805	Case cohort	n=88 pts	2.6 y	Inclusion criteria: aortic root, repair vs. replacement	Aortic root or redo surgery	● 4 redo after repair, 2 after replacement.	● Moderate/severe aortic insufficiency 79% in repair vs. 94% in replacement.
Svensson LG, et al. 2014 (382) 24680032	Case series	n=728 pts	9.0 y	Inclusion criteria: BAV repair	Clinical events	● 3 early deaths, 2.6 y reoperation rate.	● Usually aortic root was cause of reoperation.
Biner S, et al. 2009 (383) 19520254	Observational	n=48 pts	N/A	Inclusion criteria: FDR of BAV pt	Aortic dimension by echo	● Enlargement in 32%.	● Leaflet morphology is part of a bigger phenotype.
Tutar E, et al. 2005 (384) 16169333	Observational	n=1,075 pts	N/A	Inclusion criteria: All newborns	Finding of BAV by echo	● 4.6 in 1,000 live births.	● 4 times as common in males.
Huntington K, et al. 1997 (385) 9385911	Observational	n=186 pts	N/A	Inclusion criteria: FDR of BAV pts	Aortic dimensions by echo	● 17 (9.1%) also had BAV.	● More equitable male/female ratio.

Sandhu SK, et al. 1995 (386) 8829832	Case series	n=15 pts	1.5 y	Inclusion criteria: Adolescents/young adults with congenital AS	Catheterization to measure gradient in follow-up	● Gradients unchanged in the majority of those with successful procedures.	● 3 pts with inadequate relief of obstruction. Includes both BAV and TV stenosis. 3 required surgery in follow-up.
Arora R, et al. 1989 (387) 2599541	Case series	n=25 pts	16 mo	Inclusion criteria: AS (age range 6–66 y)	Follow-up gradients	● Almost half had progression of gradients compared to immediate post procedure results.	● BAV pts more prevalent in the pts who had progressive stenosis.
Fernandes SM, et al. 2004 (388) 15489098	Case series	n=569 pts	N/A	Inclusion criteria: All pts with interpretable echos with BAV	Coarctation coexisting	● ~11% of pts had a coarctation.	● Among isolated coarctation pts, 55% had a BAV.
Nistri S, et al. 1999 (389) 10377302	Case series	n=66 pts	N/A	Inclusion criteria: BAV pts undergoing echo	Aortic diameter by echo	● AR was significantly larger than controls at all levels	● Independent of valve function, age, and body size.
Della Corte A, et al. 2007 (390) 17236783	Case series	n=280 pts	N/A	Inclusion criteria: BAV pts undergoing echo	Aortic diameter by echo	● 83% of pts had abnormal aortic dimensions.	● 43% of pts had surgical indications. Male sex, age, and severe aortic regurgitation were risk factors.

Data Supplement 35. Turner Syndrome – Section 4.2.4.1

Study Name, Author, Year	Study Type/ Design	Study Size	Follow-up time	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
Carlson M, et al. 2012 (161) 23032325	Registry pts	n=20 pts	Turner syndrome with dissection	Inclusion criteria: N/A	Size 2.7 cm/m^2 at time of dissection	N/A	N/A
Lin AE, et al. 1998 (391) 9651464	Survey of society members	n=245 pts	Turner syndrome	Inclusion criteria: N/A	CV medicine in 52%	● 15 dissections, 80% of those with CV malformation/HTN.	N/A
Sybert VP, et al. 1998 (392) 9417175	Observational	n=244 pts	Turner syndrome adults	Inclusion criteria: N/A	56% with CV medicine	● 3 aortic dissections.	N/A
Matura LA, et al. 2007 (393) 17875973	Observational MRI study	n=166 pts	Turner syndrome adults	Inclusion criteria: 3 y	N/A	● 3 dissections, all with diameter >2.5 cm/m^2.	N/A
Hjerrild BE, et al. 2010 (394) 20222980	Observational MRI study	n=102 pts	Turner syndrome adults	Inclusion criteria: N/A	23% with enlargement. Associated with BAV and BP	N/A	N/A

Cleeman L, et al. 2010 (395) 20063160	Observational MRI study	n=41 pts	Turner syndrome young adults	Inclusion criteria: N/A	Dilatation in only 4 pts	None	N/A

Data Supplement 36. Aortopathies – Section 4.2.4.2

Study Name, Author, Year	Study Type/ Design	Study Size	Cohort Studied	Follow-up Duration (Mean or Median)	Aortic Enlargement	Aortic Rupture/Dissection	Risk Factors	Comments
Conotruncal Abnormalities								
Rutz T, et al. 2012 (396) 22459299	Observational	n=39 pts	TOF, TGA	N/A	N/A	0	N/A	● Larger aortic diameter than controls.
Christensen JT, et al. 2014 (397) 24480147	Observational	n=124 pts	TOF	N/A	N/A	0	N/A	● Pulse wave velocity; correlated with age at repair.
Mongeon FP, et al. 2013 (398) 23224208	Observational	n=474 pts	TOF	N/A	29%	0	● Diameter >40 associated with male sex, PA, AR, not arch sidedness.	● 3.5% with moderate-to-severe AR.
Niwa K, et al. 2002 (399) 12221055	Observational	n=216 pts	TOF	N/A	15%	0	● Shunt-repair interval, PA, right sided arch, increased CT ratio.	N/A
Stulak JM, et al. 2010 (400) 21092798	Surgical series	n=81 pts	Conotruncal	N/A	N/A	0	● Surgeries performed. 4 reoperations. No late dissections.	● Authors argue in favor of watchful waiting.
Ross Procedure								
Aljassim O, et al. 2011 (401) 21277595	Observational	n=91 pts	AS	8.9	33%	0	N/A	● 44% had enlarged proximal aorta (native).
de Kerchove L, et al. 2009 (402) 19101277	Observational	n=218 pts	AS	7.8	17%	0	N/A	● ~17% had reoperation, most for autograft dilatation.
Luciani GB, et al. 2005 (403)	Observational	n=112 pts	AS	5.1	29%	0	N/A	● Reoperation in 5 pts.

16359057								
Luciani GB, et al. 2003 (404) 12970210	Observational	n=91 pts	AS	4	34%	0	N/A	N/A
Arterial Switch Operation								
Kempny A, et al. 2012 (405) 22884697	Observational	n=145 pts	ASO	N/A	N/A	0%	N/A	● 1% reoperation rate.
Fricke TA, et al. 2012 (406) 22607787	Observational	n=618 pts	ASO	N/A	N/A	0%	● LVOTO, arch, premier.	● 1% reoperation rate.
Lim HG, et al. 2012 (407) 22573720	Observational	n=220 pts	ASO	N/A	N/A	0%	● Size of aorta, aorta.	● 2% reoperation rate.
van der Bom T, et al. 2014 (408) 24837983	Observational	n=116 pts	ASO	7	N/A	0	N/A	● There was linear growth of the neoaorta 3 pts underwent surgery (7 y of follow-up).
Bicuspid Aortic Valve								
Avadhani SA, et al. 2015 (409) 25644322	Referral population	n=115 pts	BAV	5	N/A	0	● Age and family history were regurgitant fraction for progressive enlargement.	● Ascending aortic dilatation of 0.47 mm/y. 20% had aortic valve surgery in follow-up.
Ohnemus D, et al. 2015 (410) 24735381	referral population	n=141 pts	Adolescent and young adults with BAV	3.1	N/A	0	N/A	● Aortic change was not different in those on ACEI.
Roberts WC, et al. 2012 (411) 23117850	Autopsy study	n=218 pts	Aortic valve malformations	N/A	N/A	8%	N/A	● 13% were unicuspid valves.
Michelena HI, et al. 2011 (412) 21917581	Population study	n=416 pts	BAV	16	N/A	0.5%	● Older age (>50 y) and those with aneurysm.	● 49 underwent surgery.

Oliver JM, et al. 2009 (413) 19766771	Referral population	n=341 pts	BAV with or without CoA who had follow-up >12 mo	7	3% developed aorta >55 mm	0.9%	● BAV plus CoA was more associated with ascending aortic complications (1.3 vs. 0.2/100 pt y).	N/A
Davies RR, et al. 2007 (414) 17383337	Pts with aneurysm	n=70 pts	BAV with aneurysm	3.5	N/A	8.6%	● AS, AR, or CAD were not risk factors for rupture or dissection.	● Growth rate 0.19 cm/y. AS, AR, or CAD were not risk factors for rupture or dissection.

Data Supplement 37. Supravalvular Aortic Stenosis – Section 4.2.5

Study Name	Study Type/ Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values
Bruno E, et al. 2003 (415) 14982294	Single-center retrospective study	n=53 pts	Inclusion criteria: Pts with confirmed diagnosis of Williams syndrome	Description of the CV anomalies and clinical course of pts with Williams syndrome	● The mean age was 3.6 y and period of follow-up was 5.3 y. ● 45/53 pts (85%) had CV anomalies. ● Males presented earlier than females: 2.1 vs. 4.5 y. ● Supravalvular AS occurred in 32 pts (71%), PAS in 17 (38%), and mitral valvar prolapse in 12 (27%), 9 of these having regurgitant valves. ● Pulmonary valvar stenosis, VSD, CoA, PDA, hypertrophic cardiomyopathy, and sub-AS all occurred less frequently. ● In 21 pts (47%), 24 surgical or catheter interventions had been performed, most often for repair of supravalvular AS, undertaken on 16 occasions with just 1 recurrence, and in 4 also had surgery to the mitral valve. ● Other lesions requiring intervention were pulmonary valvar stenosis, PAS, CoA, and sub-AS. ● 3 pts died (7%), with severe supravalvular AS and moderate or severe MR, 2 early and 1 late after surgery.

Wren C, et al. 1990 (416) 2345244	Single-center retrospective study	n=35 pts	Inclusion criteria: Pts with supravalvular aortic or PAS or both that had undergone cardiac catheterization between 1973 and 1989 were included. Exclusion criteria: Pts with rubella syndrome, Alagille's syndrome, and chromosomal abnormalities were excluded.	Description of the pt characteristics and outcomes	● Data from 35 pts with supravalvular AS or PAS, or both, undergoing cardiac catheterization between 1973 and 1989 were analyzed retrospectively. ● 27 pts had supravalvular AS: Most were asymptomatic and referred for a murmur, 11 required surgery after the first investigation, and 8 (80%) of 10 others undergoing serial investigation showed an increase in the LV to aorta pressure gradient. Angiography demonstrated failure of normal growth of the ascending aortic lumen. ● 19 pts had PAS, with a RV pressure >33 mm Hg. At restudy, RV pressure had decreased in 9 (82%) of 11 pts. This decrease in RV pressure was associated with an increase in the systolic distensibility of the proximal pulmonary arteries, although there was no increase in the diastolic diameters. In 2 pts, multiple peripheral PA stenosis became evident with time and produced persistent RV HTN.
Eronen M, et al. 2002 (417) 12161592	Single center retrospective study	n=75 pts	Inclusion criteria: Pts with Williams syndrome confirmed by genetic analysis	Assessment of the prevalence and types of CV conditions present in pts with Williams syndrome and outcomes following cardiac surgery and interventions	● The diagnosis of Williams syndrome was in each case confirmed by the clinical phenotype and by a fluorescence in situ hybridization test showing elastin hemizygosity. ● CV symptoms were evident in 35 of 75 (47%) Williams syndrome children at birth. ● During follow-up, 44 of 75 (53%) Williams syndrome pts were found to have CV defects. Among them, the definitive diagnosis was made before 1 y in 23 (52%) infants, between 1 y and 15 y in 14 (32%) children, and older than 15 y in 7 (16%) adults. ● Multiple obstructive CVD were found in 6 infants. supravalvular AS was diagnosed in 32/44 (73%), PAS in 18/44 (41%), aortic or mitral valve defect in 5/44 (11%), and TOF in 1 (2%) case. ● 17/44 pts (39%) underwent surgery or intervention. Surgery was most frequently performed in the infant group (6% v 21% v 0%; p=0.004). ● After 1 y of age, 7 pts underwent supravalvular AS relief and 2 cases PAS relief. ● Postoperatively there was no mortality (median follow-up time 6.9 y). ● Arterial HTN was found in 55% of adults. ● In 3 adults, arterial vasculopathy was not diagnosed until necropsy.
Tani LY, et al. 2000 (418) 10867108	Retrospective single-center study	n=18 pts	Inclusion criteria: Pts with echo/Doppler evidence of supravalvular AS within 2.5 mo of cardiac catheterization	Description of the echocardiographic findings and assessment of the relationship of directly measured catheterization pressure	● A total of 26 paired echos and catheterizations from 18 pts (12 males, 6 females) with supravalvular AS were identified. ● Age at catheterization ranged from 1 mo–18 y (median 2.5 y). From the aortic angiograms, the supravalvular AS was discrete or localized in 20 cases, and diffuse in the other 6.

				gradients to Doppler estimated peak and mean gradients	● The Doppler peak instantaneous gradient correlated with (r=0.74), but overestimated the catheter-measured peak gradient. Correcting for the proximal velocity (available in 14 pts) did not improve the correlation (r=0.66). Doppler peak gradients were consistently greater than the catheter peak gradients with a mean difference of 30 mm Hg (SD 18 mm Hg). ● The Doppler mean gradient correlated with (r=0.72), but tended to underestimate, the catheter peak gradient. ● A significant association was found between a Doppler peak instantaneous gradient of >85 mm Hg (velocity 4.6 m/s) and a catheter peak gradient of >50 mm Hg (p<0.001). The specificity and NPV of a Doppler peak gradient of >85 mm Hg in predicting a catheter peak gradient of >50 mm Hg was 95%. The overall accuracy of a Doppler peak gradient of >85 mm Hg in separating those with catheter peak gradients above or below 50 mm Hg was 92%. ● There was no significant correlation between the Doppler peak gradient and indexed LV mass or the supravalvar aorta/annulus ratio by echo or angiography.
Thiene G, et al. 1986 (419) 3606885	Single-center retrospective autopsy review	n=6 pts	Inclusion criteria: Young pts who died suddenly and underwent post mortem autopsy were included	Description of postmortem findings	● Post-mortem findings in 6 young people who died suddenly are reported; ages ranged from 9–28 y (average 17). ● All had practiced sport, and 2 died during strenuous exercise. ● 3 cases had been under observation for mild AS, while no CV disorders had been suspected in the others. ● Autopsy studies ruled out coronary atherosclerotic diseases, myocardial disarray or myocarditis as well as any extracardiac cause of death in every case. ● A stenotic BAV was found in 2; supravalvular AS and incomplete isolation of the left coronary ostium in 1; anomalous origin of the right coronary artery from the left sinus of Valsalva in 1, and dissecting aneurysm of the ascending aorta in 2.
Stamm C, et al. 1997 (420) 9240289	Single-center retrospective review	n=37 pts	Inclusion criteria: Pts with supravalvular AS who had undergone angiographic and echocardiographic assessment were compared to a control group. Additionally, 8 pathologic specimens were described.	Description of imaging findings and pathologic findings	● Partial adhesion of the leaflets to the stenosing ridge was observed in 54% of the cases and the leaflets were thickened and less mobile in 30%. ● 45% of the angiograms showed evidence of coronary orifice stenosis. ● The sinuses of Valsalva were significantly enlarged in 75% of the cases. Changes in dimensions of the aortic root were demonstrated more clearly by angiography than by echo. ● In all anatomic specimens, a marked redundancy of the leaflets was observed and quantified.

Martin MM, et al. 1988 (421) 3337571	Single-center description of 2 surgical cases	n=2 pts	Inclusion criteria: 2 pts with supravalvular AS and left coronary ostial obstruction	Description of surgical findings	● 2 pts in whom obstruction to left coronary artery flow was caused by obliteration of the coronary ostium are described. ● This mechanism differs from the more commonly recognized cause: valve leaflet adhesion to the obstructing ridge of aortic tissue. ● The coronary artery obstruction found in these 2 pts required direct enlargement of the left coronary ostium in both.
Doty DB, et al. 1982 (422) 7083541	Single-center case control study	n=7 pts	Inclusion criteria: Pts with supravalvular AS undergoing surgical repair	Assessment of coronary flow reserve and factors determining coronary flow reserve in supravalvular AS	● To assess the relative effect of coronary ostial obstruction or LV hypertrophy on coronary reserve, 7 pts with supravalvular AS were studied intraoperatively before and after repair. ● 6 pts who underwent elective cardiac surgery for conditions that did not involve the left ventricle or the left anterior ascending coronary artery served as controls (control Group 1). ● 4 pts were studied before and after CPB to determine if CPB altered coronary reserve in normal vessels perfusing normal ventricle (control Group 2). ● Using a pulsed Doppler probe to determine coronary velocity, coronary reactive hyperemia was induced in the left anterior descending coronary artery (pts with supravalvular AS and Group 1 controls) or RV branches of the right coronary artery (Group 2 controls) during maximal coronary dilation produced by a 20-s coronary occlusion. ● All pts with supravalvular AS underwent patch aortoplasty to relieve left coronary artery ostial obstruction and outflow tract obstruction; 3 pts also underwent aortic valvotomy and 1 pt also underwent valve replacement. ● Coronary reactive hyperemia was calculated as the ratio of peak to resting velocity. This ratio was 5.0 ± 0.6 (mean ± SEM) preoperatively and 3.6 ± 0.3 postoperatively in control Group 2. Thus, coronary reserve was only modestly reduced after CPB. ● Before repair, the ratio of peak to resting velocity was markedly reduced in pts with supravalvular AS compared with control Group 1 (1.8 ± 0.3 vs. 4.9 ± 0.5; $p<0.05$) and did not change after repair (1.7 ± 0.2), even though the aortic gradient was reduced (80 ± 14 vs. 38 ± 6 mm Hg; $p<0.05$) and real or potential coronary ostial obstruction was eliminated by the operation.
Thistlethwaite PA, et al. 2000 (423) 11088024	Single-center retrospective review	n=9 pts	Inclusion criteria: Pts with LMCA stenosis complicating supravalvular AS that underwent surgical repair between 1991–	Description of surgical management	● 9 pts underwent surgical repair of supravalvular AS and left main coronary stenosis. ● 5 pts (Group 1) had obstruction from near-circumferential thickening of the left main ostium, 2 pts (Group 2) had restricted coronary flow due to fusion of an aortic valve leaflet to the supravalvular ridge, and 2 pts (Group 3) had diffuse narrowing of the LMCA.

			1998 at University of California San Diego		● Group 1 pts were treated with patch aortoplasty encompassing the left main ostium and supravalvular AS. Group 2 pts were treated with excision of the fused leaflet from the aortic wall and patch aortoplasty. Group ● 3 pts were treated with bypass grafting and aortoplasty. ● Surgical strategy was determined by coronary angiography and intraoperative assessment of coronary anatomy. ● There was 1 early death. ● All surviving pts underwent echo with or without postoperative catheterization. The mean postoperative supravalvular gradient for 7 pts was 8 mm Hg (range 2–15 mm Hg). 1 pt required reoperation for a residual aortic gradient as a result of aortic arch involvement. ● No evidence of LMCA stenosis was seen in Groups 1 and 2; bypass grafts were patent in group 3 pts at a mean follow-up of 54.8 mo.
Greutmann M, et al. 2012 (424) 22815328	Multicenter retrospective study	n=3,697 pts	Inclusion criteria: N/A	Adverse cardiac events and need for cardiac surgery in adulthood	● Little or no increased risk of stroke, VTE, or AMI associated with the use of oral or injectable progestogen-only or combined injectable contraceptives

Data Supplement 38. Coarctation of the Aorta – Section 4.2.6

Study Name, Author, Year	Study Size	Study Design	Inclusion/Exclusion Criteria	1° Endpoint	Results	Summary/Conclusions
Holzer R, et al. 2010 (425) 20882661	n=302 pts	Prospective multicenter registry	Pts that underwent coarctation stenting at 34 centers included in the consortium. Inclusion criteria: Presence of significant coarctation based on 1 or more of the following: UL/LL peak to peak gradient ≥20 mm Hg, UL/LL gradient ≥10 mm Hg plus either decreased LV function or AR, UL/LL	Evaluation of acute, intermediate- and long-term outcomes. Procedural success defined as upper extremity to lower extremity systolic peak to peak gradient <20 mm Hg, lack of recurrent obstruction and freedom from unplanned repeat intervention	● Data collected prospectively on 302 pts from 2000–2009, from 34 centers. ● Median age 15 y (2–63), median weight 58 kg (11–156). ● Arch hypoplasia in 10%, BAV in 41%, 55% native and 45% recurrent coarctation. ● 21% required >1 stent, 5% of stents were covered. 44% of pts completed intermediate follow-up with integrated imaging (catheter/CT/MRI), 21% completed long-term follow-up (>18 mo). ● Acute procedural success in 96%. ● Cumulative intermediate success was 86%, long-term success was 77%. ● Unplanned repeat interventions required in 4%. ● Aortic wall complications in 1%, other complications in 5%.	● Transcatheter stenting is an effective treatment modality for native and recurrent aortic coarctation with good immediate, intermediate- and long-term outcomes. ● There is a small risk of serious aortic wall complications ● The majority of pts have long-term benefit with reduced systolic BP and systolic gradient across the coarctation. ● In ~1/3 of pts, there continues to be a need for antihypertensive medical therapy following coarctation stenting. ● Follow-up imaging with CTA/MRI/cath is important to detect

			≥10 mm Hg plus collateral flow. Exclusion criteria: Weight <10 kg, known or suspected arteritis		● Preprocedure 77% of pts had systemic HTN >95th percentile, long-term post procedure this decreased to 23%. ● Preprocedure 59% of pts had systemic systolic BP >99th percentile, long-term post procedure 6% of pts had >99th percentile systolic BP. ● At long-term follow-up, 23% continued to have systolic BP >95th percentile, 9% had UL to lower limbs peak-to-peak gradient >20 mm Hg, and 32% were taking antihypertensive medications.	stent related complications, aneurysm formation or recurrent obstruction.
Qureshi AM, et al. 2007 (426) 17319978	n=153 pts	Single-center retrospective review	Inclusion criteria: Pts that underwent coarctation stenting between 1989–2005	Evaluation of intermediate- and long-term outcomes	● 153 pts, median age 16 y underwent coarctation stenting. 64% had prior aortic interventions (57% surgery, 7% balloon dilation along, 16% balloon dilation and surgery). ● Isolated coarctation in 50%, 74% at the isthmus, 12% in the transverse arch. ● 95% of pts had reduction of the peak to peak gradient to <20 mm Hg. ● 2% of pts with aortic wall injury, none required surgery. No deaths. ● New aneurysms observed in 6% of pts over a median follow-up of 2.5 y. ● Stent fractures noted in 12 pts. ● Reintervention performed in 50% of pts at 5 y, mostly due to deliberate multistage approach.	● Transcatheter stenting of native and recurrent aortic coarctation results in relief of the gradient. ● Serious complications are rare. ● Follow-up imaging is needed to evaluate for long-term complications such as aneurysm formation or stent fracture.
Forbes TJ, et al. 2007 (427) 17896405	n=578 pts	Multicenter retrospective case series	Inclusion criteria: Pts that underwent coarctation stenting at 17 participating institutions	Evaluation of immediate and intermediate procedural outcomes	● 578 pts at 17 institutions had 588 catheter procedures with 650 stents placed. ● 160 pts available for follow-up underwent CT/MRI/catheter follow-up. ● 10% underwent planned second procedure. ● Median follow-up of 12 mo (0.5–92). ● Of the pts with follow-up imaging, 29% had abnormalities: 11% with neo-intimal hyperplasia, 9% developed aneurysms, 3% developed dissection, 4% stent fracture. ● 22% of pts with abnormal follow-up imaging required reintervention. ● Smaller postintervention aortic diameter and persistent increased systolic pressure gradient were associated with increased risk of reintervention.	● Transcatheter stenting of coarctation is associated with good immediate and intermediate outcomes. ● 22% of pts required reintervention ● Follow-up CT/MRI/catheter imaging is important in identifying potential complications.

					● Prestent angioplasty and balloon:coarctation ratio >3.5 were associated with increased likelihood of abnormal follow-up imaging.	
Chessa M, et al. 2005 (428) 16186136	n=71 pts	Single-center retrospective case series	Inclusion criteria: Pts that underwent coarctation stenting between 1997–2004	Evaluation of mid and long-term results of stent implantation for native or recurrent coarctation	● 71 consecutive pts, mean age 22 y (7–66 y), 60% of pts >18 y, 19 pts had prior surgery. ● 74 stents implanted. ● All pts had clinical evaluation, echo, and exercise ECG at 1 and 6 mo post stent implantation. ● Peak Doppler systolic gradient decreased from 39 ± 15 mm Hg to 4 ± 6 mm Hg. ● Minimal aortic diameter increased from 8 mm to 16 mm. ● 1 death occurred due to aortic rupture immediately post stent placement. ● Reintervention performed in 3 pts.	● Transcatheter stenting of a native or recurrent coarctation is feasible and effective with a low rate of complications.
Suarez de Lezo J, et al. 2005 (372) 15868319	n=172 pts	Single-center retrospective review	Inclusion criteria: Pts that underwent percutaneous intervention over 21 y	Evaluation of clinical outcomes	● The pts were divided into 4 groups. Group 1: neonates and infants that underwent balloon angioplasty due to HF (n=54). Group 2: Balloon angioplasty in children and adults before the stenting era (n=28). Group 3: Stent palliation in infants and children <6 y old (n=17). Group 4: Stent placement in pts >6 y old (n=73). ● Outcomes of Group 2 (balloon angioplasty alone), mean age 13 ± 8 y. Decreased in peak to peak gradient immediately from 49 to 8 mm Hg. 29% of pts with intimal tears, late aneurysm formation occurred in 6%. Outcomes of Group 4 (stenting), mean age 20 ± 12 y). 1 death 3 h post stenting, likely due to aortic rupture. ● All pts had relief of the gradient with a reduction in gradient from 39–3 mm Hg. Mean follow-up of 5 y, no restenosis or aneurysm formation.	● Percutaneous interventions in coarctation are feasible and efficacious. ● Balloon angioplasty alone is associated with a higher rate of intimal tears and aneurysm formation compared to stent placement.

Hager A, et al. 2007 (429) 17723827	n=273 pts	Single-center retrospective review	Inclusion criteria: Pts that underwent surgical repair for isolated aortic coarctation	Evaluation of long-term clinical outcomes	● From 1974–2000, 404 pts born before 1985 underwent surgical intervention. ● Of the 404 pts, 21 (5%) died, 1 at surgery, 6 in the perioperative period (perioperative mortality of 1.7%). 14 pts died during follow-up (3.5%) of various causes (3 of congenital HF, 1 of ruptured aortic root aneurysm, 8 unknown). ● From 382 pt that were still alive, 273 pts underwent structured clinical evaluation. ● Surgical resection with end-to-end anastomosis was the most common surgical intervention in 199/273 pts followed by resection and tube graft placement in 62/273 pts. 29/273 (11%) underwent repeat intervention, 16 had surgery, 12 balloon angioplasty, 1 stent. Of these 29 pts, 5 needed a 2nd intervention and 1 a 3rd intervention. All reinterventions were related to restenosis. 25% of pts were taking antihypertensive drugs and another 23% had increased ambulatory BP, 10% had a BP during exercise exceeding 2 SD of reference values. ● Only 43% had normal BP. ● Of the 57% pts taking anti-HTN medication or with ambulatory or exercise-induced HTN, only 13% had UL to lower limbs systolic BP difference >20 mm Hg suggesting restenosis. ● Independent risk factors for HTN (in those without restenosis) were repair with prosthetic material, male sex, and older age at follow-up.	● Long-term follow-up following successful surgical intervention for aortic coarctation reveals that 11% of pts required reintervention for restenosis. ● Of those without restenosis, 57% either were taking antihypertensive medications, had elevated ambulatory BP or had a severely hypertensive response to exercise. ● Independent risk factors for HTN (in those without restenosis) were repair with prosthetic material, male sex, and older age at follow-up.
Toro-Salazar OH, et al. 2002 (430) 11867038	n=274 pts	Single-center retrospective review	Inclusion criteria: Pts that underwent surgical repair of CoA at the University of Minnesota	Long-term clinical outcomes following surgical repair	● 274 pts had operative repair of coarctation from 1948–1976 at the University of Minnesota. ● 7% died in the immediate perioperative period. ● 252 survivors were available for follow-up. ● 45/252 pts died late after repair. ● Of the 207 survivors, 92 pts (44%) were evaluated clinically, 115 subjects only responded to a questionnaire. Group 1: 45 pts that died late after repair. Group 2: 92 subjects with clinical evaluation. Group 3: 115 pts that responded to the questionnaire. Mean age at follow-up of the 252 long-term survivors was 40 ± 10 y mean age at operation was 10 ± 9.5 y.	● The majority of pts that underwent surgical repair survive to adulthood. Comorbidities are common and include systemic HTN in 30% of pts. ● Pts repaired late (>10 y of age) are more likely to have HTN and less likely to survive long-term. ● Pts operated on early (<1 y of age) are more likely to develop recoarctation.

					● 92% had surgical end-to-end resection and anastomosis. ● During follow-up, 20% of survivors underwent another cardiac operation, 14% died at the second operation. ● 32/92 pts in Group 2 had systemic HTN. ● Pts operated on at >10 y of age were less likely to survive into adulthood. ● Late deaths were attributable to CAD, repeat operation, aortic dissection and sudden unexplained death along with other noncardiac causes. ● Predictors of recoarctation included end to end resection technique, early era of operation (before 1960) and age at operation <1 y.	● Leading causes of death long-term include CAD, repeat operation, and aortic dissection.
Dodge-Khatami A, et al. 2000 (431) 11678458	n=271 pts	Single-center retrospective review	Inclusion criteria: Pts that underwent surgical coarctation repair	Long-term clinical follow-up	● Between 1957-1998, 271 pts had surgical coarctation repair. ● Techniques included: patch aortoplasty in 118, resection with extended end to end anastomosis in 69, subclavian flap in 61, resection with simple end to end anastomosis in 18, resection with interposition graft in 4, extra-anatomic graft in 1. ● Median age at repair was 156 d, 1% early and 2% late deaths. ● Recoarctation occurred in 11%, most frequently in the extended end to end and subclavian flap groups. Pts with aortic arch hypoplasia were more likely to have recurrent coarctation. ● No mortality for recoarctation repair	● Recoarctation following surgical repair occurs in 11% of pts, and is most common in pts that underwent surgical extended end to end resection or subclavian flap repair as well as in those with a hypoplastic aortic arch.
Zabal C, et al. 2003 (432) 12482798	n=54 pts	Single-center retrospective review	Inclusion criteria: Adult pts with native coarctation that underwent either angioplasty or stenting	Intermediate-term clinical outcomes. 1° outcome is a composite index of failure, including heart related death, a residual gradient >20 mm Hg, need for reintervention, and aneurysm formation.	● 54 consecutive pts, 32 underwent balloon angioplasty from 1995–1997, 22 underwent stent placement between 1997–1999. ● Peak systolic gradient reduced in both groups (from 63–11 mm Hg in the balloon group and from 64 mm Hg–3 mm Hg in the stent group). ● Stent implantation was associated with a successful dilation in all pts (vs. 9% unsuccessful dilation in the balloon group), resolution of the gradient (<20 mm Hg peak Doppler gradient) in all pts (vs. residual gradient in 16% of the balloon group). ● 6% of pts with balloon angioplasty had aneurysm formation, none of the stented pts developed aneurysms.	● Stenting of native coarctation is has superior outcomes when compared to balloon angioplasty alone.

