2018 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay Data Supplement

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Methodology and Evidence Review

The recommendations listed in this guideline are, whenever possible, evidence based. An extensive evidence review was conducted from January through September 2017, that included literature published through September 2017. Other selected references published through January 2018 were incorporated by the writing committee. Literature included was derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline. Key search words included but were not limited to the following: *adult, adult congenital heart disease, ACS, AF, AL amyloid, AL amyloidosis, alcohol septal ablation, ambulatory electrocardiography, aminophylline, amyloidosis, antiarrhythmic drugs, antibradycardia, aortic dissection, aortic valve, asystole, arrhythmia, atrial fibrillation, atrioventricular block, atropine, AV block, AV block symptoms, beta-adrenergic agonist, beta-blocker, Birmingham trial, biventricular pacemaker, bradyarrest, bradyarrhythmia, bradyasystole, bradycardia, bundle branch block, cardiac, cardiac AL amyloid, cardiac arrest, cardiac pacing, cardiac resynchronization therapy, cardiac sarcoidosis, cardiac surgery, cardiology, cardiovascular implantable electronic devices, catecholamines, cilostazol, clinical presentation, clinical trial, complications, conduction, conduction disturbance, congenital AV block, coronary artery bypass, cost, cost-effectiveness, cost-effectiveness analysis, CPAP, deactivation, defibrillator, defibrillator versus pacemaker, device, device implantation, devices, device therapy, digoxin, digoxin antibody, dialysis, dizziness, dopamine, drug therapy, drug induced, dual chamber, dyssynchrony, echocardiogram, electrocardiogram, endocarditis, English, EP study, epidemiology, epinephrine, evaluation studies, event monitor, event recorder, exercise induced, exercise test, exercise treadmill, first degree, first degree AV block, genetic variation, genetics, genotype, glucagon, health status, heart, heart block, heart transplant, hemochromatosis, Holter, Holter monitor, human, hypertrophic cardiomyopathy, ICD, ILR, implantable loop recorder, intraoperative bradycardia, isoproterenol, lamin A/C, left bundle branch block, life, LMNA, loop recorder, Lyme carditis, Lyme disease, magnetic resonance imaging, management, medical, medical therapy, medications, mitral valve, mortality, muscular dystrophies, myectomy, myocardial infarction, myocardial perfusion imaging, myocarditis, myotonic dystrophy, natural history, orthotopic heart transplant, OSA, pacemaker, pacemaker syndrome, pacing, pacing induced cardiomyopathy, patients nearing end, pauses, permanent pacemaker, PM, pregnancy, preoperative bradycardia, preoperative risk, procainamide, procedure, prognosis, prophylactic temporary pacing, pulmonary artery catheter, quality of life, radionuclide imaging, RCT, rejection, reversal, reversible causes, review, right bundle branch block, RV pacing, sarcoid, sarcoidosis, seizure, shared decision making, sick sinus syndrome, sinus, sinus arrest, sinus bradycardia, sinus node, sinus node dysfunction, sinus of Valsalva aneurysm, sleep apnea, sleep apnea syndromes, spinal cord dysfunction, spinal cord injury, steroid, sudden cardiac death, syncope, symptomatic, TAVR, temporary, temporary pacemaker, temporary pacing, theophylline, thyroid disease, tomography-emission-computed-single photon, tomography-X-ray computed, transcatheter aortic valve replacement, transcutaneous pacemaker, transesophageal echocardiogram, transient, treatment, vagal, vagally mediated, vagally mediated AV block, ventricular arrhythmia risk, ventricular remodeling*

Abbreviations: 1° indicates primary; 2°, secondary; AAD, antiarrhythmic drug; ABP, atrial-based pacing; ACEI, angiotensin-converting enzyme inhibitor; ACLS, advanced cardiac life support; AED, antiepileptic drug; AF, atrial fibrillation; AMI, acute myocardial infarction; AS, aortic stenosis; ASA, American Society of Anesthesiology OR alcohol septal ablation; asx, asymptomatic; ATP, antitachycardia pacing; AV, atrioventricular; AVB, atrioventricular block; AVN, atrioventricular nodal; AVR, aortic valve replacement; BB, beta blocker; BBB, bundle branch block; BiV, biventricular; BMI, body mass index; BP, blood pressure; bpm, beats per minute; C, comparator; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCB, calcium channel blocker; ccTGA, congenitally corrected transposition of the great arteries; CEA, carotid endarterectomy; CHB, complete heart block; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CIED, cardiac implantable electronic device; CMP, cardiomyopathy; CPAP, continuous positive airway pressure; CRT, cardiac resynchronization therapy; CRT-D, device that provides both cardiac resynchronization therapy and defibrillator capabilities; CRT-P, device that provides cardiac resynchronization therapy only; CSM, carotid sinus massage; CV, cardiovascular; CVA, cerebrovascular accident; Cum%VP, cumulative percentage of ventricular pacing; Cx, circumflex coronary artery; CXR, chest X-ray; DC, dual chamber; DCCV, direct current cardioversion; DM, diabetes mellitus; DOE, dyspnea on exertion; D-TGA, d-transposition of the great arteries; Dx, diagnosis; echo, echocardiogram; ECG, electrocardiogram; ED, emergency department; EEG, electroencephalogram; EF, ejection fraction; EMD,

electromechanical dissociation; EMS, emergency medical service; EP, electrophysiologic; EPS, electrophysiologic study; GDMT, guideline-directed medical therapy; HCM, hypertrophic cardiomyopathy; HDIT, high-dose insulin therapy; HF, heart failure; HFH, heart failure hospitalization; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HOCM, hypertrophic obstructive cardiomyopathy; HR, hazard ratio; HTN, hypertension; HUTT, head-up tilt test; Hx, history; I, intervention; ICD, implantable cardioverter defibrillator; ICM, ischemic cardiomyopathy; ILR, implantable loop recorder; IV, intraventricular OR intravenous; LA, left atrial; LAD, left anterior descending coronary artery; LAH, left anterior hemiblock; LBBB, left bundle branch block; LHC, left heart catheterization; LMNA, Lamin A/C; LR, lower rate; LV, left ventricular OR left ventricle; LVED, left ventricular end-diastolic; LVEF, left ventricular ejection fraction; LVES, left ventricular end-systolic; LVFS, left ventricular fractional shortening; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; MACE, major adverse cardiovascular event; MDT, Medtronic; MI, myocardial infarction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MMSE, Mini Mental State Examination; MPHR, maximum predicted heart rate; ms, millisecond; MVP, mitral valve prolapse; N/A, not applicable; nCPAP, nasal continuous positive airway pressure; nLBBB, new left bundle branch block; NICM, nonischemic cardiomyopathy; NR, not relevant; NS, not significant; NSVT, nonsustained ventricular tachycardia; NSVT, non-sustained ventricular tachycardia; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; OSA, obstructive sleep apnea; PA, pulmonary artery; PAF, paroxysmal atrial fibrillation; PCI, percutaneous coronary intervention; PerAF, persistent atrial fibrillation; PFO, patent foramen ovale; PM, pacemaker; postop, postoperative; PPI, permanent pacemaker implantation; PPM, permanent pacemaker; ppm, paced beats per minute; preop, preoperative; PSG, polysomnography; pt, patient; pVO_2, peak oxygen consumption; PVC, premature ventricular contraction; QOL, quality of life; QRSd, QRS duration; RBBB, right bundle branch block; RCA, right coronary artery; RCT, randomized controlled trial; ROSC, return of spontaneous circulation; RR, relative risk; RV, right ventricle; SA, sino-atrial; SAS, sleep apnea syndrome; SACT, sino-atrial conduction time; SAVR, surgical aortic valve replacement; SB, sinus bradycardia; SCD, sudden cardiac death; SD, standard deviation; SLE, systemic lupus erythematosus; SND, sinus node dysfunction; SNRT, sinus node recovery time; SR, sinus rhythm; SSS, sick sinus syndrome; STEMI, ST-elevation myocardial infarction; SVT, supraventricular tachycardia; sx, symptom; TAP, transesophageal atrial pacing; TAVI, transcatheter aortic valve implantation; TCP, transcutaneous pacing OR transcutaneous pacemaker; TE, thromboembolism; TIA, transient ischemic attack; TPM, temporary pacemaker; TPPM, temporary permanent pacemaker; TTT, tilt table testing; TTVP, temporary transvenous pacing; TVP, transvenous pacemaker; tx, treatment; UNOS, United Network for Organ Sharing; V, volts: VA, ventricular arrhythmia OR ventriculoatrial; VF, ventricular fibrillation; Vp, ventricular pacing; VT, ventricular tachycardia; WHO, World Health Organization.

Data Supplement 1. Nonrandomized Trials, Observational Studies, and/or Registries of 12-Lead Electrocardiography in Bradycardia or Conduction Disturbance (Section 4.2.1)

Study Acronym; Author; Year Published; PMID	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Linzer M, et al. 1997 (1) 9182479	**Study type:** Literature Review- MEDLINE search and manual review of bibliographies **Size:** 4 population-based studies evaluating diagnostic yield of ECG in syncope were included, N=902	**Inclusion criteria:** English language publications from 1980–1995 reporting on diagnostic yield of a test (e.g., Hx and physical, ECG, EEG, Holter, external LR, EPS, HUTT, SAE, ETT, carotid U/S, head CT, psych evaluation) evaluated in 10 or more subjects over 18 y with syncope (±presyncope) **Exclusion criteria:** Review articles and case reports	**1° endpoint:** Diagnostic yield of a test analyzed separately for each test **Results:** Diagnostic yield of ECG at presentation was 5% (47/902). This compares to 45% (504/1110) for Hx and physical	• Despite low yield, authors recommend ECG at presentation for virtually all pts with syncope due to its lack of risk and relatively low expense. Further they cite the value of ECG findings indicative of structural heart disease or indicative of potentially life-threatening conditions (e.g., NSVT) in this population • This review did not identify any suitable studies evaluating echocardiography in syncope
Thiruganasamb-amdamoorthy V, et al. 2012 (2) 22813399	**Study type:** Retrospective single-center evaluation of pt characteristics, 12-lead ECG and ED ECG monitoring as predictors of adverse outcomes in consecutive adult ED pts with syncope from 8/1/05–1/30/07 **Size:** 505 visits from 490 separate pts [of whom 470 (93%) had at least 1 ECG]	**Inclusion criteria:** ≥16 y with local address and syncope **Exclusion criteria:** Presyncope, LOC >5 min, ongoing altered mental status, or LOC caused by ETOH or illicit drug use, seizure, head injury, or severe trauma requiring admission	**1° endpoint:** Composite of death, MI, arrhythmias, and "cardiac procedures" over 30 d **Results:** 49 serious outcomes including 27cardiac outcomes (including 2 deaths, 18 PPM, 7 SND, 6 3rd degree AVB, 2 profound bradycardia) and 22 serious noncardiac outcomes. Of 19 primary ECG variables, 2 combination ECG variables (e.g., LBBB with 1st degree AVB) and 8 variables based on QRS or QTc duration) 16 variables were significant predictors of adverse cardiac events at 30 d by univariate analysis. Using recursive	• ECG findings in pts presenting to the ED with syncope can predict adverse cardiac events in the short term. • Bradycardia or conduction disorders are an important component to the constellation of predictive ECG findings (19/132 - 14%)

			partitioning they developed ECG criteria for risk that included 5 predictors: 2nd degree Mobitz type 2 or 3rd degree AVB, bundle branch block +first-degree AV block, right bundle branch with either left anterior or posterior fascicular block, new ischemic changes, non-SR, left axis deviation, or ED cardiac monitor abnormalities. Using these predictors yielded a sensitivity of 96% (95% CI: 80–100), a specificity of 76% (95% CI: 75–76) and an area under the ROC curve of 0.89 (95% CI: 0.82–0.95).	
Del Rosso A, et al. 2008 (3) 18519550	**Study type:** Prospective cohort of consecutive pts **Size:** 516 (260 derivation/256 validation)	**Inclusion criteria:** Unexplained syncope presenting to 1 of 14 Italian EDs **Exclusion criteria:** <18 y, syncope of known non-cardiac cause (e.g., seizure, TIA or drop attack)	**1° endpoint:** Dx of cardiac syncope or death **Results:** A risk score composed of historical features, exam findings suggesting structural heart disease/CHF, or abnormal ECG (including but not exclusively bradycardia and conduction abnormalities) was predictive of cardiac syncope or death at an avg. Follow-up of 614 d in both derivation and validation cohorts. 56/79 (71%) pts with a defined mechanism of syncope had arrhythmic syncope. Of these, 38/56 (68%) were attributed to bradyarrhythmias or conduction disturbances and 24/38 (63%) syncopal episodes attributable to bradycardia or conduction disturbances were diagnosed on 12 lead ECG.	• 12 lead ECG in the ED can identify syncope attributable to bradycardia and conduction disturbances in a majority of those with bradycardic syncope presenting to the ED. • As part of the EGSYS risk score, ECG abnormalities (both those indicative of bradyarrhythmias and those indicative of other forms of heart disease) can predict cardiac causes of syncope and all-cause mortality more than 1.5 y after initial presentation.
GESINUR Perez-Rondon J, et al. 2014 (4) 24993462	**Study type:** Multicenter prospective observational **Size:** 524 (from a total of 1,080 pts and from 14 of	**Inclusion criteria:** Pts ≥14 y presenting to ED with transient LOC within 24 h for whom initial questionnaire	**1° endpoint:** Power of specific ECG criteria to predict 12 mo mortality **Results:** 65.6% had an abnormal ECG and 6 (6.3%) died at 1 y (only 1 SCD). 22 pts	• Specific ECG abnormalities predict 1 y mortality in adolescents and adults presenting with syncope (ventricular pacing, LVH, AF, and

	19 centers participating in main trial)	data, presenting ECG and 1-y follow-up was available **<u>Exclusion criteria:</u>** N/A	(4.2%) manifested AV nodal conduction disturbance (13 first-degree, 2 second-degree and 7 third-degree AVB) which did not predict mortality (p=0.642). 108 (20.6%) manifested an intraventricular conduction disturbance [13 LBBB (2.5%), 28 RBBB (5.4%), 18 IRBBB (3.4%), 17 NSIVCD (3.3%), 13 LAFB (2.5%) and 19 assorted others (18%)]. Intraventricular conduction disturbances were 1 of 4 independently predictive indicators of mortality (OR: 3.8; 95% CI: 1.7–8.3; p=0.001). Other predictive variables included ventricular pacing, AF and LVH.	intraventricular conduction disturbance) • AV nodal block is uncommon on presenting ECG (4.2%) and is not predictive of mortality at 1 y. • Intraventricular conduction disturbances are more common (20.8%) and do predict 1 y mortality in adolescents and adults with syncope.

Data Supplement 2. Nonrandomized Trials, Observational Studies, and/or Registries of Exercise Stress Testing in Bradycardia and Conduction Disturbances (Section 4.2.2)

Study Acronym; Author; Year Published; PMID	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Lauer MS, et al. 1999 (5) 10022108	**Study type:** Prospective cohort study between 9/90–12/93 **Size:** 2953 consecutive pts referred for sx-limited ETT with thallium MPI, of whom 1078 (37%) manifested chronotropic incompetence [316 (11%) by % MPHR and 762 (26%) by low chronotropic index]	**Inclusion criteria:** Referred for sx-limited ETT thallium and with failure to achieve ≥85% MPHR or failure to achieve ≥80% of chronotropic index* **Exclusion criteria:** Prior coronary angiography or PCI, cardiac surgery, CHF, valvular heart disease, pre-excitation syndrome, ACHD, or ß-blocker therapy.	**1° endpoint:** Association of chronotropic incompetence with all-cause mortality at 2 y. **Results:** 91 deaths (8.4%) - 22 cardiac deaths. Those with chronotropic incompetence were older and sicker with more ASCVD risk factors, lower exercise capacity and more angina and perfusion defects during the test (but not more ischemic ECG changes). Cox proportional hazards analyses incorporating 13 clinical confounders (age, sex perfusion defects, etc. but not EF): chronotropic incompetence independently associated with increased risk of death (adjusted RR:1.85; 95% CI: 1.13–3.00; p=0.01) when measured by failure to achieve 85% MPHR and adjusted RR:2.19; 95% CI: 1.43–3.44; p<0.001) when measured by low chronotropic index. 612 (21%) manifested perfusion defects [reversible in 311 (11%)]. Perfusion defects predictive of mortality with a similar magnitude as chronotropic incompetence. Mortality risk of chronotropic incompetence and perfusion defects were additive (e.g., adjusted RR for combined low chronotropic index and perfusion defect: 3.31; 95% CI: 1.82–6.02; p<0.001)	• Chronotropic incompetence is independently predictive of mortality in those with known or suspected CAD
Savonen KP, et al. 2008 (6) 18556711	**Study type:** Prospective cohort study (derived from the Kuopio Ischemic Heart Disease Risk Factor Study – a	**Inclusion criteria:** Enrolled in KIHD with clinical CAD and underwent bicycle ergometry **Exclusion criteria:** Cancer, heart rate-lowering Rx	**1° endpoint:** 1) Association of chronotropic incompetence with mortality over an average follow-up of 11 y (0.8–14.8 y) of chronotropic incompetence calculated during bicycle ergometry with VO_2 testing and defined as change in heart rate	• Conclusion: Heart rate 40–100 independently predicts long-term all-cause mortality in Finnish men with known or suspected CAD • Heart rate 40–100 intended to isolate the effects of exercise-induced increases in sympathetic

	longitudinal Finnish population study-representative sample of middle-aged men from Kuopio and environs recruited 3/1984–12/1989) **Size: 294** (3235 eligible/2682 participated in primary study/2240 exercise tests/294 with CAD and no exclusions)		between 40% of maximal workload and peak exercise (heart rate: 40–100). 2) Compared ability of heart rate 40–100 to predict death with that of other indices of chronotropic incompetence **Results:** 61 (20.7%) deaths. Mean (SD) heart rate 40–100 =45 (15) bpm. Risk of death increased 41% for each 1-SD (15 bpm) decrement in heart rate 40–100. Multivariate analysis identified a heart rate 40–100 value at or below the mean (<46 bpm) as a significant predictor of all-cause mortality relative to those with a heart rate 40–100 above the mean (RR: 2.9; 95% CI: 2.0–5.0). With propensity score added to model, the risk decreased to 2.0; 95% CI: 1.22–3.70. Only 1 of 6 other indices of chronotropic incompetence that were evaluated was predictive of mortality, heart rate reserve RR: 1.30; 95% CI: 1.02–1.69. (Chronotropic index not included).	tone on CV physiology and risk from those of parasympathetic withdrawal which predominates in modulating chronotropic responses from baseline to ~100 bpm. • Heart rate 40–100 was predictive of mortality in members of this same population w/o clinical evidence of CAD (separate study, Savonen, et al.) • Bicycle exercise has a greater isometric component than treadmill walking and is usually associated with lower maximal workloads and brisker heart rate response, all of which may reduce generalizability of findings to other exercise modalities.
Doi A, et al. 2002 (7) 12368930	**Study type:** Prospective cohort study **Size:** 44 pts and 20 normal controls	**Inclusion criteria:** Unexplained syncope or presyncope (18 exercise-related, 26 exercise-unrelated) **Exclusion criteria:** Structural heart disease, PAF, thyroid disease	**1° endpoint:** Diagnostic accuracy of HUTT and modified exercise treadmill testing according to relationship of unexplained syncope to exercise. Modified ETT included abrupt termination followed by prolonged standing (positive ETT defined as syncope or presyncope with SBP<80 mm Hg and/or heart rate<40 bpm) **Results:** HUTT: Sensitivity =84% and 77%; Specificity =84% and 85%; Accuracy= 84% and 80% in exercise-related and exercise-unrelated syncope respectively. None of these differences were statistically significant Modified Exercise Test: Sensitivity =78% and 19% (p<0.05); Specificity =95 and 95% (p=NS); Accuracy =86% and 52% (p<0.05) in exercise-related and exercise-unrelated syncope respectively.	• Modified exercise testing may be as accurate as HUTT with provisional isoproterenol infusion to elicit syncope/presyncope with associated hemodynamic compromise in pts with suspected exercise-related neurally mediated syncope and presyncope. • Modified exercise testing is less sensitive but similarly specific to HUTT with provisional isoproterenol infusion to elicit syncope/presyncope with associated hemodynamic compromise in pts with suspected neurally mediated syncope and presyncope unrelated to exercise.

Woelfel AK, et al. 1983 (8) 6875122	**Study type:** Case series **Size:** 3 pts	**Inclusion criteria:** Pts with exercise-related palpitations or dizziness, or asx progressive intraventricular conduction disorder with 1:1 AV conduction at rest who demonstrate rate related 2:1 and 3:1 rate-related conduction block on exercise treadmill testing w/o overt ischemia. 2 had baseline intraventricular conduction disturbance **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** All had evidence of infranodal block on EP study. 2 of 3 underwent rapid atrial pacing with evidence of rate related infranodal block. One underwent coronary angiography revealing a 90% RCA and a 60% LAD stenosis but no ischemia on exercise, stress MUGA, no ischemic ECG changes on exercise ECG and no angina. Exercise-related symptoms were relieved with pacing in all 3.	• Exercise testing can uncover apparent rate -related infranodal conduction block in carefully selected pts with exercise related symptoms or progressive intraventricular conduction disturbance w/o clinical evidence of exercise induced ischemia. • The authors suggest such pts should be considered for PPM but acknowledge the natural Hx is undefined. They draw correlates to the high rate of subsequent symptomatic AVB in those with either spontaneous or rapid atrial pacing-induced infra-nodal advanced AVB in previous reports.
Boran KJ, et al. 1983 (9) 6837453	**Study type:** Retrospective case series **Size:** 10 of 2200 (0.45%) consecutive, clinically-referred pts who underwent symptom-limited exercise treadmill testing (9/10 Bruce protocol) at a single referral center (includes the 2 pts from Oliveros below)	**Inclusion criteria:** 1) Symptom-limited ECG showing ischemic ST segment changes and intraventricular conduction disturbance. 2) Subsequent coronary angiography **Exclusion criteria:** Reproducible rate–related intraventricular conduction disturbances w/o evidence of ischemia or a clinical Dx of CAD (N=4 – 3 LAFB and 1 LBBB)	**1° endpoint:** N/A **Results:** 1) Exercise-induced conduction abnormalities: LAFB in 4, LPFB in 2, RBBB in 2, RBBB with left axis deviation in 1, and LAFB evolving to LBBB in 1. 2) Demographics: 9/10 were men, age 37–71 y. 1 prior MI. All had angina. 3). Stress Test: All had angina and ischemic ST segment changes on ETT that preceded conduction disturbance. All conduction disturbances resolved in recovery as chest pain and ST segment changes resolved. 4) Coronary angiogram: All had proximal LAD stenosis [9/10 ≥90% (one=60%)].7/10 had anterior and/or apical regional wall motion abnormalities. EF mildly to moderately reduced in 3. 2 had LMCA stenosis ≥50%. 3 single vessel disease/3 2 V disease/4 3V disease.	• Ischemically mediated transient intraventricular conduction disturbance elicited by exercise treadmill testing is rare (<0.5%). • When present in pts with significant CAD, exercise-induced conduction abnormalities are typically preceded by angina and ischemic ECG changes • The constellation of ischemic signs, symptoms and transient conduction disturbance during exercise stress testing connotes a high probability of advanced CAD, and in particular, high-grade proximal LAD disease • Revascularization can alleviate ischemically mediated intraventricular conduction disturbances

			5) Response to therapy: 9/10 repeated ETT after CABG or institution of medical Rx. Exercise duration and peak heart rate increased. None manifested angina, ischemic ST changes or conduction disturbance on the repeat ETT.	
Oliveros RA, et al. 1977 (10) 908218	**Study type:** Case series **Size:** 2	N/A	**1° endpoint:** N/A **Results:** ETT in both revealed LAFB concomitantly with ST segment depression in the lateral leads (V5 in one and I and aVL in the other). In one, LAFB progressed to LBBB and then reverted back to LAFB in recovery before resolving. In the other LAFB resolved after 2 min of recovery.	• Exercise-induced ischemia associated with proximal LAD stenosis can be manifest as transient LAFB on treadmill stress test.
Bobba P, et al. 1972 (11) 5081145	**Study type:** Case series **Size:** 4	**Inclusion criteria:** New, transient LPFB during supine bicycle ergometry in middle-aged Italian men referred for chest pain and suspicion of CAD. **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** All had significant ECG changes with exercise. 3 had inferior ST elevation prior to LPFB (2 of whom had inferior Q waves on baseline ECG). 2 of those with inferior ST elevation also had significant lateral ST segment depression). A 4th had significant inferior and lateral ST segment depression w/o inferior ST elevation or baseline Q waves. Exercise-related symptoms were not reported. All 3 who underwent coronary angiography manifested significant proximal-mid RCA stenosis.	• Exercise-related transient LPFB accompanied by ischemic ECG changes can be associated with significant, symptomatic RCA stenosis.
Bharati S, et al. 1977 (12) 299790	**Study type:** Case report **Size:** 1	**Inclusion criteria:** 33 y woman with hypertensive urgency, LVH and pulmonary edema, and angina accompanied by inferior ST segment elevation and progressive AVB (normal conduction at baseline, to 1st degree, then 2:1 2nd degree, and ultimately CHB). Symptoms,	**1° endpoint:** N/A **Results:** EPS during cath revealed normal A-H and A-V intervals while asx. During an episode of chest pain with ST elevation, she manifested progressive AVB again, culminating in CHB. At all stages of conduction disturbance, the AV node was implicated with prolonged A-H intervals and normal H-V intervals. The pt died 1 d following emergent single vessel CABG to RCA. Pathology revealed slight fibrosis and	• Authors speculate right coronary vasospasm or ischemia due to fixed obstruction led to transient AV nodal block w/o evidence of infra-nodal block • Extrapolating from other clinical scenarios, there may be a significant component of neurally—mediated AV node dysfunction at play, as well

		ST changes and conduction disturbance were all transient and resolved together. There was no ECG evidence of associated MI. Cath revealed a 90% proximal stenosis of a dominant RCA and moderate LAD and LCx disease. Normal LV systolic function and LVEDP when asx. **Exclusion criteria:** N/A	"distinct arteriosclerosis" of the AV node and HIS bundle along with advanced "fibro-elastosis" of the main left bundle w/o ECG correlate antemortem.	• Coronary vasospasm can be elicited during exercise testing and such exercise-induced vasospasm may also be manifest as progressive AVB as seen in this case
Coplan NL, et al. 1991 (13) 1959424	**Study type:** Case report **Size:** 1	**Inclusion criteria:** 62 y woman underwent treadmill exercise test in evaluation of exertional chest pain. **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** She exercised for only 2.5 min of a Bruce protocol and stopped due to dizziness and non-sustained VT. ECG revealed marked anterior ST elevation. 2:1 second-degree AVB developed in early recovery, evolving to complete AVB. By 8 min of recovery both the ST segment changes and the AVB had resolved. She manifested no evidence of infarction related to these events while evaluated in the hospital. Coronary angiography revealed a 90% proximal RCA stenosis w/o significant obstructive CAD elsewhere. Uncomplicated balloon angioplasty of the RCA lesion was followed 3 wk later with a normal exercise thallium myocardial perfusion study w/o ischemic ST segment changes, scintigraphic evidence of ischemia, or conduction disturbance.	• Authors speculate that exercise-induced ischemia (more than coronary vasospasm or occult intrinsic conduction disease) was responsible for the transient exercise-induced AVB that resolved with revascularization. • Cause of marked anterior ST elevation in the absence of significant LAD disease was unclear. • Based on this and other case reports, exercise-induced AVB when accompanied by signs of ischemia is frequently associated with significant right CAD

*** Chronotropic index** = % heart rate (HR) reserve used **/** % of metabolic reserve used **=** $(HR_{stage} - HR_{rest})$ **/** $(220\text{-age} - HR_{rest})$ **÷** $(MET_{stage} - MET_{rest})$ **/** $(MET_{peak} - MET_{rest})$

Data Supplement 3. Nonrandomized Trials, Observational Studies, and/or Registries of Ambulatory Electrocardiography in Bradycardia or Conduction Disorders (Sections 4.2.3 and 4.2.4)

Study Acronym; Author; Year Published' PMID	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Gibson TC and Heitzman MR 1984 (14) 6702676	**Study type:** Retrospective observational **Size:** 1,512 of all ages (66% >60 y) referred for Holter for syncope (7,364 total over 5 y)	**Inclusion criteria:** 24 h 2-channel Holter monitoring in evaluation of syncope **Exclusion criteria:** Unable to keep diary or technically inadequate recordings	**1° endpoint:** Diagnostic yield of Holter for syncope and presyncope **Results:** • 7 (0.5%) experienced syncope and 23 (1.5%) experienced presyncope (total=2%) associated with a significant arrhythmia. • 225 (17%) had either syncope or presyncope unrelated to arrhythmia. • 2/7 (29%) of syncopal episodes associated with bradyarrhythmia/ conduction disorder: 1 SB, 1 AVB. • 5/23 (22%) of presyncope associated with bradyarrhythmia/ conduction disorder: 1 SB, 2 "sinoatrial abnormality", 2 AVB • 0.5% of the 1,521 pts studied had symptoms associated with bradycardia or conduction disorder. • 15 (1%) manifested Mobitz type 2 2nd degree or 3rd degree AVB. 3 (20%) were symptomatic. • Of 1,004 pts >60 y, 32 (3%) had SSS: 13 SB while awake, 2 sinus pause, 2 junctional rhythm, 2 AF, 13 tachy-brady. 2 (6%) were symptomatic	• 24 h Holter rarely yields evidence of bradycardia or conduction disorder temporally related to syncope or presyncope in pts who have previously experienced syncope. • Findings of advanced AVB were rare in this population (1%) and symptomatic only 20% of the time. • Findings of SSS increase with age but were present in only 3% of those >60 y in this cohort and symptomatic only 6% of the time
Linzer M, et al. 1997 (15) 9214258	**Study type:** Literature review- MEDLINE search and manual review of bibliographies	**Inclusion criteria:** English language publications from 1980–1995 reporting on diagnostic yield of a test (e.g., Hx	**1° endpoint:** Diagnostic yield of prolonged ambulatory monitoring in pts with syncope or dizziness **Results:**	•Authors recommend 24-h Holter monitor (or inpatient telemetry) when symptoms suggest arrhythmic syncope, the ECG is abnormal, structural heart disease is present, or

	Size: Identified 8 studies that evaluated pts with syncope or presyncope with at least 12 h of Holter monitoring and reported on symptoms, N=2612	and physical, ECG, EEG, Holter, external LR, EPS, HUTT, SAE, ETT, carotid U/S, head CT, psychiatric evaluation) evaluated in 10 or more subjects over 18 y with syncope (± presyncope) **Exclusion criteria:** Review articles and case reports	• 15% symptoms w/o arrhythmia (range: 7–39%) • 14% Arrhythmia with no symptoms (range 10–41%) • 4% symptoms with arrhythmia (range 1–26%) • Note: includes Gibson et al. (14), the largest study included	the cause of syncope remains unexplained after Hx, physical and 12-lead ECG.
Reiffel JA, et al. 2005 (16) 15842970	**Study type:** Retrospective observational **Size:** 1,800 randomly selected studies from a single year derived from ~100,000-pt ambulatory monitoring database of a commercial monitoring company. 600 studies each of 3 different classes of monitoring equipment were reviewed [24 h Holter, 30 d memory loop recording, and 30 d autotriggered loop recording]	**Inclusion criteria:** Referred for monitoring for known or suspected dysrhythmias **Exclusion criteria:** N/A	**1° endpoint:** Relative diagnostic yield of the different monitoring devices **Results:** • Groups were identical in age and symptoms that prompted monitoring • Fewer women were referred for Holter • 12% <20 y • Majority (50%) referred for palpitations • 292 (16%) referred for syncope • 80 (4%) referred for dizziness • 6 (0.3%) referred for AVB • 5 (0.3%) referred for dyspnea • 42 (23%) pts manifested bradycardia (heart rate <40 for those >10 y). 7 detected by Holter, 4 by memory loop recording, 31 by autotriggered loop recording • For other detected bradyarrhythmias/conduction disorders the events were too few and the differences too slight to suggest an advantage of 1 device over the others (7 (0.4%) pauses >3 s,15 (0.8%) 2nd degree AVB, 7 (0.4%) 3rd degree AVB) • Autotriggered loop recording produced a higher yield of diagnostic events	**Conclusions:** • Auto-triggered memory loop recorders detects a greater number of arrhythmias than Holter or pt-triggered memory loop recorder, including a greater number of asx events • It is unclear from this analysis what the clinical impact of this enhanced detection might be in the management of bradycardia and conduction disorders due to the limited scope of this analysis and the infrequency of events **Limitations:** • Selection of monitoring device was not randomized, chosen on clinical grounds by the referring practitioner. Selection bias may influence results • Statistical significance of differences in detection rates not reported – data is descriptive only. • No data available regarding associated structural heart disease or medications

			(36%) than Holter (6.2%) or memory loop recording (17%).	• Timing of bradycardia not reported (asleep vs. awake) • Proportion of arrhythmias that were symptomatic is not reported
Sivakumaran S, et al. 2003 (17) 12867227	**Study type:** Prospective randomized observational **Size:** 100 pts referred for ambulatory ECG monitoring in evaluation of syncope/presyncope randomized to 48 h 2-channel Holter (N=51) or 30 d external loop recorder (N=49)	**Inclusion criteria:** Pts with syncope or pre-syncope referred from all sources for Holter monitor or external loop recorder **Exclusion criteria:** N/A	**1° endpoint:** Relative diagnostic yield of the 2 monitoring strategies for "clinically important arrhythmias" (sinus pause >3 s, CHB, Mobitz II 2nd degree AVB, AF with slow VR, symptomatic SB <40 bpm, SVT >10 s or symptomatic, and VT). **Results:** • 31/49 (63%) pts assigned initially to external loop recorder had arrhythmia diagnosed or excluded as cause of symptoms (30 symptoms w/o arrhythmia, 1 symptomatic 5-s conversion pause in AF) • 12/51 (24%) assigned initially to Holter had arrhythmia excluded through symptoms w/o arrhythmia. No symptomatic or asx arrhythmia was diagnosed by Holter • 29/51 randomized to initial Holter accepted cross-over to external loop recorder, while 4/18 with unrevealing initial external loop recorder accepted cross-over to Holter • 13/29 (45%) of cross-over external loop recorders had symptoms w/o arrhythmia during external loop recorder. None had an arrhythmia • None of the 4 pts who underwent cross-over Holter following external loop recorder manifested an arrhythmia or symptoms w/o arrhythmia.	**Conclusions:** • Ambulatory monitoring is more likely to document the absence of arrhythmia during symptoms than symptomatic arrhythmia • In this cohort, arrhythmias, symptomatic or otherwise, were rare (1%) • The diagnostic yield of 30 d external loop recorder is more than twice that of 48 h Holter, almost exclusively through its ability to document symptoms w/o arrhythmia • Despite careful instructions and confirmatory test activations, 13/57 (23%) of pts who had symptoms during external loop recorder monitoring failed to successfully activate their device **Limitations:** • Low incidence of arrhythmias in this unselected population with syncope or pre-syncope