Brown JW, et al. 2009 (433) 19932264	n=1,012 pts with 103 requiring reintervention; only 19 adult pts (2%) at the first intervention	Single-center retrospective review	Inclusion criteria: All pts with isolated or complex coarctation	Repair of recurrent coarctation compared to balloon angioplasty	● Median age at reintervention 6.5 y (2 wk–44 y). ● 98% survival at 15 and 40 y post surgery; 91% at 15 y post balloon.	● Surgical repair is safe and has excellent results with low recurrence rate.
Reents W, et al. 2012 (434) 21476189	n=13 consecutive pts adults aged 25–69 y	Single-center cohort	Inclusion criteria: Coarctation coexistent with other cardiac disease operated on via median sternotomy; 2 pts with recurrent CoA.	Early and late results	● Early mortality 0% and 1 late death at 11 y. ● Improvement in NYHA class. ● Many pts still required antihypertensive therapy.	● Excellent operative and long-term results. ● Procedure of choice if already necessitating cardiac surgery.
Roselli EE, et al. 2012 (435) 22704801	n=110 pts: (40 open, 11 hybrid, 59 endovasc); 43 first coarctation, 42 recurrent, 25 aneurysm	Single-center retrospective	Inclusion criteria: New or recurrent coarctation, postrepair aneurysm or pseudoaneurysm	Early and late results and establish indications to guide treatment	● 100% technical success no death, stroke, paraplegia 22 pts required reinterventions; no difference in occurrence of reinterventions based on approach. ● Survival at 1/5/8 y is 95/95/90%.	● Can be safely and effectively managed with a variety of techniques. ● Optimal results require multimodality approach tailored to surgical indication and anatomy. ● Pts require lifelong surveillance.
Carr JA, et al. 2006 (436) 16545637	n=846 pts	Meta-analysis of 22 studies, including adolescents and adults; 16 endovascular; 6 surgical reports	Inclusion criteria: Treatment of coarctation in adolescents or adults	Morbidity, restenosis, need for reintervention, HTN	● 1° stenting had the lowest risk of complication but higher risk of restenosis and reintervention compared to surgery. ● Both therapies had an equal cure of HTN.	● 1° stenting or angioplasty has similar morbidity to surgical repair but reintervention rates higher.
Aris A, et al. 1999 (437) 10355415	n=8 pts aged 51–73 y	Cohort of pts >50 y	Inclusion criteria: Older pts	HTN	● Improvement in BP with p<0.001.	● Surgical repair in older pts reduces HTN and the need for meds.
Almeida de Oliveira S, et al. 2003 (438) 14667622	n=18 consecutive pts compared to 81 treated conventionally	Cohort study	Inclusion criteria: >18 y	Midterm results mortality HTN	● 4% mortality in all 99 pts. ● No mortality in extra-anatomic bypass group. ● 2/3 of extra-anatomic bypass group returned to normotensive.	● Extra-anatomic bypass is safe and effective.

	all aged 18–64 y					
Morgan GJ, et al. 2013 (439) 23428013	n=31 pts	Cohort study	Inclusion criteria: Mean age 12 y at time of stenting	HTN by ambulatory BP monitoring	● Mean time after stent implantation 5 y, HTN in 10% on single time BP, but 45% on ambulatory BP. BP correlated with LV mass by echo. Stent decreased in size from 48th percentile to 4th percentile with somatic growth, but did not relate to other parameters.	● HTN is common after stenting, without correlation to residual coarctation.
Cook SC, et al. 2013 (32) 23279961	n=43 pts	Single-center cohort study	Inclusion criteria: Over age 18 y	Cerebral aneurysms in pts with CoA	● Increased prevalence of intercranial aneurysms in pts with CoA (11%), with increased age as the sole risk factor.	● Intracranial aneurysms are more prevalent in CoA, particularly in 4th/5th decade.
Connolly HM, et al. 2003 (440) 14661678	n=277 pts	Single-center cohort study	Inclusion criteria: Mean age 41 y	Cerebral aneurysms in pts with coarctation	● Increased prevalence of intracranial aneurysm in pts with CoA, with no predictive risk factors. ● 1 needed intervention.	● Increased intracranial aneurysm prevalence in CoA, but only 1 pt of 277 (10 with aneurysms) needed intervention. Notably pt population with mean age of 40s.
Correia AS, et al. 2013 (441) 24239395	n=65 pts	Single-center cohort study	Inclusion criteria: Age >18. Mean age 30 y	Prevalence of exercise-induced HTN in pts with CoA	● 18% with medical treatment for HTN, 22% had HTN with exercise of whom only 1/3 had HTN at rest. ● Risk factors were peak aortic gradient and use of ACEI.	● Exercise-induced HTN is common in pts with CoA.
Said SM, et al. 2012 (442) 22093693	n=61 pts	Case series	Inclusion criteria: Pts between Nov. 1970—Feb. 2008 who underwent repair of DCRV	Long-term surgical outcome	● 2 early deaths from postoperative low cardiac output. ● Mean postoperative gradient: 2±4.5 mm Hg. ● Late survival was 90% at 10 y. There were 3 late deaths due to HF in 2 pts and SCD in 1 pt, all occurring before 1997. ● No pts required reoperation for residual or recurrent RV obstruction.	● Surgical correction of DCRV results in excellent functional and hemodynamic long-term results, with complete relief of the RV obstruction. The presence of a DCRV should be considered in anomalies with high or persistent RVOTO.
Kahr PC, et al. 2014 (443) 24836684	n=50 pts	Retrospective review	Inclusion criteria: Pts with DCRV under follow-up	● Survival outcomes	● 96% of pts had VSD as underlying diagnosis. ● 8 pts remained completely asymptomatic during follow-up. ● The remaining pts developed symptoms at a median age of 26 y. ● Surgical correction was performed in 33 pts (median age at operation 27 y).	● Contemporary adult DCRV pts have good survival prospects and low long-term morbidity. ● Although asymptomatic adults may be encountered even with severe obstruction; symptom development is common during adult life.

					● No residual intraventricular gradient was present at the latest follow-up in 91% of operated pts and FC improved significantly with only 6 pts remaining in NYHA class 2. ● There was no early or late operative mortality and no pt required reoperation for DCRV during a median follow-up of 8 y.	● Cardiac surgery in this cohort is inherently low risk and offers good long-term hemodynamic and functional results justifying early intervention in consideration of the progressive nature of this rare congenital lesion.

Data Supplement 39. Valvular Pulmonary Stenosis – Section 4.3.1

Study Name, Author, Year	Study Type/ Design	Study Size	Inclusion/Exclusion Criteria	Intervention	1° Endpoint	Results/p Values	Summary/Conclusions
Johnson AM, et al. 1962 (444) 14451995	Prospective observational cohort	n=32 pts (19 pts operated; 13 unoperated)	Inclusion criteria: Presence of valvar PS pre- or postoperation	Exercise catheterization	Hemodynamics	● Impaired stroke volume due to impaired filling appears common.	● Impaired exercise tolerance was found in pts with native PS and after valvotomy.
Lewis JM, et al. 1964 (445) 14172094	Prospective observational cohort	n=13 pts	Inclusion criteria: Pts ≥21 y	Exercise catheterization	Hemodynamics	● If RVP ≥80 mm Hg, abnormal exercise hemodynamics (lower stroke volume at rest, inability to augment cardiac output via stroke volume).	● Pts with subnormal response to exercise had RV pressure ≥80 mm Hg.
Jonsson B, et al. 1968 (446) 5637559	Observational cohort prospective	n=17 pts (9 pts without atrial defect, 12 pts with)	Inclusion criteria: ≥21 y postoperative valvotomy	Exercise catheterization	Hemodynamics, SV, peak O_2 pulse	● Group without atrial defect had no increase in SV or low output with exercise, whereas those with residual defect improved.	● The tendency for low CO during exercise post operatively resulted from adaptive mechanisms in peripheral circulation.
Driscoll DJ, et al. 1993 (447) 8425316	Observational cohort prospective	n=194 pts	Inclusion criteria: Second Natural History Study, valvar PS	Exercise testing	Duration	● Normal compared to controls.	● Although exercise duration was preserved, exercise tolerance was subnormal.
Romeih S, et al. 2012 (448) 22892196	Observational cohort prospective	n=20 pts (2/7 late after surgical/catheter repair, 11 without surgery)	Inclusion criteria: Moderate valvar PS	Cardiopulmonary exercise testing	CPET parameters, MRI parameters, dobutamine stress parameters	● Postoperative mod valvar PS with impaired myocardial O_2 consumption, O_2 pulse, peak heart rate, inability to augment stroke volume, native moderate PS normal.	● Impaired exercise capacity in moderate PS restenosis may be caused by inability to augment the RV stroke volume.
Luijinenberg SE, et al.	Observational cohort prospective	21 valvular PS, 12 TOF	Inclusion criteria: Valvular PS or TOF post surgery	Cardiopulmonary exercise testing	CPET parameters	● Valvular PS (with mild PR in 80%) worse peak VO_2, HR,	● Despite more PR and larger RV volumes in pt with TOF, the exercise

2012 (449) 22871643						anaerobic threshold, than controls, no different, than TOF.	capacity and biventricular function are similar in pts with valvar PS and TOF.
De Meester P, et al. 2014 (450) 24780907	Observational, cohort, prospective	n=19 pts	Inclusion criteria: ≥16 y, mild-to-moderate valvar PR	Cardiopulmonary exercise testing	CPET parameters	● Peak VO_2, heart rate reserve, peak power, VE/CO_2 slope impaired in contrast to controls; peak O_2 pulse unchanged.	● Afterload reserve vs. ventilation/ perfusion mismatch may be impaired even in mild-moderate valvar PS.
Kopecky S et al. 1988 (451) 3180374	Retrospective review	n=191 pts	Inclusion criteria: Mayo long-term results surgical valvotomy 1956–1967	Surgery	Long-term survival and functional status	● Those with operative repair prior to age 21 y had normal life expectancy. ● Those after 21 y had good outcome but earlier mortality than general population.	● Even in earlier surgical era, good outcomes for repair. ● Earlier age at repair had better outcomes.
Hayes CJ, et al. 1993 (452) 8425320	Observational cohort; retrospective	n=592 pts	Inclusion criteria: Second Natural History Study, long-term results valvar PS surgery	Surgery or medical management of valvar PS	To determine long-term outcomes of medical and surgical management	● 25-y survival of 96% unless entered study >12 y (then 80%). ● Minimal need for surgery in medical management group and minimal need for reoperation in surgical group. 97% were class NYHA I.	● Pts with low gradients can be safely medically managed and those with high gradients do very well with surgery. The optimal management of the middle gradient group remains unclear.
Roos-Hesselink JW, et al. 2006 (453) 16361324	Observational, single-center cohort; retrospective	n=90 pts	Inclusion criteria: Surgical repair of isolated PS (1968–1980) ≤15 y	Long-term follow (median 16 y)	Reoperation, death, PR, arrhythmia, ventricular parameters, FC	● 15% reoperation for symptomatic residuae (PS 6%, PR 9%), perceived health lower than expected.	● Most reoperation for PR. ● Overall good exercise ability but relatively lower NYHA class. ● Need further understanding of lower perceived health.
McCrindle BW, et al. 1991 (454) 2040044	Observational, single-center cohort, retrospective	n=46 pts	Inclusion criteria: PS for balloon valvuloplasty, 6/81–12/86	Balloon valvuloplasty	Gradient relief and sustainability	● Good relief in most pts acutely (89%) and at >2 y-follow (86%). Those <2 y of age had higher residual gradients.	● Mostly pediatric study with good results of balloon valvuloplasty in pts >2 y at this center.
Voet A, et al. 2012 (455) 21078529	Observational, single-center cohort, retrospective	n=218 pts	Inclusion criteria: PS with 79 surgical repair, 139 balloon valvuloplasty	Surgical valvotomy or balloon valvuloplasty	Gradient relief and sustainability (median 22 y-follow)	● Good acute relief in all. 20% of surgical had reintervention for regurgitation; 9% of catheter pts had reintervention, mostly for stenosis.	● Both interventions good for gradient relief. ● Surgery with more residual regurgitation and catheter with more residual stenosis.

Taggart NW, et al. 2013 (456) 23613310	Retrospective cohort.	n=132 balloon pulmonary valvuloplasty pts (89 children, 40 adults)	Inclusion criteria: PS for balloon pulmonary valvuloplasty 12/93–7/2012	Balloon pulmonary valvuloplasty	Gradient relief and reintervention	● Good gradient relief in symptomatic adults with over 80% having symptom improvement. ● At 2 y, 50% were symptom free.	● Good short-term effects of balloon pulmonary valvuloplasty for PS in adults. Minimal complications.
Kaul UA, et al. 1993 (457) 8237759	Observational cohort	n=40 pts, single center	Inclusion criteria: PS for balloon valvuloplasty, 3/85–12/91; age 18–56 y	Balloon valvuloplasty	Acute and 2 y outcomes of gradient relief	● 32 pts with good acute results and sustained at 2 y; 8 pts with high acute gradient that improved at 2 y. ● NYHA class improved, cyanosis improved, 1 pt with RVOT tear and surgery required.	● Good acute outcomes in pts with PS for balloon valvuloplasty and minimal complications.
Chen CR, et al. 1996 (458) 8637537	Retrospective cohort	n=53 pts	Inclusion criteria: PS for balloon valvuloplasty; 12/85–7/1995; ages 13–55 y	Balloon valvuloplasty	Acute and longer-term outcomes	Good immediate reduction in gradient (mean 107 mm Hg–50 mm Hg) then further decrease over time (mean 30 mm Hg)	● Balloon valvuloplasty provides satisfactory acute and long-term outcomes in adolescents/adults.
Fawzy ME, et al. 2007 (459) 17307424	Single center, retrospective observational cohort	n=90 pts	Inclusion criteria: Adults with valvar PS and infundibular PS and/or severe TR undergoing pulmonary balloon valvuloplasty	Balloon valvuloplasty	Acute and long-term outcomes	30% with ≥mild PR, preintervention, 28% more with new ≥mild PR post procedure	● Successful procedure also served to decrease infundibular PS and TR.
Earing MG, et al. 2005 (460) 16007892	Retrospective cohort	n=53 adult pts	Inclusion criteria: Long-term outcomes for surgical repair	None	Need for reintervention	● 35 interventions in 28 pts; most for residual PR.	● Survival excellent but need lifelong follow-up as many interventions quite late (up to 30 y after surgery).

Data Supplement 40. Branch and Peripheral Pulmonary Stenosis – Section 4.3.2

Study Name, Author, Year	Study Type	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results	Summary/Conclusions
Hallbergson A, et al. 2014 (461) 24433604	Review	n=104 pts (124 stents)	Inclusion criteria: Stenosis narrower or equal to distal vessel; age (0.1–64 y); average age 5.5 y	In-stent stenosis is 25% narrowing of the contrast filled lumen relative to	● In-stent stenosis in 24% of pts. ● Highest incidence in TOF with multiple collateral, Williams, and Alagilles	● In-stent stenosis more frequent than previously reported; more in inherently abnormal PA. ● Increased clinical surveillance; need investigation of preventive strategies.

				stent diameter by fluoroscopy		
Gonzalez I, et al. 2013 (462) 22843203	Retrospective	26 pts, 62 stents; 2001–2012, mean age 9.5 ± 12 y	Inclusion criteria: All pts who underwent bilateral stents; 3 pts were adults	Mortality and procedural outcomes	● Right PA gradient decreased from 35 ± 22–11 ± 12; left PA gradient decreased from 32 ± 17–10 ± 12 ● 4 intra-procedural AE. ● Mean follow-up 41 ± 23 2 deaths; further intervention in 12 pts.	● Bilateral PA stenting is effective and safe with instantaneous decrease in pressure. ● Need for reintervention is common; follow-up warranted.
Takao CM, et al. 2013 (463) 23073978	Retrospective from 1998–2005	Compared with contralateral PA	Inclusion criteria: Excluded pts with interventions on contralateral lung	● 84 pts had unilateral stent implantation ● 22 excluded for intervention on contralateral lung ● 23 excluded as did not have follow-up cath ● 39 pts met inclusion criteria	● Age single ventricle pts 3.5 y (4.6 mo–32 y). ● Age 2 ventricle pts 4.8 y (4.5 mo–17 y). ● On cath follow-up: 14 ± 9.6 mo after stent implantation). ● Stent PA diameter increased 118% approximating contralateral PA.	● Stent implantation effective to promote lobar growth in 1 and 2 ventricle pts. ● Lobar growth > in 2 ventricle pts.
Holzer RJ, et al. 2011 (464) 21521836	Prospective multicenter	n=1,315 procedures	Inclusion criteria: balloon angioplasty and/or stent implantation in a proximal or lobar PA; median age 3.5 y (range: 0–70 y)	Independent predictors of AE and need for early reintervention.	● AE in 22% (high in 10%).	● Hemodynamic vulnerability, age < 1 mo, use of cutting balloon, and operator experience of <10 y were risk factors for procedural AE. ● Reintervention during the study period occurred in 22% of pts undergoing pulmonary rehabilitation.
Kenny D, et al. 2011 (465) 21414031	Retrospective	n=15 procedures	Inclusion criteria: 23 stents, 12 adults; median age 32.5 y (range: 18.7–56.7)	Review of procedural outcome and AE	● Systolic pressure reduced from 24 mm Hg–3 mm Hg 3 pts had stent embolization (1 required surgery).	● PA stenting provided effective relief of narrowing in adults with CHD. ● Stent embolization may occur especially in pts with associated significant PR.
Angtuaco MJ, et al. 2011 (466) 20853358	Retrospective review	n=67 pts (96 stents)	Inclusion criteria: Pts who underwent intraoperative PA stent placement for branch PA stenosis	Long-term outcomes and risk for reintervention	● Actuarial freedom from reintervention at 2, 5, and 10 y was 68%, 49%, and 40%, respectively.	● Analysis showed age <2 y ($p<0.005$) and diagnosis of TOF ($p<0.002$) or truncus arteriosus ($p<0.007$) to be significant risk factors for reintervention.
Menon SC, et al. 2008 (467) 19064034	Retrospective analysis	n=24 pts (27 stents)	Inclusion criteria: 1997–2006; hybrid PA stent procedures;	Review of the clinical data,	● There were 2 cases of distal stent migration. Repeat stent	● Hybrid PA stenting can play an important role in the management of CHD with complex branch PA anatomy.

			median age 15 y (range: 3–67 y)	procedural, and long-term outcome	dilations within 6 mo were performed in 3 pts.	● Hybrid procedures were safe and effective in most pts, although stent positioning remains critical. Intraoperative fluoroscopy and active suture fixation of the proximal stent may reduce the need for late reintervention.
Bergersen L, et al. 2011 (468) 22042887	Prospective, randomized, multicenter, investigational	n=73 pts (173 vessels)	Inclusion criteria: Included is 1) > 1/2 systemic RV pressure, 2) regional decrease in pulmonary blood flow by lung scan, 3) elevated PA pressures (20 mm Hg mean), or (4) cyanosis due at least in part to PA obstruction. Exclusion criteria: If pregnant or if PA surgery in the prior 6 wk	Review of the safety and efficacy of cutting balloon	● Cutting balloon had greater increase in lumen diameter. ● Only 1 adult pt.	● Cutting balloon therapy for PA stenosis not responsive to low-pressure balloon is more effective than HPB therapy and has an equivalent safety profile.
Monge MC, et al. 2013 (469) 23228407	Retrospective review	n=16 pts (7 Williams, 6 Alagille syndrome, and 3 no identifiable syndrome)	Inclusion criteria: Pts who had surgery; median age was 14 mo, and concomitant procedures performed in 9/16 pts.	Review the results and outcome after surgical reconstruction of peripheral PA stenosis	● The mean preoperative RV/LV pressure ratio was 0.88 ± 0.07. All peripheral stenoses were augmented with PA homograft tissue. ● There was a 55% reduction compared with the preoperative values with median 5-y follow-up.	● Surgical reconstruction of the peripheral PA stenosis resulted in a significant decrease in RV pressure.
Badiu CC, et al. 2010 (470) 19695893	Retrospective cohort, single center	n=130 pts	Inclusion criteria: Pts who underwent surgical repair for Ebstein's anomaly between 1976—2007	Repair feasibility	● 2 hospital deaths. ● Overall survival was 87.2%+/-3.6%, 85.1%+/-4.1% and 81.2%+/-5.4% at 10, 20, and 25 y, respectively, without significant difference between	● Repair, as opposed to replacement, is feasible in the vast majority of pts presenting with Ebstein's anomaly with a low early mortality rate. ● Outcome, in terms of survival and freedom from reoperation in the long term is

					the repair and replacement group (p=0.31). ● NYHA FC >II (p=0.01) and cardiothoracic ratio >0.6 (p=0.02) were significant risk factors for mortality. ● Overall freedom from reoperation was 79.9+/-4.6%, 61.9+/-6.8% and 58.0+/-7.4% at 10, 20, and 25 y, respectively. ● Age ≤12 y (p=0.005) and cardiothoracic ratio >0.6 (p=0.009) were significant risk factors for reoperation.	determined by the clinical state at the time of surgery.

Data Supplement 41. Double-Chambered Right Ventricular – Section 4.3.3

Study Name, Author, Year	Study Type/ Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
Hachiro Y, et al. 2001 (471) 11722036	Single center, retrospective	n=40 pts	Inclusion criteria: Surgical repair DCRV, age 3 mo–52 y (only 4 pts >30 y)	Mortality, reintervention	● Surgical success with reduction in gradient. ● No deaths, no reinterventions.	● Surgery can be performed successfully at multiple ages.
McIhenney DB, et al. 2000 (472) 10921695	Single center, retrospective	n=3 pts	Inclusion criteria: New diagnosis DCRV in adulthood	Descriptive	N/A	N/A
Kveselis D, et al. 1984 (473) 6507300	Single center, retrospective	n=20 pts	Inclusion criteria: DCRV surgery in 1959–1966 (mean age 14 y, 33 y-follow-up)	Descriptive: survival, cardiac residual disease, FC	● No late deaths. ● Mild residual disease.	N/A
Steadman CD, et al. 2009 (474) 19925548	Dual case report	n=2 pts	Inclusion criteria: N/A	Descriptive	● Stents placed successfully with relief of RVOTO in the short term.	● May be an option for selected pts deemed unable or unlikely to tolerate surgery.
Said SM, et al. 2012 (442) 22093693	Retrospective review	n=61 pts	Inclusion criteria: DCRV surgery 1970–2008; (mean 13 y, range 2 mo–64 y); associated VSD in 82%	Descriptive, survival	● 92% follow-up. ● 90% survival at 10 y. No reintervention. ● Pts were symptomatic or had gradient >40 mm Hg at rest.	● Surgical relief of DCRV and closure of VSD can be done successfully at multiple ages.

Data Supplement 42. Ebstein Anomaly – Section 4.3.4

Study Name, Author, Year	Aim of Study	Study Type (Size, N)	Patient Population	Study Intervention (n)	Results
Chauvaud S 2000 (475) 11005596	Surgery outcome	n=142 pts	Age 1–65 y, mean 25 y	● TV repair ± BDCPA	● All repaired; BDCPA 21%. ● Plication 79%; ring 64%. ● 1 y 88%; 10 y 75%. ● Late TR: I: 15%, II: 73%, III: 4%, IV: 8%. ● Late reoperation n=13 at 3.4 y; free of reoperation 87% at 14 y.
Chen JM, et al. 2004 (476) 15052195	Surgery outcome	n=25 pts	Mean age 14 y	● TV repair	● All repaired; 2 reoperation had TV replace at 4 and 8 y; 40% had grade III TR early postoperation. ● Exercise capacity improve 83%; 2 late SCDs.
Dearani JA, et al. 2013 (477) 23200240	Surgery outcome	n=89 pts	Age 19 d–68 y; mean age 19 y	● Cone repair	● All repaired. ● Modifications: ring 64%; leaflet augmentation 31%, autologous chordae 19%. ● BDCPA 24%. ● Early reoperation 13%; rerepair 50%, TV replace 50%. ● Ringed annuloplasty less TR p=0.01.
Dearani JA, et al. 2013 (478) 23743062	Surgery outcome	n=20 pts	Age 4–68 y; mean 15 y	● Cone. ● TV rerepair.	● Preoperation congestive HF 40%. ● RV plication 30%. ● Ring annuloplasty 80%. ● BDCPA 15%. ● Maze 50%. ● No reoperations. ● No late deaths.
Malhotra SP, et al. 2009 (479) 19932271	Surgery for congestive HF	n=57 pts	Mean age 8 y	● TV repair – "play it where it lies." ● TV replace 5.4%; BDCPA 55%.	● Protocol for BDCPA. ● 7% early reoperation. ● 4 y free of TV replace 92%.
Raju V, et al. 2014 (480) 24811983	Surgery for congestive HF	n=62 pts	Age 9 mo–57 y; mean age 21 y	● 73% children. ● 27% adults. ● BDCPA 100%.	● Severe RV enlargement or dysfunction 100%. ● NYHA III/IV 70%. ● Heart therapy evaluation 32%. ● TV repair 52%; TV replace 48%. ● BDCPA planned 86%; added intraoperation after CPB 11%; added early postoperation 3%. ● 1 late death. ● Late reintervention 8%.

					● Operation mortality 1.6%; mean follow-up 3.6 y NYHA I/II in 88% late follow-up.
Al-Najashi KS, et al. 2009 (481) 19559211	1.5 valve repair outcomes	n=40 pts	Mean age 42 y	● 23 pts with cavopulmonary shunt (42 y ± 12); 17 pts without (39 y, ± 19).	● 2 early death (right HF); arrhythmia most common complication; groups with similar 5 y survival (83%–86%)/HF/arrhythmia; differ in need for reoperation concomitant operation.
Stulak, JM, et al. 2012 (177) 22098921	AF surgery outcomes	n=245 pts	Age 1–75 y; mean age 45 y; 134 female; 43 pts with Ebstein anomaly	● Success of AF surgery during redo operation.	● Endpoint of sinus rhythm: 39 pt with pacemaker, in CHD pts 89% in sinus rhythm at median 4-y follow-up.
Khositseth A, et al. 2004 (482) 15573066	SVT management	n=130 pts with Ebstein anomaly and history of tachyarrhythmia	Retrospective review mean age 25 y	● Evaluate SVT therapy.	● 24 with AF/atrial flutter + 106 with EP majority >1 mechanism. ● 83/130 had surgical intervention for arrhythmia combined with surgery: 75% recurrence free at 4 y.
Wei W, et al. 2014 (483) 24614573	Description of accessory pathways in Ebstein anomaly	n=17 pts	Inclusion criteria: Adult Ebstein anomaly; referral for EPS from November 2011–May 2013	● Type of arrhythmia substrates.	● 35.3% had multiple accessory pathways. ● 91% of pathways were manifest. ● 26% were broad and 87% were nondecremental. ● All were right-sided.
Iturralde P, et al. 2006 (484) 17239096	ECG changes before and after ablation of accessory pathway in pts with Ebstein anomaly	n=60 pts	Ebstein anomaly; accessory pathway	● ECG characteristics before and after ablation of accessory pathway.	● Of 30 pts with recurrent tachycardia and single right-sided accessory pathway, 62% had typical preexcitation, although none had right bundle branch block in sinus rhythm. ● Catheter ablation resulted in appearance of right bundle branch block in 94% 1/3 of pts with Ebstein anomaly and symptomatic tachyarrhythmias have minimal or absent ventricular preexcitation. ● The absence of right bundle branch block pattern is a strong predictor of an accessory pathway.
Reich JD, et al. 1998 (485) 9869537	Radiofrequenc y ablation outcomes	n=65 pts; multicenter retrospective registry	Inclusion criteria: Pediatric Ebstein pts	● Arrhythmia mechanisms and acute success rates.	● 29% of pts had multiple accessory pathways. Other common arrhythmia mechanisms included Mahaim pathways (n=5), IART (n=4), and AVNRT (n=7). ● Acute success rates ranged from 75%–89% depending on arrhythmia substrate with recurrence rates of 27%–32% on follow-up life-threatening arrhythmias and multiple EP substrates are commonly encountered in pts with Ebstein anomaly referred for catheter ablation.
Shivapour JK, et al. 2014 (486) 24513916	Utility of preoperative EPSs	n=74 pts; retrospective review	Inclusion criteria: All pts at Boston Children's Hospital	● Preoperation and postoperation arrhythmias.	● 29/42 (69%) with significant findings on EPS ● 17/29 with successful ablation.

			with Ebstein's anomaly who had cone procedure Dec. 2006–Sept. 2012		
Bharucha T, et al. 2010 (487) 20085664	Prospective comparison	n=23 pts	3D multiplanar echocardiography in pts with Ebstein anomaly compared to 2D TTE and surgical anatomy	● Agreement between 3D echocardiography and TTE/operative findings.	● Use of 3D resulted in reclassification of 11 pts as TV dysplasia. ● Surgery undertaken on 10/23 with good correlation. ● Rotational abnormalities identified on 3D, other findings were similar to 2D.
Attenhofer Jost CH, et al. 2012 (488) 21822629	Comparison of echocardiography and MRI in Ebstein anomaly	n=16 pts	Inclusion criteria: Pts with Ebstein anomaly undergoing MRI and echocardiography	● Comparison of imaging data with operative findings.	● MRI better demonstrated right heart chamber size, degree of TR and valve anatomy, echocardiography better showed small shunts.
Zachariah JP, et al. 2013 (489) 23237138	Characteristics of multiple accessory pathways	n=1,088 pts	Inclusion criteria: Pediatric pts with accessory pathways	● Outcomes of ablation were negatively influenced by multiple pathways and structural HD.	● Multiple accessory pathways were present in 10% of pediatric pts and more common in pts with structural HD.
Brown ML, et al. 2008 (490) 18455593	Long term outcomes of surgery for Ebstein anomaly	n=539 pts (604 surgeries)	Single -center case series	● Survey sent to pts who underwent TV surgery at Mayo Clinic from 1972–2006. 30-d mortality of 5.9%, late survival 84.7% at 10 y, 71.2% at 20 y. 83% of pts responding to surveys had NYHA I and II symptoms. TV repair and replacement were associated with good long-term survival.	● Single center but very large experience in operations for Ebstein anomaly. ● Suggests both repair and replacement have similarly good long-term outcomes.
Hasan BS, et al. 2011 (491) 22075926	n=30 pts	Pts at 5 centers in the U.S: 23 pulmonary, 5 native aortic, 1 LV to Ao, 1 mitral n=30 pts	Melody valve implantation in high pressure systems	● Short-term outcomes.	● High pressure environment in PA circulation defined as mean PAP >25 mm Hg. ● In the pulmonary position 10 implants in homografts and 13 in bioprosthetic valves or bioprosthetic valved conduits. ● 3 pts died; 2 with Melody valves in the systemic circulation, 1 in the pulmonary circulation who died 8 mo after the procedure of drug overdose. ● At 1 y, freedom from moderate-to-severe regurgitation was 100%, freedom from mild regurgitation was 90%

Roberts PA, et al. 2011 (492) 21718905	n=15 pts; multi-institutional	Clinical and procedural data	Inclusion criteria: Prior TV prosthesis or RA to RV conduit	● Procedural outcomes.	● Mean tricuspid gradient 13 mm Hg preoperation; mean tricuspid gradient 4 mm Hg postprocedure. ● 1 major complication – complete heart block. ● 1 pt developed IE 2 mo postoperation. ● 1 pt with preoperation multiorgan failure did not improve and died 20 d later. ● Remaining pts doing well at 4 mo postoperation.
Cullen MN, et al. 2013 (493) 23683739	n=19 pts; single center	Pts with degenerated mitral or tricuspid bioprosthetic valves	Median age 65 y; degenerated mitral (9); tricuspid (10); valve-in-valve implantation with Melody; mean STS mortality score 13	● Procedural outcomes.	● Mitral gradient decreased from 12–5 mm Hg; residual MR mild (6), mild-to-moderate (2), moderate (1). ● Tricuspid gradient decreased 10–5 mm Hg; residual TR trivial-mild (9), mild-to-moderate (1). ● No periprocedural deaths, MI, stroke or valve embolization. ● Vascular access site complications in 4 pts.
Badiu CC, et al. 2010 (470) 19695893	Retrospective cohort, single center	n=130 pts	Inclusion criteria: Pts who underwent surgical repair for Ebstein's anomaly between 1976—2007	Repair feasibility	● 2 hospital deaths. ● Overall survival was 87.2%+/-3.6%, 85.1%+/-4.1% and 81.2%+/-5.4% at 10, 20, and 25 y, respectively, without significant difference between the repair and replacement group (p=0.31). ● NYHA FC >II (p=0.01) and cardiothoracic ratio >0.6 (p=0.02) were significant risk factors for mortality. ● Overall freedom from reoperation was 79.9+/-4.6%, 61.9+/-6.8% and 58.0+/-7.4% at 10, 20, and 25 y, respectively. ● Age ≤12 y (p=0.005) and cardiothoracic ratio >0.6 (p=0.009) were significant risk factors for reoperation.

Data Supplement 43. Tetralogy of Fallot – Section 4.3.5

Study Name, Author, Year	Study (Size, N)	Study Design	Inclusion/Exclusion Criteria	1° Endpoint	Results	Conclusions
Valente AM, et al. 2014 (494) 24179163	n=873 pts; TOF/PA 131 (15%)	Retrospective, Multicenter (4)	Inclusion criteria: TOF, CMR and ECG within 1 y apart Exclusion criteria: PV replacement prior to CMR; outcome prior to CRM	Sustained VT, death	● 32 (3.7%) reached the 1° outcome (28 deaths, 4 sustained VT. ● Cox proportional hazards regression identified RV mass-to-volume ratio ≥0.3 g/mL (HR: 5.04; 95% CI: 2.3–11.0; p<0.001), LVEF z-score <-2.0 (HR: 3.34; 95% CI: 1.59–7.01; p=0.001), and history of atrial tachyarrhythmia (HR: 3.65; 95%	● RV hypertrophy, ventricular dysfunction, and atrial tachyarrhythmias are predictive of death and sustained VT in adults with repaired TOF.