			• In all 55 pts had Holter. None had an arrhythmia identified as the cause of presenting symptoms, 12 (22%) had arrhythmia excluded as a cause. • In all 78 pts underwent external loop recorder monitoring. 1 had an arrhythmia thought to be the cause of the presenting symptoms and 43 had arrhythmia excluded as a cause [Diagnostic yield 44/78 (56%; p<0.0001 vs. Holter)]	
Brown AP, et al. 1987 (18) 3663425	**Study type:** Retrospective observational **Size:** 100 unselected pts experiencing palpitations, dizziness, or syncope (collected from 106 pts who underwent external loop recorder over 3 y). 39% had some form of structural heart disease	**Inclusion criteria:** Unselected pts who had undergone pt-activated ambulatory electrocardiography for up to 3 wk. 42 had undergone prior 24 h Holter of which 17 (40%) were abnormal **Exclusion criteria:** Incomplete case notes (N=6)	**1° endpoint:** Diagnostic yield of external loop recorder **Results:** • "Clinically useful information" was obtained in 68% • Of 56 diagnostic recordings and 13 recordings "of some diagnostic value" there were 6 bradyarrhythmias (4 reflecting sinus node dysfunction and 2 implicating conduction disorder) • 6 of 17 pts with paroxysmal arrhythmias had returned to SR by the time the event button was pressed	• Early study of pt-activated external loop recorder • Authors noted the advantages of a pt-activated external loop recorder over pt-activated recorders w/o a looping memory available at the time • Study demonstrates the feasibility and utility of pt-activated external loop recorder in a population with a relatively high prevalence of structural heart disease and Holter-documented arrhythmias • Authors suggested that the pt-activated external loop recorder was complimentary to 24 h Holter, not a substitute, in part due to the pt-activated external loop recorder's inability to capture asx events.
Cumbee SR, et al. 1990 (19) 2300833	**Study type:** Retrospective observational **Size:** N=39 Derived from first 48 pts referred for pt-activated external cardiac loop recorder	**Inclusion criteria:** Unexplained syncope or presyncope, referred for pt-activated external loop recorder **Exclusion criteria:** No documented Hx of syncope or presyncope	**1° endpoint:** • Diagnostic yield of external loop recorder • Frequency with which external loop recorder provided relevant information missed by preceding Holter and EPS • Extent to which external loop recorder influenced pt management	• Small early evaluation of pt-activated external loop recorder suggesting diagnostic utility • Diagnostic yield in this highly selected population referred to an academic medical center for syncope and presyncope that remained unexplained after fairly extensive testing was understandably lower

	at an academic medical center (see exclusion criteria)	(1), cause of syncope already established (1), inaccessible medical record or loop recorder ongoing at the time data collection was completed (7)	**Results:** • 92% had prior Holter, 46% had prior EPS • 35/39 (90%) wore the monitor (2 pts. declined, 1 stopped due to skin irritation, 1 device malfunctioned) • 32/35 (91%) pts were able to successfully record symptomatic events (others were incapacitated) • Diagnostic in 14/39 (yield=36%; 95% CI, 21%–53%). 11/39 (28%) = syncope w/o arrhythmia and 3/39 (7.6%) symptomatic arrhythmia (asystole, junctional bradycardia, and paroxysmal atrial tachycardia) • External loop recorder led to management changes in all 3 pts with symptomatic arrhythmia including PPM implantation in 2.	than some other studies of external loop recorder (36%). Most of the diagnostic yield was derived from those with syncope or presyncope w/o associated arrhythmia (11/14, 78.5%) • 7/39 (17.9%) pts referred for external loop recorder either couldn't/wouldn't tolerate wearing the monitor, had it malfunction, or were too incapacitated to capture symptomatic events
SYNAAR-Flash Locati ET, et al. 2016 (20) 26519025	**Study type:** Prospective observational multicenter **Size:** 392 pts; 282 (72%) enrolled for palpitations and 110 (28%) for syncope	**Inclusion criteria:** Recent (within 1 mo) episode of syncope or sustained palpitations (index event), after being discharged from emergency room or hospitalization w/o a conclusive Dx, and a suspected arrhythmic origin **Exclusion criteria:** N/A	**1° endpoint:** Evaluate the role of 4 wk auto-triggered external loop recorder in the clinical evaluation of unexplained syncope or sustained palpitations of suspected arrhythmic origin. Analyzed rhythm at the time of symptoms and asx arrhythmias predefined as significant (sustained SVT or VT, advanced AVB, SB <30 bpm, pauses >6 s) **Results:** • 27/110 (25%) of pts. evaluated for syncope had a diagnostic test. Of these 11/110 (10%) experienced a conclusive event regarding the arrhythmic nature of the symptoms and 16/110 (15%) had an asx significant arrhythmia • Of the 11 pts. with a conclusive event, 5 manifested recurrence of symptoms	**Conclusions:** • Authors conclude that the 4 wk external ECG monitoring can be considered as first-line tool in the diagnostic work-up of syncope and palpitation. Early recorder use, Hx of supraventricular (tachy and brady) arrhythmia, and frequent previous events increased the likelihood of diagnostic events during the 4 wk external ECG monitoring **Limitations:** • Reliance on pt diary in efforts to correlate rhythm and symptom introduces potential error • The precise mechanism of a syncopal event associated with arrhythmias documented on external loop

			w/o significant arrhythmia and 6 had symptomatic arrhythmia (all 6 were either bradycardia or conduction disorder) • Of the 16 asx significant arrhythmias, one third (5/16) were either pauses, advanced AVB, or sinus bradycardia • Predictors of diagnostic events in those evaluated for syncope were early start of recording (≤15 d between index event and enrollment vs. >15 d) (OR: 3.2; 95%CI: 1.3–26.6; p=0.021) and previous Hx of supraventricular arrhythmias (OR: 3.6; 95% CI: 1.4–9.7; p=0.018) • 202/282 (72%) of pts referred for palpitations had a diagnostic test (68% conclusive event and 23% symptoms w/o arrhythmia). Less than 3% of referred pts experienced a conclusive event due to bradycardia or conduction disorder. • Predictors of a diagnostic test in those evaluated for palpitations were Hx of recurrent palpitations (p<0.001) and early start of recording (p=0.001).	recorder can be uncertain despite the associated arrhythmia • The clinical benefit of external loop recorder remains undefined in the absence of data documenting improved outcomes predicated on therapy guided by external loop recorder results
Barrett PM, et al. 2014 (21) 24384108	**Study type:** Prospective observational **Size:** N=146 pts referred for ambulatory ECG monitoring who underwent simultaneous 24 h Holter monitor and a novel, single-lead 14-d	**Inclusion criteria:** Pts ≥18 y referred for evaluation of cardiac arrhythmia able to provide consent and comply with continuous ECG monitoring for 14 d **Exclusion criteria:** Skin allergies, conditions, or sensitivities to any of the components of the	**1° endpoint:** Comparative diagnostic utility of the 2 devices **Results:** • Adhesive patch monitor detected 96 pre-defined arrhythmic events over total wear time compared to 61 arrhythmia events by Holter (p<0.001) • Median wear time for Holter =1.0 d (range 0.9–1.0) and for adhesive patch monitor =11.1 d (range 0.9–14)	• Despite slightly lower sensitivity to supraventricular tachyarrhythmias during simultaneous monitoring, 14 d adhesive patch monitor provided greater diastolic yield than 24 h Holter monitoring, primarily through the benefit of prolonged monitoring time • The adhesive patch monitor was considered preferable to wear by the pts in this study with less impact on QOL

	adhesive patch monitor (Zio Patch). 238 screened, 88 declined, 150 enrolled, 4 lost to follow-up.	adhesive patch monitor, receiving or anticipated to receive pacing or external DCCV during the monitoring period, or the anticipation of being exposed to high-frequency surgical equipment during the monitoring period	• During the 24 h period of simultaneous monitoring with both devices, Holter monitor detected more of the pre-specified arrhythmias than the patch monitor. However, in nearly all such pts, the patch monitor subsequently detected the missed arrhythmia through prolonged monitoring. None of the discrepancies related to bradycardia or conduction disorders. • 81% of pts preferred to wear the adhesive patch to the Holter monitor and the participants found the adhesive patch more comfortable with less impact on their activities of daily living.	
Rosenberg MA, et al. 2013 (22) 23240827	**Study type:** Prospective observational **Size:** N=74 consecutive pts. referred for Holter monitor for the evaluation of PAF who underwent simultaneous 24 h Holter monitor and 14 d single-lead adhesive patch monitor (Zio Patch)	**Inclusion criteria:** PAF, referred for Holter monitor as part of clinical management **Exclusion criteria:** 1 potential participant was excluded because the adhesive patch monitor was inadvertently not activated during placement	**1° endpoint:** Comparative diagnostic utility of the 2 devices **Results:** • Mean wear time for adhesive patch monitor =10.8±2.8 d (range 4–14) and the mean monitoring time for the Holter was 22.5±1.8 h) • All 25 AF events detected by Holter in the first 24 h were detected by the adhesive patch monitor. Recorded AF burden during simultaneous monitoring was comparable (58.4±42.7% on Holter and 54.7±41.2% on adhesive patch monitor (r=0.96; p<0.0001) • During prolonged monitoring, the adhesive patch monitor identified AF in 18 (24%) additional individuals in whom it was not detected by 24 h Holter and reclassified pts' pattern of AF (i.e., persistent or paroxysmal) in	**Conclusions:** • 14 d adhesive patch monitoring is a useful tool to refine assessment of PAF, due to the benefits of prolonged monitoring • When compared to simultaneous Holter monitoring, the adhesive patch monitor performs in a comparable fashion in the detection of AF and in the quantitation of cumulative AF burden. • The adhesive patch monitor fell off of 16 pts, was removed by 6 others, or had battery malfunction in one. In all, 23/74 (49%) of participants in this trial failed to complete 14 d of monitoring for non-medically directed reasons. Mean wear time for those whose device fell off was 7.9±1.8 d (range 5.8–12.2 d).

			21 (28%). The prolonged adhesive patch monitoring also documented from 1 to 99 pauses of 3.1–9.7 s in 4 pts, as well as Mobitz type 1 second-degree AVB in 1 pt. Of the pauses only 2 were >5 s and only 1 of these was only detected by prolonged adhesive patch monitoring.	
Turakhia MP, et al. 2013 (23) 23672988	**Study type:** Cross-sectional retrospective observational **Size:** N=26,751 consecutive pts. who underwent first-time, clinically-indicated prolonged adhesive patch monitoring (Zio Patch) during 2011. Investigators used de-identified data obtained from the manufacturer/servicer (iRhythm Technologies)	**Inclusion criteria:** Consecutive pts referred for first-time, clinically indicated Zio Patch monitor **Exclusion criteria:** Excluded data from repeated or subsequent studies	**1° endpoint:** Analyzed compliance, analyzable signal time, interval to arrhythmia detection and diagnostic yield of the Zio patch **Results:** • Mean wear time =7.6±36 d • Median analyzable time =99% of total wear time • Arrhythmia was detected in 60.3% of pts. • 29.9% of all arrhythmias occurred after the first 48 h of monitoring and 51.1% of symptom-triggered arrhythmias occurred after 48 h. • Compared to the first 48 h, the diagnostic yield of the entire monitoring period for any arrhythmia was superior (62.2% vs. 43.9%; p<0.0001) as was the yield for any symptomatic arrhythmia (9.7% vs. 4.4%; p<0.0001) • 3.7% of pts manifested pauses >3 s (42.9 % of which occurred after 48 h) and 1.4% of pts manifested Mobitz II or complete AVB (36.6% of which occurred after 48 h)	**Conclusions:** • ≤14 d of Zio Patch monitoring is feasible, with high compliance, a high percentage of analyzable signal time and incremental diagnostic yield beyond 48 h for all arrhythmia types • The incidence of significant bradycardia or conduction disorders in a large unselected population referred for Zio Patch monitoring on clinical grounds is very low (5.1%). Only 4% of those studied were referred for evaluation of bradycardia, pauses, or advanced AVB
Joshi AK, et al. 2005 (24) 15781022	**Study type:** Retrospective observational	**Inclusion criteria:** Referred for clinically	**1° endpoint:** Diagnostic yield **Results:**	• Early evaluation of new technology at the time

	Size: First 100 consecutive pts. monitored by 2-channel MCOT for a mean of 9.9 d (range 2–28 d).	indicated MCOT monitoring **Exclusion criteria:** N/A	• "Clinically significant" arrhythmia detected in 51 (51%) pts, 25 (49%) of which were asx. • 3 pts manifested "sinus node disease," 2 symptomatic sinus bradycardias, 2 2nd degree AVB, 1 CHB, 1 junctional rhythm, and 1 PM malfunction • Monitoring led to a change in management in 34 (34%) pts., including implantation of PPM in 5 and ICD in 2, as well as 1 PPM replacement.	• MCOT detected clinically significant" arrhythmias in approximately half of those referred and led to a change in management in a third • Authors note that 30 of their pts had previously undergone Holter monitoring or event recorder. In 16 of these MCOT detected an arrhythmia not previously detected.
Rothman SA, et al. 2007 (25) 17318994	**Study type:** Prospective, multicenter observational **Size:** N=266 randomized to pt-activated external loop recorder (132) or MCOT (134) in evaluation of syncope, presyncope or severe palpitations	**Inclusion criteria:** Symptoms of syncope, presyncope or severe palpitations (less frequent than once per 24 h) with a nondiagnostic 24 h Holter or telemetry monitor within 45 d of enrollment. **Exclusion criteria:** NYHA class IV HF; MI within past 3 mo; USA; candidate for or recent valvular cardiac surgery; h/o sustained VT or VF; ≥10 VPCs/h and EF ≤35%; <18 y; inability to complete or comply with protocol	**1° endpoint:** Confirmation or exclusion of a probable arrhythmic cause of their symptoms **Results:** • 266/305 randomized pts completed at least 225 d of monitoring • 114/266 (43%) presented with syncope or presyncope • Overall diagnostic yield: MCOT =88%. external loop recorder =75% (p=0.008) • For those presenting with syncope or presyncope, comparison of diagnostic yield was similar: MCOT =89%. external loop recorder =69% (p=0.008) • MCOT was superior in confirming the Dx of clinically significant arrhythmias [55/134 (41%) vs. 19/132 (15%); p<0.001] • 8/266 (3%) manifested bradycardia or conduction disorder, 6 pauses, 1 complete AVB, 1 Mobitz II 2nd degree AVB, and no symptomatic bradycardia.	**Conclusions:** • MCOT provided a higher diagnostic yield than pt-activated external loop recorder in this cohort of pts referred for syncope, presyncope, and severe palpitations in a randomized head-to-head comparison • Authors speculate this likely relates to pt inability to properly use the external loop recorder, compliance, and/or the ability of MCOT to detect asx arrhythmias. **Limitations:** • external loop recorder w/o auto-trigger functionality was utilized which could bias results toward MCOT • Pt and investigator unblinded • Noncompliance =12.7% (23 randomized to MCOT did not complete 25 d of monitoring vs. 16 in the external loop recorder group)
Linzer M, et al. 1990 (26) 2371954	**Study type:** Prospective observational	**Inclusion criteria:** ≥1 episode of unexplained syncope	**1° endpoint:** Utility of external loop recorder after indeterminate Holter	**Conclusions:** • Early study of external loop recorder in syncope that suggests utility, but

	Size: N=57 pts	**Exclusion criteria:** Prior EPS	**Results:** In 14 /57 (25%) of pts, external loop recorder was diagnostic. • Half of these diagnoses (7/14) came from symptoms w/o associated arrhythmia • Symptomatic arrhythmias include VT (1 pt), high-grade AVB (2 pts), SVT (1 pt), asystole or junctional bradycardia from neurally mediated syncope (3 pts)	only rarely by identifying non-neurally mediated bradycardia or conduction disorder (<4% of those studied). **Limitations:** • Referral bias • Small sample size
Framingham Schneider JF, et al. 1979 (27) 154870	**Study type:** Prospective observational community-based study **Size:** N=55 cases of new LBBB. N=110 age/sex-matched controls w/o incident LBBB N=5,209 total cohort followed biennially up to 18 y	**Inclusion criteria:** New LBBB detected on biennial exams **Exclusion criteria:** 17 with LBBB at start of the study	**1° endpoint:** Describe the incidence of new LBBB, describe the prevalence of antecedent, coincident and subsequent CV disease and risk factors in those with vs. w/o incident LBBB (HTN, CHF, CHD, DM, cardiac enlargement) **Results:** • 31 men, 24 women • Mean age at LBBB=62 y (36–78) • Mean follow-up = 18 y (12 pre- and 6 post-LBBB) range: 4–22 y • Those with LBBB had a higher prevalence of HTN (65%), cardiac enlargement (44%), CHF, CAD, DM vs. those w/o LBBB • Only 27% of LBBB group was free of obvious CVD at the time of Dx • 5/15 (33%) free of antecedent CVD, developed evidence thereof coincident to or following the detection of LBBB • 6/15 of those with incident CVD had evidence thereof at the time of the new LBBB (all CAD) • 14/55 (28%) developed new CHF with (N=4) or after (N=10) LBBB first noted	**Strengths:** • Large population-based study with lengthy follow-up and rigorous data collection **Limitations:** • Small number of incident cases of LBBB with wide confidence margins of estimated rates of events • No echocardiogram or other assessment for structural heart disease with incident LBBB **Conclusion:** Incident LBBB in middle aged populations is often associated with antecedent or subsequent clinically apparent CV disease, and is associated with increased CV mortality in men

			• Rate of incident CAD in those with LBBB =2x controls during follow-up • Rate of incident CHF in those with LBBB=7x controls during follow-up • Median time to first recognized CAD=3.7 y • Median time to first recognized CHF=3.3 y • 11% of LBBB group and 48% of controls remained free of any evidence of CVD during follow-up (p<0.001) • No advanced AVB or PPM in those with LBBB • LBBB: 50% mortality at 10 y • Controls 11.6% mortality at 10 y (p=not provided) Prevalence cohort (17 with LBBB at initial screening) were younger (mean age=49 y), but had similar incidence of CVD (94% developed one or more forms of CVD on average 3 y after initial Dx)	
Framingham Schneider JF, et al. 1980 (28) 7350871	**Study type:** Prospective observational community-based study **Size** N=70 cases of newly diagnosed RBBB N=140 sex and age-matched controls N=5,209 total cohort followed biennially up to 18 y	**Inclusion criteria:** New RBBB **Exclusion criteria:** Extant RBBB (N=16) at first visit	**1° endpoint:** Compare the prevalence of antecedent, coincident and subsequent CV disease and risk factors in those with incident RBBB (HTN, CHF, CHD, DM, cardiac enlargement) **Results:** • Mean age at Dx of RBBB=60 y (38–77) • Prevalence increased with age • At all ages <70 y, RBBB more common in men than women • 70% of cases of RBBB associated with antecedent CVD, most commonly HTN (60%)	**Strengths** • Large population-based study with lengthy follow-up and rigorous data collection **Limitations:** • Small number of incident cases of RBBB with wide confidence margins of estimated rates of events rendering several trends statistically insignificant • No echocardiogram or other assessment for structural heart disease with incident LBBB **Conclusion:**

			• Only the prevalence of HTN and valvular heart disease antecedent to the Dx of RBBB were significantly greater than controls (roughly twice as common for both) • 15/53 (28%) of those w/o evidence of CHD at the time RBBB was diagnosed developed CHD subsequent to the development of RBBB, (OR: 2.5; p<0.001) • 7/64 (11%) of those w/o evidence of CHF at the time RBBB was diagnosed developed CHF subsequent to the development of RBBB, (OR~4; p=0.02) • Multivariate analysis suggests the relationship between RBBB and subsequent CHD and CHF remains valid for women but not men when age, SBP, and DM are considered. • 20 individuals (15 men) had no evidence of CVD at the time RBBB was noted. Of these, CHD developed in 25% (2/5 women and 2/15 men), CHF developed in 5%, and 75% remained free of clinical CVD. • In these 20 individuals free of apparent CVD at the time RBBB is first diagnosed, subsequent 10-y CV mortality=9% vs. 40% for the 50 individuals with at least 1 CV abnormality prior to the Dx of RBBB (p=not reported) • Total prevalence of most CV abnormalities at any time during the study was higher in RBBB than in controls: CHF=19% vs. 4 % (p<0.001), Cardiac Enlargement=31% vs. 14% (p<0.01), CHD=46% vs. 24% (p<0.01),	• Incident RBBB is commonly associated with CV abnormalities at the time of Dx. • Incident RBBB associated with a 2.5-fold increased risk of subsequent CHD and 4-fold increased risk of CHF. • Incident RBBB is associated with a 3-fold increased 10-y risk of CV death compared to those w/o RBBB, however, most of that risk is attributable to underlying CV disease. • Those with QRSD >130 ms and LAD (frontal plane axis: -45°–-90°) identified those with RBBB Most likely to have underlying CV abnormalities

			valvular heart disease=6% vs.1% (p<0.05) • No statistically significant difference in total prevalence of HTN, DM, or absence of all CV abnormalities. • Those with RBBB had "about 3 times greater" 10 y CV mortality compared to those w/o conduction disorder (p<0.001). 34% in men and 23% in women vs. 11% in controls (p=NS for men vs women with incident RBBB). • 10 y rate of SCD: RBBB=11%, controls=3% (p=0.05). • RBBB was a univariate predictor of CV mortality but not by multivariate analysis incorporating age, SBP, DM, CHD, CHF. In the 50 individuals with evidence of CV abnormalities prior to or coincident with the Dx of RBBB, 10 y CV mortality=40% vs. 9% in the 20 individuals free of such abnormalities prior to or coincident with the Dx of RBBB (p=not reported)	
Framingham Schneider JF, et al. 1981 (29) 6452050	**Study type:** Prospective observational community-based study **Size:** N=55 cases of new LBBB and N=70 cases of new RBBB. N=5,209 total cohort followed biennially up to 18 y	**Inclusion criteria:** New LBBB or RBBB **Exclusion criteria:** Extant L (N=17) or R (N=16) BBB at first visit	**1° endpoint:** Compare the prevalence of antecedent, coincident and subsequent CV disease and risk factors in those with incident LBBB vs. incident RBBB (HTN, CHF, CHD, DM, cardiac enlargement) **Results:** • No difference in prevalence of HTN, CAD or DM in LBBB vs. RBBB • Trend toward higher CV mortality in LBBB vs. RBBB that was stronger in men than women (p>0.05)	**Strengths:** • Large population-based study with lengthy follow-up and rigorous data collection **Limitations:** • Small number of incident cases of LBBB and RBBB with wide confidence margins of estimated rates of events rendering several strong trends statistically insignificant • No echocardiogram or other assessment for structural heart disease with incident LBBB