					CI: 1.75–7.62; p=0.001) as outcome predictors. RV dysfunction was predictive of the outcome similar to LV dysfunction. ● TOF/PA was a univariate predictor of outcome (HR: 3.3).	
Aboulhosn JA, et al. 2013 (495) 23369488	n=325 pts; TOF/PA 8.3% of 556	Retrospective, cross-sectional, multicenter (11)	Inclusion criteria: Age ≥18 y, Doppler data to assess LV diastolic dysfunction Exclusion criteria: Complex coexisting congenital abnormalities or uninterpretable ECG	Clinical variables: figure 1 is sustained VT	● Sustained VT was present in 28.9% with LV diastolic dysfunction vs. 10.6% without LV diastolic dysfunction (p<0.0001); sustained VT was present in 24.1% with RV diastolic dysfunction vs. 14.3% without RV diastolic dysfunction (p=0.04).	● LV and RV diastolic dysfunction are associated with a higher prevalence of VT.
Bonello B, et al. 2013 (496) 23643427	n=154 pts, not known TOF/PA	Retrospective single-center cohort study	Inclusion criteria: Age ≥18 y, CMR 2002–2008 Exclusion criteria: Prior history of atrial arrhythmias	Sustained atrial arrhythmia (atrial flutter or fibrillation; paroxysmal or established). Sustained VT (≥30 s), VT associated with presyncope or syncope or VF. SCD	● During a median follow-up of 5.6 y, sustained VT occurred in 9 pts and was predicted by CMR RVOT akinetic area length (cut off value 30 mm) and decreased RVEF.	● RVOT akinetic region length predicts ventricular arrhythmia in late follow-up of surgically repaired TOF.
Diller GP, et al. 2012 (497) 22496160	n=413 pts not known TOF/PA	Multicenter retrospective cohort study	Inclusion criteria: Echocardiograph 2004–2010	Sustained VT, SCD, or appropriate ICD therapy	● Pts were followed for a median of 2.9 y. ● On bi-variable analysis, mitral annular plane systolic excursion, and LV global longitudinal 2D strain were related to outcome. Independently of QRS duration.	● LV longitudinal dysfunction was associated with greater risk of VA and SCD.
Broberg CS, et al. 2011 (498) 21349477	n=511 pts, not known TOF/PA	Retrospective, multicenter cross-sectional	Inclusion criteria: Age ≥18 y, adequate echocardiographic images Exclusion criteria: PA with VSD, complex abnormalities	LV systolic dysfunction	● LV systolic dysfunction prevalent in 20.9%, with moderate/severe dysfunction in 6.3%; VT was more common with moderate or severe LV dysfunction (OR: 2.3; p=0.030).	● VT is associated with an LVEF <45% in adults with TOF.

Ortega, M, et al. 2011 (499) 21414597	n=39 pts, not known TOF/PA	Retrospective cohort	Inclusion criteria: CMR >10 y between repair and CMR	Sustained VT or death	● LV dyssynchrony.	● Tissue tracking applied to CMR images identifies indexes of LV synchrony associated with death and VT in pts with repaired TOF.
Khairy P, et al. 2010 (500) 20713900	n=556 pts, 8.1% TOF/PA	Retrospective, multicenter, cross-sectional	Inclusion criteria: Age ≥18 y Exclusion criteria: PA with VSD, complex abnormalities	Atrial and VA	● VT was prevalent in 14.6% and independently associated with number of cardiac surgeries (OR: 1.3), QRS (OR: 1.02 per 1 mo), and LV DD (OR: 3.3). ● Prevalence markedly increased after 45 y.	● Prevalence of VT increases with age (especially over 45 y) and is associated with prior cardiac surgeries, QRS duration, and LV diastolic dysfunction.
Lu JC, et al. 2010 (501) 21126623	n=62 pts, not known TOF/PA	Cross-sectional	Inclusion criteria: Age >14 y, CMR 2008–2009 Exclusion criteria: AVC, cognitive impairment	QOL	● Low RVEF. ● Age at repair >1 y.	● RVEF and age of repair were the best predictors of QOL in this population, in whom end-diastolic forward flow; and associated diastolic parameters appeared to reflect an overdistended ventricle, which might suggest a role for early PV replacement.
Wald RM, et al. 2009 (502) 19255342	n=62 pts, not known TOF/PA	Retrospective Cohort	Inclusion criteria: CMR Exclusion criteria: No follow-up, PV replacement before CMR	Peak O_2 consumption	● Decreased RVOT EF.	● A greater extent of regional abnormalities in the RVOT adversely affects global RV function and exercise capacity after TOF repair
Hickey EJ, et al. 2009 (503) 18848456	n=1,181 pts, 81 (8%) TOF/PA	Inception cohort	Inclusion criteria: All-inclusive inception, cohort of children with TOF born prior to 1984 Exclusion criteria: PA/VSD	Death, reoperation, PV replacement	● Pulmonary atresia variant (n=88) was associated with 3-fold higher late risk of death than classic TOF (n=1069). ● Presence of associated branch PAS or AVSD conferred a less optimal late prognosis.	● Reduction of early surgical mortality to <2% is responsible for excellent late survival >90% overall
Rosianu S, et al. 2009 (504) 18611966	n=52 pts not known TOF/PA	Retrospective cohort	Inclusion criteria: Adults, ECG	Atrial and VA	● In univariate analyses of pts with VT, LVEDD, left arterial size, and QRS duration are significantly higher than pts without VT.	● VT is associated with LVEDD, left arterial size, and QRS duration in univariate analyses.
Knauth AL, et al.	n=88 pts, 29 TOF/PA	Retrospective cohort	Inclusion criteria: Sub-study of Geva T, et al., 2004 (507) 15028368	Composite of sustained VT,	● RVEDV z ≥7. ● LVEF <55%. ● RVEF <45%.	● Severe RV dilatation and either LV or RV dysfunction

2008 (505) 17135219			Exclusion criteria: Incomplete follow-up	death, decrease NYHA class		assessed by CMR predicted major adverse clinical events.
Khairy P, et al. 2008 (506) 18172030	n=121 pts, not known TOF/PA	Retrospective cohort multicenter (11)	Inclusion criteria: ICD implanted before 2006 Exclusion criteria: Unrepaired TOF, AVC	ICD shock	● LVEDP ≥12 mm Hg. ● Nonsustained VT.	● Factors that predict appropriate shocks in 1° prevention ICD recipients with TOF.
Babu-Narayan SV, et al. 2006 (507) 16432072	n=92 pts, not known TOF/PA	Cross-sectional	Inclusion criteria: ACHD clinic 2002–2005 Exclusion criteria: Pacemakers		● Older age at repair. ● Decreased exercise tolerance. ● Increased neurohormonal markers, clinical arrhythmias.	● RV and LV late gadolinium were common after TOF repair and were related to adverse clinical markers, including ventricular dysfunction, exercise intolerance, and neurohormonal activation. ● Furthermore, RV LGE was significantly associated with clinical arrhythmia.
Khairy P, et al. 2004 (508) 15051640	n=252 pts	Retrospective cohort multicenter (6)	Inclusion criteria: Programmed ventricular stimulation between 1985–2002 Exclusion criteria: Unrepaired TOF, PA, AVC	Composite of sustained VT or SCD	● Age at EPS ≥18 y, palpitations, prior palliative surgery, modified Lown ≥2, cardiothoracic ratio ≥0.6.	● Programmed ventricular stimulation is of diagnostic and prognostic value in risk stratifying pts with repaired TOF.
Geva T, et al. 2004 (509) 15028368	n=100 pts; 29 TOF/PA	Cross-sectional	Inclusion criteria: >10 y after repair, CMR, 1997–2001 Exclusion criteria: Incomplete clinical follow-up	NYHA >III	● Older age at repair. ● Decreased LV or RVEF. ● Increased RV mass-to-volume ratio.	N/A
Davlouros PA, et al. 2002 (510) 12475468	n=26 pts control, not known TOF/PA	Cross-Sectional	Inclusion criteria: Age ≥15 y Exclusion criteria: PV replacement	RV wall motion	● Pts had larger CMR volumes, mass, and lower EF.	● PR and RVOT aneurysm were independently associated with RV dilation.
Ghai A, et al.	n=137 pts; 12 cases not	Case-control	Inclusion criteria: TOF	SCD	● ≥ Moderate LV dysfunction. QRS duration.	● The combination of QRS 180 mo and significant LV systolic

2002 (511) 12427422	known TOF/PA		Exclusion criteria: Death before 30 d following initial repair; incomplete follow-up			dysfunction has high positive and NPV for SCD.
Bacha EA, et al. 2001 (512) 11436049	n=57 pts	Retrospective cohort	Inclusion criteria: 1° repair between 1972–1977 prior to less than 24 mo at time of primary repair Exclusion criteria: Prior shunts, TOF/PA, absent PV, AVC	Death	● Early death (8). ● Late death (1).	● No difference in survival between transannular patch and nontransanular patch.
Gatzoulis MA, et al. 2000 (513) 11041398	n=793 pts	Retrospective	Inclusion criteria: All rTOF pts alive in 1985 Exclusion criteria: TOF/PA, complete heart block (9); prior arrhythmias (2)	Arrhythmias and SCD	● VT (33). ● SCD (16). ● AF (29).	● QRS duration ≥180 ms. ● Older age at repair. ● Transannular patch.
Nollert G, et al. 1997 (514) 9323819	n=490 pts	Retrospective cohort	Inclusion criteria: rTOF 1958–1977, University of Munich Exclusion criteria: TOF/PA	N/A	● Mortality increased 25 y postoperatively from 0.24%–0.94%.	● Preoperative polycythemia RVOT patch. ● Date of repair <1970.
Harrison DA, et al. 1997 (515) 9350941	n=210 pts; 18 cases not known TOF/PA	Case control	Inclusion criteria: 1990–1994 at Toronto Exclusion criteria: Atrial arrhythmia (17), PVCs (11), prior tachycardia (16)	1) VT >30 s 2) Palpitations with syncope or near-syncope	● Frequent ectopic beats. ● Low CI. ● RVOT aneurysm. ● ≥Moderate TR or PR.	● ≥ Moderate TR or PR. ● RVOT aneurysm.
Gatzoulis MA, et al. 1995 (516) 7600655	n=178 pts	Retrospective cohort	Inclusion criteria: Surgery between 1958–1979 Exclusion criteria: <15-y follow-up	VT	● VT (9). ● RVRP (20/41).	● QRS>180 m.

Murphy JG, et al. 1993 (517) 7688102	n=163 pts	Retrospective cohort	Inclusion criteria: Surgical repair between 1955 –1960, Mayo Clinic Exclusion criteria: Did not survive 30 d post repair (50), international pts (33), CHB (5)	N/A	● 32-y actuarial survival rate 86%	● Older age at repair. ● Increased RV:LV systolic pressure ratio. ● History of HF.
Mongeon FP, et al. 2013 (398) 23224208	n=474 pts	Retrospective, multicenter cross-sectional study (11)	Inclusion criteria: Age ≥18 y; adequate echocardiographic images Exclusion criteria: PA with VSD, complex abnormalities	Aortic size	● The aortic root dimension was ≥40 mm in 28.9% (95% CI: 26.9%–30.9%). ● In multivariate analyses, the only independently associated factor was male sex (OR: 4.48; 95% CI: 1.55–12.89; p=0.006). The prevalence of an observed-to-expected aortic root dimension ratio >1.5 was 6.6% (95% CI: 5.3%–7.9%). It was associated with pulmonary atresia and moderate or severe aortic regurgitation in univariate analyses, but no independent predictor was identified. ● The prevalence of moderate or severe aortic root was 3.5% (95% CI: 2.7%–4.2%)	● Although nearly 1/3 of adults with repaired TOF have an aortic root diameter ≥40 mm, the prevalence of a dilated aortic root, when defined by an indexed ratio of observed-to-expected values, is low. ● Similarly, moderate or severe aortic root is uncommon.
Ait-Ali L, et al. 2014 (518) 25260437	n=109 pts; 9 (7.3%) TOF/PA	Prospective study ex-echocardiography CMR, CPET, BNP	Inclusion criteria: Consecutive pts, mean age 26 y Exclusion criteria: Age <10 y, contraindication CMR, complex anomalies (AVC)	Death for all causes, cardiac death, development or progression of HF, and tachyarrhythmias.	● Tricuspid annular plane systolic excursion increased significantly during peak exercise in responders from 17.2 ± 3.4 mm at rest to 19.7 ± 4.3 mm (p<0.0001) but did not in nonresponders (from 16.9 ± 4.7–18.1 ± 4.6 mm; p=0.20). ●LV end-diastolic volume at rest and LVEF <50% were related to the lack of increased RV fractional area change on exercise.	● Exercise echocardiography is feasible in pts with repaired TOF and allows the integrated assessment of variation in RV systolic pressure, area, and function during exercise, which usefully complement more conventional indices of hemodynamic burden in these pts.
Freling HG, et al. 2014 (519) 24355311	n=42 pts	Retrospective	Inclusion criteria: Echo, CMR and CPET within 6 m	Peak VO_2	● Multivariate analysis showed that the peak RVOT gradient was the only independent predictor of exercise capacity.	● Exercise capacity is lower in pts with RVOTO compared with those without RVOTO despite a less dilated RV and comparable degree of PR.

			Exclusion criteria: Other significant valve regurgitation or shunts			
Babu-Narayan SV, et al. 2014 (520) 24146254	n=220 pts, 11 with TOF/PA	Retrospective	Inclusion criteria: rTOF with surgical PV replacement	All-cause mortality	● Peak VO_2, VE/CO_2 slope (ratio of min ventilation to CO_2 production), and heart rate reserve during CPET predicted risk of early mortality when analyzed with logistic regression analysis; peak VO_2 emerged as the strongest predictor on multivariable analysis (OR: 0.65/1 $mL/kg^{-1} \cdot min^{-1}$; p=0.041)	● Preoperative CPET predicts surgical outcome and should, therefore, be included in the routine assessment of these pts.
Ferraz Cavalcanti PE, et al. 2013 (521) 24080109	n=3,118 pts not known TOF/PA	Meta-analysis	Inclusion criteria: Pts enrolled from 1960–2011 Exclusion criteria: Repaired TOF with moderate insufficiency undergoing PV replacement	N/A	● 30-d mortality of 0.87% ● 5-y mortality of 2.2% ● 5-y re-PV replacement 4.9%	● PV replacement post TOF repair results in: - Decrease in regurgitant factor - Improved RV volume but not EF - Improved LVEF, decreased LVEDV - Decrease QRS duration - Improvement of symptoms.
Morray BH, et al. 2013 (522) 24065444	n=404 pts; 226 TOF, 84 TOF/PA	Multicenter, (4) retrospective	Inclusion criteria: Pts referred for TPVR	Presence or absence of coronary artery compression	● 21 (5%) had evidence of coronary artery compression with simultaneous RVOT angioplasty and coronary angiography. 68 (17%) had abnormal coronary angiography anatomy.	● Preimplantation coronary angiography with simultaneous test angioplasty is an important step to evaluate for the presence of coronary angiography compression during TPV.
Ong K, et al. 2013 (523) 23481618	n=49 pts; 106 conduits 16 (33%) TOF/PA	Retrospective	Inclusion criteria: Review from 1974–2011 Exclusion criteria: RV to PA conduit reoperations in pts with TOF or PA/VSD	Reoperation	● Significant independent predictors of shorter conduit longevity included smaller conduit and conduit type (homograft and other vs. Dacron).	● Multiple RV-PA conduit revisions were required in pts who survived to adulthood, with many replacements taking place during adolescence.
Adamson L, et al. 2009 (524) 19567499	n=1,070 pts; not known TOF/PA	"Best Evidence" Meta-analysis	Inclusion criteria: 1950–2009; 19 papers selected	Explore clinical and imaging result of PV replacement	● PV replacement improves RV function and offers symptomatic benefit. ● Consistent reduction in RVEDV and RVESV.	● PV replacement improves RV function and offers symptomatic benefit. ● Consistent reduction in RVEDV and RVESV.

					● PV replacement improves clinical outcome and is performed with low mortality.	● PV replacement improves clinical outcome and is performed with low mortality.
Cheung EW, et al. 2010 (525) 20691315	n=1,083 pts	Meta-analysis	Inclusion criteria: PubMed Inception: 2009; 15 papers selected Exclusion criteria: Case reports and review articles; percutaneous valves; image and biomarker studies; comparison studies	Children and adults following outcomes measures after surgical PV replacement	● Early mortality 2.1%. Late mortality 0.5%/pt y. RVEDV reduction of 63 mL/m^2. RVESV reduction of 37 mL/m^2. No change in RVEF or QRS duration.	● Low early and late mortality. ● Significant decreases in RV volume. ● No change in RVEF or QRS duration.
Lee C, el al. 2012 (526) 22921969	n=170; 139 TOF (82%), 15 PA with VSD (9%)	Retrospective cohort	Inclusion criteria: Undergoing PV replacement for chronic PR after TOF repair or similar physiology from January 1998–March 2011 Exclusion criteria: Pts with valvar or subvalvular PS, RV to PA conduits, other confounding HD	Prosthetic PV failure, prosthetic PV dysfunction, arrhythmias	● More PR associated with increasing RV volumes but not function. ● 2 early deaths (1.2%). ● 10-y survival 97.5 ± 1.6%. ● Freedom from redo PV replacement at 10 y 74.7±10.0%. ● Freedom from prosthetic valve failure at 10 y was 50.3 ± 10.1% MRI cutoff for RVED volume indexed normalization after surgery was 168 mL/m^2.	● Midterm outcomes of PV replacement acceptable. ● PV replacement should be considered before RVEDV is >163 mL/m^2, or RVESV >80 mL/m^2.
Fiore AC, et al. 2008 (527) 18442571	n=82 pts not known TOF/PA	Retrospective cohort	Inclusion criteria: PV replacement with tissue prosthesis between January 1995–August 2006 Exclusion criteria: Extracardiac conduits; Ross; monocuspid valves	Valve dysfunction	● Mean age 22.7 y with mean 15.3 y after initial repair. ● All 3 reduced PR but late insufficiency greater with homograft's (54%) followed by porcine (19%) and pericardial (5.5%) p<005. ● RV dimension reduced in stented but not allografts. ● FC and TR improved with PV replacement; early and late mortality 3.6% and 1.2%.	● All 3 prostheses perform similarly for 3 y. ● PR developed more frequently in homografts albeit longer follow-up.
Gengsakul A, et al.	n=164 pts	Matched cohort	Inclusion criteria: PV replacement after TOF compared with non-PV	N/A	● SCD in 4 non- PV replacement with none in PV replacement group. PV replacement pts more likely to be	● Symptoms and FC improved after late PV replacement with reduction in PV and TV

2007 (528) 17627832			replacement pts from Jan 1974–Dec 2003, DORV of TOF type Exclusion criteria: Ventricular arrhythmia, automatic intracardiac cardioverter defibrillator, multiple aortopulmonary collaterals, nonconfluent PA, Single ventricle; PV replacement occurring at time of initial repair		symptomatic, non-VA, lower FC, longer QRS, lower RVEF, higher RV pressure and reduced exercise duration.	insufficiency and RV size and function improved; no SCDs in PV replacement population but no impact on arrhythmia.
Oosterhof T, et al. 2007 (529) 17620511	n=71 pts	Prospective, nationwide	Inclusion criteria: Corrected TOF undergoing PV replacement from 1993–2007	RV volumes	● RV volumes decreased a mean of 28%. ● RVEF did not change significantly. ● RVOT reduction altered RV volume by 25%. ● Cutoff values RVEDV 160 mL/m^2 RVESV 82 mL/m^2.	● RV volume decreased in all pts, especially with RVOT reduction Cutoff values RVEDV 160 mL/m^2 RVESV 82 mL/m^2.
Frigiola A, et al. 2008 (530) 18539471	n=36 (25 PV replacement, 11 PPVI)	Prospective	Inclusion criteria: 1 y after PV replacement or PPVI Exclusion criteria: For PPVI: <20 kg, presence of a transannular patch	To evaluate EF and volumes after RVOT reconstruction with PV replacement and PPVI	● Significant reduction in RVEDV in both groups. ● Improvement in RV and LV stroke volume.	● Significant reduction in RV volume and function. ● LV effective stroke volume should be used to judge benefit of procedure. ● Supports PPVI as intervention for RVOT management.
Yin S, et al. 2005 (531) 15905342	n=10 pts	Retrospective	Inclusion criteria: June 2002–April 2004 undergoing late PV replacement	LVEF, RV size, QRS duration, QT interval	● Interval between repair and PV replacement 20 ± 12.3 y. ● LVEF improved significantly from 62.1%–70.2% QT decreased (460.9 vs. 451.9 ms);2 pts required defibrillators; only 3 pts underwent MRI.	● Significant benefits with low operative risk.
Mainwaring RD, et al. 2012 (532) 22269747	n=5 pts	Case series	Inclusion criteria: March 2009–April 2011, with previous TOF repair undergoing pulmonary valvuloplasty	Pulmonary insufficiency	● Median age 9 y. ● For bicuspid native PV s and had undergone transannular patch with retention of native leaflets and no pulmonary stenosis and transannular gradient of <10 mm.	● New technique of bicuspidization of the native PV leaflets.

					● Majority of pts went from severe to trace pulmonary insufficiency.	
Graham TP, et al. 2008 (533) 18557878	n=93 pts	Retrospective multi-institutional (7 centers)	Inclusion criteria: >18 y of age, TOF post repair with main artery present and isolated PV regurgitation Exclusion criteria: Multiple aortopulmonary collaterals TOF with absent PV	Death, reoperations RV size, ability index	● PV replacement at 2.61 y. ● No operative deaths. ● Overall mortality 2.1% (1 from V Fib). ● Median follow-up 3 y (4 d–26 y) so 10 pts underwent 2 PV replacements, 3 pts with 3 PV replacements. ● Valve durability 50% at 11 y.	● PV replacement is low mortality. ● Decrease in RV size and improvement in ability index. ● Average durability 11 y. ● Criteria for PV replacement not clear.
Ovcina I, et al. 2011 (534) 21429868	n=24 pts (17 with RV volume reduction plasty)	Prospective	Inclusion criteria: April 2004–2009; pts were offered mechanical valve as an option: symptomatic with moderate-to-severe PV dysfunction: asymptomatic with moderate-to-severe dysfunction and significant RV dysfunction: RV volume reduction plasty for RVEDV of >170 mL/m^2): pts given choice of mechanical valve Exclusion criteria: Candidates for Melody since 2006	Midterm surgical results for use of mechanical prosthesis with and without RV volume reduction plasty	● Follow-up 6.9–67.1 m. ● Mean age 23.1 ± 6.6 y. ● Perioperative and midterm mortality is 0. ● 1 prosthetic thrombosis at 11 mo postop due to Coumadin cessation for procedure.	● Aggressive PV replacement at >160 mL/m^2 ● Concomitant RV volume reduction plasty safe and effective to remove inactive fibrous tissue.
Dave HH, et al. 2005 (535) 16242426	n=39 pts	Prospective using valved conduit: homograft or bovine jugular	Inclusion criteria: RVEDV >150 mL/m^2	Define objective guidelines for timing of PV replacement MRI changes in morphology and function at 6 m	● No early nor late deaths. ● Good conduit function at 15 m. ● Significant reduction in RV size Increase in LVEF. ● Pts who achieved post op RV size of <100 mL/m^2 had beginning RVEDVi of 170 vs. 203.	● Improvement in ventricular function and size correlates with timing of PV replacement with early insertion leading to normalization. ● Low morbidity justifies earlier reintervention. ● RVEDV <150 mL/m^2.

Meijboom FJ, et al. 2008 (536) 18179918	n=67 pts	Retrospective follow-up study	Inclusion criteria: Repair between 1968–1990	Long-term results of selective strategy towards PV replacement looking at improvement in ECG, echocardiography, exercise, and no deterioration in pts treated conservatively	● Follow-up 15 ± 3 y–27 ± 3 y 45 pts with severe PR: 62% remained symptom free and did not undergo PV replacement and had no changes in RV size or exercise capacity. ● 17 pts had symptoms and underwent PV replacement; of these 54% improved clinically and echocardiographically.	● Only operate on symptomatic pts Refraining from PV replacement in asymptomatic pts led to no measurable deterioration.
Van Huysduynen BH, et al. 2005 (537) 15716288	n=26 pts	Retrospective analysis	Inclusion criteria: 1997–2002	Effects of PV replacement on QRS and RV volume	● QRS duration shortened by 6 ± 8 mo (p=0.002) overall. QRS duration decreased in 18/26 pts. ● RVEDV significantly reduced from 305 ± 87 to 210 ± 62 (p=0.000004). ● QRS duration correlated with RVEDV changes (r=0.54; p=0.01).	● PV replacement reduces QRS duration and expressed also by reduction of RVEDV.
Lee C, et al. 2011 (538) 21281951	n=181 pts	Retrospective analysis	Inclusion criteria: 1993–2004, bioprosthetic PV replacement Exclusion criteria: Valved conduit or homograft	Long-term results of PV replacement; mean age 14.2 y	● 3 early and 7 late deaths. ● Mean follow-up duration was 7.3 ± 2.9 y. ● 43 pts underwent redo PV replacement. ● Freedom from redo PV replacement at 5 and 10 y was 93.9% and 51.7%. ● Freedom from valve failure and dysfunction at 5 and 10 y was 92.2% and 20.2%. ● Risk factors are younger age, PAVSD, stentless valves.	● Durability of bioprostheses are suboptimal. ● Valve function was stable until 5 y postoperation. ● By 10 y 80% will require reoperation or manifest dysfunction. Stentless valve less durable.
Chen PC, et al. 2012 (539) 22153723	n=227 pts	Retrospective analysis	Inclusion criteria: 1994–2009, stented bioprosthetic Exclusion criteria: Pulmonary homograft or mechanical valve	Predictors of structural deterioration	● No early mortality. ● Freedom from reintervention and single ventricle defects 94% and 74% at 5 y. ● Younger age and higher indexed valve internal diameter were predictors of reduced time to single ventricle defects.	● Younger age at time of PV replacement and oversizing of valve in pts less than 20 y were significant predictors of single ventricle defects.
Discigil B, et al. 2001 (540) 11174741	n=42 pts	Retrospective analysis	Inclusion criteria: 1974–1998	Review experience with	● Interval between TOF repair and PV replacement was 10.8 y (1.6 mo to 33 y).	● Late PV replacement improves RV function, FC, atrial arrhythmia.

				late PV replacement	● Decreased exercise tolerance was indication in 58%. ● 1 early death and 6 late (3 cardiac) Survival was 95.1% and 76.4% at 5 and 10 y. ● FC improved significantly. ● Moderate-to-severe reduction in RV function improved from 59% pre to 18% post. ● Freedom to rereplacement 9.0 ± 4.2 y; freedom from rereplacement 93.1% and 69.8% at 5 and 10 y. ● Risk factor for rereplacement was younger age at time of initial PV replacement (p=0.023).	● Can be performed with low mortality. ● Rereplacement may become necessary.
Zubairi R, et al. 2011 (541) 21256315	n=169 pts	Retrospective analysis	Inclusion criteria: 1987–2007 after prior repair of PV replacement	Identify risk factors of PV Failure	● Indication for PV replacement was insufficiency in 79%. ● Median follow-up 8 y. ● Freedom from failure at 10 y overall 72% and best for bovine pericardial at 78%. ● Risk factors for PV failure are young age, use of homograft for early failure and younger age for late.	● Excellent freedom from reoperation at 10 y. ● Risk factors for PVF are young age, use of homograft for early failure and younger age for late.
Babu-Narayan, SV, et al. 2012 (249) 20970202	n=64 pts; not known TOF/PA	Double-blinded, placebo-controlled, RCT	Inclusion criteria: Moderate-severe PR; CMR Exclusion criteria: PS, drug allergy, renal dysfunction	CMR RVEF	● There was no difference in the 1° endpoint RVEF. RV long-axis shortening significantly improved in the ramipril group compared to placebo (RV: 2.3 ± 3.8 vs. 0.02 ± 2.7 mm; p=0.017) as did LV long-axis shortening (1.9 ± 4.5 vs. -0.2 ± 3.7 mm respectively; p=0.030). No clear differences were detected between ramipril and placebo for other measures. In a subgroup of pts with restrictive RV physiology, ramipril resulted in decrease in LV end systolic volume index and increase in LVEF (-2.4 ± 5.0 vs. 2.7 ± 3.6 mL/m^2; p=0.005, 2.5 ± 5.0 vs. -1.3 ± 3.5%; p=0.03).	● Ramipril is a well-tolerated therapy, improves biventricular function in pts with rTOF and may have a particular role in pts with restrictive RV physiology. ● Larger, longer-term studies are needed to determine if ACEIs can improve both ventricular remodeling and clinical outcomes.

					● Ramipril did not cause AE and was well tolerated.	
Norozi, K, et al. 2007 (248) 17572925	n=33 pts	Double-blinded, placebo-controlled, RCT	Inclusion criteria: Pts 14–50 y Exclusion criteria: Significant bradycardia, average heart rate <50 beats/min, already on BB	Cardiac failure: present if level of BNP significantly >100 pg/mL	● Beta blockade with bisoprolol seems to have no beneficial effect on asymptomatic or mildly symptomatic pts with RV dysfunction secondary to rTOF with residual PR and/or PS.	● Beta blockade with bisoprolol seems to have no beneficial effect on asymptomatic or mildly symptomatic pts with RV dysfunction secondary to rTOF with residual PR and/or PS.
Geva T, et al. 2010 (542) 20837914	n=64 pts	Randomize, prospective clinical trial	Inclusion criteria: Older than 10 y of age with chronic PR referred for PV replacement Exclusion criteria: Severe RVOTO, severe RV HTN, additional sources of RV volume overload, contraindications to CMR	CMR RVEF	● No significant difference in RVEF or in any of the secondary outcomes at 6 mo postoperative. Multivariable analysis identified preoperative RVEDV >90 mL/m^2 and QRS duration <140 ms to be associated with optional postoperative outcome.	● The addition of surgical remodeling of the RV to PV replacement in pts with chronic PR did not result in an early measurable benefit.
Therrien J, et al. 2005 (543) 15757612	n=17 pts	Retrospective	Inclusion criteria: TOF pts who underwent PV replacement	RV volumes	● RV volumes decreased after PV replacement, yet RVEF systolic function remain unchanged.	● Pts with an RVEDV >170 mL/m^2 or RVESV >85 mL/m^2 before PV replacement "normalized" after pulmonary valve replacement.
Quail MA, et al. 2012 (544) 22959579	n=87 pts	Propensity score matching cohort	Inclusion criteria: TOF with severe PR from 2003–2010	Ventricular size and function	● No significant deterioration in RV or LV measurements in the matched untreated pts over a median of 1.8 y. ● No absolute ceiling beyond which the RV did not normalize could be discerned.	● TOF pts with intermediate RV dilation and severe PR are at low risk for significant progression in the short term.
Blalock SE, et al. 2013 (75) 23418153	n=30 pts	Prospective study	Inclusion criteria: TOF undergoing CMR from 2009–2010 Exclusion criteria: CMR under sedation/anesthesia, imaging artifact or arrhythmia	Ventricular size and function	● Agreement for measurements better with a single observer. ● Effect was most prominent on measurement of RV mass.	● CMR measurements of ventricular size and function have acceptable reproducibility in pts with repaired TOF. ● RV mass measurements are subject to higher variability.

Mercer-Rosa L, et al. 2012 (545) 22869820	n=143 pts	Prospective	Inclusion criteria: Repaired TOF 8–18 y of age; echocardiography and CMR within 3 mo	RV function and PR	● Echocardiography had good sensitivity identifying cases with regurgitant fraction >20% but overestimated the amount of PR when regurgitant fraction <20%. ● The diastolic and systolic time-velocity integrals on echo showed moderate correlation with regurgitant fraction on CMR.	● Echocardiography has a limited ability to quantify PR and RV function as compared to CMR. Diastolic and systolic time-velocity integrals ratio make a modest contribution to the overall assessment of PR.
Hallbergson A, et al. 2014 (546) 25483002	n=101 pts	Retrospective	Inclusion criteria: TOF with surgical PV replacement, pre and post CMR, RVEDV z-score ≥3 Exclusion criteria: Age at PV replacement <4 y; prior surgical or catheter PV replacement; acute dysfunction of bioprosthetic PV	RV dimensions, PR	● By 7–10 y after PV replacement, RVEDV index and RVESV index were significantly increased and had returned to 84% and 104% of pre-PV replacement volumes, respectively, and RV EF had declined further.	● Early reduction in RV size showed a gradual return toward preoperative values by 7–10 y after PV replacement. ● The late adverse RV remodeling was associated with increased RV volume and pressure loads.
Harrild DM, et al. 2009 (547) 19139389	n=77 pts	Case control study	Inclusion criteria: TOF with PV replacement >5 y prior Exclusion criteria: Confounding structural HD (AVC, Ebstein)	Death, VT	● No significant differences were found in age, QRS duration, type or decade of initial repair, age at TOF repair, or presence of pre- PV replacement VT between the 2 groups.	● Late PV replacement for symptomatic PR did not reduce the incidence of VT or death.
Tsai SF, et al. 2010 (548) 20723654	n=80 pts	Retrospective cohort	Inclusion criteria: CHD pts with screening EPS	Positive screening EPS for ventricular arrhythmia	● 23 pts with positive screening EPS and correlated with QRS duration, fibrosis on CMR and exercise capacity.	● Almost 30% of pts had a positive screening EPS for VA and combined exercise capacity and myocardial fibrosis predicted a positive study.
Lucron H, et al. 1999 (549) 10235097	n=89 pts	Retrospective cohort	Inclusion criteria: Pts with s/p repair for TOF who underwent EPS	Positive for inducible sustained VT	● Compared the group that was positive n=21 vs. 68 that were negative. Those positive were older, had previous palliative shunt, higher RV systolic pressure, and had symptoms. In follow-up, no pt with a negative study had clinical VT.	● A negative EPS may be helpful in the management of postoperative TOF pts and a positive should be interpreted with caution.

Dietl CA, et al. 1994 (550) 7955286	n=107 pts	Retrospective cohort	Inclusion criteria: Postoperative repair TOF who underwent 24 ambulatory monitor	Comparing RV vs. right atrial approach for TOF repair for atrial and VA on 24h ambulatory monitor.	● Pts who underwent RV approach to TOF repair vs. right atrial approach had significantly greater atrial and VA, RV dysfunction and pulmonary insufficiency.	● Right atrial approach had significantly reduced risk for life threatening VA.
Khairy P, et al. 2007 (551) 17522719	N/A	Applying Bayesian theory to screening EPS for repaired TOF	Inclusion criteria: N/A	N/A	● To identify pts with TOF in whom inducing VT would increase the risk category sufficiently to contemplate ICD implantation, the minimum pretest probability for SCD should be 0.95%, which corresponds to a positive post-test probability of 3.5%. ● A combination of static and dynamic noninvasive risk factors, such as age, transannular patch, nonsustained VT, syncope, and hemodynamic or echocardiographic data is, however, likely to identify a subgroup with a sufficiently high pretest probability to warrant further stratification with EP testing.	● Bayesian perspective indicates that PVS need not be routinely performed to risk-stratify all pts with TOF.
Koyak Z, et al. 2013 (552) 22608897	n=36 pts	Retrospective cohort	Inclusion criteria: TOF pts with ICD for 1° prevention	Appropriate ICD shocks and compare to risk model	● 7 pts (19%) received ICD shock during median follow-up of 5.5 y. Only NSVT was associated with appropriate shock. The risk model predicted low, medium and high-risk pts.	● The risk model was able to stratify risk, but event rates were lower than predicted.
Witte KK, et al. 2008 (553) 18442962	n=29 TOF pts and 39 with DCM	Retrospective cohort	Inclusion criteria: TOF and DCM pts with an ICD	Death, ICD therapy delivery	● TOF pts had a higher incidence of inappropriate therapies and lower death rate	● TOF pts have a higher risk of inappropriate therapies and other complications yet a lower incidence of appropriate therapies from their ICD than DCM pts.
Geva T, et al. 2013 (554) 24065609		Opinion	Inclusion criteria: Repaired TOF	Indication for PV replacement	● Indications for PV replacement.	● Large multicenter trials will be necessary to better determine optimal timing for PV replacement.
Gengsakul A, et al. 2007 (528)	n=82 pts	Retrospective cohort	Inclusion criteria: TOF pts with PV replacement	PV replacement on clinical outcomes	● Symptoms, FC, pulmonary and TV regurgitation improved in the PV replacement group.	● Symptoms and functional status are improved after late PV replacement, with a

17627832			matched control TOF pts without PV replacement			reduction in pulmonary and TV regurgitation and RV size and dysfunction.

Data Supplement 44. Right Ventricle to Pulmonary Artery Conduit – Section 4.3.6

Study Name, Author, Year	Study Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results	Summary/Conclusions
Boshoff DE, et al. 2013 (555) 22887796	Retrospective case review	n=23 pts	Inclusion criteria: Conduit free RVOT or undersized RV to PA conduit (<16 mm)	Procedural efficacy and safety	● 21 Melody valves and 2 Sapien valves implanted successfully in 23 pts. ● Mean age is 17 y, range 6–81 y. ● Group 1 (n=8) had conduit free RVOT and all had presenting prior to valve placement. ● Group 2 (n=2) elderly pts with severe native PS and RVOT calcification. ● Group 3 (n=13) with existing conduit (nominal 16 mm, range 10–20 mm), all had presenting.	● PPVI safe and feasible in selected pts with an off-label indication. ● Creating an adequate "landing zone" by presenting makes the procedure safe and predictable.
Buber J, et al. 2013 (556) 23756696	Retrospective single-center review	n=147 pts	Inclusion criteria: Consecutive pts from 2007—2012 that underwent Melody valve placement at Boston Children's Hospital	Blood stream infections defined as bacterial infection treated with ≥4 wk of antibiotics	● Mean age at implant was 21.5 ± 11 y, 59% with TOF. ● During median follow-up of 19 mo, 14 pts (9.5%) had blood stream infection. ● Of these, 4 (2.7%) had Melody valve IE. ● 2 pts died during the event, neither had known valve involvement. ● Medical procedure to infection time was 15 mo. ● Univariate predictors were male sex, previous IE, in situ stents in RVOT, and presence of outflow tract irregularities at the implant site	● Blood stream infections occurred in 9.5% of pts following Melody placement. ● Minority (2.7%) had proven Melody valve IE. ● Pt and nonvalve anatomic factors may be associated with blood stream infections.
Butera G, et al. 2013 (557) 22718682	Multicenter registry prospective, observational study	n=63 pts	Inclusion criteria: Between 2007—2010, 63 pts were included in this Italian registry of Melody valve implants	Immediate and intermediate-term outcomes	● 63 pts were included in the registry (median age: 24 y; range 11–65 y). ● 40 pts were in NYHA class I–II while 23 were in NYHA class III-IV. Pts included had a history of a median 3 previous surgeries (range 1–5) and a median of 1 previous cardiac catheterization (range 0–4). ● A conotruncal disease was present in 39 pts, previous Ross operation in 9, and other diagnosis in 15.	● Early results suggest Melody implant is successful. 11% risk of early complications. ● Major concerns are related to stent fracture and bacterial IE.

					● Indication to valve implantation was pure stenosis in 21 pts, pure regurgitation in 12, association of stenosis and regurgitation in 30. ● Implantation was performed in 61 subjects (97%). Presenting was performed in 85% of cases. ● No significant regurgitation was recorded after procedure while the transpulmonary gradient reduced significantly. Early major complications occurred in 7 subjects (11%). 1 death occurred in the early postoperative period in a severely ill subject. ● At a median follow-up of 30 mo (range 12–48 mo), 3 pts died due to underlying disease. ● Major complications occurred in 6 pts during follow-up (external electric cardioversion: 1 pt; herpes virus encephalitis: 2 pts; Melody valve IE needing surgical explant: 2 pts; major fractures of the stent and need second Melody valve implantation: 2 pts). ● Freedom from valve failure at latest follow-up was 81.4% ± 9%.	
Cheatham SL, et al. 2013 (558) 23359563	Retrospective chart review	n=11 pts	Inclusion criteria: Melody valves implanted on a 24-mm balloon or postdilated to 24 mm following implantation	Immediate and intermediate-term outcomes	● Between April 2008—Dec 2011, 13 Melody valves were successfully implanted in 11 pts, median age 35 y (range 16–61 y), in the pulmonary (bioprosthetic valve, right ventricle to PA conduit, native valve) position (n=9), tricuspid position (bioprosthetic valve n=3), and aortic position (bioprosthetic valve n=1). ● 10 valves were delivered on a 24-mm balloon in balloon catheter, and 3 were implanted using a 22-mm Ensemble balloon delivery system, followed by post dilation using a 24 mm × 2 cm Atlas balloon catheter. ● Post-implant, the median peak systolic gradient across the PV was 7 mm Hg and median gradient across the TV was 3 mm Hg. There was no change in gradient across the Melody valve in the aortic position where valve prosthesis pt mismatch was present.	● The Melody valve can be implanted at 24 mm in the stenotic/regurgitant bioprosthetic pulmonary, tricuspid, and aortic valve, dysfunctional right ventricle to PA conduit, and the native RV outflow tract. ● At 9.5 mo median follow-up the valve remains competent with mild regurgitation.

					● Post-implant ICE demonstrated none or mild valve regurgitation. ● No more than mild regurgitation was noted at a median follow-up of 9.5 mo	
Faza N, et al. 2013 (559) 23008193	Retrospective data analysis of pts undergoing TPVR between 2008 and 2012	Melody (n=13) Sapien (n=20) Total=33	Inclusion criteria: All TPVRs performed at Rush University between April 2008—April 2012	Short- and intermediate-term outcomes	● 33 pts underwent successful TPVR (SAPIEN n=20, Melody n=13). ● Pt age and weight were similar between the 2 groups. 1° indication included regurgitation (SAPIEN [n=2], Melody [n=3]), stenosis (SAPIEN [n=13], M [n=7]), or mixed (SAPIEN [n=5], Melody [n= 3]). ● There was no difference in preprocedural peak Doppler gradients across the pulmonary outflow (SAPIEN = 47.73 ± 21.14 mm Hg, Melody = 42.62 ± 15.59 mm Hg; p=0.46). ● All but 1 pt underwent presenting prior to valve implantation. Immediately following valve deployment, the transvalvar gradient was not statistically different between the 2 groups (SAPEIN = 11.5 ± 8.07 mm Hg, Melody = 8.15 ± 4.56 mm Hg; p=0.18). ● There were no procedural deaths. Follow-up mean pulmonary Doppler gradients were higher with the SAPIEN cohort (18.43 ± 9.06 mm Hg (SAPIEN) and 11.17 ± 5.24 mm Hg (Melody); p=0.016); however, no differences were seen when similar procedural epochs were assessed. ● All but 1 pt remained with PR grade ≤2.	● In a single-center series, the SAPIEN and Melody valves demonstrated comparable medium-term valve function. ● Greater residual gradients with the SAPIEN valve may represent a more conservative early presenting approach with this valve.
Haas NA, et al. 2013 (560) 22932954	Retrospective case review	n=22 pts	Inclusion criteria: All SAPIEN PV replacement cases at a single center over 1 y	Immediate and short-term outcomes	● 22 pts with various RVOT morphologies transannular patch (n=4), bioprosthesis (n=2), homograft (n=5), and Contegra conduit (n=11). PS (n=2), PR (n=11) and a combined PS/PR (n=9). ● 21/22 pts with successful PV replacement, mean age 21.7 y. ● Decrease in mean RV systolic pressure from 61 mm Hg to 41 mm Hg, reduction in peak systolic gradient from 37 mm Hg to 7 mm Hg. Resolution of PR in all cases.	● TPVR with Edwards-Sapien valve can be performed safely with good immediate and short-term results in pts with PS/PR.

					● 5.7 mo follow-up, no change in valve function.	
Hainstock NR, et al. 2013 (561) 24254707	Single-center, retrospective analysis of angioplasty of obstructed RVOT homograft conduits	n=70 pts	Inclusion criteria: Pts that underwent homograft conduit angioplasty with ultra-noncompliant balloons	Immediate outcomes	● 70 pts underwent 76 procedures. ● All pts with RV to PA obstructed homografts, underwent angioplasty with ultra-noncompliant balloons, outcomes compared to 81 pts who had angioplasty with conventional balloons. ● Acute hemodynamic changes after angioplasty of homografts with ultra-noncompliant balloons included significantly reduced RV:aorta pressure ratio ($p=0.02$) and RV outflow tract gradients ($p\leq0.001$). Balloon waist resolution was more frequently achieved with noncompliant balloons ($p=0.04$), and balloon rupture occurred less often ($p<0.001$). ● Conduit tears of any severity occurred in 22% of pts overall and were more common in the ultra noncompliant balloon group ($p=0.001$). Pts with any conduit tear had significantly greater reduction in their RV: aorta pressure ratio ($p<0.001$) and RVOT gradient ($p=0.004$) than those with no tear. ● There were 4 unconfined tears, all in the ultra-noncompliant balloon group, with no acute decompensations or deaths, 1 pt needed surgical intervention	● Ultra-noncompliant balloon angioplasty of stenotic RV-PA homografts is more effective than angioplasty with conventional balloons in reducing stenosis. ● The risk of conduit tears is higher with noncompliant balloons. Unconfined tears only occurred with noncompliant balloons.

McElhinney DB, et al. 2013 (562) 23735475	Cross-sectional case series Multicenter case series from 3 ongoing prospective multicenter trials in the U.S. and Europe	n=311 pts	Inclusion criteria: Pts at multiple centers who have undergone Melody PV replacement as part of 3 prospective multicenter center trials	intermediate- and long-term outcomes	● Any clinical episode with positive blood cultures and fever was considered IE regardless of valve involvement. ● 3 trials included 311 pts with a median follow-up of 2.5 y 16 pts diagnosed with IE between 50 d and 4.7 y post Melody implant, median of 1.3 y. ● 6 pts with evidence of valve related IE (3 with vegetations, 2 with valve dysfunction, 1 with both). Annualized rate of IE episodes is 2.4% per pt y. ● All pts treated with IV antibiotics, 4 with valve explanted and 2 received a second transcatheter valve. ● 1 pt died of sepsis, 1 pt died of sudden hemoptysis, and 2 pts developed recurrent IE.	● IE occurred in 5% of pts post-Melody implantation with an annualized rate of 2.4%/pt y, valve related IE occurred in 2% of pts. ● Most cases respond well to IV antibiotic treatment.
Batra AS, et al. 2012 (563) 22305848	Multicenter case series	n=150 pts	Inclusion criteria: Pts at multiple centers who underwent CPET testing before and 6 mo following Melody PV placement	Change in cardiopulmonary exercise performance post Melody valve placement	● No significant change in peak VO_2 or O_2 pulse. ● Small but significant improvements noted in work rate achieved and VE/ VO_2 ratio at the anaerobic threshold. ● Post-Melody improvement in peak VO_2 was greatest in pts with the lowest baseline peak VO_2.	● Transcatheter Melody PV replacement is associated with modest improvements in exercise capacity and gas exchange efficiency.
Muller J, et al. 2014 (564) 24713459	Single-center retrospective case review	n=59 pts	Inclusion criteria: Between 2007—2013, pts at a single center who underwent TPVR and underwent CPET testing, MRI and QOL assessment pre and post valve replacement	Changes in cardiopulmonary exercise performance and QOL pre- and post-valve replacement	● 59 pts, mean age 22.8 y, 46 with PS, 13 with PR. 56 had Melody valve placement, 3 with Sapient valve placement. ● All pts had dysfunctional conduits. ● Peak VO_2 improved from 27.2 to 29.2 mL/kg/min ($p<0.001$), improvements seen in both PS and PR subgroups. ● QOL was good before valve replacement but improved in multiple domains post- PV replacement, especially in physical function, general health perception, and health transition.	● QOL improvements are noted post-TPVR. ● There is a modest improvement in peak O_2 consumption following transcatheter PVR.

Gillespie MJ, et al. 2012 (565) 23212395	Multicenter case series	n=104 pts	Inclusion criteria: Pts at 8 U.S. Centers who underwent Melody TPVR in a failing bioprosthetic valve between 2007—2012	Short- and intermediate-term outcomes following TPVR	● 104 pts underwent TPVR in dysfunctional bioprosthetic PV s. ● 100% procedural success rate. ● Peak RV-PA conduit gradient decreased from 39 mm Hg to 11 mm Hg mean. ● No serious procedural morbidity or mortality. ● Median of 12 mo follow-up, no significant PR, 4 pts with PS. ● 2 stent fractures during follow-up. ● 3 cases of IE, 2 needing surgical explant.	● Melody TPVR in dysfunctional bioprosthetic valves can be accomplished with a high success rate and good short- and intermediate-term outcomes.
Eicken A, et al. 2011 (566) 21273201	2 center retrospective case series	n=102 pts	Inclusion criteria: Combined TPVR experience of 2 German Centers (Munich and Berlin)	Short- and intermediate-term outcomes following TPVR	● 102 pts with dysfunctional RVOTs, median age 21.5 y. ● Median follow-up 352 d ● Prestenting performed in 95% of pts. ● Median peak systolic RVOT gradient decreased from 37 mm Hg to 14 mm Hg. ● Median MRI measured RVEDV index decreased from 106 mL/m^2 to 90 mL/m^2. ● PR significantly reduced in all pts. ● 1 pt died of left coronary compression. ● 5% incidence of stent fracture. ● 1 pt with IE on the Melody valve requiring surgical removal. ● Repeat intervention needed in 8/102 pts, 4/102 pts with valve in valve procedure.	● Melody TPVR in dysfunctional RVOT conduits is feasible and effective in improving stenosis and relieving regurgitation. ● The rate of short- and intermediate-term complications is low.
Hasan BS, et al. 2011 (491) 22075926	Multicenter case series	n=30 pts	Inclusion criteria: Melody valve implantation in high pressure systems	Short-term outcomes	● 30 pts at 5 centers in the U.S. ● 23 pulmonary, 5 native aortic, 1 LV to Ao, 1 mitral high pressure environment in PA circulation defined as mean PAP >25 mm Hg. ● In the pulmonary position 10 implants in homografts and 13 in bioprosthetic valves or bioprosthetic valved conduits. ● 3 pts died; 2 with Melody valves in the systemic circulation, 1 in the pulmonary circulation who died 8 mon after the procedure of drug overdose. ● At 1 y, freedom from moderate-to-severe regurgitation was 100%; freedom from mild regurgitation was 90%.	● Short-term performance of the Melody valve in high pressure environments is good.

Kenny D, et al. 2011 (567) 22078433	Case series, prospective multicenter, nonrandomized	n=36 pts	Inclusion criteria: Edwards-Sapien TPVR	Immediate and short-term outcomes	● 36 pts from 4 centers. ● All pts with dysfunctional RVOT conduits. ● Mean age 30 y. ● Successful TPVR in 33 of 34 attempts (97%). ● Valve migration in 3 pts, 2 required surgical retrieval. ● Pulmonary hemorrhage in 1 pt. ● Decreased RV to PA peak gradient from 27 mm Hg to 12 mm Hg, reduction in PR. ● No deaths. All pts alive at 6 mo. Improved FC noted in most pts	● The Edwards-Sapien transcatheter heart valve can be used safely and effectively in dysfunctional RV to PA conduits.
Lurz P, et al. 2011 (568) 21292132	Case series Retrospective single- center review	n=65 pts	Inclusion criteria: Pts who had TPVR who had MR imaging and cardiopulmonary exercise testing within 1 mo before TPVR, within 1 mo post TPVR and 12 mo after TPVR	Immediate and intermediate outcomes	● 65 pts included, divided into predominant PS (n=35) or PR (n=30). ● Significant early decrease in RVEDV in both groups. ● Improved early RVEF by MRI in PS group (51%>58%). ● No late improvements or changes by MRI in either group. ● Improved early peak VO_2 in PS group, no further change with retesting at 1 y. ● No VO_2 changes noted early or late in the PR group.	● Early (1 mo) reductions are noted in RV size in both PS and PR groups following TPVR, these are maintained at 1 y. ● Pts with preprocedural PS show early improvements in RVEF and peak VO_2 post TPVR. ● No evidence of further positive functional remodeling noted beyond 1 mo following TPVR.
McElhinney DB, et al. 2011 (569) 22075927	Case series; prospective multicenter nonrandomized trial	n=150 pts	Inclusion criteria: Pts who underwent Melody TPVR as part of the Melody Valve Investigational Device Exemption Trial	Immediate and intermediate-term outcomes	● 150 pts, median age 19 y, all with dysfunctional RV-PA conduits. ● Existing conduit stents in 37 pts (25%), 12 of these already fractured. ● 1 or more stents placed at the time of Melody valve placement in 51 pts. ● Median follow-up of 30 mo, 39 pts with stent fracture (26%). Freedom from stent fracture was 77% at 14 mo and 60% at 39 mo. ● Multivariable analysis demonstrated that implantation of the Melody valve within an existing stent, new prestent, or bioprosthetic valve are associated with longer freedom from stent fracture.	● Melody stent fracture is common following TPVR implant and is more likely with severely obstructed conduits that are adherent to the anterior chest wall. ● Prestenting and implantation of a Melody within a previously stented conduit or within a bioprosthetic valve all lower the risk of Melody stent fracture.

					● TPV compression and conduit apposition to the anterior chest wall were associated with shorter freedom from stent fracture.	
McElhinney DB, et al. 2010 (570) 20644013	Prospective multicenter nonrandomized trial	n=124 pts	Inclusion criteria: Pts with dysfunctional RVOT conduits that underwent Melody PV replacement at 5 U.S. centers between 2007–2009	Short- and intermediate-term outcomes	● 136 pts underwent catheter for Melody implant, 124 pts had Melody implanted in a dysfunctional RVOT conduit. ● Mean age 19 y. ● 1 death after coronary artery dissection. ● 1 conduit rupture requiring valve explant. ● RVOT peak gradient decreased from 27 mm Hg to 12 mm Hg after TPV placement. ● No pt with more than mild PR post Melody or up to 1 y follow-up. ● Freedom from stent fix was 78% at 14 mo, freedom from Melody valve dysfunction or reintervention was 93.5% at 1 y. ● All reinterventions were for RVOTO, mostly due to stent fracture.	● High rate of procedural success, low morbidity and mortality rates, encouraging short- and medium- term outcomes following Melody valve placement in dysfunctional RV-PA conduits. ● Melody stent fracture is the major cause for reintervention.
Zahn EM, et al. 2009 (571) 19850214	Prospective multicenter nonrandomized trial	n=34 pts	Inclusion criteria: Pts with dysfunctional RVOT conduits that underwent Melody PV replacement at 3 U.S. centers in 2007	Procedural and short-term outcomes	● 34 pts underwent catheter for Melody implant, successful implant in 29 pts. ● Mean age 19 y. ● Procedural complications were 1 conduit rupture requiring surgical intervention, 1 wide complex tachycardia, 1 distal PA guide wire perforation. ● Peak conduit gradient decreased from 37 mm Hg to 17 mm Hg, no pt had more than mild PR.	● Melody valve implantation can be performed with high procedural success, low mortality rates, and results in improved hemodynamics. ● Melody stent fracture is common and occurred in 27% of pts.
Nordmeyer J, et al. 2011 (572) 20965979	Retrospective single-center analysis of prospectively collected data	n=108 pts	Inclusion criteria: Pts with CHD who underwent Melody valve placement in the pulmonary position at a single institution	Short- and intermediate-term outcomes	● 108 consecutive pts underwent Melody TPVR from 2005–2008 for dysfunctional RV-PA conduits. ● 54 pts with Melody alone, 54 pts with prestenting prior to Melody placement. ● Prestenting associated with lower RVOT velocities. Prestenting associated with a lower risk of stent fracture (HR: 0.35; p=0.024). ● The probability of freedom from serious adverse follow-up events (death, device explanation, repeat intervention) was not statistically different at 1 y.	● Prestenting of dysfunctional RV to PA conduits prior to Melody TPVR reduces the risk of Melody stent fracture.
Frigiola A, et al. 2008 (530)	Prospective single-center	n=36 pts	Inclusion criteria: Pts with severe PR due to	Short- and intermediate-	● 25 pts (mean age 21 y) with dysfunctional RVOT conduits underwent surgical TPVR.	● Surgical or TPVR for severe PR caused by a

18539471	case series with surgical and TPVR arms		dysfunctional RV-PA conduit that underwent surgical or TPVR and had pre and post intervention MRI data	term outcomes	● 11 pts (mean age 20 y) underwent TPVR. ● MRI performed prior to and 1 y following intervention. ● Following intervention, there were significant reductions in RV volumes in both groups. ● Both groups had improvements in LV and RV stroke volume.	dysfunctional RV-PA conduit results in decreased RV volume and improved RV and LV stroke volume.
Lurz P, et al. 2008 (573) 18391109	Retrospective analysis of TPVR performed at 2 European centers between 2000—2007	n=155 pts	Inclusion criteria: Pts with dysfunctional RV-PA conduits who underwent TPVR	Short-, intermediate- and long-term outcomes	● 155 pts with PS and/or PR due to dysfunctional conduit had TPVR. ● Significant reduction in RVOT gradient (37 mm Hg to 17 mm Hg) and RV systolic pressure (63 mm Hg to 45 mm Hg). Follow-up ranged from 0–83.7 mo, median 28.4 mo. ● Freedom from reoperation was 95% at 10 mo, 87% at 30 mo and 73% at 50 and 70 mo. ● Survival at 83 mo was 97%. ● Time dependent analysis demonstrated that the first 50 cases performed and pts with a residual gradient >25 mm Hg were associated with a higher risk of reoperation. ● Reintervention was primarily for the “hammock” effect in 7 pts and stent fractures in 9 pts.	● Long-term follow-up post TPVR demonstrates that 73% of pts do not require reintervention at 70 mo. Excellent long-term survival post TPVR. ● There is a higher risk of reoperation if the residual RVOT gradient is >25 mm Hg and in the first 50 cases performed.
Nordmeyer J, et al. 2007 (574) 17339542	Retrospective single-center case series	n=123 pts	Inclusion criteria: Pts with dysfunctional RVOT who underwent PV replacement and had structured follow-up with CXR and echo	Short-, intermediate- and long-term outcomes	● 123 pts included, 26 (21%) developed Melody stent fracture 0–843 d post procedure. ● Melody stent fracture free survival at 1 y is 85%, at 2 y is 75%, and at 3 y is 69%. ● The majority (n=17) of pts had mild type 1 stent fractures with no loss of stent integrity, 8 pts had type II stent fractures with loss of integrity and restenosis, 1 pt had type III stent fracture with separation of fragments and embolization. ● Multivariate analysis demonstrated that implantation into “native” RVOT, absence of conduit calcification, and recoil of the Melody stent were associated with an increased risk of stent fracture.	● Melody stent fracture occurs in 21% of pts and is associated with “native” RVOT, absence of RVOT calcification and stent recoil.

Coats L, et al. 2006 (575) 16636174	Retrospective single-center case series	n=18 pts	Inclusion criteria: Pts with RVOTO (defined as RVOT peak gradient >50 mm Hg by echo/Doppler) who underwent TPVR and underwent MRI and CPET. Excluded if they had more than mild PR	Short-term outcomes	● 18 pts with RVOTO, 17 with conduits, 1 with native RVOTO, median age 20 y. ● TPVR reduced RVOT gradient from 51 mm Hg to 22 mm Hg and RV systolic pressure from 73 mm Hg to 47 mm Hg. Improved peak VO_2 and anaerobic threshold. ● Decreased RV volume, improved RVEF, and RV stoke volume by MRI.	● TPVR is effective in relieving RVOT stenosis and results in improved hemodynamics, decreased RV size, improved RV stroke volume and RVEF. ● Peak VO_2 and anaerobic threshold are also improved.
Coats L, et al. 2005 (576) 15784347	Retrospective multicenter case review	n=129 pts	Inclusion criteria: Pts that underwent surgical or TPVR between 1998–2004	Short- and intermediate-term outcomes	● 94 pts underwent surgical reintervention for RVOT dysfunction (median age 26 y). ● 35 underwent TPVR (median age 16 y). ● 1.1% early mortality in the surgical group, no mortality in the TPVR group. ● Procedural complications in 8.5% of the surgical group vs. 5.7% in the TPVR group. ● Freedom from reintervention was 100% at 1 y in the surgical group and 86% in the TPVR group, due to late stenosis/stent fix. ● Median hospital stay was 7 d in the surgical group vs. 2 d in the percutaneous group.	● Both surgical and TPVR are safe and effective ways of intervening upon dysfunctional RVOT.
Brown JW, et al. 2008 (577) 19049758	Retrospective single-center review	n=186 pts	Inclusion criteria: All pts undergoing Ross AVR from June 1993–May 2007	Long-term outcomes	● 183 consecutive pts underwent Ross AVR with RVOT reconstruction (median age 23.3 y). ● 156 pts with cryopreserved pulmonary homograft; 22 pts decellularized; 5 bovine jugular. ● Mean follow-up 5.7 y. ● 3 deaths. ● 24 pts (13%) with peak RVOT >20 mm; 5 (3%) with gradient >40 mm; 7 (4%) had more than 2+ RVOT insufficiency. ● Freedom from reoperation and RV dysfunction at 10 y 96%. ● Predictors of dysfunction are grafts <14 mm.	● Good outcomes with pulmonary homograft in RVOT position in Ross procedure.
Niemantsverdriet MB, et al. 2008 (578) 18557880	Multicenter international study retrospective review	n=194 pts	Inclusion criteria: Pts undergoing 1°RVOT reconstruction using RV to PA conduit from Jan 1987—March 2003	Long-term outcomes	● 194 pts with median follow-up 4.7 y. ● 57% had aortic homografts, 25% pulmonary, and 12% Contegra. ● Average size of conduits between 11 and 13 mm. ● Freedom from conduit failure at 5 y was 50% with 128 pts having surgery for obstruction.	● Longevity increased in those with pulmonary homograft, largest possible conduit. ● Consider transcatheter intervention for conduit obstruction.

Ong K, et al. 2013 (523) 23481618	Retrospective case review	n=49 pts	Inclusion criteria: TOF with pulmonary atresia or stenosis undergoing RV to PA conduits from 1974—2011	Long-term outcomes	● 106 conduits in 49 pts. ● Freedom from reoperation in 10 y: first conduit = 50%, second = 74%, third = 86%.	● Most pts undergo revision in adulthood. ● Most conduits in adults meet criteria for percutaneous PV.
Morray BH, et al. 2013 (522) 24065444	Multicenter, (4) retrospective	n=404 pts: 226 TOF, 84 TOF/PA	Inclusion criteria: Pts referred for transcatheter PV replacement	N/A	● Presence or absence of coronary artery compression.	● 21 (5%) had evidence of coronary artery compression with simultaneous RVOT angioplasty and coronary angiography. ● 68 (17%) had abnormal coronary angiography anatomy.
Ait-Ali L, et al. 2014 (518) 25260437	Prospective study ex-echocardiography CMR, CPET, BNP	n=109 pts, 9 (7.3%) TOF/PA	Inclusion criteria: Consecutive pts; mean age 26 y; age <10 y; contraindication CMR; complex anomalies (AVC)	Death for all causes, cardiac death, development or progression of HF, and TAs.	● Tricuspid annular plane systolic excursion increased significantly during peak exercise in responders from 17.2 ± 3.4 mm at rest to 19.7 ± 4.3 mm ($p<0.0001$) but did not in nonresponders (from 16.9 ± 4.7–18.1 ± 4.6 mm; $p=0.20$). ● LV end-diastolic volume at rest and LVEF <50% were related to the lack of increased RV fractional area change on exercise.	● Exercise echo is feasible in pts with repaired TOF and allows the integrated assessment of variation in RV systolic pressure, area, and function during exercise, which usefully complement more conventional indices of hemodynamic burden in these pts.
Freling HG, et al. 2014 (519) 24355311	Retrospective	n=42 pts; not known TOF/PA	Inclusion criteria: Echo, CMR and CPET within 6 m. Other significant valve regurgitation or shunts	Peak VO_2	● Multivariate analysis showed that the peak RVOT gradient was the only independent predictor of exercise capacity.	● Exercise capacity is lower in pts with RVOTO compared with those without RVOTO despite a less dilated RV and comparable degree of PR.
Babu-Narayan SV, et al. 2014 (520) 24146254	Retrospective	n=220, 11 with TOF/PA	Inclusion criteria: rTOF with surgical PV replacement	All-cause mortality	● Peak VO_2, VE/ CO_2 slope (ratio of minute ventilation to CO_2 production), and heart rate reserve during CPET predicted risk of early mortality when analyzed with logistic regression analysis; peak VO_2 emerged as the strongest predictor on multivariable analysis (OR: 0.65/1 mL/kg^{-1}·min^{-1}; $p=0.041$).	● Preoperative CPET predicts surgical outcome and should therefore be included in the routine assessment of these pts.

Mainwaring RD, et al. 2012 (532) 22269747	Case series	n=5 pts	Inclusion criteria: March 2009—April 2011; 5 pts with previous TOF repair undergoing pulmonary valvuloplasty	Pulmonary insufficiency	● Median age 9 y ● For bicuspid native PV s and had undergone transannular patch with retention of native leaflets and no PS and transannular gradient of <10 mm. ● Majority of pts went from severe to trace pulmonary insufficiency.	● New technique of bicuspidization of the native PV leaflets.
Fraisse A, et al. 2014 (579) 24619978	Case series	n=100 pts	Inclusion criteria: Consecutive pts undergoing transcatheter PV implantation between 2008—2012. Incidence, diagnosis and outcome of coronary compression.	Coronary compression	● 6 pts, median age 24.5 y, compression of left main in 4, of left anterior descending from right coronary in 2. Diagnosis made by coronary angiogram or aortic root angiogram	● Recommend aortic root angio during balloon inflation to ensure proximal compression isn't missed by selective coronary angiography.
Bauer BS, et al. 2014 (580) 25363190	Case series	n=42 pts	Inclusion criteria: Pts who underwent Melody valve implantation. Comparison of echocardiographic and invasive measures of RVOT gradients.	RVOT gradient following Melody implantation	● Mean age 22 y. ● Echo using Doppler had higher estimates of RV-PA gradients than those assessed invasively immediately after Melody implantation.	● Echo estimated higher gradients than cath after Melody valve implantation, though measurements were not simultaneous.

*Aortic homografts calcify more quickly.

Data Supplement 45. Transposition of the Great Arteries with Atrial Switch – Section 4.4.1.1

Study Name, Author, Year	Study Type/ Design	Study Size	Inclusion Criteria	1° Endpoint	Results/p Values	Summary/Conclusions
Hesslein PS, et al. 1982 (581) 7064768	Prospective	n=29 pts	Inclusion criteria: TGA s/p Mustard	Exercise response	● 83% demonstrated depression of maximum HR.	● Maximal exercise testing may be a sensitive noninvasive method to identify sinoatrial node dysfunction in postoperative children.
Flinn CJ, et al. 1984 (582) 6727935	Retrospective	n=372 pts	Inclusion criteria: Mustard procedure survivors	Rhythm at follow-up	● 43% loss of sinus rhythm by 8 y.	● Over time, decreasing prevalence of sinus rhythm.
Duster MC, et al. 1985 (583) 4003242	Retrospective	n=120 pts	Inclusion criteria: Mustard procedure survivors over 3 surgical eras	Rhythm at follow-up	● After 8 y, less than 50% of the rhythms were sinus.	● Despite efforts to protect the sinus node, late occurring dysrhythmias remain a significant problem in the postoperative Mustard pt.