			• Overall those with LBBB had a 4-fold increased 10-y CV mortality after Dx and those with RBBB had a 3-fold increased 10 y CV mortality compared to those w/o conduction disorder (p<0.001 for both) • Men with incident LBBB had a higher cumulative prevalence of "advanced CV abnormalities" before or after the development of LBBB than men who develop RBBB • Women with incident LBBB had similar prevalence of "advanced CV abnormalities" before or after the development of LBBB than women who develop RBBB • In both men and women and for both RBBB and LBBB, the development of BBB was a univariate predictor of incident CHD or CHF • Multivariate analysis: LBBB and RBBB remained predictive for incident CHD and CHF in women but not men (p<0.05 for LBBB in women and P<0.001 for RBBB in women) • Only 11% of those with LBBB and only 21% of those with RBBB remained free of all CV abnormalities during follow-up • Multivariate analysis: LBBB in men was independently predictive of 10-y CV mortality (p<0.01). RBBB in men and both LBBB and RBBB in women were not predictive of 10 y CV mortality independent of age, SBP, DM, CHD and CHF • Amongst the 33 individuals with LBBB or RBBB at first visit (excluded form	**<u>Conclusion</u>:** • Both LBBB and RBBB are associated with increased 10-y risk of CV death in a middle aged unselected population than those w/o BBB • Strong trend toward higher CV mortality in LBBB than RBBB that was stronger in men than women • The vast majority of individuals with incident LBBB or RBBB manifest some form of CV abnormality (most commonly HTN) during follow-up. • Although LBBB and RBBB are univariate predictors of incident CHD and CHF in both men and women, controlling for age, SBP, DM, CHD and CHF renders LBBB and RBBB independently predictive of incident CHD and CHF only in women but not in men

			analysis above), there was a 2-fold higher prevalence of HTN (p<0.05) and a 4-fold higher prevalence of radiographic cardiac enlargement (p<0.01) in LBBB vs. RBBB. • 2-fold higher rate of CHD, CHF, and DM was also evident in those with BBB at baseline (p=NS) • Overall there was a trend toward increased prevalence of all CV abnormalities during follow-up for LBBB vs. RBBB (94% vs. 75%; p=NS) in those with BBB at baseline exam.	
Eriksson P, et al. 1998 (30) 9832497	**Study type:** Longitudinal prospective community-based study **Size:** N=855	**Inclusion criteria:** • Sample of men living in Göteborg, Sweden born on days divisible by 3 in 1913 obtained from the county census bureau's register of names (N973) • Agreed to participate (N=855) • Followed for 30 y with serial exams at 4–8 y intervals starting in 1963 when all were 50 y. **Exclusion criteria:** N/A	**1° endpoint:** Describe the cumulative incidence of BBB and its relationship with CV disease, risk factors, and prognosis based on ECGs obtained at baseline and 3 subsequent exams in 1980, 1988, and 1993. **Results:** • follow-up 98% complete • Prevalence of BBB=82/855 (9.6%), 22 (2.6%) LBBB, 60 (7.0%) RBBB, 86% after age 50 y. • 26% of LBBB and 6% of RBBB showed LVH on ECGs prior to development of BBB (p<0.01 for comparison) • At age 80 y, cumulative incidence rate: LBBB=6.5% RBBB=12.9% • Prevalence of LBBB in survivors: 0.4% at 50 y. and 5.7% at 80 y • Prevalence of RBBB in survivors: 0.8% at 50 y and 11.3% at 80 y • No difference in baseline CV risk factors between those with and w/o incident BBB, except greater	**Strengths**: • Long-term prospective follow-up of moderately large and homogeneous population **Limitations:** • Too few LBBB cases rendering statistical significance elusive as it relates to underlying structural heart disease and outcomes. • Small number of cases also precludes meaningful comparison between LBBB and RBBB. • Combining RBBB and LBBB likely dilutes the potential impact compared to LBBB alone • Limited to men **Conclusion:** • Prevalence of LBBB and RBBB increases with age • RBBB is twice as common as LBBB • Those who develop LBBB are more likely to have LVH on ECGs preceding the development of LBBB than those

			radiographic heart volume in those with BBB (794 vs. 746 ml; p<0.05) • Those with incident BBB: higher prevalence of CHF in follow-up (36 vs. 14%; p<0.01 vs. no BBB) and higher prevalence of DM (36 vs. 17%; p<0.05 vs. no BBB) • No apparent difference between LBBB and RBBB in baseline risk factors or outcomes • Trend toward increased mortality and CV mortality with BBB vs. no BBB, but p=NS. 73/262 (28%) CV deaths associated with prior Dx of CHF in those w/o BBB vs. 14/23 (61%) of CV deaths associated with prior Dx of CHF in those with BBB (p<0.01)	who develop RBBB (a potential indicator that underlying structural heart disease is more likely with LBBB vs. RBBB) • Those who develop BBB have greater radiographic cardiac volume at baseline compared to those who do not (again suggesting greater likelihood of underlying structural heart disease in those who develop BBB) • Those with BBB are more likely to develop clinically evident CHF or DM • BBB associated with a trend towards higher mortality that fails to reach statistical significance.
Fahy GJ, et al. 1996 (31) 8651093	**Study type:** Prospective observational community-based study **Size:** • N=110,000 participants in an Irish CV prevention screening study over 25 y. • N=310 with BBB but w/o suspected CVD	**Inclusion criteria:** • BBB at baseline exam (N=480, 0.44%) • Age and sex matched controls w/o BBB **Exclusion criteria:** • HTN at baseline exam (N=109) • H/o CVD at baseline exam (N=84) • Both HTN and CVD=23	**1° endpoint:** Determine the prevalence of isolated BBB and the associated long-term prognosis over a 25-y period **Results:** • Prevalence of isolated BBB=0.28% • RBBB: N=198 (0.18%) more common than LBBB: N=112 (0.1%); p<0.001. • Those with LBBB (51±13 y) older than RBBB (44±13 y); p=0.001. • RBBB but not LBBB was more common in men than women (p<0.001) • Mean follow-up=9.5 y. median follow-up=87.5 y. • 49 total deaths • No difference in mortality rate between BBB vs. no BBB and between RBBB and LBBB	**Strengths:** • Long-term prospective follow-up of large middle-aged population including men and at least some women (<25% in this analysis) • Larger number of cases of LBBB and RBBB compared to other studies • Protracted prospective follow-up **Limitations:** • Lack of physical exam, CXR, echo, or CAD screening at baseline **Conclusion:** • RBBB and LBBB rare in middle age (~0.1–0.2%) • RBBB more common than LBBB • RBBB (but not LBBB) more common in men than women.

			• Actuarial freedom from CV death up to 15 y worse in LBBB vs. controls (p=0.01) • Actuarial freedom from CV death up to 15 y worse in LBBB vs. RBBB (p=0.001). • When age included in Cox multiple regression model, differences in CV mortality were no longer significant (p=0.08) • Overt CV disease developed in more individuals with LBBB than controls (21% vs. 11%; p=0.04). Not so with RBBB • No increased rate of PPM implantation	• Overt CV disease develops in ~20% in those with LBBB during follow-up (nearly twice as often) than in controls w/o conduction disorder. • CV death (but not all-cause mortality) more common in combined left and right bundle branch block than in those w/o conduction disorder • CV death (but not all-cause mortality) more common in those with LBBB vs. RBBB • In multivariate analyses, the differences in CV death associated with BBB and amongst types of BBB are no longer significant when age is considered.
Imanishi R, et al. 2006 (32) 16923453	**Study type:** Case-control **Size:** N=17,361 (6,663 men) screened N=110 incident LBBB (41 men) N=456 (156 men) randomly selected age and sex-matched controls w/o LBBB, 3–5 controls per incident case of LBBB	**Inclusion criteria:** Atomic bomb survivors in Hiroshima and Nagasaki, Japan, participants in biennial health exams (including CXR and ECG) from 1958–2002 **Exclusion criteria:** LBBB at initial exam (N=9) Controls with PPM or AF (no cases of LBBB had AF)	**1° endpoint:** Incidence and mortality of LBBB **Results:** • Mean age at LBBB=69.6 ± 10.0 y in men and 68.3±10.9 y in women • LBBB increased with age • Incident LBBB associated with HTN (54.6% of LBBB vs. 43.2% of controls; p=0.033), ischemic heart disease (22.7% vs. 5.7%; p<0.001), and non-cardiac disease (43.6% vs. 33.3%; p=0.045) • Incident LBBB associated with: • Radiographic cardiothoracic ratio: (51.9±6.1 at Dx of LBBB vs. 50.3±5.5 in controls; p=0.010) • ECG-derived LVH (60.9% of LBBB vs. 22.3% of controls; p<0.001) • ST-T abnormalities (39.1% of LBBB vs. 16.2% of controls; p<0.001)	**Strengths**: • Large population-based study with lengthy follow-up and rigorous data collection • 40-y follow-up **Limitations**: • Although larger than Framingham study, still a limited number of cases of incident LBBB to analyze • Lack of echo or cath data may underestimate the prevalence of underlying CMP or valvular heart disease **Conclusion**: • Incident LBBB is independently predictive of CHF-related mortality (RR >3) but not all-cause mortality • Incident LBBB is associated with antecedent or coincident markers of

			• antecedent to the development of LBBB • LBBB independently predictive of CHF mortality; RR: 3.08 (1.62–5.87; p<0.001) but not all-cause mortality; RR: 1.22 (0.90–1.65; p=0.206)	structural heart disease such as increased radiographic CT ratio or electrocardiographic LVH or ST-T abnormalities

Framingham
Dhingra R, et al. 2006 (33)
16585411
	Study type:
	Prospective, longitudinal, community-based study
	
	Size: N=1,759 (1,113 women)
		Inclusion criteria:
		Attendees of the 16th (1979–1981) or 17th (1982–1984) biennial exam of the Framingham Heart Study with available ECG and echo data (2-D guided M-mode)
		
		Exclusion criteria:
		Prevalent HF or previous MI (N=135)
		Anti-arrhythmic therapy or PPM (N=187)
			1° endpoint:
			Assess the relationship of QRSd to CHF incidence during mean follow-up of 12.7 y; range 0.4–22.3 y.
			
			Results:
			• 324 participants developed CHF (205 women); 231 (17.3%) of 1339 with QRS <100 ms, 62 (20.2%) of 307 with incomplete BBB (QRS=100–119 ms), and 31 (27.4%) of 113 with complete BBB (QRS ≥120 ms).
			• Survival free of CHF decreased with increasing QRSd category (log-rank p<0.001)
			• In multivariable time-dependent Cox models, BBB associated with a 1.74-fold risk of CHF (p<0.001) compared to the referent group.
			• In multivariable analyses LBBB had the highest incidence of CHF during follow-up compared to QRS <100 msec.
			  ○ LBBB: adjusted HR: 4.45 (95% CI: 2.33–8.51; p=0.0001)
			  ○ Indeterminate BBB: adjusted HR: 2.18 (95% CI: 1.13–4.20; p=0.02)
			  ○ RBBB: adjusted HR: 1.73 (95% CI: 0.93–3.21; p=0.08)
				Strengths:
				• Large community-based population
				• Long duration of follow-up (up to 22 y)
				• Prospective, systematic data acquisition
				• Both sexes well represented
				
				Limitations:
				• Limited statistical power to analyze relations of BBB type to CHF incidence
				• Single assessment of QRSd
				• Predominantly Caucasian population
				
				Conclusion:
				• There is a positive association between ECG QRSd with CHF risk in a large community-based population free of CHF or MI at baseline
				• Association strongest for complete BBB who experienced a 2-fold risk of CHF compared to those with QRS <100 msec.
				• Baseline incomplete and complete BBB accounted for only 30% of incident CHF during follow-up.
				• In an exploratory analysis of a subgroup (N=82, 25% of CHF cases) of pts undergoing echo within 30 d of CHF Dx, incomplete and complete

				BBB both associated equally with HFrEF and HFpEF.
Rotman M, et al. 1975 (34) 1132086	**Study type:** Retrospective observational cohort study **Size:** N=237,000 with ECGs in the United States Air Force Central Electrocardiographic Library, 1957–1972 N=394 RBBB N=125 LBBB	**Inclusion criteria:** Routine initial ECGs obtained on a heterogeneous group of Airforce Academy cadets and applicants for flight training and serial ECGs on rated flying personnel taken throughout their Air Force career. The population that was critically examined included only those subjects that had had either an initial clinical evaluation and/or available complete follow-up information. **Exclusion criteria:** N/A	**1° endpoint:** Review clinical status and mortality of those with BBB at the United States Air Force School of Aerospace Medicine. Compare and contrast those with RBBB with LBBB and explore various combinations of fascicular blocks for their impact on findings at initial evaluation and subsequent clinical course. **Results:** • Mean age=36±9 (range 17–58) y for RBBB • Mean age=40±7 (range 20–56) y for LBBB (higher % of RBBB were <25 y and a higher % of LBBB was >45 y; p<0.001) • 251/394 (63.7%) RBBB present on initial ECG and 143/394 (36.3%) were noted on subsequent ECG • 44/125 (35.2%) LBBB present on initial ECG and 81/125 (64.8%) were noted on subsequent ECG • 372/394 RBBB had complete evaluation at time of initial Dx, 97% of these were asx, 94% had a normal CV evaluation, 10/372 (2.7%) had evidence of CAD, 9/372 (2.4%) had hypertension, 5/372 (1.3%) congenital heart disease • 121/125 LBBB had complete evaluation at the time of initial Dx, 95% of these were asx, 89% had a normal CV evaluation, 11/121 (9.1%) had evidence of CAD (4 confirmed by cath), 8/121 (6.6%) had hypertension	**Strengths:** • Large pool of routine screening ECGs in a young, generally healthy, predominantly asx population • Fairly long duration of follow-up **Limitations:** • Exclusively male population • Low prevalence of BBB and of underlying structural heart disease renders the study largely descriptive **Conclusion:** • The majority of young airmen with right and left bundle branch block are asx and free of underlying structural heart disease/CAD. • Although underpowered to allow conclusions, LBBB may be more predictive of CV death than RBBB • The prognosis of BBB relates more to the underlying structural heart disease than the conduction abnormality itself. • "Significant progressive electrical dysfunction is a rare occurrence" in this population (1 PPM for advanced AVB in each group, and 1 additional PPM for unexplained syncope w/o advanced AVB in the RBBB group).

			• 54 subjects with RBBB and 29 with LBBB had a complete cardiac catheterization • LBBB had a significant higher rate of CAD ($p<0.01$) and HTN ($p<0.05$) than RBBB, independent of age. • Mean follow-up: RBBB=10.8±4.7 y, LBBB=8.8±4.8 y • During follow-up of those with RBBB, 21 (6%) new cases of CAD and 21 new cases (6%) of HTN developed. • During follow-up of those with LBBB, 6 (5%) new cases of CAD and 7(6%) new cases of HTN developed • 14 (4%) of those with RBBB died, all but 3 from non-cardiac causes • 9 (8%) of those with LBBB died, all but 2 from cardiac related causes. Combinations of fascicular blocks did not inform clinical status at the time of initial evaluation or subsequent prognosis.	
Froelicher VF, et al. 1977 (35) 831426	**Study type:** Retrospective cross – sectional study **Size:** N=34 with asx LBBB N=41 with asx RBBB Derived from 325 airmen referred for cardiac catheterization	**Inclusion criteria:** Airmen who underwent coronary angiography for clinical indications between 2/1971 and 12/1974. All but 27 with possible angina were asx. **Exclusion criteria:** Declined catheterization (N=not provided)	**1° endpoint:** Prevalence of significant CAD (>50% stenosis) according to referral Dx (e.g., abnormal ETT, angina, BBB, etc.) **Results:** • Mean age=42±7 y • Significant CAD: LBBB=8/34 (24%) RBBB=8/41 (20%) All pts=98/325 (30%) • 5/34 (14.7%) with LBBB and no significant CAD had “generalized LV dyskinesia” and LVEDP >12 mm Hg • 1/34 (2.9%) with LBBB and normal coronary arteries manifested overt HFrEF subsequent to catheterization and died suddenly 2 months after Dx	**Strengths:** • Coronary angiography performed in asx pts with isolated LBBB and no other indication of CV disease (justified by public safety concerns) **Limitations:** • Small size • Potential selection bias (clinically referred for cardiac evaluation) • No systematic follow-up **Conclusion:** ECG abnormalities are “poorer predictors of heart disease in asx apparently healthy men than in hospital or clinic populations.”