Kramer HH, et al. 1991 (584) 1864669	Retrospective	n=47 Mustard procedure pts	Inclusion criteria: Mustard procedure in infancy or older age	Rhythm at follow-up	● Normal findings were present in only 51% of the cases at follow-up repaired by the Mustard procedure in infancy, and in 29% of the group having the Mustard repair at an older age.	● The arterial switch procedure essentially solved the problem of SND after surgery for d-TGA, and that problem is biggest in pts who had the Mustard procedure outside of infancy.
Hucin B, et al. 2000 (585) 10901527	Retrospective	n=177 pts	Inclusion criteria: Exercise response Mustard 1979–1984, follow-up 12–18 y	Rhythm at follow-up	● 10 SCDs. SND in 51%.	● SND is very common following the Mustard procedure.
Khairy P, et al. 2004 (586) 15680022	Meta-analysis	n=885 pts (369 Mustard, 474 Senning)	Inclusion criteria: 7 studies	SND	● No separate analysis.	● Sinus nodal dysfunction was more common after the Mustard procedure than the Senning.
Diller GP, et al. 2006 (376) 16979014	Retrospective	n=727 pts	Inclusion criteria: Consecutive adult CHD pts without pacemakers, 1999–2005 with exercise testing for heart rate reserve	All-cause mortality	● Heart rate reserve predicted mortality independently of antiarrhythmic therapy, FC, and peak VO_2. A lower heart rate reserve was associated with a greater risk of death in pts with complex anatomy, Fontan circulation, and TOF ($p<0.05$ for each).	● An abnormal heart rate response to exercise identifies ACHD pts with a higher risk of mortality in the midterm.
Diller GP, et al. 2009 (587) 18495265	Retrospective	SRV (n=32), univentricular circulation (n=32)	Inclusion criteria: Adult CHD pts with SRV or univentricular circulation, age 28 ± 11.3 y who underwent exercise testing. Paced pts excluded	Exercise capacity, chronotropic competence	● Chronotropic incompetence in 59% of systemic RV pts, 84% of univentricular circulation pts.	● Chronotropic incompetence is common and associated with exercise limitation in pts with a SRV or univentricular circulation.
Champsaur GL, et al. 1973 (588) 4705569	Retrospective	n=123 pts	Inclusion criteria: Pediatric survivors of atrial switch in Toronto	Early and late deaths	● 21% died, 12 late deaths, 2 sudden attributed to arrhythmia.	● Some deaths following the Mustard procedure are sudden.
Thornback P, et al.	Retrospective	n=18,000 pts	Inclusion criteria: Children	Sudden unexpected death	● 33 SCDs, 3 in transposition pts.	● Some deaths following the Mustard procedure are sudden.

1975 (589) 803125			with HD in Toronto			
Flinn CJ, et al. 1984 (582) 6727935	Retrospective	n=372 pts	Inclusion criteria: Mustard procedure survivors	Rhythm and death	● 9 SCDs.	● Over time, a small risk of SCD.
Vetter VL, et al. 1987 (590) 3680795	Retrospective	n=64 pts	Inclusion criteria: Mustard children undergoing EPS	Inducible flutter	● 51% had IART inducible, 48% of them went on the have clinical flutter.	● Alone or in combination, these abnormalities, which result in severe bradycardia or rapid atrial arrhythmia, may lead to SCD.
Hayes CL, et al. 1986 (591) 3941200	Retrospective	n=95 pts	Inclusion criteria: Mustard survivors	Arrhythmia and SCD	● 75% with atrial arrhythmia by 6 y. 3% incidence of SCD.	● Elimination of arrhythmias caused by extensive intra-atrial surgery is 1 of the potential advantages of the ASO for correction of TGA.
Deanfield J, et al. 1988 (592) 3172804	Retrospective	n=100 pts	Inclusion criteria: Mustard and Senning survivors	Arrhythmias and SCD comparing Mustards and Sennings	● 4% SCD, equally divided.	● Because late death could not be predicted by ECG analysis; an alternative approach involving detailed hemodynamic and EP measurements may be required to identify high-risk pts.
Janousek J, et al. 1994 (593) 7846933	Retrospective	n=359 pts	Inclusion criteria: Mustard and Senning survivors	Arrhythmias and SCD	● SND in 63%, 4.2% died suddenly.	● By multivariate analysis severe TR and/or RV dysfunction and uncontrolled SVT were identified as the 2 significant risk factors for SCD.
Helbing WA, et al. 1994 (594) 8041184	Retrospective	n=122 pts	Inclusion criteria: Mustard and Senning survivors	Arrhythmias and SCD comparing Mustards and Sennings	● 6% incidence of SCD in both groups.	● Apart from the difference in the loss of sinus rhythm, no differences were found in the long-term clinical results of the 2 types of operations.
Gelatt M, et al. 1997 (595) 8996314	Retrospective	n=534 pts	Inclusion criteria: Mustard survivors, single center	Risk factors for late mortality, loss of sinus rhythm and atrial flutter after the Mustard operation	● SCD in 31/534 (5.8%) Independent risk factors for unexpected SCD among operative survivors were smaller size at operation (OR: 1.28; 95% CI: 1.07–1.53; $p<0.008$ for each 0.1 m^2 decrement in body surface area); presence of atrial tachyarrhythmia during the operative period (OR: 3.56; 95% CI: 1.56–8.12; $p<0.003$); and presence of permanent heart	● Ongoing loss of sinus rhythm and late peaks in the risk of atrial flutter and death necessitate continued follow-up.

					block (OR: 5.71; 95% CI: 1.32–24.8; p<0.02).	
Puley G, et al. 1999 (596) 10190524	Retrospective	n=86 pts	Inclusion criteria: Adult survivors of Mustard procedure	Arrhythmia and survival	● 48% with SVT, 2 SCD	● Adult survivors of the Mustard procedure continue to be at risk for premature death, congestive HF and supraventricular tachyarrhythmia.
Sun ZH, et al. 2004 (597) 15219528	Retrospective case-control	n=22 pts	Inclusion criteria: SCD victims with Mustard or Senning	QT dispersion, loss of sinus rhythm	● QT dispersion p<0.01 vs. control, loss of sinus rhythm p<0.002	● A combination of increased QT dispersion with loss of sinus rhythm increases the positive predictive value for SCD in pts with TGA after Mustard and Senning procedures.
Khairy P, et al. 2008 (598) 19808416	Multicenter cohort study	n=37 pts	Inclusion criteria: TGA atrial baffle with ICD	Risk factors for shocks	● Annual rates of appropriate shocks were 0.5% and 6.0% in 1° and 2° prevention, respectively (p=0.0366).	● High rates of appropriate shocks are noted in secondary but not 1° prevention. SVA may be implicated in the etiology of ventricular tachyarrhythmias; beta-blockers seem protective, and inducible VT does not seem to predict future events.
Van Hare GF, et al. 1996 (599) 8644650	Retrospective case series	n=10 pts	Inclusion criteria: Children s/p Mustard/Senning undergoing ablation for IART	Success/failure	● 10/13 IARTs successfully ablated.	● Ablation of IART after the Senning or Mustard procedure is feasible using concealed entrainment mapping techniques, but requires a detailed knowledge of the individual surgical anatomy and the ability to approach the pulmonary venous atrium.
Kanter RJ, et al. 2000 (600) 10676691	Retrospective case series	n=11 pts	Inclusion criteria: Children s/p Mustard/Senning undergoing ablation for IART	Success/failure	● 8/11 pts successfully ablated.	● Radiofrequency catheter ablation can be effectively and safely performed for certain SVT types in addition to intra-atrial reentry.
Kriebel T, et al. 2002 (601) 12395221	Retrospective case series	n=13 pts	Inclusion criteria: Pts s/p Mustard/Senning undergoing ablation for IART	Success/failure	● 14/15 IARTs successfully ablated.	● In the majority of our pts, curative treatment was feasible by induction of linear radiofrequency current lesions by primarily targeting electrical protected areas of atrial tissue in the systemic venous atrium.
Zrenner B, et al.	Retrospective case series	n=12 pts	Inclusion criteria: Adults	Success/failure	● 12/14 IARTs successfully ablated.	● In Mustard pts, the TA serves as the most frequent central barrier of IART.

2003 (602) 14678105			s/p Mustard/Senning undergoing ablation for IART			● Biatrial electroanatomic mapping combined with entrainment mapping facilitates delineation of IART circuits in relation to their anatomic barriers and enables the design of individual ablation strategies to achieve high success.
Wu J, et al. 2013 (603) 23355133	Retrospective case series	n=26 pts	Inclusion criteria: Adults s/p Mustard/Senning following ablation for IART	Recurrence	● Recurrence rate 30%.	● Catheter ablation of IART or AVNRT in pts post-Mustard/Senning operation for d-TGA has a high acute success rate. ● The recurrence rate for IART is about 30%; however, after a second ablation, long-term results are excellent.
Correa R, et al. 2013 (604) 24052498	Retrospective case series	n=29 pts (Mustard and Senning)	Inclusion criteria: Use of transbaffle puncture	Success/failure and complications	● Overall success 77%.	● Transbaffle access is feasible in this population; its use was not associated with a higher incidence of AE.
Testing						
Giardini A, et al. 2009 (605) 19389567	Observational	n=274 pts	Inclusion criteria: Adults with d-TGA after atrial redirection surgery	Assess prognostic value of CPET	● If ventilatory equivalent of elimination rate of CO_2 >35.4 and peak VO_2<52%, predicted high-risk 4-y event (78%).	● CPET good prognostic value. Pts with enhanced ventilator response or with poor exercise capacity had a substantially higher 4 y risk of death or emergency admission.
Plymen CM, et al. 2010 (606) 20720248	Prospective longitudinal observational study	n=35 pts	Inclusion criteria: Adults with d-TGA after atrial redirection surgery	Evaluate Systemic RV performance using ECG and NT-proBNP	● Mean age 29 ± 6.5 y ● Relationship between diastolic and systolic RV function and NT-proBNP and QRS duration.	● Circulating NT-proBNP and ECG Parameters offer safe and cost effective surrogate markers for systemic RV failure and HF.
Westhoff-Bleck M, et al. 2013 (126) 24207068	RCT	n=48 pts	Inclusion criteria: Adults with d-TGA after atrial redirection surgery. 24 wk of structured exercise training or usual care	Change in Peak VO_2 Secondary endpoint was systemic RV diameter by CMR	● Exercise training increased exercise capacity (peak VO_2 3.8 mL/kg/min, work load, maximum exercise time and NYHA). ● No change in RV volume and function.	● Aerobic exercise improved exercise capacity and HF symptoms.
Westhoff-Bleck M, et al.	Prospective longitudinal	n=116 pts	Inclusion criteria: Adults	Evaluation of NT-proBNP relative to	● Observational time was 7.3 y (± 2.4 y).	● In systemic RV, NT-proBNP is a useful predictor for all causes of

2013 (607) 24169536	observational study		with d-TGA after atrial redirection surgery	all cardiac causes of hospitalization, HF, transplantation and death	● NT-proBNP detected pts at risk for HF, transplantation and death.	hospitalization, and HF, transplantation and death. It may be a useful risk assessment tool.
Diller GP, et al. 2012 (608) 22607865	Observational	n=87 with d-TGA and 42 with CCTGA	Inclusion criteria: Adult pts with systemic RV	Biventricular myocardial deformation was compared with healthy pts	● Systemic ventricular longitudinal 2D peak systolic strain was significantly reduced compared with controls. ● Systemic 2D-longitudinal strain was related to adverse clinical outcome independently of EF on CMR, history of relevant arrhythmia or FC.	● Global longitudinal systolic strain is significantly reduced in pts with systemic RV, is related to subpulmonary ventricular function and predicts clinical outcome in adults with atrial switch.
Hoffman P, et al. 2008 (609) 18651400	Observational	n=60 pts	Inclusion criteria: Atrial switch pts who had Mustard or Senning from 1982–1990. Pts were 14.9 ± 3.5 y at the time of the study	Echocardiography and myocardial perfusion imaging performed. Systolic RV function assessed from subcostal view	● 21 pts had significant impairment of RV systolic function. ● RV area change ≤0.35 detected moderate to severe perfusion abnormalities with 78% sensitivity and 62% specificity.	● RV fractional area change evaluated from subcostal view provides significant clinical information. ● A cutoff value of 0.35 can be used as an indicator of RV impairment associated with significant perfusion abnormalities.
Khattab K, et al. 2013 (610) 23276471	Observational	n=37 pts (56 echos)	Inclusion criteria: Adults with d-TGA and previous atrial switch (26.9 ± 7.4 y)	Fractional area change, lateral tricuspid annular plane systolic excursion, lateral RV systolic motion velocities by tissue Doppler, RV myocardial performance index, and dp/dt assessed and compared with RVEF by CMR	● Routine nongeometric echocardiography parameters correlate weakly with CMR derived EF.	● RV pressure increase should be preferentially used to assess systemic systolic function in adults with subaortic RV.
Poerner TC, et al. 2007 (611) 17604961	Observational	n=24 pts	Inclusion criteria: Pts with d-TGA after atrial switch. Aged 12–33 y. 10 controls	Evaluate regional myocardial function	● In d-TGA both ventricles showed reduced peak systolic strain rate at rest. ● The increase in peak early diastolic velocity was reduced in	● Exercise tissue Doppler echocardiography/strain rate imaging identified reduced relaxation reserve of both ventricles after atrial switch for d-TGA.

			subjects. Tissue Doppler echocardiography at rest and during bicycle exercise.		the systemic ventricle and absent in the subpulmonary ventricle	
Winter MM, et al. 2008 (612) 18713464	Observational	n=29 pts (17 Mustards, 12 CCTGA)	Inclusion criteria: Measure of RV volumes including our excluding trabeculation and papillary muscle	Compare methods of cavity delineation in systemic RV	● Including structures resulted in shorter time and better inter observer reproducibility of EF	● Choice of method for systemic RV delineation affected RV volumes. Recommend delineation outside the trabeculation (less time and more reproducible).
Dore A, et al. 2005 (252) 16216961	Multicenter randomized double-blind	n=29 pts	Inclusion criteria: Adult pts (21 Mustard, 8 CCTGA)	Impact of ARB on systemic RV	● Losartan and placebo did not show any difference in VO_2, exercise duration or NT-proBNP.	● Losartan did not improve exercise capacity or reduce NT-proBNP.
Dos L, et al. 2013 (259) 23972966	Double-blind, placebo-controlled	n=26 pts	Inclusion criteria: Atrial switch pts, 14 eplerenone, 12 placebo, and 14 healthy volunteers	CMR parameters (systolic RV mass and EF) and neurohormonal and collagen turnover biomarker levels.	● Pts had good baseline profile (systemic RV mass and EF) Elevated NT-proBNP, C-terminal propeptide of type I procollagen, and C terminal telopeptide. ● After 1 y of therapy, a trend towards reduction of C-terminal propeptide of type I procollagen, NT-pro Metalloproteinase.	● Eplerenone pts improved baseline collagen turnover biomarkers, suggesting reduction of myocardial fibrosis. No other improvements.
Hill KD, et al. 2012 (613) 22419517	Retrospective	n=22 pts	Inclusion criteria: Adults with Mustard with baffle leak or obstruction	Assess safety and efficacy of percutaneous interventions	● 29 interventions. ● Stent placement successful in all 18 pts. ● 1 death secondary to arrhythmia 2 d post pulmonary baffle angioplasty.	● Stent placement for SVB obstruction is effective and safer than surgical intervention. ● Baffle leak occlusion can be safely accomplished but residual leaks common in short term.
Van Der Bom T, et al. 2013 23247302	Multicenter RCT	n=88 pts	Inclusion criteria: Pts with surgical or congenital systemic RV	Role of ARB on systemic RV	● No effect of 3 y Valsartan therapy on RVEF, exercise capacity or QOL. ● The RVEDV and mass increased more in the placebo group.	● No significant treatment effect of Valsartan on RVEF, exercise capacity, or QOL. ● Small differences seen in RV volume and mass.
Winter MM, et al. 2012 (258) 22036871	Multicenter RCT	n=54 pts	Inclusion criteria: Adults with systemic RV	Assess whether exercise training in adults with systemic RV improves	● 46 pts analyzed. At 10 wk, Improved VO_2 (3.4 mL/kg/min) and decreased BP (-7 mm Hg) in exercise group.	● In adults with systemic RV, exercise training improves exercise capacity.

				exercise capacity and QOL and lowers NT-proBNP	● No significant change in QOL or NT-proBNP. ● None had to discontinue exercise due to AE.	
Josephson CB, et al. 2006 (614) 16835671	Observational	n=8 pts	Inclusion criteria: Adults with d-TGA after atrial redirection surgery	Events after 3 y of follow-up	● 2 of 5 had improved systemic ventricular dysfunction, 2 of 4 had improved TR and 4 of 6 had improved FC, as determined by history or exercise testing.	● 1 pt not accounted for in follow-up. Medication given for RV dysfunction or arrhythmia.
Khairy P, et al. 2006 (615) 16702467	Retrospective, multicenter	n=37 pts	Inclusion criteria: TGA s/p atrial switch with ICD implantation	Appropriate ICD therapies	● Annual rate of shock was 6% in those with a secondary indication for a device. 0.5% in those with 1° indication.	● SVT preceded or coexisted with VT in 50% of those with appropriate shocks.

Data Supplement 46. Transposition of the Great Arteries with Arterial Switch – Section 4.4.1.2

Study Author, Year, Location	Aim of Study	Study Size (N)	Surgical Era	Mean follow-up	Late Death	Late complications	Risk Factors	Comments
DiDonato RM, et al. 1989 (616) 2598431	Long-term outcomes	n=62 pts	83–87	2.3	5%	3 with coronary problems, pulmonary stenosis in 7%	N/A	N/A
El-Segaier M, et al. 2010 (617) 20506518	Coronary screening (angiography) in survivors	n=81 pts	80–2010	N/A	N/A	7% with coronary problems	N/A	● Coronary interventions with stents performed in 6 pts, 3 pts asymptomatic.
Fricke TA, et al. 2012 (406) 22607787	Long-term outcomes	n=618 pts	83–00	10.6	1%	Neoaortic valve intervention in 1%, mild aortic root in 26%	LVOT obstruction, arch abnormalities, and prematurity	● No arrhythmia or congenital HF.
Kempney A, et al. 2013 (405) 22884697	Long-term outcomes	n=145 pts	N/A	N/A	3%	Neoaortic valve intervention in 1%, PV intervention in 6%, no late coronary events.	Cardiac interventions during childhood	● All adult survivors, not children. ● Mild root enlargement in the majority.
Khairy P, et al. 2013 (618) 23239839	Long-term outcomes	n=400 pts	83–99	18.7	2%	5% coronary problems including several deaths, 3.4% with 3+ neoaortic insufficiency, 10% with pulmonary stenosis.	Single coronary, postoperative HF	● Most events occurred in childhood.

Kim H, et al. 2011 (619) 22263137	Long-term outcomes	n=158 pts	94–10	4.3	0%	8.9% with intramural coronary arteries, 1 intervention	N/A	● Coronary problems at time of ASO, but rarely after.
Lalezari S, et al. 2011 (620) 21871285	Long-term outcomes	n=332 pts	N/A	15	4%	Moderate-severe neoaortic valve regurgitation in 3-4%	Older age, arch abnormalities, and coronary problems.	N/A
Legendre A, et al. 2003 (621) 12970230	Coronary events	n=1198 pts	82–01	5		7% with coronary events, most in first y after repair, multiple stenosis on angiography	Coronary pattern, perioperative events. Perfusion abnormalities often not present despite stenosis.	● 324 pts underwent angiography. ● Sensitivity for ECG, treadmill, echo, or nuclear study were all low (<50%), better combined.
Lim HG, et al. 2013 (407) 22573720	Long-term outcomes	n=220 pts	87–11	8.6	3%	88% free of coronary events after 23 y, neoaortic valve problems in 2%, PS in 5%	Aortic size, Tausig-Bing anomaly, or single coronary artery	● Of 95 pts undergoing coronary assessment, 5 had abnormalities.
Losay J, et al. 1990 (622) 2225399	Long-term outcomes	n=138 pts	84–87	4.3	1%	2 deaths due to coronary problems within first 2 mo. PS intervention in 1%	N/A	N/A
Oda S, et al. 2012 (623) 22334628	Long-term outcomes	n=387 pts	84–10	10	8%	Coronary issues in ~5%, neoaortic valve problems in 8%, PS in 17%.	LV outflow obstruction was risk factor for neoaortic valve dysfunction	● Use of equine patch was a risk for PS.
Ou P, et al. 2013 (624) 22795438	CT scanning	n=190 pts	N/A	N/A	N/A	Coronary problems in 9%	N/A	● Describes problems with proximal coronaries predominantly.
Planche C, et al. 1988 (625) 9636253	Long-term outcomes	n=110 pts	84–87	N/A	2%	Both late deaths were coronary related.	N/A	N/A
Popov AF, et al. 2012 (626) 22958234	Long-term outcomes	n=52 pts	91–99	5	N/A	Coronary problems in 2%, neoaortic valve intervention in 4%, pulmonary stenosis intervention in 6%.	Age at time of repair, need for other surgery	N/A
Raju V, et al. 2013 (627) 23618522	Reoperations	n=32 pts (reoperations)	84–2012	N/A	0%	Coronary problems in 9%	N/A	N/A

Serraf A, et al. 1991 (628) 2072712	Long-term outcomes	n=118 pts	83–90	2.5	1%	PS intervention in 6%	Coarctation, VSD	● 2 pts needed pacemakers.
Soszyn N, et al. 2011 (629) 21801920	Long-term outcomes (Taussig-Bing)	n=57 pts	83–90	9.8	0%	24% reoperation rate	Surgery prior to ASO	N/A
Stoica S, et al. 2012 (630) 22365263	Long-term outcomes	n=101 pts	03–11	4.1		Coronary problems in 2%	Arch abnormalities and malaligned commissures.	● Arch and malaligned commissures.
Schwartz ML, et al. 2004 (22) 15364851	Long-term outcomes	n=335 pts	96–09	5.5	N/A	Neoaortic valve intervention in 5%, pulmonary stenosis intervention in 5%	VSD, age at repair, and need for PA banding	● Average peak PS gradient was 23 mm Hg.
Thrupp SF, et al. 2012 (631) 22981257	Long-term outcomes	n=215 pts	96–06	N/A	N/A	Coronary problems in 8%	5.6% death if coronary problem	● Focus exclusively on those with intramural coronary arteries.
van der Bom T, et al. 2014 (408) 24837983	Reoperations	n=116 pts	<95	7.2	N/A	4% neoaortic valve intervention	Linear growth of the neo-aortic root in adult survivors	● Showed some progressive root dilatation over time.
Vouhe PR, et al. 2013 (632) 22564800	Long-term outcomes	n=101 pts	03–11	N/A	5%	5.3% coronary problems	N/A	N/A
Delmo Walter EM, et al. 2010 (633) 21044157	Long-term outcomes	n=324 pts		14.4		Neoaortic valve intervention in 1%	VSD, PA banding, and postoperative neoaortic valve regurgitation	N/A

Data Supplement 47. Congenitally Corrected Transposition of the Great Arteries – Section 4.4.1.4

Study Name, Author, Year	Study (Size, N)	Study Design	Inclusion/Exclusion Criteria	1° Endpoint	Results	Conclusions
Cui B, et al. 2014 (634) 25173927	n=14 pts between 2.5–72 mo of age	Observational	Inclusion criteria: Consecutive	N/A	● 2 pts died after ASO. The causes of death included serious cardiac arrhythmia with circulatory collapse and SCD. The others were followed up for 2–8 y: 1 pt died from serious cardiac	● For CCTGA children with degraded morphologic LV, the 2-stage double switch procedure can be

	(mean: 34.4 ± 24.0 mo)				arrhythmias with circulatory collapse in the follow-up period. With regard to the others, 8 were evaluated as NYHA FC I and the other 3 as class II. Moderate aortic valve regurgitation was noted in 3 pts and moderate MR in 1 pt.	performed with low mortality and morbidity and may be an appealing alternative to conventional repair. ● Morphologic LV retraining should be performed as early as possible.
Ma K, et al. 2014 (635) 24529731	n=40 pts; (15 double switch; 25 PA band)	Comparison	Inclusion criteria: Child pts with CCTGA	In-hospital mortality, long-term mortality, and heart function	● Overall survival rate was 66.7% in the double-switch group vs. 96.0% in the PA band group (p=0.03). The ratio of NYHA FC I-II (80.0% vs. 95.9%; p=0.02) and the mean functional LVEF (51.4% ± 9.6% vs. 61.0% ± 6.4%; p=0.01) were higher in the PA band group at follow-up. ● In univariate analysis, age at PA band was the only risk factor for late deaths (OR: 7.30; p=0.01) and LV dysfunction (OR: 4.77; p=0.03) after the double switch.	● Compared with the double-switch procedure after PA band, prolonged palliative PA banding provided a lower mortality rate and indicated better cardiac function.
Myers PO, et al. 2014 (636) 24267780	n=106; median age at surgery was 1.2 y (range, 2 mo–43 y)	Retrospective, single center	Inclusion criteria: Surgery between 1992–2012	Moderate or greater TR and TV reoperation after anatomic repair	● Of the 106 pts, 6 (5.6%) with TR underwent tricuspid valvuloplasty at anatomic repair, 5 with (21%) and 1 without (11%) Ebsteinoid dysplasia (p<0.001). ● During a median follow-up period of 32 mo, of the 24 pts with TR before anatomic repair, all 6 who had undergone tricuspid valvuloplasty had mild TR or less at the latest follow-up visit; 15 of the 18 (83%) without valvuloplasty had mild TR or less (p=0.4) and 3 (16.7%) had moderate or greater TR. Of the 14 pts with Ebsteinoid dysplasia and TR, 5 underwent valvuloplasty and had no significant TR during follow-up; 2 of the	● TV function significantly improved after anatomic repair, independent of direct surgical intervention. For significant TR associated with Ebsteinoid dysplasia, valvuloplasty should be considered.

					9 (22.2%) without valvuloplasty had moderate or greater TR (p=0.51). ● Valvuloplasty was associated with an absolute risk of TR reduction of 16.7%, which was further reduced by 22.2% in pts with associated Ebsteinoid dysplasia.	
Bautista-Hernandez V, et al. 2014 (637) 24100093	n=106 pts; median age at surgery, 1.2 y; range, 2 mo–43 y	Retrospective, single center	Inclusion criteria: Surgery between 1992–2012	LV dysfunction	● 12 pts (12%) developed moderate or severe LV dysfunction. ● Factors associated with LV dysfunction were age at repair older than 10 y, weight greater than 20 kg, pacemaker implantation, and severe neo-aortic regurgitation.	● Late LV dysfunction after anatomic repair of CCTGA is not uncommon, occurring most often in older pts and in those requiring pacing.
Van der Bom T, et al. 2013 (638) 23850923	n=88 pts, mean age was 33 ± 10 y	Double-blind, randomized, placebo-controlled trial of valsartan	Inclusion criteria: 2006–2009	Composite endpoint of clinical events: death; NSVT, VT; vascular events (CVA, TIA, MI) TR requiring invasive treatment; worsening NYHA FC, or hospital admission for worsening symptoms of HF; and arrhythmia requiring DCCV, ablation, implantation of a pacemaker, or a permanent change of antiarrhythmic medication	● During a follow-up period of 4.3 y, 31 pts (35%) experienced 46 clinical events for an annual risk of 12%.	● RVEDV index >150 mL/m^2 and peak exercise systolic BP below 180 mm Hg had a 20-fold higher annual event rate than pts without these risk factors.
Book W, et al. 2013 (639) 23350927	n=51 pts; median age was 30 y	Prospective	Inclusion criteria: TGA pts with systemic RV	6MWT	● The pt's self-assessment of poor health, as measured by an increased NYHA FC (p=0.003) and a decreased	● Pt's self-assessment of functional status did

	(range 19–65); 11 with CCTGA				Minnesota Living With Heart Failure Questionnaire score (p>0.0001) correlated with a shorter 6MWT.	correlate with objective functional status.
Mongeon FP, et al. 2011 (640) 21565637	n=46 pts; mean age of 40.8 ± 14.8 y	Retrospective	Inclusion criteria: 1) Systemic AV regurgitation that required valve replacement performed at Mayo Clinic; and 2) a known systemic ventricular EF at the time of systemic AV valve replacement.	Late mortality or cardiac transplant. 2 groups: preoperative systemic ventricular EF >40% in 27 pts and <40% in 19 pts)	● Preoperative variables associated with late mortality were systemic ventricular EF <40%, a subpulmonary ventricular systolic pressure >50 mm Hg, AF, and NYHA FC III–IV.	● For best results, operation should be considered at an earlier stage, before the systemic ventricular EF falls below 40% and the subpulmonary ventricular systolic pressure rises above 50 mm Hg.
Graham TP, et al. 2000 (641) 10898443	n=182 pts	Retrospective, multicenter	Inclusion criteria: Group I: 132 pts with significant associated lesions (large VSD, moderate or severe PS, PA moderate or severe TR and Ebstein-like anomaly of the TV. Group II consisted of 50 pts with no significant lesions	Mortality, HF, RV, and LV dysfunction	● By age 45, 67% of pts with associated lesions had congestive HF, and 25% of pts without associated lesions had this complication. ● The rates of systemic ventricular dysfunction and HF were higher with increasing age, the presence of significant associated cardiac lesions, history of arrhythmia, pacemaker implantation, prior surgery of any type, and particularly with tricuspid valvuloplasty or replacement.	● Tricuspid (systemic AV) valvular regurgitation is strongly associated with RV (anatomical right ventricle connected to aorta in CCTGA pts; systemic ventricle in CCTGA) dysfunction and HF.
Prieto LR, et al. 1998 (642) 9737520	n=40 pts	Retrospective	Inclusion criteria: Since 1958, 40 consecutive pts with CCTGA and 2 normal-sized ventricles have been followed at Columbia	Death	● Poor long-term postoperative outcome was due to TI(s) in all but 1 pt; 20-y survival rates for operated pts with and without TI(s)were 34% and 90%, respectively (p=0.002). ● Similarly, 20-y survival rates for unoperated pts with and without TI(s) were 60% and 100%, respectively, whether or not attempts to repair the tricuspid insufficiency were made (p=0.08).	● Significant tricuspid insufficiency represents the major risk factor for CTGA pts; RV dysfunction appears to be almost always secondary to long-standing TR.
Lewis M, et al. 2014 (643) 24814545	n=33 pts; mean age at CMR was	Retrospective observational study	Inclusion criteria: Pts with CCTGA who had undergone CMR	RV size and function	● Mean RVEF (45% vs. 41% vs. 42%; p=0.68) and mean indexed RVEDV (122 mL/m^2 vs. 136 mL/m^2 vs.138	● No association between the degree of

	38 y (23–64 y).				mL/m^2 p=0.36) were not significantly different for pts with ≥ mild TR, moderate TR or severe TR.	TR and RV volume or EF.
Grewal J, et al. 2012 (644) 22981226	n=26 pts; mean age, 38 ± 16 y: 20 controls	Prospective study	Inclusion criteria: Echo, CMR and CPET Exclusion criteria: Devices of mechanical valves	RV volumes and EF, fibrosis, RV strain, exercise capacity	● There was a significant difference in diastolic volumes among those with RVEFs >40% vs. 40% (173 ± 6 29 mL vs. 233 ± 65 mL; p=0.02) and moderate or severe vs. no or mild TR (240 ± 80 mL vs. 190 ± 38 mL; p=0.04). ● RV apical longitudinal and mid free wall circumferential strain was decreased compared with these.	● Exercise capacity was significantly reduced in pts with CCTGA compared with normal subjects (20.9 ± 6 6.0 vs. 30.8 ± 6 9.2 mL/kg/min; p=0.001). ● The majority of pts (61%) had RVEF 40%.
Diller GP, et al. 2012 (608) 22607865	n=129 pts; mean age 35 ± 12 y); 42 with CCTGA	Retrospective	Inclusion criteria: Echocardiography	Combined endpoint: an increase in NYHA FC to ≥3 or new signs and symptoms of HF - occurrence of clinically relevant arrhythmia (i.e., symptomatic arrhythmia requiring medical or interventional therapy); or death during follow-up. Predictors of outcome were determined separately for pts with TGA after atrial switch and pts with CCTGA	● Systemic ventricular longitudinal 2D peak systolic strain (RV 2D-longitudinal strain) was significantly reduced compared with controls (−12.9 ± 3.6 and −15.4 ± 5.1 vs. −21.0 ± 5.5 in TGAs, CCTGAs, and controls; p<0.0001). Systemic and pulmonary 2D-longitudinal strain were correlated in pts with TGA (r=0.46; p<0.0001) and CCTGA (r=0.64; p<0.0001), suggesting interventricular interaction, and this was confirmed when EF on MRI was assessed (r=0.53; p<0.0001).	● Global longitudinal systolic strain is significantly reduced in pts with a systemic RV is related to subpulmonary ventricular function.
Yeo WT, et al. 2014 (645) 24374205	56 (22 with LV pacing; 7 with biventricular	Retrospective	Inclusion criteria: 2 echocardiographs at least 6 mo apart were included	Deterioration in systemic RV function measuring RV	● The LV-paced group experienced deterioration in the RV fractional area change (RV fractional area change) (28.7 ± 10.0 vs. 21.9 ± 9.1%; p=0.003),	● Univentricular subpulmonary LV pacing in pts with CCTGA predicted

	pacing) age 39 ± 16 y			fractional area change, systemic, RV size (RVEDA) and systemic AV valve regurgitation by at least 1 grade	systemic AV valve regurgitation (p=0.019) and RV dilatation (end diastolic area 32.7 ± 8.7 vs. 37.2 ± 9.0 cm^2; p=0.004). ● There was a corresponding deterioration in NYHA FC (p=0.013). ● Multivariate Cox regression analysis showed that pacing was an independent predictor of deteriorating RV function and RV dilation (HR: 2.7 [10–7.0] and 4.7 [1.1–20.6], respectively). ● None of these parameters changed significantly in the Un-paced Group. ● The CRT Group showed improvement in RV fractional area change (22.0%–30.7% (p=0.030) and NYHA FC (p=0.030), despite having lower baseline RV fractional area change (22.0 ± 5.7 vs. 31 ± 9.7%; p=0.025) and greater dyssynchrony (RV total isovolumic time 13.4 ± 2.1 vs. 9.3 ± 4.2 s/min; p=0.016) when compared to the unpaced group.	deterioration in RV function and RV dilatation over time associated with deteriorating NYHA FC.
Winter MM, et al. 2012 (646) 22036871	n=54 pts mean age 32.5 ± 9.9; 18 with CCTGA	Multicenter parallel RCT to 10 wk of exercise training 3 times/wk	Inclusion criteria: Adult pts with systemic RV Exclusion criteria: Incapability to participate in a home-based exercise training program, the presence of exercise-induced arrhythmia, symptomatic MI, a resting systolic BP >200 mm Hg and/or diastolic BP >110 mm Hg, NYHA FC III or IV,	Peak VO_2	● A significant difference in VO_2 peak (3.4 mL/kg/min; 95% CI: 0.2–6.7; p=0.04) and resting systolic BP (-7.6 mm Hg; 95% CI: -14.0–1.3; p=0.03) in favor of the exercise group. ● No significant changes were found in serum NT-proBNP levels or QOL in the intervention group or in the control group nor between groups.	● In pts with systemic RV, exercise training improves exercise capacity.

			pregnancy, and noncardiac comorbidity that could aggravate by exercise			
Van der Bom T, et al. 2013 (258) 23247302	n=88 pts, 25 with CCTGA	Multicenter, double-blind, parallel, RCT of angiotensin II receptor blocker valsartan 160 mg twice daily compared with placebo	Inclusion criteria: Systemic RV Exclusion criteria: Incapability of giving informed consent; hypersensitivity to valsartan or any of its help substances; hypersensitivity to IV contrast agent; known bilateral renal artery stenosis; MI, stroke, or open heart surgery in the previous 4 wk; previous heart transplant, or expected heart transplant within the next 6 mo; plasma creatinine level >mcmol/L; plasma potassium level >5.5 mmol/L; Current treatment of HTN with an ACEI or an angiotensin II receptor blocker, which cannot be discontinued; pregnant or nursing women (a pregnancy test was offered to every female pt within fertile age); desire to have children during follow-up	RVEF measured by CMR	● There was no significant effect of 3-y valsartan therapy on systemic RVEF (treatment effect, 1.3%; 95% CI: -1.3%–3.9%; p=0.34), maximum exercise capacity, or QOL. There was a larger increase in RV end-diastolic volume (15 mL; 95% CI: 3–28 mL; p<0.01) and mass (8 g; 95% CI: 2–14 g; p=0.01) in the placebo group than in the valsartan group.	● There was no significant treatment effect of valsartan on RVEF, exercise capacity, or QOL.

Dore A, et al. 2005 (252) 16216961	n=29 pts 30.3 ± 10.9 y of age; 8 (28%) CCTGA	A multicenter, randomized, double-blind, placebo-controlled, crossover clinical trial with losartan	Inclusion criteria: Echocardiography, CPET, BNP Exclusion criteria: Adults with systemic RV	(NYHA class III or IV), unable to exercise, were pregnant, had a fixed-rate pacemaker, had a creatinine level >250 mmol/L, or had a history of angioedema, right-to-left shunting; substantial left-to-right shunting (Qp/Qs>1.5); severe mitral, aortic, or PR; systemic or pulmonary inflow obstruction with a peak velocity >1.5 m/s by TTE; and severe outflow tract obstruction with a peak systolic gradient >80 mm Hg	● Comparing losartan to placebo showed no differences in VO_2 max (29.9 ± 5.4 vs. 29.4 ± 6.2 mL · kg/min; p=0.43), exercise duration (632.3 ± 123.0 vs. 629.9 ± 140.7 s; p=0.76), and NT-proBNP levels (201.2 ± 267.8 vs. 229.7 ± 291.5 pg/mL; p=0.10), despite a trend toward increased angiotensin II levels (15.2 ± 13.8 vs. 8.8 ± 12.5 pg/mL; p=0.08).	● In adults with systemic RVs, losartan did not improve exercise capacity or reduce NT-proBNP levels.
Huhta C, et al. 1983 (647) 6851033	n=107 pts	Retrospective study	Inclusion criteria: Confirmed AV discordance with 2 ventricles seen at Mayo Clinic between January 1951 –June 1981 Exclusion criteria: Situs ambiguous	Complete AV block	● 23 pts (22%) had complete AV block. This condition was present in 4 pts at birth and developed in 19 pts at ages 4 mo–53 y (mean 18.1 y).	● Pts with AV discordance are at risk of developing complete AV block throughout their lives.
Green CE, et al. 1983 (648)	N/A	Review article		N/A	N/A	● The majority of adults with CHD will

6544144						have some telltale abnormality on the chest radiograph that will occasionally furnish the first clue to the presence of a congenital anomaly.
Silverman NH, et al. 1995 (649) 7503010	n=14 pathologic specimens	Descriptive	Inclusion criteria: N/A	N/A	● The TV plane was rotated 47 ± 21 degrees from its usual position into the ventricle. ● The TV tissue was variably attached to the underlying myocardium, with the most severely affected lesion being the mural leaflet followed by the septal leaflet, and the anterior leaflet attachment the least affected.	● The plane of displacement of the valve in corrected transposition appears less amenable to 4-chamber echocardiography than other forms of Ebstein anomaly. ● Changes in the echo planes should display the morphology and also provide some hemodynamic information.
MacDonald ST, et al. 2010 (650) 21108556	N/A	Review	Inclusion criteria: N/A	N/A	N/A	● ACHD pts offer distinct challenges such as unusual anatomy and demands, such as pregnancy and exercise tolerability not found in conventional pediatric or traditional adult interventional pts.
Buber J, et al. 2015 (651) 25661908	n=38 pts	Retrospective study	Inclusion criteria: (S,L,L) or (I,D,D) segmental anatomy and AV discordance: either TGA or DORV Exclusion criteria: Surgical TV repair prior to or at the time	TR severity and RV function	● Worsening TR was associated with the degree of change in RV and LV diameters, change in tricuspid annulus size and tethering distance, and the degree of septal shift, as reflected by the RV sphericity index (all p≤0.04).	● Intervention for LV to PA conduit dysfunction may result in worsening TR and RV function, likely due in part to altered septal shift due to changes in the interventricular pressure ratio.

			of conduit intervention; operations involving switching the LV to the systemic circulation, single ventricle conversion, deliberate banding of LV-PA conduit, residual shunting or aortic coarctation			
Casso P, et al. 1998 (652) 9453520	n=12 pts	Prospective	Inclusion criteria: LTGA	N/A	● The chordal attachments of both valves were clearly elucidated by TEE in all pts; whereas, TTE could obtain images of these in only 3 pts.	● TEE is superior to transthoracic imaging in studying LTGA in adult pts; the horizontal plane is best suited to the evaluation of atrial situs and the AV junction; whereas, the longitudinal plane is most valuable in the study of the morphologic features of the ventriculoarterial connections.

Data Supplement 48. Fontan Palliation of Single Ventricle Physiology Including Tricuspid Atresia and Double Inlet Right Ventricle – Section 4.4.2

Study Name, Author, Year	Study Design	Study Size	Inclusion/Exclusion Criteria	1° Endpoint	Results	Summary/Conclusions
Hebert A et al. 2014 (653) 25446057	Randomized trial of bosentan × 14 wk	n=69 pts	Inclusion criteria: Adolescent/adult Fontan	QOL, Exercise, NYHA	● Improved peak VO_2	N/A
Giardini A et al. 2008 (261) 18534975	Single dose, randomized controlled study	n=27 pts	Inclusion criteria: Adolescent/adult Fontan	Exercise testing in cath lab	● Peak VO_2 ● Pulmonary blood flow ● PVR	N/A

Goldberg DJ et al. 2011 (262) 21382896	RCT--cross over of sildenafil	n=28 pts	Inclusion criteria: Adolescent Fontan	Exercise testing	● MV ● RR ● O_2 consumption at AT ● Peak VO_2 and peak HR were not significant	N/A
Ovaert C et al. 2009 (654) 19519964	Prospective non-randomized trial of bosentan × 16 wk	n=10 pts	Inclusion criteria: Failing Fontan	O_2 sat at rest and exercise	● No improvement	● 5 pts had improvement in O_2 sat or exercise capacity (worsened after drug cessation)
Bowater SE et al. 2012 (655) 22348734	Prospective non-randomized trial of bosentan × 6 mo	n=8 pts	Inclusion criteria: Adult Fontan	Exercise testing, echo	● Improved NYHA and ventricular ejection fraction	● Only 6 completed 6 mo of therapy
Derk G et al. 2015 (656) 24890846	Bosentan × 4 mo, observational	n=10 pts	Inclusion criteria: Adult Fontan	6MWT, BNP, CMR	● 6MWT distance improved, cardiac output improved	● 7 completed study
Schuuring MJ et al. 2013 (657) 23361871	Randomized trial (3 mo delay in bosentan therapy), total 6 mo therapy	n=32 pts	Inclusion criteria: Adult Fontan	VO_2, BNP, NYHA, QOL scores	● No significant findings	● 10 pts didn't complete the study, and half of eligible pts declined to participate.
Cordina R et al. 2013 (120) 23846614	Cohort study	n=16 pts	Inclusion criteria: NYHA class I/II Fontan adults	Reduced skeletal muscle mass and/or metabolic abnormalities	● Peak VO_2 was 1.9±0.1 L/min (66±3% of predicted values). ● Skeletal muscle mass assessed by relative appendicular lean mass index was significantly reduced compared with age-matched and sex-matched reference values (Z-score -1.46±0.22; p<0.0001). Low skeletal muscle mass correlated with poorer VO_2 max (r=0.67; p=0.004). ● Overall, skeletal muscle mass T-score (derived from comparison with young normal reference mean) was -1.47±0.21; 4/16 Fontan subjects had sarcopenic range muscle wasting (T-score <-2.0) and 9/16 had less marked, but clinically significant wasting (T-score <-1.0 but ≥-2.0).	● Fontan pts have reduced skeletal muscle mass and intrinsic muscle metabolic abnormalities.

					● Muscle aerobic capacity, measured by the rate constant (k) of post-exercise phosphocreatine resynthesis, was significantly impaired in Fontan adults vs. controls (1.48±0.13 vs. 2.40±0.33 min^{-1}; p=0.02).	
Brassard P, et al. 2006 (658) 16046016	Matched case-control	n=14 pts (7 cases; 7 healthy controls)	Inclusion criteria: Fontan procedure	Skeletal muscle functioning and exercise tolerance	● The ergoreflex contribution to absolute DBP was higher (12.5+/-4.8 vs. 5.6+/-4.2 mm Hg; p=0.04) in Fontan pts vs. healthy subjects; whereas, a trend was encountered regarding the ergoreflex contribution to absolute SBP (9.0+/-7.0 vs. 0.4+/-9.0 mm Hg; p=0.09). Furthermore, time to fatigue of the nondominant forearm muscles was shorter in Fontan pts vs. healthy subjects (431+/-290 vs. 847+/-347 s; p=0.03). ● Following exercise training, there was a significant reduction of the ergoreflex contribution to absolute values of SBP (9.8+/-0.9 vs. 0.3+/-2.7 mm Hg; p<0.05). There was an association between muscle strength and VO_2 peak in Fontan pts (upper limb: r=0.895; p<0.01; lower limbs: r=0.838; p<0.05, respectively).	● Skeletal muscle function in Fontan pts is abnormal which may have an impact in the reduced exercise tolerance encountered in these pts. ● Exercise training may be beneficial on skeletal muscle function in this population.
Inai K, et al. 2004 (659) 15019898	Cohort study		Inclusion criteria: Fontan operation	Exercise capacity		● In Fontan pts, diminished exercise capacity was related to a reduced blood flow supply and an attenuated post-exercise O_2 resaturation of the working skeletal muscle, which also was related to impaired endothelium-dependent vasodilation.
Wang A, et al. 2007 (195) 17920376	Cohort study	n=198 pts	Inclusion criteria: All ACHD pts with surgery prior to 1992	Hepatitis C antibody testing	● 17 (8.6%) had positive Hepatitis C antibody results, and 8 (4.0%) had positive Hepatitis C ribonucleic acid results.	● Positivity rate was nearly 5-fold higher than general population.
Kiesewetter CH, et al. 2007 (660) 17005713	Cohort study, retrospective	n=12 pts	Inclusion criteria: Prior Fontan palliation	Liver assessment protocol with CT and histology	● Various pathologic findings in 4–7 of the 12 pts. ● Degree of hepatic fibrosis correlated with duration of Fontan.	● PLE in 5/12 pts.

Potter BJ, et al. 2013 (661) 23870650	Cohort study, retrospective	n=210 pts	Inclusion criteria: Prior Fontan palliation	Thromboembolic events	● 24.3% received aspirin, and 25.7% warfarin. ● Use of either was protective against thromboembolic events (HR: 8.5)	● No difference between aspirin or anticoagulation. ● AF or atrial flutter were also risk factors for events.
Davies RR, et al. 2012 (272) 22500594	Cohort study	n=43 pts	Inclusion criteria: Fontan undergoing transplant	Mortality	● 90-d mortality was greater in Fontan pts.	● Renal failure was a predictor of early mortality.
Aboulhosn J, et al. 2010 (662) 21087427	Cohort study	n=27 pts	Inclusion criteria: Pts undergoing Fontan conversion surgery	Arrhythmia recurrence	● 2 postoperative deaths, both with liver failure. Early postoperative atrial arrhythmia in 22%.	● 14% of those who had concomitant arrhythmia surgery had recurrence >3 mo later.
Elder RW, et al. 2014 (663) 25130602	Retrospective observational, single center	n=123 pts	Inclusion criteria: Adult pts >15 y post Fontan	Late major AE in adult survivors	● Major AE in 15%; transplant free survival rate 95%, 83%, 60% at 20, 25, and 30 y, respectively. ● No difference in adverse outcome based on morphology of systemic ventricle, Fontan type, or systolic ventricular function. Independent risk factors for major AE were portal HTN ($p<0.0001$), need for permanent pacemaker ($p=0.002$), systemic O_2 desaturation ($p=0.02$).	● Portal HTN, desaturation, need for permanent pacemaker were predictive of AE
Said SM, et al. 2014 (664) 24786860	Retrospective observational, single center	n=70 pts	Inclusion criteria: Fontan conversion surgery, median age 23 y, 5 y median follow-up.	Risk factors for Fontan conversion	● Early mortality 14%; independent risk factors for early death, age >20 y ($p=0.009$); AV valve regurgitation ($p=0.016$); lack of Maze procedure ($p=0.04$); male sex ($p=0.02$). ● Late survival at 1, 5 10 y was 81%, 70%, 67%.	● Older age and AV valve regurgitation increased risk of poor outcome.
Khairy P, et al. 2008 (665) 18071068	Retrospective observational, single center	n=261 pts	Inclusion criteria: Fontan, pts, median age 7.9 y	Risk factors for mortality	● Late survival free of death or transplant was 94%, 90%, 87%, 83% at 5, 10, 15, 20 y respectively. ● No difference between right aortic peripheral artery vs. total cavopulmonary connection; independent risk factors for thromboembolic death were lack of antiplatelet or anticoagulant medication ($p=0.0041$) and clinically diagnosed intracardiac thrombus ($p=0.0002$). ● Independent predictors for HF death were PLE ($p=0.0043$), single morphologic RV ($p=0.04$), and higher RA pressure (0.0016).	● Right aortic peripheral artery connection in 52%; right atrial to RV in 10%; total cavopulmonary connection 39%.

Mavroudis C, et al. 2007 (666) 17954046	Retrospective observational, single center	n=111 pts	Inclusion criteria: Fontan conversion, mean age 22.5 y	Identify risk factors for Fontan conversion with Maze	● Early mortality, 0.9%; late deaths, 5.4%; need for cardiac transplantation, 5.4%. ● Mean hospital stay: 14 d. ● Risk factors for death or transplantation were RV or ambiguous ventricle, preop PLE, preop moderate-to-severe aortic valve regurgitation, and long bypass time.	● Late recurrence of atrial tachycardia was ~15%.
Ono M, et al. 2006 (667) 17074498	Retrospective observational, single center	n=121 pts	Inclusion criteria: Fontan, mean age, 5.8 y	Late morbidity and mortality after Fontan	● Late survival, 87% at 20 y; 10 early deaths, 5 late deaths. ● Heterotaxy and AV valve anomaly were risk factors for late failure and tachyarrhythmias. ● Fenestrated total cavopulmonary connection and aortopulmonary collaterals had reduced incidence of late tachyarrhythmias.	● Fenestrated Fontan provided better cardiac output and lower incidence of late tachyarrhythmias.
Kaulitz R, et al. 2002 (668) 12238839	Retrospective observational, single center	n=88 pts	Inclusion criteria: Fontan survivors >5 y postoperatively. Mean follow-up 9.6 y.	Need for reintervention after Fontan palliation	● Freedom from reop at 5 y=82%; 8 y=76%. Interventions included total cavopulmonary connection conversion in 2, PPM in 11%; Coil occlusion of aortopulmonary collaterals in 6/17 pts. ● Freedom from transcatheter interventions was 94% and 82% at 5 and 10 y respectively	● All pts had cardiac cath as part of regular postop protocol or symptomatic atrial tachycardia or increase in cyanosis.
Yeh T, et al. 1999 (669) 10485406	Retrospective observational, single center	n=407 pts	Inclusion criteria: Adult pts >15 y post Fontan	Long-term survival after Fontan vs. cavopulmonary shunt	● Long-term survival, 20 y survival for cavopulmonary shunt-Fontan 65% (n=220); whereas, 20 y survival cavopulmonary shunt-no Fontan 50% (n=187). On multivariable analysis, proceeding to Fontan has small survival benefit.	● Independent risk factors for death for common aortic valve or PA banding.
Harper AR, et al. 2013 (274) 22588032	Single center	n=126 pts	Inclusion criteria: Median 1.2 y	Comparison of transplant vs. nontransplant surgical intervention	● 14 pts who underwent surgery instead; still 1 y mortality 28%.	● Best outcomes in those with normal 2 ventricle anatomy.
Bradyarrhythmias and Pacemakers						
Takahashi K, et al. 2009 (670) 19545341	Retrospective single-center cohort study	n=78 pts	Inclusion criteria: Fontan surgery; atrial lead implantation between 1992—2007	Comparison of lead performance and longevity between transvenous and epicardial leads	● Acute complication rates were similar (8% transvenous vs. 19% epicardial), but hospital stay was shorter for transvenous (2 vs. 5 d; p=0.03). ● Lead survival was similar (transvenous 9.9 vs. epicardial 7.8 y). Thresholds were lower at implant for transvenous leads (0.9 vs. 2.2	● Compared to epicardial leads, transvenous atrial pacing leads may be placed in Fontan pts with lower procedural morbidity and equivalent expectation of

					microjoule; p=0.049), but similar at follow-up (1.2 vs. 2.6 microJ). ● Atrial sensing was unchanged over time for transvenous (2.2 to 2.1 mV) but decreased for epicardial (3.3 to 2.5 mV; p=0.02).	lead performance and longevity.
Dodge-Khatami A, et al. 2005 (671) 16181884	Retrospective single-center cohort study	n=9 pts	Inclusion criteria: Fontan surgery; dual chamber pacemaker between 1997—2004	Morbidity and mortality	● There was no mortality or morbidity. Lead survival was 100% at 3.3 y. Arrhythmias subsided in all and no longer required medication in 3 pts. Protein-losing enteropathy improved in 1 pt and disappeared in another. Exercise intolerance diminished, and HF was controlled.	● Dual chamber pacing improves single ventricle hemodynamics and can help decompensated Fontan pts.
Hansky B, et al. 2005 (672) 15679644	Single-center case series	n=7 pts	Inclusion criteria: Fontan surgery; implantation of endocardial pacing leads via a transvenous or transatrial approach.	Feasibility	● Endocardial leads were successfully implanted in all pts.	● Transvenous endocardial lead implantation avoids the problem of increasing capture thresholds typically observed with epicardial leads.
Cohen MI, et al. 2001 (673) 11279424	Retrospective single-center cohort study	n=31 Fontan pts, 56 controls	Inclusion criteria: Epicardial lead implanted between Jan 1983—June 2000; Fontan surgery or non-Fontan control	Perioperative course and epicardial lead survival	● There was no difference in the perioperative course for Fontan pts and controls and no difference in epicardial lead survival (1 y, 96%; 2 y, 90%; 5 y, 70%).	● Epicardial leads can be safely placed in Fontan pts at no additional risk compared to pts with biventricular physiology.
Cohen MI, et al. 1998 (674) 9852926	Retrospective single-center cohort study	n=287 pts	Inclusion criteria: Staged Fontan surgery between Jan 1990—Dec 1995	Early incidence of SND	● Overall, 23% had SND in the early postoperative period after Fontan surgery. Of the 95 pts followed for >4 y, 44% had SND, 6.7% had received a PM, and 4.1% had documented atrial flutter.	● Perioperative SND is common after the Fontan procedure.
Fisberger SB, et al. 1996 (675) 8623749	Retrospective single-center cohort study	n=500 pts	Inclusion criteria: Fontan surgery between April 1973—July 1991	Prevalence of pacemaker implanted	● Overall, 9.2% of pts received pacemaker 5.4 y post Fontan. ● Pts with pacemaker compared favorably with nonpaced pts with respect to survival. ● In pts with AV block, dual chamber pacing was superior to ventricle paced, ventricle sensed, pacing inhibited pacing.	● PM are often required post Fontan surgery are associated with favorable survival.
Dodge-Khatami A, et al. 2005 (671)	Retrospective single-center cohort study	n=9 pts	Inclusion criteria: Fontan surgery; dual	Morbidity and mortality	● There was no mortality or morbidity. Lead survival was 100% at 3.3 y.	● Dual chamber pacing improves single ventricle hemodynamics and can

16181884			chamber pacemaker between 1997—2004		● Arrhythmias subsided in all and no longer required medication in 3 pts. Protein-losing enteropathy improved in 1 pt and disappeared in another. Exercise intolerance diminished, and HF was controlled.	help decompensated Fontan pts.
Atrial Tachyarrhythmias (Excluding Anticoagulation)						
d'Udekem Y, et al. 2014 (676) 25200053	Retrospective multicenter cohort study prior to 2008, prospective until 2013	n=1,006 pts	Inclusion criteria: Fontan procedure between 1975—2010; follow-up in Australia or New Zealand	Long-term outcomes following Fontan surgery (SVT, mortality, failure, pacemaker, thromboembolism)	● A total of 94 pts required a pacemaker. ● Sustained episodes of SVT were reported in 100 pts. ● SVT was associated with atrial isomerism. ● Arrhythmias were not associated with late mortality or late failure.	● While brady and tachyarrhythmias are prevalent following Fontan surgery, they are not associated with late mortality or late Fontan failure.
Correa R, et al. 2013 (604) 24052498	Retrospective catheter ablation case series	n=89 Fontan pts	Inclusion criteria: Mustard, Senning, or Fontan; Referred to Boston Children's Hospital for catheter ablation; Jan 2006—Dec 2010	AE; changes in clinical score	● AE rates similar with and without transbaffle access. ● Pts with and without transbaffle access experienced clinical improvement.	● Transbaffle access for catheter ablation is feasible and not associated with a higher incidence of AE. ● Desaturation is observed in some and warrants monitoring.
Giannakoulas G, et al. 2012 (17) 21196055	Single-center retrospective cohort	n=98 pts	Inclusion criteria: Fontan operation; follow-up at Royal Brompton since 1999	All-cause mortality; hospitalization	● Atrial tachyarrhythmia was an independent predictor of death (adjusted HR: 9.35; 95% CI: 1.10–79.18; p=0.04) and composite of death or hospitalization (adjusted HR: 5.00; 95% CI: 2.47–10.09; p<0.0001).	● The presence of atrial tachyarrhythmias is associated with higher morbidity and mortality at midterm follow-up.
Khairy P, et al. 2008 (665) 18071068	Single-center retrospective cohort	n=261 pts	Inclusion criteria: Born before Jan 1, 1985; reside within New England area; Fontan surgery	Long-term survival; modes of death; predictors of mortality	● AF was associated with a 5.4-fold increased risk of thromboembolic death. SCD occurred at a median age of 20.2 y. ● IART with rapid 1:1 conduction was identified as a cause of cardiac arrest.	● Atrial tachyarrhythmias with rapid AV conduction are a rare cause of SCD following Fontan surgery.
Abrams DJ, et al. 2007 (677) 17372177	Single-center catheter ablation case series	n=26 pts	Inclusion criteria: Fontan surgery; documented atrial tachyarrhythmia resistant to at least 1 antiarrhythmic	Comparisons of contact and reconstructed unipolar electrograms from electroanatomic	● A significant decrease in electrogram cross correlation (p=0.003), timing (p=0.012), and amplitude (p=0.003) of reconstructed electrograms, but not of contact electrograms (p=0.742), was seen at endocardial sites >40 mm from the multielectrode array.	● Electroanatomic mapping is superior to noncontact mapping, particularly >40 mm from for arrhythmia mapping late after the mo from the multielectrode array.

			medication (including amiodarone)	mapping vs. noncontact mapping systems	● Successful arrhythmia mapping by electroanatomic vs. noncontact mapping was superior in 15 pts (58%), the same in 6 (23%), and inferior in 5 (19%; p=0.044).	Areas of scar and low-voltage endocardium are less well identified.
Friedman RA, et al. 2005 (678) 15673382	Single-center retrospective case series	n=7 pts	Inclusion criteria: Fontan; IART; attempted regurgitant fraction ablation of the AV junction	Feasibility	● Ablation of the AV junction was successful (n=6) or partially successful (n=1) in all. ● Normal AV conduction was not seen during follow-up. ● The number of antiarrhythmic medications decreased from 2.8 ± 1.5–0.7 ± 0.8 (p<0.05).	● In Fontan pts with drug-resistant IART, regurgitant fraction ablation of the AV junction with prior pacemaker implant is a feasible therapeutic option.
Wong T, et al. 2004 (679) 15136502	Single-center cross-sectional analysis	n=33 pts	Inclusion criteria: Fontan surgery; follow-up at Royal Brompton in 2000	Mechanico-electrical interactions	● Pts with atrial tachyarrhythmia had longer p-wave duration (159 ± 28 vs. 123 ± 28 m; p<0.001), greater p-wave dispersion (9 ± 30 vs. 50 ± 19 m; p<0.001), and larger right atrial dimensions (6.4 ± 1.4 vs. 5.0 ± 1.0 cm; p=0.01).	● Pts with atrial tachyarrhythmia s late after Fontan operation have longer p-wave duration and p-wave dispersion and larger right atrial dimension than those without arrhythmias.
Van den Bosch AE, et al. 2004 (680) 15110207	Single-center retrospective cohort study	n=36 pts	Inclusion criteria: Fontan procedure; followed in Thorax Center, Netherlands	Long-term outcomes and QOL	● Atrial tachyarrhythmias were observed in 56% and were associated with impaired QOL.	● Atrial tachyarrhythmias are highly prevalent and, along with reoperations and thromboembolic events, are associated with a reduction in QOL.
Weipert J, et al. 2004 (681) 14762355	Single-center retrospective cohort study	n=162 pts	Inclusion criteria: Fontan procedure; follow-up at German Heart Center, Munich	Late Fontan failure; Incidence of IART	● At 20 y, overall freedom from tachycardia was 46%. Acute success of catheter ablation was (83%; 25 of 30) with freedom from recurrent tachycardia of 81% at 3 y. ● Duration of Fontan circulation was the only independent predictor of IART.	● IART is highly prevalent and associated with duration of the Fontan circulation. ● Catheter ablation outcomes are reasonable in Fontan pts.
Davos CH, et al. 2003 (682) 12970229	Single-center cross-sectional analysis	n=22 pts	Inclusion criteria: Fontan operation; age- and sex-matched controls	Heart rate variability and baroreflex sensitivity	● Baroreflex sensitivity and heart rate variability were significantly depressed in Fontan pts.	● Relative suppression of the sympathetic- compared with the parasympathetic-system

					● Those with a history of sustained atrial tachyarrhythmia stronger baroreflex than those without (p=0.005).	was observed in Fontan pts. ● Stronger baroreflexes were seen in those with sustained atrial tachyarrhythmia, implying that SND is unlikely to be the dominant mechanism.
Ghai A, et al. 2001 (683) 11216983	Single-center retrospective cohort study	n=94 pts	Inclusion criteria: Fontan surgery between 1977—1994; follow-up at Toronto ACHD center	Prevalence of atrial tachyarrhythmia	● 39 pts (41%) had sustained atrial tachyarrhythmia compared to pts without atrial tachyarrhythmia, those with atrial tachyarrhythmia were more likely to develop HF (46% vs. 13%) and right atrial thrombus (31% vs. 4%), exhibit right and left atrial enlargement, and have moderate-to-severe systemic valve regurgitation (31% vs. 7%).	● Atrial tachyarrhythmia is highly prevalent post Fontan and is associated aortic valve regurgitation, biatrial enlargement, right atrial thrombus, and HF.
Tuzcu V, et al. 2000 (684) 10933377	Prospective 2-group cohort study	n=24 Fontan pts; 15 healthy controls	Inclusion criteria: Fontan surgery; age-matched healthy controls.	P-wave signal-averaged ECG and atrial tachyarrhythmia	● Filtered p-wave duration was significantly longer in Fontan pts with atrial tachyarrhythmias compared to no atrial tachyarrhythmias. A filtered p-wave duration cut point of 135 mo resulted in a sensitivity of 71% and a specificity of 81%. ● The p-wave vector integral was significantly greater in Fontan pts with and without ATs compared with controls	● Signal-averaged p-wave duration is significantly prolonged in postoperative Fontan pts and is associated with atrial tachyarrhythmias.
Betts TR, et al. 2000 (685) 10908214	Retrospective single-center case series	n=6 pts	Inclusion criteria: Fontan surgery; IART; Referred for catheter ablation	Acute success of catheter ablation using noncontact system; arrhythmia recurrence	● Noncontact mapping improved recognition of arrhythmia substrates. Acute success was achieved in 3 of 5 pts with regurgitant fraction ablation. 2 had a recurrence at 6.4 mo of follow-up.	● Noncontact mapping can identify arrhythmia circuits and guide placement of ablation lesions. ● Arrhythmia recurrence is high.
Durongpisitkul K, et al. 1998 (686) 9736597	Single-center retrospective cohort study	n=499 pts	Inclusion criteria: Fontan surgery between 1985—1993	Determine prevalence of SVA after Fontan surgery	●17% of pts developed SVA by 5 y of follow-up. Arrhythmias were associated with older age and systemic aortic valve replacement, but not type of Fontan.	● SVA are common after Fontan surgery but do not appear to be related to type of Fontan procedure.

Backer CL, et al. 2013 (687) 23987899	Single center	n=22 pts	Inclusion criteria: Transplant in pts with Fontan repairs	Outcomes of transplant for those with Fontan repairs	● Median age 12.2 y at transplant, interval from Fontan, 7.1 y. ● 5/22 died (23%) early, 1 graft failure, 1 pulmonary HTN, 1 infection. Those with PLE or plastic bronchitis had complete resolution of their symptoms. 1, 5, 10 y survival were 77%, 66%, 45%	● Transplantation in pts with Fontan repair has high mortality, and this series is relatively young.
Seddio F, et al. 2013 (265) 22733841	Single center	n=33 pts	Inclusion criteria: Mean 7.8 y post-transplant	Risks factors for survival	● PLE and pretransplant mechanical ventilation were risk factors for mortality, but transplant was also curative.	● Data also presented for pediatric age groups, but not all results differentiated by age.
Gatzoulis MA, et al. 2000 (688) 10618336	Single center	n=50 pts	Inclusion criteria: Pts palliated with cavopulmonary or aortopulmonary shunts but not Fontan palliated. Mean 13 y of follow-up at center	Morbidity and mortality	● Survival was 89% at 10 y, 52% at 20 y. ● Arrhythmias were common, mean SpO_2 82%, 42% in NYHA II-II, 50% NYHA III. ● Arrhythmias and decline in ventricular function more common in aortopulmonary shunting.	● Aortopulmonary or cavopulmonary (or both) shunts have survival comparable to Fontan series. ● Cavopulmonary shunt have a beneficial effect on ventricular function compared to aortopulmonary shunts.
Dulfer K, et al. 2014 (689) 244918733	RCT	n=71 pts	Inclusion criteria: Teens with TOF or Fontan circulation, randomized to exercise program or usual habits	Emotional and behavioral problems as assessed by questionnaire	● 3 training sessions, 1 h/wk resulted in no significant difference between exercise and control groups in behavioral/emotional problems. Such problems were infrequent in the groups at baseline.	● Though randomized, the study may not have selected pts for whom the intervention would be of benefit and only 71 of 362 eligible teens participated.
Gamba A, et al. 2004 (690) 14762368	Retrospective case series	n=14 pts	Inclusion criteria: Mean age at transplant 17 y	Mortality after transplantation in pts with Fontan physiology	● 7 pts transplanted for PLE 5 for ventricular dysfunction. ● 2 hospital deaths, 1 of graft rejection the other of a neurologic event. 2 late deaths, 1of acute rejection, the other of chronic rejection and IE. ● 10 survivors are NYHA class I without PLE.	● Transplantation is a good option for failing Fontan's and results in resolution of PLE in this relatively small group.
Jayakumar KA, et al. 2004 (691) 15542293	Retrospective case series	n=35 pts	Inclusion criteria: Mean age at transplant 15 y	Mortality after transplant in pts with Fontan or Glenn shunt	● Mean follow-up 54 mo, 11 pts with Glenn, 24 with Fontan. ● Indications for transplant included ventricular dysfunction, Fontan failure, and cyanosis. 1-y survival 71%, 5-y survival 67%.	● Transplant in Glenn or Fontan pts has similar mortality to other indications for transplant.