Manitoba Heart Study Rabkin SW, et al. 1980 (36) 6444828	**Study type:** Prospective, observational cohort study **Size:** N=29 Derived from 3,983 male pilots from the Royal Canadian Air Force or licensed by the Canadian Dept. of Transport participating in regular health exams (including ECG) every 3–5 y from 1948–1977	**Inclusion criteria:** Participants in regular annual medical exams with no clinical evidence of CHD or valvular heart disease antecedent to or coincident with the discovery of LBBB **Exclusion criteria:** One participant with LBBB at entry exam was excluded from analysis of factors contributing to the development of LBBB but was included in the prognostic study	**1° endpoint:** Death, including sudden death during follow-up, association of ECG findings antecedent to the Dx of LBBB with the development of subsequent LBBB **Results:** • Mean age at entry=30.8 y. • Average follow-up=29 y • Only 1 case of LBBB present at entry • 13/28 (46.4%) who developed LBBB after the initial exam had some antecedent ECG abnormality (14% had LVH, 14% has ST-T abnormalities, and 14% had some form of conduction abnormality such as PR prolongation, IVCD, LAD, etc) • Only the prevalence of LVH was significantly different from the population free of incident LBBB (14% vs. 3.5%; p<0.05) • Risk of SCD: 6/29 (20.7%) was >10 fold higher than in those w/o LBBB (1.6%); p<0.01	**Strengths:** • Long period of close follow-up **Limitations:** • Highly selected population • Exclusively male • Young at the start with predictably very low prevalence of LBBB • Low number of cases of LBBB **Conclusion:** • Incident LBBB is associated with LVH on prior ECGs • LBBB in a relatively young, male population is associated with a >10-fold risk of sudden cardiac death.
Women's Health Initiative Zhang ZM, et al. 2012 (37) 22858187	**Study type:** Prospective observational cohort study **Size:** N=66,450 (1,739 with BBB, of which 708 had clinical evidence of CV disease) Derived from 68,133 participants in the Women's Health Initiative study	**Inclusion criteria:** Participants in the Women's Health Initiative with interpretable ECG **Exclusion criteria:** • No available electronic ECG (N=960) • Inadequate quality ECG (N=614) • PPM or WPW (N=109)	**1° endpoint:** CHD-related and all-cause mortality associated with L and R BBB **Results:** • Mean follow-up=14.2 y • Avg. age=63 y; 10% African American • 19% had h/o CVD or ECG evidence of prior MI • 2.6% BBB (714 LBBB, 832 RBBB, 122 NSIVCD, 71 RBBB with LAFB) • 18% with BBB died • 8% with LBBB had fatal CHD events	**Strengths:** • Relatively large number of cases of LBBB and RBBB • Long systematic follow-up **Limitations:** • Exclusively women **Conclusion:** • In women with baseline CVD, after adjusting for potential confounders, LBBB and RBBB were predictive of CHD death, but only LBBB was predictive of all-cause death

			• HR for CHD death for LBBB in women with CVD: 2.92 (95% CI: 2.08–4.08; p<0.01). • HR for CHD death for RBBB in women with CVD: 1.62 (95% CI: 1.08–2.43; p<0.05) • HR for all-cause mortality for LBBB in women with CVD: 1.43 (95% CI: 1.11–1.83; p<0.01) • HR for all-cause mortality for RBBB in women with CVD: 1.1 (95% CI: 0.84–1.44. p=NS) • HR for CHD death for LBBB in women free of baseline CVD: 2.17 (1.37–3.43; p<0.01)	• In women free of CVD, only LBBB was predictive of CHD death, and neither BBB was a predictor of all-cause death • NSIVCD and RBBB with LAFB is associated with a 2.5- to 3-fold increased risk of CHD death in those with baseline CV disease. • Most repolarization parameters do not predict CHD or all-cause mortality.
OPTIMAAL Bogale N, et al. 2007 (38) 17317365	**Study type:** Prospective observational study derived from an RCT of losartan vs. captopril in pts with AMI and HF or asx impaired LVEF **Size:** N=356 (6.5%) with LBBB at baseline or subsequently developing LBBB during 2.7 y mean follow-up N=354 (6.5%) with RBBB at baseline or subsequently developing RBBB during 2.7 y mean follow-up N=5,477 in the RCT	**Inclusion criteria:** Acute MI (average time to enrollment=3 d), ≥50 y, HF, impaired LVEF <35%, or LVEDD >65 mm and anterior Q waves on ECG (old or new) **Exclusion criteria:** • Supine SBP <100 mm Hg at the time of enrollment • Rx with an ACEI or ARB • Unstable angina • Hemodynamically significant valvular stenosis • Hemodynamically significant arrhythmia • Planned revascularization • Unable/unwilling to give consent	**1° endpoint:** All-cause death. Outcomes and crude rates were stratified according to presence of LBBB or RBBB at baseline. Kaplan–Meier curves plotted for death and SCD stratified by BBB pattern at baseline. Cox regression models assessed effect of BBB pattern at baseline on death and SCD and the effect of the development of BBB during follow-up adjusted for age, pulse rate, h/o CABG, DM, CHF or prior MI **Results:** • Pts with BBB patterns were older, fewer were smokers at time of inclusion, and more had previous HTN, AMI, CABG, and DM. • 946/5477 (17.3%) all-cause deaths. 442/5477 (46.7%) were SCD • Baseline: 203/5477 (3.7%) had LBBB and 235/5477 (4.3%) had RBBB	Strengths: • Relatively large number of cases of LBBB and RBBB • Systematic follow-up for fatal outcomes Limitations: • No core lab interpretation of ECGs • No data to correlate BBB with EF • No data on presence or absence of BBB before index AMI • No ability to assess reversion rates of BBB back to normal after AMI (reported to be >10% after revascularization in some studies) • Only 10% received PCI (54% received thrombolysis) Conclusion: • In middle-aged and older pts with high-risk findings after acute MI, LBBB present at time of MI is independently predictive of all-cause

		• Participation in another research trial	• Follow-up: additional 153 (2.8%) developed LBBB and 119 (2.2%) developed RBBB. • LBBB at baseline independently predictive of all-cause death (HR: 1.48; 95% CI: 1.25–1.77; p<0.01) and CV death (HR: 1.53; 95% CI: 1.17–1.99; p<0.01), but not SCD/resuscitated cardiac arrest (HR:1.28; 95% CI: 0.96–1.71; p=NS) • Late onset LBBB independently predictive of all-cause death (HR: 2.06; 95% CI: 1.49–2.90; p<0.01), CV death (HR:2.70; 95% CI: 1.68–4.35; p<0.0001), and SCD/resuscitated cardiac arrest (HR: 2.38; 95% CI, 1.48–3.83; p=0.01) • RBBB at baseline independently predictive of SCD/resuscitated cardiac arrest (HR:1.60; 95% CI: 1.25–2.04; p<0.01) but not all-cause death (HR:1.16; 95% CI, 0.96–1.39; p=NS) or CV death (HR: 1.25; 95% CI: 0.95–1.64; p=NS) • Late-onset RBBB independently predictive of SCD/resuscitated cardiac arrest (HR: 2.02; 95% CI: 1.22–3.34; p=0.05) but not all-cause death (HR: 1.26; 95% CI: 0.84–1.89; p=NS) or CV death (HR: 1.42; 95% CI: 0.76–2.67; p=NS)	death and CV death, but not SCD/resuscitated cardiac arrest. Subsequently developing LBBB during an average of 2.7-y follow-up is associated with all 3. • In middle-aged and older pts with high-risk findings after acute MI, RBBB present at time of MI and subsequently developing RBBB during an average of 2.7-y follow-up is independently predictive of SCD/resuscitated cardiac arrest but not all-cause death or CV death.
Baldasseroni S, et al. 2002 (39) 11868043	**Study type:** Retrospective, observational registry study **Size:** N=5,517	**Inclusion criteria:** Participants in the Italian Network CHF Registry, created in 1995 by the Italian Association of Hospital Cardiologists and	**1° endpoint:** 1-y, all-cause mortality rate **Results:** • Mean age=63±12 y • 1295/5517 (23.5%) women • 1544/5517 (28.0%) NYHA class 3–4 • LBBB 1391/5517 (25.2%)	**Strengths:** • Large prospective outpatient registry of pts referred to cardiologists for management of CHF • Standardized definitions and data collection methods (for most elements)

		derived from 150 Italian medical facilities. **Exclusion criteria:** • CHF due to valvular heart disease (N=745) • Inadequate quality ECG (N=270) Cardiac transplantation within the 1st year of follow-up	• RBBB: 336/5517 (6.1%) • Other forms of IVCD: 339/5517 (6.1%) • Those with LBBB more likely to be female, have non-ischemic CM, NYHA 3–4 status, S3, cardiomegaly on CXR, EF <30%, or receive diuretics, ACEI, digoxin, and amiodarone, and less likely to have AF and receive nitrates, BBs, antiplatelet agents, and CCBs • Overall 1-y mortality: 659/5517 (11.9%) • 306/659 (46.4%) deaths attributed to sudden death • LBBB 1-y all-cause mortality: 224/1391 (16.1%) • RBBB 1-y all-cause mortality: 40/336 (11.9%) • Other IVCD 1-y all-cause mortality: 30/339 (8.8%) • By multivariable analysis, LBBB remained independently predictive of all-cause mortality (HR: 1.360; 95% CI: 1.148–1.610; p=0.0004) • By multivariable analysis, LBBB remained independently predictive of sudden death (HR: 1.348; 95% CI: 1.051–1.729; p=0.0188)	**Limitations:** • No core lab interpretation of ECGs • Chose QRSd >140 ms to reduce likelihood of false classification of IVCD as LBBB. This may exaggerate the prognostic impact of LBBB as QRSd itself is predictive of outcome with higher mortality with longer QRSd. • No systematic coronary angiogram to determine etiology of CM • No systematic definition of sudden death **Conclusion:** Amongst outpatients referred to Italian cardiologists for HF management, LBBB is associated with both a higher risk population (as indicated by clinical status and co-morbidities) and an approximate 35% increased 1-y risk of both all-cause death and sudden death, independent of a large number of other CHF risk indicators.
Erne P, et al. 2017 (40) 28224924	**Study type:** Retrospective observational registry study **Size:** • N=29,114 in registry • N=28,421 had presenting ECG data • N=26,090 STEMI w/o LBBB	**Inclusion criteria:** • Participants in the AMIS Plus Registry, an ongoing Swiss nationwide prospective cohort of pts admitted with ACS, founded by the Swiss Societies of Cardiology, Internal Medicine, and Intensive Care Medicine in 1997.	**1° endpoint:** All-cause, in-hospital mortality **Results:** • Age: STE=64.3 [SD 13.2], LBBB=75.0 [10.7]; p<0.001 • Those with LBBB at the time of acute MI were more likely to be female, present later, have less chest pain and more dyspnea as chief complaint, have higher heart rate, and higher	**Strengths**: • Largest prospective registry of unselected pts with suspected acute MI and LBBB to date • Standardized definitions and data collection methods **Limitations:** • No core laboratory for ECG analysis • No systematic algorithm to differentiate isolated LBBB from LBBB associated with transmural

	2,295 had LBBB with or w/o concomitant STE	• Definitive acute MI with either STE or new/ presumed to be new LBBB **Exclusion criteria:** N/A	prevalence of AF, Killip class 3–4 status, DM, HTN, hyperlipidemia, and prior MI, HF, CVA, PAD, or CKD (p<0.001 for all) • Those with LBBB had higher prevalence of impaired EF (354/1530 [23.1%] vs. 1582/18622 [8.5%]; p<0.001). • Those with LBBB were less aggressively treated with antiplatelet, antithrombotic, BB, statin, and revascularization therapies (p<0.001 for all) • All-cause in-hospital mortality: LBBB=371/2,295 (16.2%); STE=1,707/26,090 (6.5%); p<0.001 • Cardiogenic shock after admission: LBBB=286/2252 (11.6%) STE=1642/25,834 (6.4%); p<0.001 • MACCE: LBBB=394/2244 (17.6%) STE=2102/25,751 (8.2%); p<0.001 Multivariate analysis: LBBB no longer an independent predictor of in-hospital mortality, HR: 1.01 (95% CI: 0.86–1.19; p=NS)	Ischemia (e.g. Sgarbossa criteria) • No prior or subsequent ECGs after admission to know if the LBBB was new or not and whether the LBBB was transient • No assessments of clinical eligibility for each therapeutic option. Therefore, hard to interpret differences in treatment rendered between those with and w/o LBBB **Conclusion:** • LBBB identifies a pt subset with a higher baseline CV risk profile and greater burden of preexisting CV diseases and comorbidities compared with pts with STE • Pts with LBBB are less likely to receive evidence-based antithrombotic therapy and invasive treatment strategy compared with STE pts LBBB is associated with a higher incidence of unadjusted in-hospital MACE, mortality, and cardiogenic shock rates but the same adjusted risk
Yeo KK, et al., 2012 (41) 22152973	**Study type:** Retrospective registry study utilizing the NCDR's ACTION registry-GTWG **Size:** • N=46,006 in registry with STEMI (STE or nLBBB)	**Inclusion criteria:** • Participants in the ACTION registry from January 2007 to March 2009 from 343 participating US hospitals, enrolling 117,781 pts with ACS presenting within 24 h of symptom onset **Exclusion criteria:**	**1° endpoint:** • Prevalence of presumed nLBBB in the setting of AMI • Compare characteristics and treatments of those with AMI and either nLBBB or persistent STE • Compare the risk for adverse in-hospital CV outcomes in the 2 groups **Results:**	**Strengths:** • Large prospective registry of unselected pts with suspected acute MI and LBBB • Standardized definitions and data collection methods **Limitations:** • No core laboratory for ECG analysis • No systematic algorithm to differentiate isolated LBBB from LBBB associated with transmural Ischemia (e.g. Sgarbossa criteria)

	• N=44,405 (96.5%) had STE w/o LBBB N=1,601 (3.5%) AMI with nLBBB	• NSTEMI (N=71,536) • Missing ECG data or isolated posterior MI (N=160) • Subsequent admissions in those with multiple admissions (only the index admission was used; N=79)	• Median age: STE=60 [interquartile range 51.0, 71.0], nLBBB=74.0 [63.0, 82.0]; p<0.0001 • Those with nLBBB at the time of acute MI were more likely to be female, non-smoker, have h/o DM, HTN, hyperlipidemia, prior MI, CABG, HF, CVA, PAD, or CKD, have higher heart rate, or present with signs of CHF (p<0.001 for all) • Also those with nLBBB were more likely to have prior PCI (p=0.0013), or cardiogenic shock at presentation (p=0.0052) • Those with nLBBB were less aggressively treated with antiplatelet therapy, beta blocker, and statin medications and were less likely to receive reperfusion therapy, including primary PCI (p<0.0001 for all) • Time to primary PCI was delayed on average 33 min for those with nLBBB relative to those with STEMI (p<0.0001) • More pts in the STEMI group had LVEF ≥50% compared to the nLBBB group (47.9% vs. 27.2%) and fewer pts with LVEF <25% (4.8% vs. 17.4%; p<0.0001) • Median peak troponin and creatine kinase-MB levels were higher in pts with STEMI compared to those with nLBBB (131.9 vs. 32.3; p<0.0001, and 21.8 vs. 6.0; p<0.0001, respectively) • **Unadjusted all-cause in-hospital mortality:** nLBBB compared to STEMI (13.3% vs. 5.6%; p<0.0001)	• Insufficient angiographic data to distinguish AMI with LBBB vs. other causes of biomarker elevation in the setting of LBBB • No data on pre-existing LBBB prior to incident AMI **Conclusion:** • LBBB identifies a pt subset with a higher baseline CV risk profile and greater burden of preexisting CV diseases and comorbidities compared with pts with STE • Pts with LBBB are less likely to receive evidence-based antithrombotic therapy and invasive treatment strategy compared with STE pts LBBB is associated with a higher incidence of unadjusted in-hospital mortality but the same adjusted risk

			Multivariate analysis: nLBBB no longer an independent predictor of in-hospital mortality, (OR: 0.91; 95% CI: 0.75–1.12; p=0.38)	
Framingham Dhingra R, et al. 2005 (42) 15734611	**Study type:** Prospective, cross-sectional, community-based study **Size:** N=4,534 (2,583 women)	**Inclusion criteria:** Attendees of the 16th or 17th biennial exam of the Framingham Heart Study or the 2nd exam of the Framingham Offspring Study with available ECG and echo data (2-D guided M-mode) **Exclusion criteria:** • Prevalent HF (N=51) • Previous MI (N=146) • Digoxin or quinidine use (N=206) PPM (N=3)	**1° endpoint:** Gender-specific linear regression models to assess the relationship of QRSd to echo parameters of LV size, mass and fractional shortening and left atrial size at end-systole. **Results:** • In linear regression models, LV mass, end-diastolic dimension, and septal and posterior wall thickness were positively related to log-QRSd (p<0.001) • Fractional shortening was inversely related to log-QRSd (p<0.001) • LBBB (N=32) was associated with higher LV mass and lower fractional shortening compared to a normal QRSd (p<0.001) • RBBB (N=92) was not associated with significant differences in LV mass, dimensions, wall thickness or fractional shortening in men, but was associated with higher LV mass (p=0.02) and greater septal (p=0.01) and posterior (p=0.001) wall thickness in women. A stronger association of LV mass with QRSd was seen in obese men, older women, and in hypertensive women	**Strengths**: • Large community-based population • Long duration of follow-up • Prospective, systematic data acquisition • Both sexes well represented **Limitations:** • Limited statistical power to analyze relations of BBB type to LV measurements • Use of M-mode for EF estimation (reflects only basal function of 2 segments) • Single assessment of QRSd • Predominantly Caucasian population **Conclusion:** There is a positive association between ECG QRSd, as well as LBBB pattern, and LV mass, dimensions and wall thickness, and an inverse relation to systolic function in a large, community-based cohort free of MI and HF.
Talreja D, et al. 2000 (43) 10689252	**Study type:** Prospective case-control study **Size:** N= 300	**Inclusion criteria:** Consecutive inpatients referred for echocardiographic assessment of LV systolic	**1° endpoint:** Predictive value of historical features, symptoms, physical findings, chest radiography and/or ECG findings to predict LVEF <45%	**Strengths:** • Systematic assessment of clinical features including ECG features that might predict LVSD in those referred for echocardiography

		function of which 124 (41%) had LVEF <45%. **Exclusion criteria:** No ECG within 1 wk prior to echo (N=30)	**Results:** • LBBB was the most predictive ECG finding to suggest LVSD; p<0.0001 • Multivariate predictors of LVSD: Radiographic cardiomegaly. OR: 3.8 (95% CI: 1.6–4.6; p<0.01) LBBB. OR: 3.7 (3.6–67.2; p<0.01) Male sex. OR: 3.45 (1.4–4.9; p<0.01) Normal ECG: OR: 0.30 (0.02—0.45, p<0.004)	**Limitations:** • Small sample size with wide confidence margins **Conclusion:** The presence of LBBB is an independent predictor of echocardiographically-determined LVSD in inpatients for whom LVSD is a clinical concern
Mendu ML, et al. 2009 (44) 19636031	**Study type:** Retrospective observational **Size:** N=2106 consecutive admissions for 1920 individuals ≥65 y admitted following syncope from 7/2002 to 12/2006	**Inclusion criteria:** ≥65 y admitted following syncope **Exclusion criteria:** Documented pre-syncope, 103 cases omitted for complete lack of data	**1° endpoint:** Diagnostic yield of a broad spectrum of clinical assessments **Results:** • 163 (8.5%) had more than 1 admission • 32% known CAD, 18% h/o AF, 9% h/o MI, 5% h/o AVB • 980 (47%) etiology unknown, 453 (22%) vasovagal, 282 (13%) orthostatic hypo. • 821 (39%) had echocardiogram, abnormal in 516 (63%), "affected Dx" in 35 (4%), "helped determine etiology" in 13 (2%)- most frequently aortic stenosis, affected management in 36 (4%) • Yield in defining etiology for echocardiogram similar to ECG (3%), ETT (2%), Head MRI (2%), Carotid US (2%) but less than telemetry (5%) and orthostatic VS (15%). • Of 11 tests analyzed, echo yielded the 4th lowest cost per test affecting Dx ($6,272/ influential test) after postural BP, telemetry and ECG Diagnostic impact of echo was greater and cost per test affecting Dx were lower	**Strengths** Sample size, standardized abstraction, consistent definitions, blinded re-abstraction (mean bias-adjusted κ statistic = 87% (SD 20%) for the diagnostic test variables), inclusion of effect on management not just Dx yield **Limitations**: Reliance on administrative database to identify cases, reliance on chart documentation to assess impact of tests on clinical management (? underestimated effect of negative tests), using charges adjusted by cost-charge ratio rather than actual costs. Test ordering was not protocol driven and at the discretion of the clinicians, likely affecting the yield of the tests (echocardiogram likely ordered more indiscriminately than some others). **Conclusion**: Echocardiogram was a frequent part of syncope evaluation in elderly hospitalized pts (39%) at an academic