					● Survival not different between Glenn and Fontan pts.	
Triedman JK, et al. 2002 (692) 12039499	Retrospective case series	n=134 pts, 177 procedures	Inclusion criteria: Pts with CHD and IART undergoing ablation	Factors influencing outcomes of ablation	● Acute success associated with irrigated ablation and lack of AF. Mean follow-up of 25 mo, 42% had recurrence of IART and 28% required cardioversion. ● Better outcomes seen with higher RA saturations, use of electroanatomic mapping, fewer IART circuits and acute procedural success.	● IART frequently recurs, though this is an older series and improved technology may improve outcomes
Yap SC, et al. 2010 (693) 21029876	Retrospective case series	n=130 pts with 193 procedures	Inclusion criteria: Pts with CHD and IART undergoing ablation	Acute and long-term outcomes and predictors of IART ablation	● Mean age 40 y, 69% initially with successful IART. ● Use of electroanatomic mapping associated with successful ablation, Fontan and Mustard repairs associated with unsuccessful ablation. Median follow-up of 3.7 y in 77 pts had recurrence in 48%, cardioversion or reablation in 42% and death in 4%. ● Age and Fontan were risks for recurrence.	● IART ablation is successful in short term, but recurs commonly, particularly in older pts and those with Fontan repairs.
de Groot NM, et al. 2010 (694) 20194797	Retrospective case series	n=53 pts	Inclusion criteria: Pts with CHD and atrial tachyarrhythmia	Characteristics of recurrent atrial tachyarrhythmia after ablation in pts with CHD	● Mean age 38 y, mean follow-up 5 y. ● AT recurred in 59% in the first y. Different arrhythmogenic substrates were found as cause of recurrence in majority. 31 pts were in sinus rhythm at follow-up, with 57% on antiarrhythmic medications.	● Atrial tachyarrhythmia is frequently recurrent and cause is not usually arrhythmogenicity of prior ablative lesions. ● Sinus rhythm is able to maintain in many, though with use of antiarrhytmic medications in most.

Data Supplement 49. Severe Pulmonary Arterial Hypertension – Section 4.4.6.1

Study Name, Author, Year	Study Design	Study Size	Study Design	Inclusion/Exclusion Criteria	1° Endpoint	Results	Summary/Conclusions

D'Alto M, et al. 2013 (339) 23850317	Single-center open-label cohort	n=22 pts		Inclusion criteria: Presence of PAH after closure of ASD, VSD, PDA, AVSD, with pre- and post-closure hemodynamics	Demographics, hemodynamics (catheterization) pre- and post- defect closure	● Mean age at closure 25.3 ± 20.1 y (3 mo–56.7 y). mean age at PAH diagnosis 37.0 ± 20.8 y (5–61.2 y). ● At preclosure catheterization 18/22 subjects had PVR ≥5 U, 21/22 had PVR index ≥6 U × m^2, 21/22 Rp/Rs≥0.33.	● Preclosure PVR (≥5 U), PVR index (≥6 U × m^2) and Rp/Rs≥0.33 appeared to correlate with PAH late after shunt closure.
Barst RJ, et al. 2014 (695) 24176071	Multicenter prospective registry	n=353 pts with CHD-PAH of 1979		Inclusion criteria: New and previously defined subjects with WHO Group 1 PAH (catheterization based diagnosis) followed at PAH treatment centers	Survival (4 y, 7 y of follow-up) Secondary EP: demographics, hemodynamics, 6MWT	● Survival was similar between idiopathic PAH and CHD associated PAH cohorts (74 ± 1 vs. 78 ± 4% p=0.69) at 4 y, (55 ± 2 vs. 70 ± 8% p=0.3). ● For the CHD associated PAH cohort 4 y survival was correlated with (univariate) 6MWT (HR:0.68 per 100 m; 95% CI: 0.56–0.83; p<0.001), lower mean RA pressure (HR: 1.09; 95% CI: 1.04–1.14; p<0.001), BNP <50 pg/mL (HR<0.28; 95% CI: 0.11–0.69; p<0.006), and the presence of vasoreactivity at entry catheterization (HR: 0.33; 95%CI: 0.11–0.98; p<0.046) and (multivariate) age at diagnosis (HR: 1.11 per 5 y; 95% CI: 1.04–1.18; p<0.002) and mean RA pressure (HR: 1.05; 95% CI: 1.00–1.10; p<0.042).	● CHD associated PAH in subjects cared for at PAH treatment centers carries similarly profound diagnosis as idiopathic PAH. ● Time from diagnosis and higher RA pressure carry worse long-term prognosis.
Duffels MG, et al. 2007 (696) 17182132	Multicenter retrospective registry	n=112 with CHD-PAH of 5,970		Inclusion criteria: Echocardiographic estimation of systolic PAP ≥40 mm Hg	Demographics, prevalence, FC	● PAH prevalence by echo estimation of PAP was 4.2%. Of subjects with a septal defect 6.1% had PAH; of subjects with previously closed septal defect, 3% had PAH. ● Female sex (OR=1.5; p=0.001) and echo estimation of PAP (OR=0.04; p=0.001) were associated with decreased FC.	● PAH occurs with reasonable frequency in adults with CHD and shunts. ● Decreased FC may be a marker for higher PAP.

Engelfriet PM, et al.
2007 (697)
17164490
	Multicenter retrospective registry	n=1,877 pts		Inclusion criteria:
				All pts with ASD, VSD, cyanotic HD; PAH defined either by catheterization systolic PAP ≥25 mm or echocardiography systolic PAP ≥35 mm
					Demographics, prevalence, FC, RV contractile function (echo), survival	● Open defects: 34% with ASD and 28% with VSD had PAH.
						● Closed defect, 12% with ASD and 13% with VSD had PAH.
						● 5-y survival with vs. without PAH:
						closed ASD: 94.8% vs. 98.4%, (p=0.036);
						open ASD: 97.2% vs. 99.6% (p=0.118);
						closed VSD: 93.1% vs. 99.1% (p=0.021);
						open VSD: 96.7% vs. 98.7% (p=0.299).
						● Each increase in systolic PAP of 1 mm Hg, increased the probability of RV dysfunction by a factor of 1.073 (95% CI: 1.045–1.102; p=0.001).
							● CHD associated PAH in subjects with open or closed septal defects cared for at ACHD treatment centers appear to carry less mortal prognosis than expected in 5-y follow-up. Incremental elevation of systolic PAP is associated with worsened RV systolic function.

Gabriels C, et al. 2014 (698) 25149406	Multicenter retrospective registry	n=47 pts with PAH of 295		Inclusion criteria: All subjects with ASD; PH defined by TR velocity ≥2.9 m/s.	Demographics, hemodynamics at past catheterizations, echocardiographic estimate of TR velocity and RV systolic function, atrial arrhythmia	● PH prevalence was 15.9% in all subjects with open or closed ASD, vs. 13.3% in subjects after ASD closure. ● Mean PAP at catheterization prior to ASD closure was related to PH after closure (HR: 1.09). ● Age at ASD closure was related to PH after closure (HR: 1.11). ● PH after ASD closure was related to mortality (p=0.001), atrial arrhythmia (p<0.001) and right HF (p=0.019).	● PH as defined by TR velocity elevation may be more common than expected in adults with ASD, whether open or closed. ● Age at ASD closure and mean PAP at time of ASD closure may be related to late presence of PH after closure.
Lowe BS, et al. 2011 (27) 21777753	Provincial administrative retrospective registry: longitudinal cohort multivariate analysis matched by age and CHD lesion type	n=2212 pts with PH of 3,843		Inclusion criteria: PH defined by treating physician specialists.	Mortality, HF, health resource utilization: 23-y follow-up	● PH: - All-cause mortality was increased (HR: 2.69; 95% CI: 2.41–2.99). - HF and arrhythmia burden were increased (HR: 3.01; 95% CI: 2.80–3.22) - Overall health resource utilization was increased (RR: 5.04; 95% CI: 4.27–5.93) - Coronary and intensive care hospitalizations were increased (RR 5.03; 95% CI: 4.86–5.20).	● Clinician-based categorization of PH in adults with CHD raises use of health resources, risks of HF and arrhythmia and all-cause mortality.

Manes A, et al. 2014 (699) 23455361	Single-center retrospective cohort	n=192 pts		Inclusion criteria: Presence of current or repaired CHD and catheterization based PAH	Demographics, hemodynamics, FC,1-, 5-, 10-, and 20-y survival	● Overall population, 1-, 5-, 10-, 20-y survival rates (95% CI) were 99% (96%–100%), 91% (85%–94%), 85% (78%–90%), and 77% (68%–84%). ● Eisenmenger Syndrome, 1-, 5-, 10-, 20-y survival rates were 99% (92%–100%), 93% (85%–97%), 89% (79%–94%), and 87% (77%–93%). ● PAH associated with systemic-to-pulmonary shunts, 1-, 5-, 10-, 20-y survival rates were 100%, 93% (76%–98%), 93% (76%–99%), and 86% (60%–96%). ● PAH associated with small defects, 1-, 5-, 10-,15-y survival rates were 100%, 88% (39%–98%), 8% (39%–98%), and 66% (16%–91%), respectively. ● PAH after cardiac defect correction, 1-, 5-, 10-, 20-y survival rates were 98% (85%–100%), 83% (66%–92%), 65% (43%–80%), and 36% (12%–62%).	● Pts with PAH after congenital heart defect repair may have worse survival than subjects who remain with open septal defects.
O'Donnell C, et al. 2010 (700) 20869312	Single-center open-label retrospective cohort	n=11 pts		Inclusion criteria: Mean PAP >30 mm at time of ASD closure	Survival, FC symptomatic HF, echocardiographic TR velocity	● 8/11 post closure with symptomatic improvement with no evidence of progressive PH. 1/11 with death of unrelated causes. 2/11 with progressive PH with ½ deaths associated with PH. ● Recurrent PH appeared to correlate with lesser Qp/Qs at time of catheterization.	● Pts with PH at the time of ASD closure may be at increased risk for later development of PH and worse outcome after ASD closure.
Van de Bruaene A, et al. 2011 (701) 20674051	Multicenter retrospective open-label case control	n=155 pts (24 surgical closure, 131 transcatheter closure)		Inclusion criteria: ASD closure, clinical presentation with atrial arrhythmia during follow-up	Demographics, hemodynamics at time of ASD closure, clinical arrhythmia within 5 y of post closure follow-up	● 25.2% of subjects undergoing ASD closure developed atrial arrhythmia >1 mo after closure. ● Univariate risks for development of atrial arrhythmia were male (p=0.008), creatinine (p=0.002), atrial arrhythmia either for closure (p<0.0001) or during the 1 mo after closure (p=0.001), and mean PAP) ≥25 mm Hg (p<0.0001). ● Multivariate risks for development of atrial arrhythmia were mean PAP ≥25 mm at the time of closure (HR: 3.72; 1.82–7.59; p<0.0001) and either the presence of atrial	● Presence of PH at the time of ASD closure may correlate with late development of atrial arrhythmia.

						arrhythmia prior to closure (HR: 3.22; 1.56–6.66; p=0.002) or during the 1 mo after closure (HR: 2.08; 2.08–15.92; p=0.001).	
Van de Bruaene A, et al. 2013 (702) 21802750	Multicenter retrospective open-label case control: Cox regression to define a multivariate weighted risk model	n=155 pts (24 surgical closure, 131 transcatheter closure)		Inclusion criteria: ASD closure, clinical presentation with atrial arrhythmia during follow-up	Demographics, hemodynamics at time of ASD closure, clinical arrhythmia within 5 y of post closure follow-up	● Multivariate risks for development of atrial arrhythmia were mean PAP ≥25 mm at time of closure (HR: 4.39; 2.17–9.09; p<0.0001), and either the presence of atrial arrhythmia prior to closure (HR: 3.52; 1.75–7.14; p=0.002) or during the 1 mo after closure (HR: 6.62; 2.38–20.00; p<0.0001), and male (HR: 2.18; 1.11–4.35). ● A points system was developed to predict the risk for developing atrial arrhythmia >1 mo after ASD repair and at 1, 2, 3, 4, and 5-y (integrated Brier score 0.10 with R^2: 0.41).	● Presence of PH at the time of ASD closure may correlate with late development of atrial arrhythmia.
Balint OH, et al. 2008 (703) 17932093	Single-center retrospective open-label cohort	n=54 pts (11% of all adults referred for ASD closure)		Inclusion criteria: Moderate (50–59 mm) or severe (≥60 mm) PH by echo determined TR velocity prior to transcatheter ASD closure	Demographics, echocardiographic TR velocity, measures of RV systolic dysfunction, subjective FC, survival	● 31 ± 15 mo follow-up. ● RV systolic pressure decreased from 58 ± 10 mm to 44 ± 16 mm (p=0.004), and were not related to duration of follow-up; only 44% had normalization of RV systolic pressure. ● While NYHA class decreased regardless of pre- and postprocedure RV systolic pressure, subjects with residual PH by RV systolic pressure were more frequently symptomatic after device closure (15% vs. 67%; p=0.02). ● RV dilation and subjectively described systolic dysfunction decreased from presence in 96% and 41% to 36% and 23% (p<0.001).	● Presence of severe PH at the time of ASD closure and impaired subjective NYHA postclosure FC may correlate with greater likelihood of moderate-to-severe PH post procedure.

Balzer DT, et al. 2002 (704) 12354713	Multicenter open-label prospective cohort: children	n=124 pts		Inclusion criteria: Preoperative congenital or acquired HD, hemodynamics sufficient to calculate Rp, Rs, under all test conditions, Rp:Rs≥0.33 during baseline measurements.	Demographics, hemodynamics, postoperative HF or death	● Ability to demonstrate Rp/Rs<0.33 with or without iNO yielded positive and NPVs of 95% (87, 99) and 32% (19, 51) for survival without right HF and 92% (84, 97) and 78% (52, 97) for survival without right HF or death over 26 (3–97) mo of follow-up.	● Ability to lower Rp/Rs<0.33 during preoperative evaluation using O_2 and iNO may predict postoperative survival without HF in adults with CHD and severe PAH.
Berner M, et al. 1996 (705) 8629600	Single-center open-label retrospective cohort: children	n=13 pts		Inclusion criteria: Preoperative hemodynamic assessment of children with CHD with baseline Rp/Rs≥0.3	Demographics, hemodynamics (selective pulmonary vasoreactivity defined as simultaneous decrease in both PVR and Rp/Rs of >10% to administration of iNO); postoperative survival	● 9/13 had decrease in PVR from 9.5 + 1.5–7.2 ± 1.2 WU l m^2 (-24 ± 7%; p<0.05), and in Rp/Rs from 0.46 + 0.11–0.35 + 0.10 (-25 + 8%; <0.05), with height of preoperative Rp/Rs and older age correlated with lack of selective pulmonary vasoreactivity. ● Presence of selective pulmonary vasoreactivity correlated with survival in 2–5 mo of follow-up.	● Ability to lower preoperative PVR and Rp/Rs>10% with iNO as well as Rp/Rs<0.3 may predict short-term survival after surgery to correct congenital septal defects with intracardiac shunting in children.
Gorenflo M, et al. 2010 (706) 20424447	Single-center open-label retrospective cohort	n=46 pts		Inclusion criteria: Preoperative hemodynamic assessment of subjects with CHD with intravascular shunting and preoperative PVR index indicative of "severe PAH" (implied ≥10 WU*m^2)	Demographics, hemodynamics (pulmonary vasoreactivity defined as reduction in PVR index ≥20% compared to baseline without decreaseof systemic arterial BP to administration of inhaled iloprost)	● Ages 9 mo–43 y. ● 29/46 pts had positive preoperative pulmonary vasoreactivity with PVR index 14.91 ± 5.98 reduced to 8.92 ± 4.09 WU*m^2 (p<0.05); 21/29 underwent surgical correction with 21/21 alive at 3 y of follow-up.	● Ability to lower preoperative PVR index ≥20% compared to baseline using inhaled iloprost may predict short- and intermediate-term survival after surgery to correct congenital septal defects with intracardiac shunting.
Huang JB, et al. 2011 (707) 20494465	Single-center open-label retrospective cohort: children	n=49 pts		Inclusion criteria: Preoperative hemodynamic assessment of pts with CHD with intravascular shunting and preoperative PAM	Demographics, hemodynamics, open lung biopsy findings, survival	● In 49 pts (mean age at operation 36.5 ± 23.8 mo (8–96), who met "treat and repair criteria" after use of PAH therapy for 16–150 d, all survived surgical defect closure; at 117.6 ± 56.6 mo (range, 13–167) of follow-up. ● 49/49 were alive; 98% were WHO class I. 1 pt with residual PH was WHO class II.	● Ability to raise systemic arterial saturation by defined criteria using PAH therapy in children with CHD and intravascular shunting with preoperative severe PAH may predict intermediate-term survival after surgery to

				>50 mm who received preoperative "treat and repair" with PAH therapy leading to a) systemic arterial saturation rise in subjects with "simple CHD" to >93%, or b) increase in systemic arterial saturation by ≥5% in pts with "complex CHD"			correct congenital septal defects.
Neutze JM, et al. 1989 (708) 2913735	Single-center open-label retrospective cohort: children	n=87 pts, 36 with moderate or severe preoperative PAH (>7 U* m^2)		Inclusion criteria: Preoperative hemodynamic assessment of subjects with congenital VSD	Demographics, hemodynamics, vasodilator testing to administration of isoproterenol (positive response defined as ability to lower PVR index <7 WU* m^2), survival	● Positive pulmonary vasodilator response to isoproterenol correlated with survival (1.8–162 mo). ● Rp/Rs<0.75 did not correlate with positive pulmonary vasodilator response; Rp/Rs≥0.75 correlated with lack of positive pulmonary vasodilator response to isoproterenol.	● Ability to lower PVR index to <7 U/m^2 using isoproterenol in children with CHD with preoperative moderate-to-severe PAH may predict short- and intermediate-term survival after surgery.
Steele PM, et al. 1987 (709) 3664992	Single-center open-label retrospective cohort	n=702 pts, 40 with pulmonary vascular disease		Inclusion criteria: Isolated secundum or venous ASD; surgery at discretion of treating clinician	Demographics, hemodynamics (preoperative total peripheral resistance), preoperative systemic arterial saturation	● Median follow-up 12 y, 17/40 dead at follow-up. ● In 26 pts undergoing surgical repair, correlates of longer-term survival included total peripheral resistance (p<0.00001), PA resistance (p<0.00001), Rp/Rs (p=0.004), systemic arterial SpO_2 (p=0.005), PA SpO_2 (p=0.007). ● Both systemic arterial and PA SpO_2 varied inversely with PVR. ● Longer-term survival after surgical defect closure appeared correlated with total peripheral resistance <15 U/m^2 or systemic arterial SpO_2 ≥92%.	● Preoperative resting total peripheral resistance <15 U/m^2 or systemic arterial O_2 saturation ≥92% may predict intermediate-term survival after secundum ASD or VSD surgical repair.

Yong G, et al. 2009 (710) 20031756	Single-center open-label retrospective cohort	n=215 pts		Inclusion criteria: Isolated secundum ASD undergoing catheter-based ASD closure	Demographics, hemodynamics, echocardiographic estimates of TR, RV systolic function, TR velocity, subjective NYHA FC Moderate PH defined as PASP 50–59, severe PAH defined as PASP ≥60 mm	● Mean follow-up 15 mo. ● Pts with moderate and severe PAH had higher Qp/Qs, 2.8 (1.8, 3.4) and 3.5 (2.0, 4.1), respectively (p=0.0045) ● Independent predictors of preclosure moderate or severe PH were older age (OR: 1.10 per y; p=0.0001), larger ASD (OR: 1.13 per mm; p=0.0052), female (OR: 3.9; p=0.0313), ≥ moderate TR (OR: 3.6; p=0.0043). ● Increasing preclosure PASP correlated with post closure lowering of PASP ≥5% (p<0.0001) but also with inability to normalize post closure PASP (p<0.0001). ● NYHA FC improved post ASD closure in subjects with moderate or severe PH, lower preclosure PASP (OR: 0.91 per mm Hg; p=0.0418) and ≤ mild TR (OR: 0.14; p=0.0420) correlated with ability to normalize post closure PASP.	● Preoperative moderate-to-severe PH may carry risk of late PH in adults undergoing transcatheter ASD closure.

Data Supplement 50. Eisenmenger Syndrome – Section 4.4.6.2

Study Name, Author, Year	Study Type/ Design	Study Size	Inclusion/Exclusion Criteria	Intervention	1° Endpoint	Results/p Values	Summary/Conclusions
Bosentan							
Galiè N, et al. 2006 (264) 16801459	Double-blind, placebo-controlled RCT	54 (37 bosentan, 17 control)	Inclusion criteria: ≥12 y, WHO III, echocardiography diagnosis Eisenmenger syndrome, catheter diagnosis Eisenmenger syndrome, SpO_2 70%–90%, 6MWT 150–450 mo, stable Rx	Bosentan 62.5 mg PO BID × 1 mo, 125 twice a d × 3 mo	● 1°: SpO_2 baseline to wk 16 s-1°: PVR if first 1°endpoint met. ● 2°: hemodynamics, 6MWT	● Bosentan Rx: SpO_2 (corrected for placebo effect) =1.0% (95% CI: -0.7–2.8). Bosentan Rx: PVR index 472.0 dynes (p=0.0383). ● Bosentan Rx: mPAP 5.5 mm Hg (p=0.0363), Bosentan Rx: 6MWT 53.1 min (p=0.0079).	● Bosentan improves 6MWT and hemodynamics without worsening systemic arterial saturation in pts with typical Eisenmenger Syndrome and FC III after administration for 4 mo.

			Exclusion criteria: PDA, complex CHD, LVEF <40%, total lung capacity <70%, forced expiratory volume in 1 s <70%, forced expiratory volume in 1 s/forced vital capacity <60%, known CAD. No prior use prostanoids, PDE5 inhibitors, ERA's within 1 mo screening				
Gatzoulis MA, et al. 2008 (711) 17658633	OLE (of RCT), observational, cohort, retrospective	n=37 pts	Inclusion criteria: Participation within BREATHE-5	Bosentan in BREATHE-5: continuation × 24 wk Bosentan naïve: bosentan 62.5 mg PO BID × 4 wk, 125 mg PO BID thereafter	6MWT, O_2 saturations, Borg dyspnea class	● 6MWT: + 33.2 ± 23.9 min ex-placebo group (95% CI: [-21.9–88.4]; n=9) +6.7 ± 10.0 mo for open-label extension period for ex-Bosentan group (95% CI: -13.9–27.4; n=26) and overall improvement (OLE + B5) + 61.3 ± 8.1 mo (95% CI: 44.7–78.0; n=26). ● SpO_2: +0.8 ± 1.3% (95% CI: -2.3–3.9; n=9) ex-placebo group -1.0 ± 0.8% (95% CI: -2.5–0.6]; n=26) for ex-Bosentan group for open-label extension period, and overall +1.4 +/= 0.7% (95% CI: 0.0–2.8; n=26) for open-label extension and BREATHE-5. ● BORG: -0.9 ± 0.3 (95% CI: -1.5– -0.3; n=9) for ex-placebo +0.4 ± 0.3 (95% CI: -0.1–1.0; n=26) for ex-Bosentan in open-label extension study, overall -0.5 ± 0.4 (95% CI: -	● Sustained use of Bosentan in subjects who participated in the original RCT involving this medication for typical Eisenmenger Syndrome and FC III maintains improvement over 5 additional y of follow-up in 6MWT.

						1.3–0.2; n=26) for open-label extension + BREATHE-5.	
Berger RM, et al. 2010 (712) 19464064	Post hoc analysis of double-blind, placebo-controlled RCT	n=54 pts (37 Bosentan, 17 control)	Inclusion criteria: Participation within BREATHE-5	Bosentan 62.5 mg PO BID × 1 mo, 125 mg PO BID × 3 mo	PVR index 6MWT, mPAP, Qpi, SpO_2	● PVR index: -544.0 dynes (95% CI: -1593.8–344.7) ASD, -436.4 dynes (95% CI: -960.0–167.0) VSD. 6MWT +32 min (95% CI: -16.3–325.5) ASD +34 min (95% CI: -1.9, 65.5) VSD mPAP. -9.0 (85% CI: -26.6–1.1) ASD: -4.0 (95% CI: -8.6–1.0) VSD. ● No changes in SpO_2 or Qpi in Bosentan or placebo subgroups.	● No difference in improvement in hemodynamic or functional outcomes were apparent between pts with pre- or post-tricuspid shunts with Eisenmenger Syndrome and FC III who participated in RCT of Bosentan therapy.
Abd El Rahman MY, et al. 2014 (713) 24682249	Observational cohort multiple center uncontrolled open-label prospective	n=40 pts	Inclusion criteria: ≥18 y, O_2 saturation ≤93%; PAH (catheter) Rp:Rs ≥0.75 presence of PAH due to noncorrected large congenital shunting defect at atrial, ventricular or arterial level. Exclusion criteria: PH for other reason, acute decompensated HF within 7 d, LV or non-TV or PV valvular diseases, bronchopulmonary dysplasia or other chronic lung diseases, poor echocardiography windows.	Bosentan 24 wk 62.5 mg PO BID × 4 wk then 125 mg PO BID × 20 wk, catheterization pre and post, echocardiography parameters pre and post	Echocardiography parameters of RV and LV function, 6MWT, BNP	● Pre vs. post measures: -TAPSE 19 (15–21) vs. 20 (16–22); p=0.01; RV Tei index 0.55 (0.45–0.65) vs. 0.48 (0.41–0.63); p=0.043; LV Tei index 0.46 (0.35–0.6) vs. 0.37 (0.28–0.52); p=0.001; RV mean strain (%) 18 (13–22) vs.19 (15–25); p=0.004; LV mean strain (%) 16 (12–21) vs. 17 (16–22); p=0.0001.	● Echocardiographic parameters of RV and LV function appeared improved after Bosentan therapy for typical Eisenmenger syndrome in open-label uncontrolled study.

Baptista R, et al. 2013 (714) 23351920	Single-center open-label prospective	n=14 pts	Inclusion criteria: Eisenmenger syndrome, FC II-IV, nonisolated ASD or isolated VSD, iron-deficiency corrected	Bosentan 62.5 mg PO BID × 4 wk, then 125 mg PO BID, sildenafil addition allowed for clinical worsening	6MWT, SpO_2 at 6 min, FC, Borg	● Pre vs. bosentan: 6MWT: 371.9 ± 90.3 vs. 428.4 ± 98.3; p=0.005; SpO_2: 82.0 ± 6.9 vs. 81.9 ± 6.6; p=0.956; SpO_2 peak exercise: 73.4 ± 13.2 vs. 72.8 ± 10.6; p=0.832; BORG baseline: 2.4 ± 1.7 vs. 3.3 ± 2.3; p=0.271; BORG end exercise: 6.7 ± 1.8 vs. 7.5 ± 1.5; p=0.108.	● In pts with complex CHD (truncus, TOF/PA, PDA, TGA) and Eisenmenger syndrome with FC I–IV, observed in open-label prospective study, improvement in 6MWT with Bosentan was sustained to 4 y of follow-up.
Díaz-Caraballo E, et al. 2009 (715) 24775365	Single-center open-label prospective	n=10 pts	Inclusion criteria: Eisenmenger syndrome, >18 y, FC II–IV, nonisolated ASD or isolated VSD	Bosentan 62.5 mg PO BID × 4 wk, then 125 mg PO BID	6MWT, SpO_2 at 6 mo, FC	● Pre vs. bosentan: 6MWT: 266 ± 161 to 347 ± 133 min p=0.015; SpO_2: No change; NYHA: 3.3 ± 0.7–2.5 ± 0.9; p=0.002.	● In pts with complex CHD (truncus or pseudotruncus, single ventricle, TGA, AVC, TOF/PA) and Eisenmenger syndrome with FC II-IV followed in open-label prospective fashion, improvement in 6MWT and subjective FC without worsening of systemic arterial saturation, was noted at 6 mo of follow-up.
Sildenafil							
Zhang ZN, et al. 2011 (716) 21948962	Multicenter, open-label, prospective	n=84 pts	Inclusion criteria: Eisenmenger syndrome, WHO FC II–IV	Sildenafil, 20 mg PO TID × 12 m	6MWT SpO_2, hemodynamics	● 12 m: 6MWT: + 56 min (95% CI: 42–69; p<0.0001); SpO_2: + 2.4% (95% CI: 1.8%–2.9%; p<0.0001); mPAP: -4.7 mm Hg (95% CI: -7.5– -1.9; p=0.001). ● PVR index: -474 dynes m^2 (95% CI: -634– -314; p<0.0001).	● Sildenafil appeared to improve 6MWT and systemic arterial oxygenation at 12 mo of follow-up in pts with typical Eisenmenger syndrome and FC II–IV followed in open-label prospective fashion.