			in those who met SFSR criteria for increased risk	medical center and only occasionally provided information that affected management (4% of those studied) or established an etiology of syncope (2%). Compared to the litany of diagnostic tests used in this population, however, it was relatively cost-effective.
Recchia D, et al. 1995 (45) 8770716	**Study type:** Retrospective observational **Size:** N=128	**Inclusion criteria:** All pts admitted to a university teaching hospital due to syncope over a 7 mo period **Exclusion criteria:** Syncope of known cause, presyncope, obvious seizure, referred for EPS	**1° endpoint:** Dx yield of echo beyond that provided by Hx, physical, and ECG **Results:** • 48/128 (37.5%) had a cause of syncope identified. Of these 37/48 (77%) were diagnosed by Hx, physical and ECG. • 82/128 (64%) underwent echo • Echo normal in 52% of total population and 63% of those with no clinical evidence of heart disease (46% of population had no clinical evidence of heart disease) • Echo confirmatory in 48% of those with suspected heart disease and refuted it in 52% • Echo provided no etiology of syncope that was unsuspected on clinical grounds	• **Limitations**: Small sample size, test ordering at the discretion of the clinicians, did not address the impact of echo on management in those with clinically suspected heart disease in whom it was confirmatory half the time
Sarasin FP, et al. 2002 (46) 12231593	**Study type:** Prospective observational with 18 mo-follow-up **Size:** N=650 consecutive pts presenting to the ED of a university teaching	**Inclusion criteria:** Syncope with clinical suspicion of cardiac valve disease or unexplained syncope after Hx, physical and ECG **Exclusion criteria:** Those presenting with syncope	**1° endpoint:** Diagnostic yield of echo, either confirming a suspected Dx or revealing an unexpected one **Results:** • 61/650 (9%) had a systolic murmur and severe AS was suspected in 20 (3% of total). Echo confirmed severe AS in 8 (40%). In 18 months of follow-	Conclusions • Echo is most useful to assess the severity of suspected underlying cardiac disease and for risk stratification in those whose syncope is unexplained but have a Hx of heart disease or an abnormal ECG. • Echo is unlikely to yield a clinically unexpected etiology of syncope in

	hospital who underwent a standardized initial clinical evaluation, and for those with syncope of undetermined etiology thereafter, a stepwise testing algorithm that started with echocardiography.	who did not complete the standardized evaluation (105) or refused to participate (33)	up no further cases of severe AS emerged • 155/650 (24%) had unexplained syncope and echo revealed no abnormalities that established a cause in them (this group was older with more comorbidities than those with an established cause of syncope) • 71/155 (46%) had "abnormal but not-relevant" echo findings that include clinically relevant findings such as severe MR, moderate PH, moderate MS, LVH • In those with a normal ECG (N=67), echo was normal or "non-relevant" in all • In those with a cardiac Hx or abnormal ECG (88/650=13.5%), echo revealed EF ≤40% in 24/88 (27%) and minor non-relevant findings in the rest • Arrhythmias were diagnosed in 12/24 (50%) of those with Hx of heart disease or abnormal ECG and low EF on echo and 12/64 (19%) of those with EF >40% on echo (P<0.01)	those w/o evidence of cardiac disease on initial evaluation • Comment: Echo has greater relevance than these conclusions suggest due to the possibility that the clinically relevant but not definitively diagnostic abnormalities (other than low EF) will influence management
Dagres N, et al. 2013 (47) 24280765	**Study type:** Descriptive survey of member institutions of the EHRA EP research network **Size:** 43 centers from 17 countries from Europe (and Argentina)	**Inclusion criteria:** EHRA members who responded to the survey **Exclusion criteria:** N/A	**1° endpoint:** Define current practice habits regarding the work-up and management of pts with syncope **Results:** • ECG used "always or almost always" by 98% of respondents ("in most case" =2%) • Echo used "always or almost always' by 66% ("in most cases" =27%, "only if specific indication" =7%)	• Offers little regarding appropriate use of tests but does define current practice suggesting stubborn reliance on echo in contemporary practice despite data to suggest relatively low yield in unselected pts • 42% of respondents used formal diagnostic algorithms and only 26% had a dedicated syncope unit • Compared to other tests, there was relative uniformity of utilization of echo, second only to ECG

			• Holter used "always or almost always" by 59% • All other tests queried <50% "always or almost always"	
Badheka AO, et al. 2013 (48) 23726176	**Study type:** Retrospective cohort study on prospectively collected data from NHANES III **Size:** 8,527 of 8,561 individuals >40 y who underwent resting 12-lead ECG as part of NHANES III.	**Inclusion criteria:** NHANES III enrollee with available ECG data **Exclusion criteria:** Missing QRS data (N=30) Missing mortality data (N=4)	**1° endpoint:** Describe the relationship between QRSd on routine ECG and CV mortality **Results:** • Mean age was 60.5±13.6 y • "White" race: 87% • Female: 53% • Follow-up: 106,244.6 person-y • HR for risk adjusted CV mortality of highest quartile of QRSd: 1.3; 95% CI: 1.01–1.7; p=0.04 • LBBB HR: 2.4; 95% CI: 1.3–4.7; p=0.009) • RBBB HR: 1.9; 95% CI: 1.2–3.0; p=0.008) • Adding QRSd in 10-ms increments to Framingham Risk Score yielded 4.4% overall net reclassification improvement (95% CI: 0.02–0.04; p=0.00006)	**Strengths:** • Large representative cross section of US population (part of a cohort of 72,062,796 in NHANES III). • Prospectively acquired data **Limitations:** • Retrospective and observational analysis • Single ECG at baseline interpreted by software • Diagnoses based on death certificate w/o chart review • No data on SCD **Conclusions:** Increased QRSd in general and LBBB and RBBB specifically are all associated with increased risk of risk-adjusted CV death.
Chiu DT, et al. 2014 (49) 24698512	**Study type:** Secondary analysis of a prospective, observational, cohort study **Size:** 570 consecutive ED pts aged ≥18 y presenting with syncope between 9/2003 and 6/2006	**Inclusion criteria:** Presented to a single, large urban teaching hospital emergency department with syncope **Exclusion criteria:** Near syncope Persistent altered mental status Syncope due to alcohol or illicit drugs	**1° endpoint:** Diagnostic yield of tests performed in ED, during hospitalization, or during 30 d of follow-up. Tests chosen at clinician discretion. Positive tests identified a serious condition deemed responsible for the index syncopal event **Results:** • Mean age was 57.2 ± 24.5 y • Female: 64% • Admitted to hospital: 60.2%	**Strengths:** • Busy ED with 55,000 annual visits • Prospectively acquired data • 99% follow-up • Assessed current clinical practice (tests ordered according to clinical suspicion) **Limitations:** • Observational • Testing not ordered systematically (not all pts had all tests)

		Seizure Coma due to hypoglycemia or head trauma Lost to follow-up (n=5)	• 330 (58%) underwent in-hospital telemetry, 317 (55%) serum troponin, 150 (26%) echocardiography, 56 (10%) ambulatory monitoring • Overall yield of all tests analyzed: 73 pts (8%; 95% CI: 7–10%) Diagnostic yield: Echo – 22% (5.8% overall yield for the entire syncope population – κ=0.78); Telemetry – 5.8% (overall yield 3.3% – κ=0.66); Ambulatory Monitoring – 3.6% (overall yield 0.4% – κ=0.5); Serum troponin – 3% (overall yield 3.3% – κ=1)	• Single center • Small sample size • Short-term follow-up • Limited range of commonly employed testing studied (i.e., no head CT, routine blood tests, CXR, EEG, etc.) **Conclusions:** Although routine testing is prevalent in ED pts with syncope, the diagnostic yield is relatively low. Nevertheless, some testing, particularly echocardiography, may yield critical findings.
Menozzi C, et al. 1998 (50) 9832095	**Study type:** Prospective observational study of the placebo arm of an RCT of oral theophylline and permanent pacing in pts with symptomatic SND (THEOPACE trial) **Size:** 162 screened 55 excluded (12 for "severe" SSS) N=107 randomized to 3 treatment arms 35 randomized to no treatment	**Inclusion criteria:** Symptomatic SND, age ≥45 **Exclusion criteria:** • Severe SSS (heart rate <30 bpm or sinus pauses >3 s) • Refractory HF • Recent MI or CVA (<3 mo) • "Very severe general diseases" • "Significant renal or hepatic disease" • H/O sustained VT • Secondary bradycardia (e.g., hypothyroidism/drugs) • Need for BB or CCB • Other causes of syncope besides SND • Pt refusal Unable to follow up	**1° endpoint:** 1st episode of syncope, CHF requiring hospitalization, persistent AF, "poorly tolerated" sustained paroxysmal tachyarrhythmia requiring treatment, thromboembolic event **Results:** • Mean age was 71 ± 11 y • Female: 49% • "Organic" heart disease: 63% • H/O Syncope: 57% • Mean ambulatory heart rate: 51 ± 8 bpm • Follow-up: 17 ± 15 months • 20 (57%) experienced CV events requiring treatment [8 (23%) syncope, 6 (17%) CHF, 4 (11%) AF, 2 (6%) paroxysmal tachyarrhythmia] • Actuarial rates at 1, 2, and 4 y for any CV event: 35%, 49%, and 63% respectively • Actuarial rates at 1, 2, and 4 y for syncope: 16%, 31%, and 31% respectively	**Strengths:** • Prospective • Up to 4-y follow-up **Limitations:** • Small sample size **Conclusions:** Clinical CV events occur in most untreated SSS pts during long-term follow-up. The outcome can be "partly predicted" on initial evaluation. Along with age ≥65, echocardiographic parameters of LV size and EF help identify those at risk for CV events (but not necessarily syncope per se). A prior Hx of syncope and a corrected SNRT ≥800 ms identifies those at increased risk of syncope during follow-up.

			• Predictors of any CV event by multivariate analysis: age ≥65 y (HR: 7.80 [95% CI:1.97–30.9]; p=0.001), LVEDD ≥52 by **echo** (HR: 2.89 [1.07 to 7.81]; p=0.04), EF <55% by **echo** (HR: 3.68 [1.28 to 10.52]; p=0.01) Predictors of syncope by multivariate analysis: corrected sinus node recovery time ≥800 ms (HR: 7.80 [0.94–65]; p=0.02), h/o syncope (HR: 5.96 [0.71–49.7]; p=0.05)	

Data Supplement 4. Nonrandomized Trials, Observational Studies, and/or Registries of Ambulatory Electrocardiography in Bradycardia or Conduction Disorders (Section 4.2.4)

Study Acronym; Author; Year Published' PMID	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Mendu ML, et al. 2009 (44) 19636031	**Study type:** Retrospective observational **Size:** N=2106 consecutive admissions for 1920 individuals ≥65 y admitted following syncope from 7/2002 to 12/2006	**Inclusion criteria:** ≥65 y. admitted following syncope **Exclusion criteria:** Documented pre-syncope, 103 cases omitted for complete lack of data	**1° endpoint:** Diagnostic yield of a broad spectrum of clinical assessments **Results:** • 163 (8.5%) had >1 admission • 32% known CAD, 18% h/o AF, 9% h/o MI, 5% h/o AVB • 980 (47%) etiology unknown, 453 (22%) vasovagal, 282 (13%) orthostatic hypotension. • 821 (39%) had echo, abnormal in 516 (63%), "affected Dx" in 35 (4%), "helped determine etiology" in 13 (2%)- most frequently AS, affected management in 36 (4%) • Yield in defining etiology for echo similar to ECG (3%), ETT (2%), Head MRI (2%), Carotid US (2%) but less than telemetry (5%) and orthostatic VS (15%). • Of 11 tests analyzed, echo yielded the 4th lowest cost per test affecting Dx ($6,272/ influential test) after postural BP, telemetry and ECG • Diagnostic impact of echo was greater ad cost per test affecting Dx were lower in those who met SFSR criteria for increased risk	• 87% (SD 20%) for the diagnostic test variables), inclusion of effect on management not just Dx yield • **Limitations**: Reliance on administrative database to identify cases, reliance on chart documentation to assess impact of tests on clinical management (? underestimated effect of negative tests), using charges adjusted by cost-charge ratio rather than actual costs. Test ordering was not protocol driven and at the discretion of the clinicians, likely affecting the yield of the tests (echo likely ordered more indiscriminately than some others). • **Conclusion**: Echo was a frequent part of syncope evaluation in elderly hospitalized pts (39%) at an academic medical center and only occasionally provided information that affected management (4% of those studied) or established an etiology of syncope (2%). Compared to the litany of diagnostic tests used in this population, however, it was relatively cost-effective.
Recchia D, et al.1995 (45) 8770716	**Study type:** Retrospective observational	**Inclusion criteria:** All pts admitted to a university teaching hospital due to	**1° endpoint:** Dx yield of echo beyond that provided by Hx, physical, and ECG	• ●Limitations: Small sample size, test ordering at the discretion of the clinicians, did not address the

	Size: N=128	syncope over a 7 mo period **Exclusion criteria:** Syncope of known cause, presyncope, obvious seizure, referred for EPS	**Results:** • 48/128 (37.5%) had a cause of syncope identified. Of these 37/48 (77%) were diagnosed by Hx, physical and ECG. • 82/128 (64%) underwent echo • Echo normal in 52% of total population and 63% of those with no clinical evidence of heart disease (46% of population had no clinical evidence of heart disease) • Echo confirmatory in 48% of those with suspected heart diseases and refuted it in 52% • Echo provided no etiology of syncope that was unsuspected on clinical grounds	impact of echo on management in those with clinically suspected heart disease in whom it was confirmatory half the time
Sarasin FP, et al. 2002 (46) 12231593	**Study type:** Prospective observational with 18-mo follow-up **Size:** N=650 consecutive pts presenting to the ED of a university teaching hospital, who underwent a standardized initial clinical evaluation, and for those with syncope of undetermined etiology thereafter, a stepwise testing algorithm that started with echocardiography.	**Inclusion criteria:** Syncope with clinical suspicion of cardiac valve disease or unexplained syncope after Hx, physical and ECG **Exclusion criteria:** Those presenting with syncope who did not complete the standardized evaluation (105) or refused to participate (33)	**1° endpoint:** Diagnostic yield of echo, either confirming a suspected Dx or revealing an unexpected one **Results:** • 61/650 (9%) had a systolic murmur and severe AS was suspected in 20 (3% of total). Echo confirmed severe AS in 8 (40%). In 18 mo of follow-up no further cases of severe AS emerged • 155/650 (24%) had unexplained syncope and echo revealed no abnormalities that established a cause in them (this group was older with more comorbidities than those with an established cause of syncope) • 71/155 (46%) had "abnormal but not-relevant" echo findings that include clinically relevant findings such as severe MR, moderate PH, moderate MS, LVH	**Conclusions** • Echo is most useful to assess the severity of suspected underlying cardiac disease and for risk stratification in those whose syncope is unexplained but have a Hx of heart disease or an abnormal ECG. • Echo is unlikely to yield a clinically unexpected etiology of syncope in those w/o evidence of cardiac disease on initial evaluation • **Comment**: Echo has greater relevance than these conclusions suggest due to the possibility that the clinically relevant but not definitively diagnostic abnormalities (other than low EF) will influence management

			• In those with a normal ECG (N=67), echo was normal or "non-relevant" in all • In those with a cardiac Hx or abnormal ECG (88/650 =13.5%), echo revealed EF ≤40% in 24/88 (27%) and minor non-relevant findings in the rest • Arrhythmias were diagnosed in 12/24 (50%) of those with Hx of heart disease or abnormal ECG and low EF on echo and 12/64 (19%) of those with EF >40% on echo (p<0.01)	
Dagres N, et al. 2013 (47) 24280765	**Study type:** Descriptive survey of member institutions of the EHRA EP research network **Size:** 43 centers from 17 countries from Europe (and Argentina)	**Inclusion criteria:** EHRA members who responded to the survey **Exclusion criteria:** N/A	**1° endpoint:** Define current practice habits regarding the work-up and management of pts with syncope **Results:** • ECG used "always or almost always" by 98% of respondents ("in most case" =2%) • Echo used "always or almost always' by 66% ("in most cases" =27%, "only if specific indication" =7%) • Holter used "always or almost always" by 59% • All other tests queried <50% "always or almost always"	• Offers little regarding appropriate use of tests but does define current practice suggesting stubborn reliance on echo in contemporary practice despite data to suggest relatively low yield in unselected pts • 42% of respondents used formal diagnostic algorithms and only 26% had a dedicated syncope unit • Compared to other tests, there was relative uniformity of utilization of echo, second only to ECG

Data Supplement 5. Nonrandomized Trials, Observational Studies, and/or Registries of Nocturnal / Sleeping Bradyarrhythmias and Sleep Apnea (Section-4.2.7)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
NORMALS				
Brodsky M, et al. 1977 (51) 65912	**Study type:** Prospective observational – 24h Holter	**Inclusion criteria:** Healthy, Caucasian, male medical students, age 23–27 y with	**1° endpoint:** Define rates of arrhythmia on 24 h Holter in normal young Caucasian men	• Sinus bradycardia <40 bpm is common in healthy young men (none trained athletes),

	Size: 50	normal exam, ECG, cardiac silhouette on CXR, and echo **Exclusion criteria:** Of 61 volunteers, 9 excluded and 2 did not complete study. Excluded: 2 with DM,1 each with ASH on echo, MVP, WPW, h/o pericarditis, IVCD, MVP and HTN, QRS axis of -100°	**Results:** • 50% marked sinus arrhythmia • 24% SB <40 bpm at least once/night • 28% >1.75 s pause • 4% pause >2 s • 8% 1° AVB (1/2 exclusively nocturnal. 1/2 both d and night) • 6% type 1 2nd degree AVB-virtually all nocturnal	• Pauses >2 s and type 1 second-degree AVB are uncommon (4%–6%) • No specific screening for OSA and no information regarding obesity.
Bjerregaard P, 1983 (52) 7160388	**Study type:** Prospective observational – 24 h Holter **Size:** 260	**Inclusion criteria:** Healthy middle age and older volunteers (40–79 y). 65% male. Mean age: male =53 y; female =56 y **Exclusion criteria:** • technically inadequate tracings (N=9) • HTN (N=17) • Abnormal 12-lead ECG x 2 min except for arrhythmias (N=9) • CV Sx (N=7) • Illness within 3 mo (N=3) • Abnormal CV physical exam (N=5) • CM or pul. venous congestion on CXR (N=0)	**1° endpoint:** Establish norms for mean 24 h heart rate, minimal HR, and pauses **Results:** • Mean heart rate =74±18 bpm (range 53–95) • Mean min heart rate =56±16 bpm (range 36–78) • 30% had pause ≥1.5 s • <1% had pause >2 s (longest =2.24 s) • 60% of those with pauses had longest pause at night • 4.6% sinus arrest • 3.5% blocked PACs • 0.8% Wenckebach (both nocturnal) • 1.1% marked SB (heart rate <40 bpm) • Males, non-smokers, and physically active had lower mean and minimal HR by ANOVA (no p value reported). Age differences NS.	• Nocturnal pauses >2 s, marked sinus brady, and type 1 2nd degree AVB are rare in a middle aged, healthy population (1% or less) • Sinus arrest is more common but still uncommon in this population (~ 5%) • No information on obesity or screening for OSA
Clarke JM, et al. 1976 (53) 74472	**Study type:** Prospective observational, 2 separate 24 h Holter	**Inclusion criteria:** Healthy volunteers (16–65 y) with normal clinical exam, ECG, and biochemical/hematologic screening	**1° endpoint:** Describe the distribution and frequency of arrhythmias in 2 separate 24 h Holter monitors in healthy subjects (41 male, 45 female) **Results:**	• In healthy adolescents and adults, 2nd degree AVB is rare and exclusively nocturnal (2.5%) • Heart rate drops ~20 bpm during sleep relative to