Garg N, et al. 2011 (717) 21729508	Open label single-arm prospective	n=22 pts	Inclusion criteria: Eisenmenger syndrome, age >12 y, FC II, III, stable medications, no other PAH targeted medical Rx. Exclusion criteria: PDA or complex CHD	Sildenafil 12.5 PO TID × 1 mo, then 25 mg PO TID	6MWT, O_2 saturations, mPAP, PVR index	● 6MWT: 305.3 ± 60.1 to 476.9 ± 73.6 min; (p<0.0001). ● SpO_2: 86% ± 2% to 91.1 ± 1.1%; (p<0.001). ● mPAP: 69.6 ± 10.0 to 62.2 ± 11.5 mm Hg; (p<0.001). ● PVR index: 21.4 ± 3.9–15.4 ± 3.9 WU; p<0.0001.	● Pts with typical Eisenmenger Syndrome and FC II–III treated with sildenafil improved 6MWT, hemodynamics, and systemic arterial saturation after 6 mo of open-label prospective follow-up; ASD pts appeared to have greater response than VSD pts.
D'Alto M, et al. 2012 (718) 21081251	Single-center, open-label, single-arm, prospective	n=28 pts; Eisenmenger syndrome of 32 CHD-PH	Inclusion criteria: Clinical worsening on Bosentan for CHD-PH or Eisenmenger syndrome: death from any cause, nonelective hospitalization for PAH and/or disease progression = 15% decrease from baseline in 6MWT on 2 tests performed within 2 wk in association with worsening FC; weight >40 kg	Right heart catheterization followed by Sildenafil 20 mg PO TID	FC, SpO_2, 6MWT, hemodynamics, serologies	● WHO FC 2.9 ± 0.3–2.1 ± 0.4; p=0.042. ● SpO_2: no change 80 ± 9–82 ± 8; p=0.48. ● 6MWT: 293 ± 68 to 3–60 ± 51; p=0.005. SpO_2 post 6MWT 63 ± 15–72 ± 10; p=0.047. ● Borg 4.4 ± 2.3–2.9 ± 1.5; p=0.036. ● Qp: 3.1 ± 1.2–3.4 ± 1.0; p=0.0002. ● RA: 13 ± 4–11 ± 3; p=0.09. ● mPAP: 73 ± 20–71 ± 17; p=0.09. ● PVR index: 24 ± 16–19 ± 9; p=0.003. ● ProBNP: 760 ± 943–303 ± 366; p=0.008	● Combination therapy of sildenafil added to baseline Bosentan in the setting of clinical worsening appeared to improve 6MWT, hemodynamics, BNP and subjective FC without worsening of systemic arterial saturation during 6 mo of open-label prospective follow-up.
Iversen K, et al. 2010 (719) 20202971	Randomized placebo-controlled, double-blinded, cross-over, single center	n=21 pts (19 complete)	Inclusion criteria: ≥18 y, Eisenmenger syndrome, defined as PH by cath right to left shunting through nonrestrictive defect	Bosentan 62.5 mg PO BID × 2 wk, 125 mg PO BID thereafter × 9 mo, at 12 wk, after repeated measures, sildenafil 25 mg PO TID added × 2 wk, then 50 mg	1°6MWT, 2° SpO_2 rest and exercise, NT-BNP, NYHA FC, MRI blood flow, Qp, Qp/Qs, PVR index	● Bosentan alone: 6MWT 377–414 min (95% CI: 17–58 min); p=0.01; Qp (catheter) 2.6–3.5 change 0.9; (95% CI: 0.3–1.6); p=0.01; Qp/Qs 0.64–0.79 change 0.16; (95% CI: 0.03–0.28); p=0.02;	● In randomized controlled crossover study, the addition of sildenafil to Bosentan in subjects with typical Eisenmenger syndrome followed for 3 mo of combination therapy improved only systemic arterial saturation without

				PO TID × 10 wk vs. placebo; repeated measures, sildenafil switched for placebo or vice versa × 2 wk, then 10 wk, repeat measures		PVR index: 28.3–21.8 change -6.5; (95% CI: 11.3–1.7); p=0.01; With add on therapy: SpO_2 placebo vs. sildenafil -1.8–2.9 change 4.7; (95% CI: 1.9–7.5); p=0.01; SpO_2 end exercise -2.9–3.9 change 6.8; (95% CI: 20.5–14.2); p=0.07; No change 6MWT, Qp, Qp/Qs.	evidence of improved hemodynamics or exercise capacity when compared to baseline measures performed while taking Bosentan.
Singh TP, et al. 2006 (720) 16569546	Randomized, double-blind, placebo-controlled, crossover	n=10 PAH pts, 10 Eisenmenger syndrome pts	Inclusion criteria: All ages, PAH or Eisenmenger syndrome; clinical exclusion of other causes	Adults: 25 mg sildenafil trial dose, then 100 mg PO TID × 6 wk, 2 wk washout, then placebo × 6 wk	1°6MWT 2°: SBP exercise tolerance test, TTE Doppler measures of TR velocity and RVOT velocity	● All Comers Only: 6MWT: baseline vs. placebo 31.4 ± 9.2; (95% CI: 7.2–55.6; p=0.009); Baseline vs. sildenafil: 96.9 ± 11.3; (95% CI: 67.2–126.6; p=0.0001); Placebo vs. sildenafil: 65.5 ± 11.0; (95% CI: 36.7–94.4; p=0.0001). ● Echocardiography PAP: Baseline vs. placebo - 3.9 ± 2.0; (95% CI: -9.2 – 1.3; p=0.189); Baseline vs. sildenafil - 20.6 ± 2.9 (95% CI: -28.2– -13.0; p=0.0001); Placebo vs. sildenafil -16.6 ± 2.2 (95% CI: -22.4– -10.9; p=0.0001). ● No change SBP exercise tolerance test exercise duration, metabolic equivalent improved (p=0.0001). ● No data regarding Eisenmenger syndrome other	● Use of sildenafil for 6 wk in pts with typical Eisenmenger syndrome appeared, when assessed in aggregate with other subjects with idiopathic PAH, in randomized crossover fashion, to improve 6MWT and echo-derived estimates of PA pressure, without change in measured exercise parameters.

						than NS differences on substudy.	
Bharani A, et al. 2007 (721) 19126937	Blinded crossover study	n=11 pts, 8 analyzed	Inclusion criteria: PAH in pts with prior shunt lesions	Tadalafil 20 mg daily or placebo	6MWT, PASP, Who class and Borg Dyspnea Index	● 8 pts analyzed. Tadalafil was compared to Tadalafil associated with an increase in 6MWT (mean: 409.25, SD: 40.25 m vs. 319.37 SD: 42.39 m; p<0.0001), reduction in PASP (88.75 SD: 23.26 mm Hg vs. 109.5 SD 23.78 mm Hg; p<0.0001), improvement in BMI (4.62 SD 2.56 vs. 6.37 SD 2.61; p=0.021) and WHO Class (6 pts vs. 2 pts), compared to placebo.	● Use of Tadalafil associated with improvement in small series, short-term follow-up.
Ambrisentan							
Zuckerman WA, et al. 2011 (722) 21371683	Open label, cohort, single center, retrospective	n=17 pts	Inclusion criteria: Eisenmenger syndrome, treated with ambrisentan	Ambrisentan 5–10 mg PO daily, after pretreatment either with bosentan or sitaxsentan	6MWT, SpO_2	● 6MWT: 389 ± 74 vs. 417 ± 77 min at 3–9 mo follow-up (p=0.03). ● 420 ± 88 vs. 401 ± 68 mo at >1 y follow-up (p=0.15). ● SpO_2: No change in 3–9 mo or >1 y follow-up.	● Use of ambrisentan in subjects with typical Eisenmenger syndrome studied in open-label retrospective fashion demonstrated decline at >1 y of follow-up from early improved 6MWT

							measured at 3–9 mo, without worsening of systemic arterial saturation during therapy.
Tadalafil							
Mukhopadhyay S, et al. 2006 (723) 17030688	Open label, single-arm, prospective	n=16 pts	Inclusion criteria: Clinical Eisenmenger syndrome, cath when necessary, symptomatic Exclusion criteria: WHOFC IV, overt HF, pulmonary capillary wedge pressure >15, abnormal serologic profile, AF, hypersensitivity to PDE5 inhibitors	Acute: PA catheter, 1 mg/kg tadalafil followed by measures, then 40 mg daily tadalafil measure mo × 12 wk	Acute: Systemic vascular resistance, PVR/systemic vascular resistance ratio, SpO_2 systemic and PA, mPAP, sPAP, right-to-left shunt, Qpeff, FC, 6MWT	12 wk results: ● Tadalafil vs. baseline: PVR: 17.02 ± 6.19 vs. 24.75 ± 8.49; p<0.005; PVR/systemic vascular resistance: 0.71 ± 0.26 vs. 1.09 ± 0.34; p<0.005; mPAP: 75.5 ± 15.09 vs. 81.75 ± 14.21; p<0.005; SpO_2: 89.16 ± 3.8 vs. 87.39 ± 4.34; p<0.005; Qpeff: 2.82 ± 0.88 vs. 2.46 ± 0.69; p<0.08; Right-to-left shunt: 1.16 ± 0.62 vs. 1.71 ± 0.92 mo; p=0.018; FC: 1.25 ± 0.44 vs. 2.31 ± 0.47; (p<0.0001); 6MWT: 387.56 ± 117.18 vs. 344.56 ± 119.06; (p<0.001).	● Tadalafil for 3 mo in subjects with typical clinically defined Eisenmenger syndrome FC II–III followed in open-label prospective fashion appeared to improve hemodynamics and systemic arterial saturation.
Mukhopadhyay S, et al. 2011 (724) 21914136	Single-center randomized controlled crossover	n=28 pts	Inclusion criteria: Catheterization-based diagnosis of Eisenmenger syndrome with mPAP >40 mm, pulmonary capillary wedge pressure <15 mm, and PVR >10 U/m^2, systemic pulse oximetry 70% and 90, baseline 6MWT 150–450 m	Pts given 40 mg of tadalafil or matching placebo for 6 wk followed by washout of 2 wk followed by crossover to the other drug	1°EP: 6MWT compared with baseline after 6 wk Rx. 2° EP: SpO_2, pulmonary blood flow, PVR, systemic vascular resistance, WHO FC	● 6MWT: tadalafil was associated with improvement 404.18 ± 69.54 m vs. placebo 357.75 ± 73.25 m; p<0.001. ● PVR: tadalafil treatment was associated with lowering by 7.32 ± 1.58 U*m^2; p<0.001 with increase in EPBF 0.12 ± 0.05; p=0.03. ● SpO_2%: tadalafil treatment was associated with increased by 1.72 ± 0.58%; p=0.007. ● WHO FC: tadalafil therapy was associated with	● Short-term therapy with tadalafil for subjects with typical Eisenmenger syndrome WHO FC II–III appeared to improve 6MWT and subjective FC, and PVR, without worsening of systemic arterial SpO_2.

			Exclusion criteria: WHO IV, clinical HF or pulmonary capillary wedge pressure >15 mm, LVEF <40%, AF, PDA or other complex congenital heart defects, restrictive lung disease (total lung capacity <70%), obstructive lung disease (forced expiratory volume in 1 s <70% with forced expiratory volume in 1 s/forced vital capacity <60%), previously diagnosed CAD requiring nitrates, abnormal biochemical profile, hypersensitivity to PDE5 inhibitors.			improvement, 1.96 ± 0.18 vs. 2.14; 0.44; p=0.025). ● Systemic vascular resistance: tadalafil was not associated with change in systemic vascular resistance (p=NS).	
Dual/Combination PAH Therapy							
Diller GP, et al. 2013 (725) 22390966	Single institution open-label cohort observational	79 total (63 ES, 16 DS+ES)	Inclusion criteria: All Eisenmenger syndrome on dual targeted therapy	Dual targeted therapy by clinician preference	6MWT, SpO_2, FC	Post dual targeted therapy vs. before: ● 6MWT 50 mo increase at 8 y; p=0.009. ● Increase correlates to worse baseline 6MWT p=0.0047. ● Improved with up-titration or 3rd therapy SpO_2. ● Nonsignificant rise in SpO_2. ● In those who rose SpO_2, baseline SpO_2 correlated with rise p=0.0047. ● FC:	● Use of dual or triple targeted PAH specific therapy in subjects with clinically defined Eisenmenger therapy followed in open-label prospective fashion appeared to have improved 6MWT and subjective FC, correlating in inverse fashion with baseline 6MWT.

						FC "appeared" to increase early, sustained, correlated with worse 6MWT at baseline, on uptitration did not improve.	
Dimopoulos K, et al. 2010 (30) 20026774	Retrospective single center propensity matched observational cohort	n=229 pts	Inclusion criteria: Clinical diagnosis of Eisenmenger syndrome as PAH in the setting of nonrestrictive cardiac defect (not catheterization based) allowing inclusion if surgical closure had occurred in past but subject had near systemic levels of PAP	Targeted PAH medical therapy (68) v no targeted PAH Rx (161)	Propensity adjusted survival	● Risk of death: targeted medical PAH Rx use: Unadjusted HR: 0.21; 95% CI: 0.05–0.86; p=0.03. Adjusted HR: 0.16; 95% CI: 0.04–0.71; p=0.015.	● Mortality appeared lessened in pts with clinically defined typical Eisenmenger when using targeted PAH therapy based upon care provider determination of appropriateness for treatment. Pts receiving PAH specific treatments were more likely to be receiving anticoagulants (p=0.0001), statistically older, more likely to be FC impaired, or to have had syncope. ● 74% using Bosentan; 25% using sildenafil. ● Results similar after exclusion of 13 pts who had shunts repaired, not pure Eisenmenger syndrome.
Pulmonary Vasoreactivity Testing							
D'Alto M, et al. 2010 (726) 20668108	Open label single-center retrospective	n=40 pts	Inclusion criteria: Clinical nonrestrictive defect consistent with Eisenmenger syndrome and right-to-left or bidirectional shunting, FC II–IV, SpO_2>60%, not pregnant, age ≥16 y, >40 kg	Epoprostenol 2 ng increments to max 12 ng/kg/min q 10 min	Clinical worsening: death from any cause, heart-lung or lung transplantation (or waiting list), hospital for PAH, symptoms worsening by ≥20% decrease in 6MWT on 2 tests,	● Initial response of lowering of PVR index to acute testing of pulmonary vasoreactivity with epoprostenol appeared to predict occurrence of clinical worsening regardless of use of PAH therapy after mean 33 mo of follow-up for pts with clinically defined Eisenmenger syndrome with	● Benefit of epoprostenol.

					increase WHO FC or worse right HF	FC II–IV followed in open-label retrospective fashion.	
Therapy for Adults With Down Syndrome and Eisenmenger Syndrome							
Duffels MG, et al. 2009 (727) 18579234	Observational, cohort, retrospective	n=24 pts	Inclusion criteria: >18 y, DS	Bosentan	6MWT, QOL	● 11.5-mo follow-up: 6MWT increased 296 to 325 m; p<0.05 after 12 wk. ● 276 m; p=0.6 after 26 wk, 287 m; p=0.3 at 52 wk. QOL stable during Rx.	● Use of Bosentan for subjects with Down syndrome and Eisenmenger syndrome treated up to 1 y and followed in open-label retrospective fashion appeared to improve 6MWT and to sustain such improvement during follow-up.
Monfredi O, et al. 2011 (728) 21943933	Observational, cohort, retrospective	n=10 Down syndrome pts, 29 non-DS pts	Inclusion criteria: ≥18 y, Eisenmenger syndrome	Bosentan 62.5 mg PO BID × 4 wk, 125 mg PO BID thereafter	6MWT, O_2 saturations	● 2.1 ± 1.5 y, 6MWT not reported for DS, O_2 saturations did not change.	● Team did not feel that 6MWT could be tested in Down syndrome population.
Troost E, et al. 2011 (160) 21744698	Observational cohort, retrospective	n=134 pts (60 DS)	Inclusion criteria: Adult Eisenmenger syndrome	Standard of local care	Survival, medications, arrhythmia, thrombosis, bleeding	● DS pts were younger at latest follow 28.6 ± 11.1 vs. 36.9 ± 14.4 y, less likely to be treated with diuretics 20% vs. 40.5% (p=0.004) or Vitamin K antagonists 0 vs. 17.6% (p=0.0001); equal distribution of ERA and PDE5 inhibitor Down syndrome vs. non-Down syndrome (18.3 vs. 24.3%; p=0.335 ERA and 3.3 vs. 10.8 sildenafil p=0.084). ● Equal survival between Down syndrome and non-Down syndrome 44.5 ± 2.6 vs. 44.5 ± 2.9 y (p=0.8). No difference arrhythmia, thrombotic events, major bleeding, CVA Down syndrome and non-Down syndrome.	● When assessed in open-label retrospective fashion, no difference in survival was noted between pts with Eisenmenger syndrome with or without Down syndrome when controlled for other factors.

						● Diuretic use, creatine, BMI, cigarettes correlate with survival.	
Serino G, et al. 2013 (729) 23440179	Observational cohort, retrospective	n=7 pts	Inclusion criteria: Adult Down syndrome pts; Eisenmenger syndrome	Bosentan, 62.5 mg PO BID × 4 wk then 125 mg PO BID	6MWT, SpO_2, echocardiography parameters, WHO FC	● 68 min improvement in 6MWT (p=0.1), no change in SpO_2; improvement in WHO FC (p=0.01). ● No change echocardiography indices.	● When assessed in open-label retrospective fashion, Bosentan treatment appeared to improve 6MWT in subjects with Down syndrome and Eisenmenger syndrome.
Crepaz R, et al. 2013 (159) 24047157	Observational cohort retrospective, open-label	n=7 pts	Inclusion criteria: DS, Eisenmenger syndrome with clinical diagnosis	Open label Bosentan 62.5 mg PO BID × 1 mo then 125 mg PO BID thereafter	6MWT	● 52.2 ± 3.9 min; 6MWT increased from 199.6 ± 69.1 min to 303.7 ± 99.9 min ($p<0.05$); SpO_2 at end of the 6MWT increased from 61.6 ± 7.6% to 74.7 ± 6.2% ($p<0.05$). ● TTE acceleration time increased from 62.9 ± 11.6 m/s to 83.0 ± 9.6 m/s (p=0.0156), acceleration time/ejection time ratio from pulmonary flow increased from 0.24 ± 0.04 at baseline to 0.30 ± 0.02 (p=0.0156).	● Recognizing limited numbers of studied subjects, when assessed in open-label retrospective fashion, adults with Down syndrome and Eisenmenger syndrome appeared to improve functional ability and SpO_2 after exercise after use of Bosentan for mean 52 mo.
D'Alto M, et al. 2013 (730) 21802156	Observational cohort retrospective	n=18 with Down syndrome (56 without DS)	Inclusion criteria: Adults >16 y with Eisenmenger syndrome	Bosentan	6MWT, NYHA, hemodynamics	● WHO FC, 6MWT, hemodynamics improve with bosentan: WHO FC 2.9 ± 0.6 to 2.5 ± 0.5; p=0.005; 6MWT 239 ± 74 to 288 ± 71 min; p=0.0007; Qp 3.5 ± 1.4 vs. 4.0 ± 1.6 l/m/m^2; p=0.006; Qp/Qs 1.0 ± 0.4 vs. 1.4 ± 0.7; p=0.003; PVR index 20 ±13 vs. 15 ± 9 WU m^2; p=0.007; no difference in benefit Down syndrome vs. control.	● The presence of Down syndrome did not appear to alter benefits of Bosentan therapy in pts with Eisenmenger syndrome when studied in open-label retrospective fashion.

Diller GP, et al. 2012 (731) 22397941	Observational cohort, retrospective	n=181 pts (56 with DS)	Inclusion criteria: Adults with DS	PAH therapies	BNP, death	● 20 deaths (7 DS).	● BNP absolute and temporal predicted survival independent of renal function, DS, 6MWT (p<0.0004).
Data Regarding Palliative Medical Therapies							
Tay EL, et al. 2011 (732) 20304507	Observational, cohort, prospective, open-label, single-arm	n=25 pts (14 Eisenmenger syndrome)	Inclusion criteria: >18 y, cyanotic complex CHD, O_2 saturation ≤90, able to undergo exercise testing serum ferritin <30 mcg/L or serum ferritin <50 mcg/L and transferrin saturation <15% Exclusion criteria: Pregnant, anemic, hypersensitivity to iron, recent start PAH therapy, "hyperviscosity symptoms"	Ferrous fumarate 200 mg PO QD × 1 wk, then 200 mg PO BID × 1 wk, then 200 mg PO TID; if "not tolerated," single dose IV iron sucrose 200 mg followed by repeat iron chemistries and if still deficient repeated IV dose at 1 mo	6MWT, QOL (Camphor Scale), CPET	● 3-mo follow-up: improved. ● CAMPHOR score (20.7 ± 10.9 to 16.2 ± 10.4; p=0.001). ● 6MWT (371.7 ± 84.7 min to 402.8.0 ± 74.9 min; p=0.001). ● Unchanged: peak VO_2 (40.7 ± 9.2% to 43.8 ± 12.4% of predicted; p=0.15).	● Iron repletion in subjects with cyanotic CHD, the majority of whom had Eisenmenger syndrome appeared to improve 6MWT and subjective QOL index when tested in open-label prospective fashion 3 mo after repletion.
Sandoval J, et al. 2001 (733) 11719310	Randomized, controlled, prospective	n=23 pts (14 Eisenmenger syndrome)	Inclusion criteria: Age 20–50 y, clinical diagnosis of post tricuspid Eisenmenger syndrome, severe pulmonary HTN and predominant right-to-left shunt Exclusion criteria: Obstructive sleep apnea, obesity, cigarette use, restrictive or obstructive lung disease"	≥8 h/night O_2 at flow rate sufficient to raise O_2 saturation 79 to 88 for the group as a whole (typically 2–3 L nasal cannula); therapy was withheld from control group (12)	Mortality, 6MWT, pulmonary function tests	● 19.8-mo follow-up: no change: Survival: (20.7 vs. 20.8 mo; chi-square log rank, 0.08; p=NS). ● No change over course of study or between not and controls in 6MWT, QOL, PFTs, Hob and hematocrit, blood urea nitrogen or creatinine	● The use of overnight O_2 failed to improve measured indices of mortality, 6MWT, QOL when tested in randomized controlled fashion in very limited numbers of clinically defined pts with Eisenmenger syndrome followed for short term (<2 y).

Sandoval J, et al. 2012 (301) 22360787	Retrospective cohort study	n=144 Eisenmenger syndrome pts (48 anticoagulant, 44 nonanticoagulant)	Inclusion criteria: Adults, clinical diagnosis of Eisenmenger syndrome, saturation ≤90%, predominant right-to-left shunt, ≥2 y-follow-up	Comparison between anticoagulated vs. nonanticoagulated pts, anticoagulation at discretion of treating clinician	Mortality since referral	● 7-y follow-up: no change: Survival Log rank = 0.19–0.22.	● The use of oral anticoagulation (without estimation of time in target range) started at the discretion of the treating physician failed to improve survival over 7 y when tested in open-label retrospective fashion in clinically defined subjects with Eisenmenger syndrome free of targeted PAH therapies.

Data Supplement 51. Anomalous Coronary Artery Evaluation – Section 4.4.7.1

Study Name	Study Design	Study Size (N)	Inclusion/Exclusion Criteria	1° Endpoint	Results	Conclusions
Sharma V, et al. 2014 (734) 25038010	Single-center retrospective case review	n=75 pts	Inclusion criteria: Pts with AAOCA who underwent unroofing from 1992—2011	Surgical outcomes	● Mean age: 39 y: 32% under age 30. ● Angina, shortness of breath, or syncope in 72%. SCD in 3%. Of 53% who had preoperative stress testing, half were abnormal. 92% had right coronary arising from left sinus, 8% with left coronary arising from right sinus. ● No early deaths, 1 late death of noncardiac causes. ● Mean follow-up 18 mo, maximum 7 y, all pts were free of cardiac symptoms.	● Surgical unroofing has low surgical morbidity and mortality with resolution of symptoms at mean follow-up of 18 mo and no SCD in that time.
Basso C, et al. 2000 (735) 10807452	Retrospective case series from 2 registries	n=27 pts	Inclusion criteria: Athletes with SCD and anomalous coronary artery origin identified at autopsy	Clinical profile of AAOCA	● 23 pts with left coronary from right sinus, 4 with right coronary from left sinus. ● Death was during (25) or immediately after (2) strenuous exercise.	● Resting ECG and stress testing may be normal in athletes at risk for SCD due to anomalous aortic origin of a coronary artery and symptoms are common prior to SCD, thus warrant evaluation.

					● 55% were not evaluated or known to have symptoms prior to death. 45%, mean age 16 y, had data prior to death: 10 with premonitory symptoms (syncope or chest pain). ● All resting ECG (9/9) and stress testing was normal (8/8).	
Frescura C, et al. 1998 (736) 9670825	Autopsy specimens	n=1,200 pts	Inclusion criteria: Coronary anomalies in autopsy population of CHD	Anatomic descriptor and cause of death	● 27 (2.2%) of specimens had isolated anomalous coronary takeoff. ALCAPA in 5, wrong sinus in 12 (left from the right in 5, right from the left in 7), median age 14, range 2 mo–53 y. SCD in all left coronary from right sinus, 43% of right coronary from left sinus and 40% of ALCAPA. SCD precipitated by effort in 50%, and first manifestation of disease in 50%. ● 5 athlete's prodromic symptoms included palpitations, syncope, VA.	● AAOCA is associated with SCD, particularly with exercise and often with premonitory symptoms.
Krasuski RA, et al. 2011 (737) 21200009	Retrospective single-center case series	n=301 pts	Inclusion criteria: Pts undergoing cardiac catheterization over 35-y period	Mortality	● 0.14% of pts undergoing catheterization had anomalous coronary origin from the opposite sinus. 79% with right from the left cusp, 18% with interarterial course. ● Pts with interarterial course were slightly younger (52 vs. 59 y) and more likely to undergo surgery. ● Surgical pts were more likely to have abnormal stress tests and more extensive atherosclerosis. ● Mortality was similar amongst groups. No operative deaths.	● Older adults with anomalous coronaries warrant further study.
Davies JE, et al. 2009 (738) 19699909	Retrospective single-center case series	n=36 pts	Inclusion criteria: Pts who underwent surgery for AAOCA	Mortality and morbidity	● Median age 47 y, angina, shortness of breath, syncope in 81%, 43% with abnormal stress test. Left from right sinus in 36%, right from left in 58% and left anterior descending from right with	● Unroofing is feasible and safe in majority of pts.

					interarterial course in 5%. Intramural course in 94%. ● 14 with prior MI. ● No pt with significant atherosclerotic disease. Unroofing in 22, CABG in 14, no cardiac deaths at mean follow-up 1 y.	
Poynter JA, et al. 2014 (739) 24403351	Congenital Heart Surgeons Society registry	n=198 pts	Inclusion criteria: Pts with AAOCA	Mortality and management	● Median age at diagnosis 10 y, 54% symptomatic at presentation. ● Diagnosed at autopsy in 2. Right from left sinus (AAORCA) in 144 pts, left from right sinus (AAOLCA) in 51. ● Surgery or autopsy without surgery in in 106 pts. Surgery more common in AAOLCA (67%) than AAORCA (52%). Most surgical reports described intramural segment. ●Surgery correlated with symptoms, older age, presence of intramural segment in AAOLCA.	● Management decisions, including surgical referral, are influenced by symptoms and coronary morphology, and surgery is more common for AAOLCA.
Frommelt PC, et al. 2011 (740) 21439578	Single-center retrospective case series	n=27 pts	Inclusion criteria: Pts undergoing surgery for AAOCA	Mortality and preoperative characteristics	● Mean age 12.6 y. Left coronary from the right in 26%, right from the left in 74%. 26/27 with diagnosis by echo. Resuscitated SCD in 3, syncope in 8, chest pain in 4, no symptoms in 12 of "serendipitous diagnosis". Unroofing performed in all. Slit-like orifice in 12 at surgery, 7 with right from left and no symptoms. Mean follow-up 1.8 y, all have normal stress testing and normal echocardiograph and no symptoms.	● Pts referred for surgery can have unroofing with low morbidity/mortality. ● Symptoms of ischemia occur in some pts prior to surgery, and are alleviated afterward.
Mumtaz MA, et al. 2011 (741) 21353004	Single-center retrospective case series	n=22 pts	Inclusion criteria: Pts undergoing surgery for AAOCA	Mortality and preoperative characteristics	● 7 pts with left from right cusp, 4 had chest pain, 1 with syncope, 1 MI, 1 asymptomatic. 15 with right from left, 11 with chest pain 4 with	● Unroofing can be done with low morbidity and mortality.

					syncope. Median age 15 y, mean follow-up 17 mo.	
Mainwaring RD, et al. 2011 (742) 21718962	Single-center retrospective case series	n=50 pts	Inclusion criteria: Pts undergoing surgery for AAOCA	Mortality and preoperative characteristics	● Median age 14 (5 d–47 y), 31 pts with right from left sinus, 17 with left from right sinus, 2 with eccentric single ostium. 26/50 had ischemic symptoms, 14 had concomitant CHD. ● Unroofing in 35, reimplantation in 6, PA translocation in 9. ● No operative mortality. ● Median follow-up 5.7 y. 2 lost to follow-up, 1 underwent transplant. ● No symptoms or SCD in 47 others.	● Surgical repair of AAOCA is safe and may be effective in alleviating symptoms.
Gulati R, et al. 2007 (743) 17976445	Single-center retrospective case series	n=18 pts	Inclusion criteria: Pts undergoing surgery for AAOCA	Mortality	● Mean age 8 y, all with intra-arterial anomalous coronary. 10 with right from left, 8 with left from right, 4 with single coronary without intramural course. 56% had symptoms. ● Unroofing in 11, reimplantation in 3, PA translocation in 4. ● No mortality at mean follow-up 2.2 y.	● Description of successful surgical options for different specific abnormalities. ● Note that this is likely an earlier report of pts also included in Mainwaring RD, et al., 2011 (742) 21718962
Brothers J, et al. 2009 (744) 19488806	Questionnaire regarding AAOCA management	n=113 responses	Inclusion criteria: Members of Congenital Heart Surgeons Society and affiliated providers	Management strategies	● Almost all agree ischemia warrants surgery. Over half believe any pt with symptoms but no ischemia warrants surgery. ● In pts awaiting surgery, activity restriction is common. ● Among medical managed pts, 6 died, with 2 deaths in surgically managed pts.	● Marked heterogeneity in physician management of AAOCA.
Angelini P, et al. 2015 (745) 26178792	Single-center case series	n=67 pts	Inclusion criteria: Pts undergoing intravascular ultrasound for AAORCA	Anatomic description	● All anomalous right coronary from opposite cusp had an intramural segment and had some proximal intramural stenosis.	● All AAORCA had an intramural segment. In this series, over half underwent PCI.

					● 62% underwent stent implantation.	
Maron BJ, et al. 2009 (746) 19221222	Registry data	n=1,866 pts	Inclusion criteria: Athletes with SCD	Clinical characteristics	● 690 confirmed cardiac deaths, coronary anomaly in 119–65 left main from right cusp, 16 right coronary from left cusp.	● Coronary anomalies are not a common cause.
Opolski MP, et al. 2013 (747) 23411107	Single-center case series	n=8,522 pts	Inclusion criteria: Pts undergoing coronary CT	Anatomic description	● Anomalous coronary arising from the opposite sinus in 0.84% (72 pts). Right from left cusp in 11, left from right in 20. 24 with interarterial course, 12 showed significant vessel compression. ●Interarterial compression was seen only in right coronary from left sinus and correlated with symptoms at 15 mo follow-up.	● Anomalous coronary arising from the opposite sinus is not common.
Lee HJ, et al. 2012 (748) 22056684	Single-center case series	n=22,925 pts	Inclusion criteria: Pts undergoing coronary CT	Anatomic description	● 124 pts with anomalous origin on right coronary artery from left sinus, 87 enrolled after excluding those with combined cardiac disease. ● Of 87, 59% had "high interarterial course" and 41% had "low interarterial course." ● High course had a higher prevalence of angina (43% vs. 6%) and MACE (28% vs. 6%).	● Typical angina and MACE are more common in pts with high interarterial course of AAORCA.
Kaushal S, et al. 2011 (749) 21871287	Single-center retrospective case series	n=27 pts	Inclusion criteria: Pts undergoing surgery for AAOCA	Mortality	● Mean age 14 y, 25 pts with AAORCA, 14 with chest pain and 4 with syncope. 2 AAOLCA had chest pain. ● Intramural coronary length correlated with preoperative symptoms.	● Length of intramural coronary segment correlates with symptoms.
Eckart RE, et al. 2004 (750) 15583223	Registry series	n=126 pts	Inclusion criteria: Nontraumatic SCDs in military recruits	Anatomic description	● 86% of deaths related to exercise, 51% of SCD had identifiable underlying cardiac cause.	● Left coronary from right sinus accounted for all coronary anomalies in this autopsy series of SCD in military recruits.

					● 61% of those had coronary anomalies (39 pts) all with left coronary from the right sinus.	
Eckart RE, et al. 2011 (751) 21903060	Registry series	n=902 pts	Inclusion criteria: Nontraumatic SCD in adults in the U.S. military	Anatomic descriptors	● Anomalous coronary artery accounted for 4% of SCD <35 y of age and 0.2% >35 y. ● Anomalous take-off defined as any left coronary from the right sinus or right coronary from the left sinus with oblique takeoff and corresponding acute or chronic ischemia.	● Coronary anomalies are not a common cause of SCD in this population.
Rajbanshi BG, et al. 2014 (752) 24079879	Observational cohort, retrospective	10 (7 with anomalous left coronary artery, 1 with anomalous left anterior descending)	Inclusion criteria: ≥18 y, ALCAPA, surgical repair	Surgical coronary transfer, interposition graft, or CABG with ostial ligation/oversew	● Survival, reoperation, LVEF, recurrent symptoms.	● Mean follow-up 8.6 y. ● 2 late deaths (noncardiac). ● 1 with recurrent ischemic symptoms: reoperation CABG for ostial stenosis. ● Postoperation all subjects were NYHA I-II. ● Postoperation no change in LVEF.
Yau JM, et al. 2011 (753) 21462214	Observational cohort, retrospective	n=151 pts, Medline review 1908—2008, retrospective case series	Inclusion criteria: ≥18 y, ALCAPA, with or without surgical repair, diagnosed pre- (133) or postmortem (18)	Coronary ligation or coronary transfer or CABG and ligation	● Description of symptoms, survival.	● Surgical repair: 119 Ligation in 21% Dual coronary repair in 79%. ● Surgical mortality was 1%–4%. ● Medical follow: 32. ● Of cohort, 103/151 <50 y (4% treated medically); 48/151 ≥50 y (37% treated medically).
Wilson CL, et al. 1979 (754) 484430	Observational cohort, retrospective	n=29 (13 with ligation of anomalous coronary artery, 16 with simultaneous ligation and coronary bypass)	Inclusion criteria: ≥13 y, ALCAPA, surgical repair all simultaneously Exclusion criteria: surgical components separated in time; coronary reimplantation	Surgical ostial ligation/oversew vs. ostial ligation/ oversew with concomitant CABG	● Survival.	● Mean follow-up 9.2 y. ● Ligation alone: 3/13 deaths at mean 5-y follow-up. ● Ligation and CABG: 0/16 deaths at mean 5-y follow-up.

El-Said GM, et al. 1973 (755) 4541750	Observational cohort, retrospective	n=10 pts, 4 medical management, and 6 with surgical management	Inclusion criteria: ALCAPA, all pediatric	SVG to ALCAPA in 6 (5 left main and 1 left anterior descending) with proximal ligation	● Survival, reoperation, graft stenosis.	● 6-mo angio and variable postoperative study with treadmill exercise test; ischemia found in pt with distal occlusion.
Lange R, et al. 2007 (756) 17383358	Observational cohort, retrospective	n=56 pts, mean age 16.2 mo	Inclusion criteria: ALCAPA	Coronary transfer (31) or subclavian artery anastomosis (25)	● Operative outcomes	● Maximum follow-up 23.8 y Pts older (mean 27.8 y) presented with higher EF (>35%)
Paridon SM, et al. 1990 (757) 2317910	Observational cohort, retrospective	n=11 pts, infants and children	Exercise testing after repair of ALCAPA	Surgical repair by SVG, Subclavian artery graft or AP window with baffle; 1 pt with ligation	● Exercise testing	● Frequently associated with ECG evidence of abnormal perfusion regardless of age and type of repair.
Cochrane AD, et al. 1999 (758) 9918975	Observational, cohort, retrospective	n=21 pts (6 wk.–26 y)	Inclusion criteria: ALCAPA	Surgical reimplantation or Takeuchi; 1 pt with coronary ligation	● Survival, exercise ability	● Median follow-up 6.5 y; all survived; all but 3 NYHA class I and normal level of exercise.

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