	Size: 86/101 G.D. Searle & Co. employee volunteers, mostly office workers	**Exclusion criteria:** HTN (6), BBB (2), heart murmur (1), epilepsy (1), sedative use (3), anemia (1), anxiety (1)	• 2/81 (2.5%) had nocturnal 2nd degree AVB: 1 had both type 1 and type 2 2nd degree AVB, the other had type 1 2nd degree AVB only • 1 subject had 1st degree AVB • 8 (10%) subjects had junctional rhythm both awake and asleep.	wakefulness in both men and women • Average daily heart rate is higher in women than men ($p<0.05$) and in smokers vs. non-smokers ($p<0.001$) • No information on obesity or screening for OSA
Fleg JL, et al. 1982 (54) 7056104	**Study type:** Prospective observational – 24 h Holter **Size:** 98/110 healthy active subjects, ages 60–85 y (69 men). 59/98 (60%) in 60s, 32/98 (33%) in 70s and 7/98 (7%) in 80s.	**Inclusion criteria:** • Participants in the Baltimore Longitudinal Study on Aging • >60 y • No CV Hx or sx • No systemic illness • NL exam • BP <160/95 • NL CXR • No MI, atrial abnormality, LVH, RVH or BBB on ECG • NL PFT • NL ETT • No meds affecting heart rate/rhythm **Exclusion criteria:** • 8/38 had abnormal thallium • 1/38 had abnormal echo • 3 technically unsatisfactory Holter	**1° endpoint:** Describe frequency and distribution of arrhythmias in healthy elderly adults **Results:** • Marked SB (heart rate <40 bpm): 2/98 (2%) • Sinus pause >1.5 s: 2/98 (2%). No pause >2 s • 2nd degree AVB: 1/98 (1%) • All bradyarrhythmias occurred during sleep	**Conclusions** • Healthy, active elderly individuals screened for significant cardiac and pulmonary disease manifest rare nocturnal bradyarrhythmias (1–2%)
ATHLETES				
Meytes I, et al. 1975 (55) 1163436	**Study type:** Prospective observational – awake 12-lead ECG **Size:** 126	**Inclusion criteria:** Athletes from Israeli national teams **Exclusion criteria:** N/A	**1° endpoint:** Frequency of conduction disturbances on awake 12-lead ECG after 15 min. of resting recumbency **Results:** • 11/126 (8.7%) 1st degree AVB (P-R ≥0.21 s)	• Wakeful type I 2nd degree AVB is rare in athletes and is presumed to be physiological • Authors point out it is, nonetheless, "much more frequent than hitherto suspected."

			• 3/126 (2.4%) type I 2nd degree AVB (abolished by sitting, standing, and atropine) • Followed the 3 athletes with Wenckebach for 6 y – Wenckebach present only during intense training and resolved consistently within a few weeks of reducing intensity of training • No heart disease or decline in performance developed over 6 y	• By comparison: 1/67,375 asx healthy male USAF fliers manifested type I 2nd degree AVB on awake routine ECG
Viitasalo MT, et al. 1982 (56) 7059398	**Study type:** Prospective observational – Nocturnal Holter **Size:** 35 Finnish male "top-class" nationally competitive endurance athletes (mean age 23.1±6.1 y) and 35 controls (age 23.0±5.8 y) who were med students and army conscripts who were not engaged in regular intensive physical training, normal ECG and CXR	**Inclusion criteria:** • ≥5 y of intensive physical training • Normal clinical exam • No "changes" in resting 12-lead ECG **Exclusion criteria:** • H/O CV disease or other disease known to affect the CV system • CXR findings other than those associated with athletic heart • "Permanently" under medication • Taking meds at the time of the study • Smoker • URI within 1 mo of the study	**1° endpoint:** Describe the range of arrhythmias including conduction disturbances on nocturnal 2-channel ambulatory ECG monitor (4pm–8am). No training or alcohol consumption during study **Results:** • Slowest heart rate =37.7±4.3 bpm (range 24–48) in athletes and 45.4±6.3 bpm (range 33–63) in controls (p<0.001) • 13/35 (37.1%) of athletes and 2/35 (5.7%) of controls had sinus pause >2 s (all from 10pm–6am). Longest pause =2.76 and 2.6 s respectively • 1st degree AVB (PR >0.22): 13/35 (37.1%) of athletes and 5/35 (14.3%) of controls (p<0.05) – 6 exclusively during sleep, 4 asleep and awake, 3 exclusively awake in athletes. All controls had 1st degree AVB exclusively during sleep • Type 1 2nd degree AVB: 8/35 (22.9%) of athletes and 2/35 (5.7%) of controls (p<0.05) – 5 exclusively while asleep, 2 awake and asleep, and exclusively while awake in 1. All controls had type 1 2nd degree AVB exclusively during sleep	• Heart rate slows substantially (>20 bpm) while asleep in athletes and non-athletes alike • Nocturnal sinus pauses >2 s are common in young male athletes (present in >1/3) and infrequent in untrained healthy young men (<6%) • 1st degree AVB at any time is common in young male athletes (present in >1/3) and occasional in untrained young men (present in ~15%) • AVN Wenckebach and SB with junctional or idioventricular escape rhythm are both fairly common in young male athletes (≥20%) and occur primarily while asleep. • AVN Wenckebach is infrequent in untrained young men (<6%) and occurs exclusively while asleep • SB with junctional or idioventricular escape rhythm and type 2 second-degree AVB are exceedingly rare in untrained healthy young men

			• Type 2 2nd degree AVB: 3/35 (8.6%) of athletes but no controls – 1 while awake and asleep, 1 only while awake, 1 only while asleep • SB with competing junctional or idioventricular rhythm in 7/35 (20%) of athletes but no controls – 3 exclusively while asleep, 3 while awake and asleep, and 1 exclusively while awake	while awake or asleep (neither demonstrated in this study).
Northcote RJ, et al. 1989 (57) 2923752	**Study type:** Prospective observational – 48 h Holter **Size:** 20 male Scottish veteran runners and 20 age-matched sedentary male controls	**Inclusion criteria:** • Age >45 y (mean =56±7) • >25 y regular running • >25 miles/wk **Exclusion criteria:** • Smoking • Medications • Hx CV disease.	**1° endpoint:** Describe distribution of ECG abnormalities and arrhythmias in middle-aged male athletes detected with resting, exercise, and 48 H ambulatory ECG **Results:** • Heart rate <35 bpm Athletes: 8/20 (40%) Controls: 1/20 (5%) • Mean nocturnal heart rate Athletes: 51±8.5 bpm Controls: 66±13.2 bpm • Sinus pauses (1.8–15 s) Athletes: 8/20 (40%) - >80% nocturnal Controls: 2/20 (10%) • 1st Degree AVB (PR >220 ms) Athletes: 6/20 (30%) Controls: 0/20 (0%) • Type 2 2nd Degree AVB Athletes: 4/20 (20%) Controls: 0/20 (0%) • CHB Athletes: 3/20 (15%) Controls: 0/20 (0%)	• In this older cohort of distance runners, bradycardia and AVB was more common than in previously studied younger cohorts of athletes • Bradycardia and AVB are more frequent in distance runners than in healthy, active age-matched controls and predominantly nocturnal in both groups
SLEEP APNEA				
Tilkian AG, et al. 1977 (58) 331948	**Study type:** Prospective observational	**Inclusion criteria:** OSA identified on PSG. All male. Mean age =44 y (30–60). Mean time in apnea	**1° endpoint:** Describe the distribution and frequency of arrhythmias while awake and asleep in pts with OSA and evaluate the	Conclusions • In pts with fairly profound OSA, bradycardia and conduction

	Size: 15 pts with OSA who underwent extensive monitoring: • 2 separate 24 h Holters and simultaneous PSG in all • 12/15 participated in overnight invasive hemodynamic monitoring • 6 underwent a third 24 h Holter to assess the effect of atropine • 6 underwent awake EPS • 8 underwent repeat Holter after tracheostomy • 4 underwent ECG monitoring while the tracheostomy was temporarily plugged during sleep.	=51% (35–72%). Mean duration =24 s (11–40 s) **Exclusion criteria:** N/A	influence of atropine and tracheostomy on those arrhythmias **Results:** • 14/15 (93.3%) marked sinus arr. (>30 bpm swing) • 6/15 (40%) marked SB (heart rate <30 bpm), all nocturnal • 5/15 (33%) "Asystole" (pauses of 2.5–6.3 s), all nocturnal • 2/15 (13.3%) 2nd degree AVB, all nocturnal • 2/15 (13.3%) VT, all nocturnal • Tracheostomy eliminated arrhythmias which recurred when transiently re-plugged • Atropine (1.2–2.4 mg) blunted degree of sinus arrhythmia but did not eliminate. It prevented marked SB in 3 of 6, 2nd degree AVB in 1 of 2, and pauses in 3 of 5. • 5 with wakeful EPS had normal SNRT, A-H and H-V intervals. Of these 2 had marked SB, 2 had prolonged pauses (3–6 s), and 1 had AVN Wenckebach	disturbances are common and can be profound • Tracheostomy can eliminate the nocturnal arrhythmias associated with OSA • The nocturnal bradycardia and conduction disturbances associated with OSA are at least partially vagally mediated based on partial suppression with atropine Confounders • No AHI reported • Highly selected population • Particularly unnatural sleeping environment • No normal comparator group
Guilleminault C, et al. 1983 (59) 6193700	**Study type:** Retrospective observational – 24 h Holter **Size:** 400 pts with SAS who underwent 24 h Holter and simultaneous PSG. 384 men, median	**Inclusion criteria:** AHI >5 (range 25–92) and had simultaneous Holter and PSG **Exclusion criteria:** No simultaneous testing or no SAS. 187 excluded of which 111 did have AHI >5	**1° endpoint:** Describe frequency and distribution of arrhythmias during sleep in pts with SAS **Results:** • 193/400 (48%) had nocturnal arrhythmias ▪ 98% of arrhythmias occurred during an obstructive event	**Conclusions** • In aggregate, nocturnal arrhythmias are common in pts with moderate to severe SAS and occur almost exclusively during obstructive events • There appears to be an O_2 sat threshold of 72% for nocturnal bradyarrhythmias in this cohort

	age =48 y (19–71 y). 16 women, median age 59 (25–68 y)		• Arrhythmias (except for PVCs) seen only with O_2 sat <72% (93% occurred with O_2 sat ≤65%). • 8/400 (2%) NSVT • 43/400 (10.8%) Sinus arrest (2.5–13 s). In 32/43 (74.4%) it lasted ≥4 s • 31/400 (7.8%) 2nd degree AVB (19 type 1 (5%) and 12 type 2 (3%) • 29/400 (7.2%) had profound SB (<30 bpm for ≥10 s) • 10/400 (2.5%) had PAF • 3/400 (1%) had AFL • 75 /400 (18.8%) >2 VPC/min during sleep • 50 with significant arrhythmias underwent trach: repeat monitoring 3–6 mo postop: no arrhythmias except VPCs in 4 (vs. 18 prior)	• Profound SB, sinus pauses ≥2.5 s, and 2nd degree AVB occur occasionally (~7–10% of pts) • Tracheostomy eliminates nocturnal bradyarrhythmias in pts with OSA **Confounders** • Highly selected population • No normal comparator group
Shepard JW Jr, et al. 1985 (60) 2411477	**Study type:** Prospective observational – nocturnal ECG only **Size**: 31	**Inclusion criteria:** Clinically referred males with OSA (apnea index 44±26/h and hypopnea index 1 ±24/h). Age 55±11 y (range 30–76) **Exclusion criteria:** N/A	**1° endpoint:** Determine the relationship between ventricular ectopy and the severity of oxyhemoglobin desaturation during sleep **Results:** • Profound SB (heart rate <30 bpm): 10% • Sinus pauses (2–13 s): 10% • 2nd degree AVB: 6%	Conclusions • Bradycardia and AVB occur occasionally during sleep in pts with moderate to severe OSA (6%–10%) Confounders • Primary data not reported in original study or in subsequent review article.
Hoffstein V, et al. 1994 (61) 7774322	**Study type:** Prospective observational – Nocturnal ECG only **Size:** 458 clinically referred for PSG (214 (46.7%) with SAS – AHI >10)	**Inclusion criteria:** Consecutive, unselected pts referred for PSG (primarily for snoring). Age 48±13 y. BMI 31±7 kg/m^2 **Exclusion criteria:** N/A	**1° endpoint:** Compare the frequency of sleep-related arrhythmias in those with and w/o SAS and examine separately the relationships between arrhythmias and the severity of apnea, hypoxemia, and snoring, **Results:** • 121 (26%) AHI 10–30, 41 (9%) AHI 30–50, 52 (11%) AHI >50) • Arrhythmia prevalence: SAS: 58%; No SAS: 42% (X^2 =16.7; p<0.0001); AHI ≥40:	**Conclusions** • AVB or junctional rhythm during sleep in adults with severe SAS is uncommon (<3%) but does not occur at all in pts referred for PSG w/o SAS • Arrhythmias in aggregate are more frequent in those with more profound SAS and in those with nocturnal hypoxemia

			70% (X^2 =9.2; p=0.002); mean O_2 sat <90%: 82%; mean O_2 sat >90%: 40% (X^2 =7.4; p=0.006) • Most frequent arrhythmias in all groups = ventricular or supraventricular tachyarrhythmias • 6/214 (2.8%) with SAS had some bradyarrhythmia (AVB, junctional) all associated with other arrhythmias and all with AHI >30. • 0/244 (0%) had AVB or junctional rhythm with AHI ≤10. • Significance for difference in prevalence of bradyarrhythmias among the groups not reported	**Confounders** • Too few bradycardic events to correlate with AHI or hypoxemia. • No data regarding profound bradycardia, sinus pauses, etc
Boudoulas H, et al. 1983 (62) 6580372	**Study type:** Prospective observational - Holter **Size:** 120 pts with sleep disordered breathing: • SAS =61 (46 males; mean age 49.6±12 y; 15 with HTN, 4 with MI) • Narcolepsy =35 • Idiopathic hypersomnolence =24	**Inclusion criteria:** Pts with sleep disordered breathing previously diagnosed by PSG admitted to a clinical research center for ≥3 d to undergo echo, 24 h Holter, and 24 h urinary catecholamines on 3 successive d **Exclusion criteria:** N/A	**1° endpoint:** Describe the incidence of primary cardiac abnormalities in pts with SDB **Results:** • 1st degree AVB: 2/61 (3.3%) of SAS • SN exit block: 2/61 (3.3%) of SAS • Neither evident in other groups • Malignant ventricular arrhythmias: 26% of SAS, 3% in narcolepsy, and 4% in idiopathic hypersomnolence • Urinary catecholamines similarly elevated in all 3 groups	**Conclusions** • First degree AVB and sinus node exit block occur occasionally in pts with SAS (~ 3%) • SDB of disparate types is associated with increased urinary catecholamines
SHHS Mehra R, et al. 2006 (63) 16424443	**Study type:** Prospective, cross-sectional, observational **Size:** 228 SAS (RDI ≥30)	**Inclusion criteria:** • Participant of original SHHS (N=6,441) who were alive, agreed to undergo repeat PSG 3–7 y after enrollment and who were not on CPAP (N=3,295) • Age ≥40 y	**1° endpoint:** Examine the association between SDB and cardiac arrhythmias **Results:** • Mean age 70.6±9.72 vs. 68.6±9.1 y (p=0.01)	• In this community-based cohort, there was no evidence of an increased prevalence of conduction disturbances in those with severe SDB and those w/o SDB

		• RDI ≥30 • Comparison group RDI <5 Matched for age, sex, race/ethnicity, and BMI (N=338) **Exclusion criteria:** BMI <18 or >40 kg/m^2	• 3.1% of SDB had PPM and 0.9% of non-SDB had PPM (p=0.05) • No difference in frequency of conduction delays (SDB vs. no SDB) • Sinus pause ≥3 s: 11 vs. 8.6%; p=0.34 • 1st degree AVB: 25 vs. 22.5%; p=0.49 • Type I 2nd degree AVB: 1.8 vs. 0.3%; p=0.07 • Type II 2nd degree AVB: 2.2 vs. 0.9%; p=0.20 • AF (OR: 4.02), NSVT (OR: 3.4), complex V ectopy (OR: 1.74) were more common in SDB than non SDB groups. • No dose response relationship noted between severity of SDB and V arrhythmia • SDB much more strongly associated with complex ectopy in younger members than older [OR:9.3 (2.8–30.6) at age 50 to 2.0 (1.3–3.1) at age 70 (p=0.002)]	• The prevalence of sinus pauses, and 2nd degree AVB was ~15% in the SDB group, however.
Miller WP, et al. 1982 (64) 7124758	**Study type:** Prospective observational - Holter **Size:** 23 SAS (AHI 12.5–62.5; 78% with AHI >43.75). Age 25–57 y, 87% male.	**Inclusion criteria:** SAS severe enough to warrant referral for tracheostomy **Exclusion criteria:** N/A	**1° endpoint:** Describe the frequency and distribution of arrhythmias during sleep in pts with SAS **Results:** • Marked sinus arrhythmia: 18/23 (78%) • Heart rate <30 bpm: 2/23 (8.7%) • Sinus pause >1.8 s: 2/23 (8.7%) • 1st degree AVB: 1/23 (4.3%) • Type 1 2nd degree AVB: 1/23 (4.3%) • Aggregate: 6/23 (26%) brady (non- sinus arrhythmia) while asleep vs. 1/23 (4.3%) while awake	**Conclusions** • Nocturnal marked sinus arrhythmia is common in pts with SAS (predominantly severe SAS) • Nocturnal profound bradycardia and sinus pauses occur occasionally in pts with SAS (~9%) • Nocturnal first degree and type I 2nd degree AVN occur infrequently in pts with SAS (<5% each) • Such bradyarrhythmias are far more common while asleep than awake in this cohort. **Comments**

				• Small sample size • No comparator • Highly selected
Flemons WW, et al. 1993 (65) 8368632	**Study type:** Prospective observational – nocturnal Holter **Size:** 173 /263 consecutive pts referred for PSG and underwent complete PSG and simultaneous Holter	**Inclusion criteria:** Completed PSG and Holter overnight. Compared 76 with SAS (AHI >10) vs. no SAS **Exclusion criteria:** • Previous assessment of or treatment for SAS (N=7) • Referred for a specific condition other than SAS (N=9) • Rx for severe psychiatric condition (N=8) • Major medical condition (N=21) • 9 technically inadequate (7 Holter and 2 PSG) • 14 no show • 3 Intercurrent illness • 1 declined to participate	**1° endpoint:** Describe the frequency and distribution of arrhythmias during sleep in pts with SAS **Results:** • Median AHI in SAS group =33 • Age of SAS group 48.5±11.3 • SAS: 87% male; mean BMI 32.9±6.1 • 26% of SAS had O_2 sat <80 more than 3% of the study time,11% has O_2 sat <70 more than 1 % of the study time, and 2.7% had O_2 sat <60 more than 1% of the study time • 2nd degree AVB: SAS =1.3% (95% CI: 0.4–6.9) vs. No SAS =4.1% (95% CI: 1.6–10.1). p=NS • Sinus arrest: SAS =5.2% (95% CI: 2.2–12.6) vs. No SAS =1.0% (95% CI: 0.2–5.6) p=NS • Complex ventricular ectopy: SAS =1.3% (95% CI: 0.4–6.9) vs. No SAS =4.1% (95% CI: 1.6–10.1). p=NS	**Conclusions:** The prevalence of nocturnal cardiac arrhythmias is low in pts w/o serious cardiac or respiratory comorbidity who are referred for assessment of sleep apnea, and no different from those w/o sleep apnea. **Comments:** • Potential referral bias • Authors speculate their population consisted of less severe SAS and less severe underlying disease (minority fell below previously suggested thresholds for arrhythmia (Guilleminault and Shepard) • Only 2 prior studies=consecutive pts (Guilleminault and Boudoulas) and the others may have been subject to selection bias • Only Boudoulas compared SAS to comparator group (albeit pts with other types of sleep disorder) • Excluded "major medical conditions" and there may be a complex interaction between CV disease and SAS
EFFECT OF CPAP ON ARRHYTHMIAS - OBSERVATIONAL				
Becker H, et al. 1995 (66) 7812557	**Study type:** Prospective observational	**Inclusion criteria:** Sleep apnea and Mobitz type 2nd degree	**1° endpoint:** Describe the frequency and distribution of arrhythmias during sleep in pts with SAS and assess the effect of nCPAP	**Conclusions** • CPAP effectively suppresses sleep and sleep apnea

	Size: 17/239 consecutive pts referred to a German sleep clinic over 17 mo who manifested both SAS and "heart block" on ambulatory screening tests. They then underwent serial PSGs with Holter monitoring, w/o and subsequently with CPAP	AVB, 3rd degree AVB or sinus pause >2 s on Holter monitor **Exclusion criteria:** N/A	on the 2nd night of treatment and after 4 wk of treatment **Results:** • Mean age =50.7 (27–78) • Median RDI =90/h (±36.1) at baseline • Median RDI =6/h (±6.2) on nCPAP • No. of HB episodes =1,575 at baseline • No. of HB episodes =165 on CPAP ($p<0.001$ vs. baseline) – an 89% reduction • 12/17 (70.6%) manifested no arrhythmia on CPAP • 3/17 (17.6%) manifested a 71–97% reduction in heart block episodes on CPAP (2 of these 3: resolution of HB at 4 wk) • 2/17 (11.8%) demonstrated increased heart block on CPAP but 1 demonstrated resolution of HB at 4 wk. • 15/17 (88%) manifested no arrhythmia after 4 wk of CPAP	associated "heart block" in pts with fairly advanced SA. **Comments** • Potential referral bias • Non-randomized, observational • 16/17 subjects were male
Koehler U, et al. 1998 (67) 9551750	**Study type:** Prospective observational **Size:** 16	**Inclusion criteria:** Sleep apnea (AHI >10/h), no evidence of SAN or AVN dysfunction on EPS, and nocturnal "heart block" who underwent baseline PSG and PSG on CPAP the following night **Exclusion criteria:** AVN blocking or AADs	**1° endpoint:** Correlate the frequency of bradyarrhythmias to stages of sleep, oxygen desaturation and apnea, as well as the effect of nCPAP/nasal bilevel positive airway pressure therapy on these arrhythmias in pts w/o EP abnormalities. **Results:** • Mean age=49.6 (±10.4) y • BMI 36.8 (±7.9) kg/m^2 • 13/16 (81.3%) HTN; 0 MI; 2/16 (12.5%) DM; 11/16 (68.8%) LVH by echo; 7/16 (43.8%) COPD • 651 episodes of HB; 87.9% during REM and 12.1% during stages 1 and 2 non-REM • ($p<0.001$)	**Conclusions** • CPAP effectively suppresses sleep apnea associated "heart block" in pts with fairly advanced SA. **Comments** • Potential referral bias • Non-randomized, observational • 14/16 subjects were male

			• 609/651 (93.5%) occurred during apnea/hypopnea with desaturation ≥4% (but no correlation to nadir O_2 sat above/below 72%) • Mean AHI =75.5±39.6/h at baseline and 3.0±6.6/h on nCPAP/BiPAP (p<0.01) • Bradyarrhythmia: 651 at baseline (432 episodes of 2nd degree AVB, 178 sinus pauses >2 s, 41 3rd degree AVB) • Bradyarrhythmia on nCPAP/BiPAP: 72 (p<0.01) – an 89% reduction in bradyarrhythmia.	
Grimm W, et al. 2000 (68) 10980227	**Study type:** Prospective observational **Size**: 29	**Inclusion criteria:** Sleep apnea, no evidence of SAN or AVN dysfunction on EPS, and ventricular asystole of 6.7±3.3 s (3.1–16.8 s) exclusively during sleep who underwent PSG with and w/o CPAP and were followed clinically for 54±10 mo **Exclusion criteria:** • AVN blocking or AADs • "Advanced" SAN or AVN disease at EPS • Symptomatic bradycardia on 24 h Holter (or symptoms of bradycardia, otherwise)	**1° endpoint:** Describe the long-term prognosis for symptomatic bradyarrhythmia in pts with asx bradyarrhythmias associated with sleep apnea and w/o significant conduction abnormalities on EPS. **Results:** • 93% male • Mean age: 49 y • BMI: 36 kg/m^2 • HTN: 19/29 (66%); CAD: 6/29 (21%); MI: 2/29 (7%) • Bradyarrhythmia: 14/29 (48%) sinus arrest, 12/29 (41%) 3rd degree AVB, 3/29 (10%) both sinus arrest and 3rd degree AVB • nCPAP abolished all pauses >3 s in 21/29 (72%) • nCPAP failed to abolish all pauses in 8/29 (28%) with persistent pauses of 3–5 s • No pt developed symptomatic bradycardia over 54±10 mo of follow-up • 58% always used CPAP • 10% never used CPAP	**Conclusions** • Pts free of significant SAN or AVN dysfunction by EPS who are chronically treated with CPAP for SA c/b nocturnal bradycardia are extremely unlikely to have symptomatic bradycardia or syncope in long-term follow-up of 4.5 y. • Such pts who receive a PM are unlikely to require pacing very much, at all, if PMs are set to low back-up pacing rates. **Comments** • Potential referral bias • Non-randomized, observational • Same group as Koehler • 93% of subjects were male

			• 23/29 had follow-up 24 h Holter: 1/14 w/o PPM had asx pauses up to 3.6 s in duration, while asleep • 12/29 (41%) received PPM at discretion of their care provider during study (including 7/8 with persistent pauses on CPAP. • 8 PPM programmed in VDI at 30–40 bpm: <1% paced at follow-up • 3 PPM programmed in DDD at 40–50 bpm: <10% paced at follow-up • 1 PPM programmed in DDD at 60 bpm: >10% paced at follow-up	
Harbison J, et al. 2000 (69) 10988177	**Study type:** Prospective observational **Size:** 45 consecutive eligible pts from a university hospital's dedicated sleep disorders unit referred to initiate nCPAP	**Inclusion criteria:** Previously diagnosed moderate-severe OSA (AHI 50±23/h) who underwent overnight oximetry and concurrent 18 h 2-channel Holter prior to and after initiating CPAP (Becker, Koehler, within 2 nights of initiating). Studies performed in hospital. **Exclusion criteria:** N/A	**1° endpoint:** Establish the frequency of pathologically significant cardiac rhythm disturbances in the group and, in particular, to determine the effect of nCPAP on these disturbances. **Results:** • 91% male • Mean age: 50 (SD: 13.1) y • BMI: 32.7 (SD: 6.0) kg/m^2 • 35/45 (78%) had some rhythm disturbance at baseline • 8/45 (18%) manifested "pathological arrhythmia (complex ectopy, SVT other than sinus tach, or pauses >2 s, 2nd and 3rd degree AVB) • 7/45 (15.6%) sinus pause >2 s (frequencies reflect individuals with more than 1 type of arrhythmia and sum is >8) • 2/45 (4.4%) from among these 7 with pauses had sinus pauses >3 s (longest =10 s) • 2 /45 (4.4%) had complex ventricular ectopy (1 NSVT, 1 ventricular bigeminy) • 1/45 (2.2%) had 2nd degree AVB	**Conclusions** • Cardiac rhythm disturbances during sleep are common in pts with OSA • Potentially significant arrhythmias during sleep are relatively common (18%) • Potentially significant nocturnal arrhythmias correlate with OSA severity • Potentially significant arrhythmias during sleep are effectively treated by nCPAP therapy. **Comments** • Small sample size • Potential referral bias • No control group • Non-randomized, observational design • 91% of subjects were male • Absence of data to suggest the presence of arrhythmias during sleep directly influences morbidity and

			• nCPAP abolished all "pathological" arrhythmias in 7/8 (87.5%) • The outlier had ischemic CM and severe AS and had both ventricular ectopy and sinus pauses with and w/o CPAP • "Pathological" arrhythmias correlated with severity of OSA as indicated by AHI (p=0.04), but not to mean oxygen saturation, BMI, age, BP, glucose, or lipids	mortality in OSA and the lack of evidence that suppression of arrhythmias with CPAP contributes to improved outcomes in OSA.
ASYX BRADYCARDIA AS A MARKER OF OSA - OBSERVATIONAL				
Stegman SS, et al. 1996 (70) 8774819	**Study type:** Prospective observational cohort study **Size:** 7 pts with clinical indications for cardiac rhythm assessment (ECG, hospital telemetry, and ambulatory monitoring) referred to an EP service for PPM for asx bradyarrhythmias	**Inclusion criteria:** Referred for PPM for asx profound SB, sinus pauses of 2.08–7.52 s, or 2nd or 3rd degree AVB detected on clinically indicated rhythm assessment. Screened clinically for SAS. Those with suggestive sx were referred for PSG. **Exclusion criteria:** • Medications include beta blocker, digoxin or verapamil. • None were trained athletes	**1° endpoint:** Prevalence of SAS as indicated by PSG in those with asx bradycardia and sx suggestive of SAS. **Results:** • All had normal resting awake heart rates during all EP clinic visits before and after enrollment • Bradyarrhythmias prompting referral were all nocturnal or during daytime sleep • OSA diagnosed in all by PSG (1 mild, 2 moderate, and 4 severe). • Mean nadir O_2 sat: 70.6% (45–88%) • 6 treated with CPAP or sleep position modification • 1 received tracheostomy after failing CPAP • Mean follow-up: 22 mo (18–32 mo) • 6/7 (86%) remained free of typical bradyarrhythmia symptoms on treatment for OSA. • 7/7 reported improved sx of OSA on treatment • 1 with AS and severe CHF had syncope during follow-up but also showed resolution of nocturnal bradycardia on hospital tele after tracheostomy. • Authors describe 1 additional subject with daytime and nocturnal profound resting	**Conclusions** • Asx bradyarrhythmias occurring during sleep should prompt screening for SAS. • Those with sx suggestive of SAS and significant nocturnal bradycardia have a high likelihood of OSA on PSG • Such pts are likely to remain asx on treatment for OSA w/o PPM implantation during 18–32 months of follow-up. • Establishing a Dx of OSA in these pts may obviate the need for PPM by facilitating treatment of the underlying cause of the bradyarrhythmia and identify pts at (potentially modifiable) increased risk for CV events. **Comments** • Small sample size • Potential referral bias • No control group with negative response to screening questions who also underwent PSG

			sinus bradycardia in the 30s with preserved chronotropic response to exercise and no sx of SAS who did not undergo PSG and refused PPM. Remained asx over 17 mo of follow-up. They highlight the distinct pattern of persistent d and night time bradycardia in this subject vs. exclusively nocturnal bradyarrhythmias in those with SAS	• Non-randomized, observational design and size preclude conclusions regarding the impact of treatment of OSA on outcomes • Most did not present definitive indications for PPM in the absence of sx
European Multicenter Polysomno-graphy Study Garrigue S, et al. 2007 (71) 17353437	**Study type:** Prospective observational cohort study **Size:** 98 consecutive pts with PPM from 11 European centers	**Inclusion criteria:** • PPM for at least a month for symptomatic SND, advanced AVB, or CRT for HFrEF and QRS >120 ms. • Mean spontaneous nocturnal atrial rate ≥50 bpm • PPM settings during PSG = DDI at lower rate of 50 bpm in all **Exclusion criteria:** • Recent (<6 mo) MI, USA, or coronary revascularization • Permanent atrially paced rhythm	**1° endpoint:** Prevalence and consequence of undiagnosed SAS as indicated by PSG in those with PPM according to indication for pacing: HF, symptomatic "diurnal" bradycardia, and advanced AVB **Results:** • Mean age 64±8 y • Pacing indication: 29/98 (30%) DCM/CRT; 33/98 (34%) advanced AVB; 36/98 (37%) for SND • 77% male • BMI 26.8±5.2 kg/m^2 • HTN: 49%; CAD: 22%; DM: 10% • Mean Epworth Sleepiness Score =7±4, similar in all pacing indications. 13/98 (25%) had ESS >11. • Prevalence of SAS: 59% (95% CI: 46–69), over twice the estimated prevalence in the general population in other studies • SND prevalence of SAS: 58% (27% severe-AHI >30/h) • AVB prevalence of SAS: 68% (27% severe) • HFrEF prevalence of SAS: 50% (5% severe) • V-pacing during PSG: AVB=97±4%; SND=15±12%, CRT: 0% (p<0.01 by ANOVA for AVB and CRT) • A-pacing rate similar in all groups at 15–20% (p=NS)	**Conclusions** • Regardless of indication for pacing, those with PPM have a significantly higher prevalence of SAS (59%) than the general population despite relatively few symptoms of SAS (mean ESS =7) • The majority of the SA is obstructive even in those with HFrEF/CRT • Authors call for systematic screening of PPM recipients for SAS due to the high prevalence and potential CV consequences of SAS **Comments** • No control group w/o PPM for comparison of ESS and PSG results • Some elements inconsistent with previous observations including lack of correlation of AHI with age or BMI and the preponderance of OSA rather than CSA in the HFrEF/CRT group

			• Prevalence of SAS was similar in those with or w/o HTN, CAD or DM, regardless of pacing indication. • 75% of SDB events were hypopneas • All pts had mixed OSA and CSA. Most apneic events were obstructive, including in the CRT group • <5% of pts had predominantly CSA, regardless of pacing indication • No correlation between ESS and AHI (r=0.01; p=NS)	• Although atrial pacing occurred <20% of the time with lower pacing rate of 50 bpm, it was not entirely eliminated atrial pacing has been linked in some studies to reductions in SDB

Data Supplement 6. RCTs of Implantable Loop Recorder in Patients With Documented or Suspected Bradycardia or Conduction Disorders (Section 4.3.1)

Study Acronym; Author; Year Published; PMID	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
RAST Krahn AD, et al. 2001 (72) 11435336	**Aim:** To find out whether prolonged monitoring strategy is better than conventional strategy in the evaluation of recurrent syncope **Study type:** Prospective randomized trial **Size:** 60 pts	**Inclusion criteria:** Recurrent unexplained syncope or syncope X 1 associated with injury **Exclusion criteria:** LVEF <35%, <1 y expected survival, unable to provide follow-up or consent, clear NMS	**Intervention:** ILR (MDT Reveal) monitoring for 1 y (N=27) **Comparator:** Conventional testing – 2 to 4 wk of external loop recorder, TTT and EP testing (SNRT, SACT, antegrade/retrograde conduction, programmed electrical stimulation) (N=30) Crossover was allowed if Dx was unable to be made.	• Dx obtained in 14 of 27 pts (ILR group) vs. 6 of 30 pts (conventional group) (52% vs. 20%; p=0.012)	
EaSyAS Farwell DJ, et al. 2004 (73) 15246645	**Aim:** Investigate the impact of ILRs on unselected population of syncopal pts presenting to one institution **Study type**: Randomized trial **Size:** 201 pts	**Inclusion criteria:** recurrent syncope but no definitive Dx following initial clinical w/u (including CSM and TTT) **Exclusion criteria:** Structural heart disease	**Interventions:** CSM+TTT+implantation of loop recorder (N=103) **Comparator:** CSM+TTT+conventional investigation (N=98) Mean follow-up 276 d	EKG Dx made: 34 (33%) in ILR group vs. 4 (4%) in conventional group (HR: 8.93; 95% CI: 3.17–25; p<0.0001)	• Total medical costs: £406 in ILR group vs. £1210 in conventional group (mean difference £809; 95% CI: 123–2730)
FRESH Podoleanu C, et al. 2014 (74) 25241220	**Aim:** To compare conventional evaluation vs. early use of ILR in low-risk pts with syncope in France	**Inclusion criteria:** Any recent unexplained syncope (after basic clinical exam)	**Intervention:** ILR group (N=39) **Comparator:** Conventional evaluation strategy group (N=39) F/u 14 mo	• Identification of cause: 18 (46.2%) pts in ILR group vs. 2 (5%) pts in conventional group (p<0.001)	• Quality of life was no different between the 2 groups

	Study type: Prospective open-label randomized multicenter study **Size:** 78 pts	**Exclusion criteria:** Significant heart disease, EF <40%, Hx of MI or unstable CAD, Hx of arrhythmia, family Hx of SCD, conduction disturbance on EKG, HOCM, AS, potentially arrhythmogenic drug use		• Days of hospitalization: 5.7 d in ILR group vs. 8.0 d in conventional group (p=0.55) • Number of advanced cardiac tests needed: 0.03/pt in ILR group vs. 0.2/pt in conventional group (p=0.05)	

Data Supplement 7. Nonrandomized Trials, Observational Studies, and/or Registries of Electrophysiology Testing in Patients With Documented or Suspected Bradycardia or Conduction Disorders (Section 4.3.2)

Study Acronym; Author; Year Published; PMID	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results	Summary/Conclusion; Comments
Denniss AR, et al. 1992 (75) 1572741	**Aim:** Electrophysiologic studies in pts with unexplained syncope **Study type:** Prospective cohort **Size:** 111 pts	**Inclusion criteria:** Unexplained syncope, prior general medical evaluation (H&P, CXR, echo, LHC, neuro exam, heart monitor, etc) **Exclusion criteria:** Documented tachy or bradyarrhythmia, Dx of vasovagal syncope, postural hypotension, AS, HOCM or prolonged QT interval Mean follow-up 20 mo	**Results:** • No mortality within 30 d of EPS • Pts with heart disease (CAD, HTN, MVP, CMP) had higher incidence of conduction disease (26%) than those w/o heart disease (8%; p<0.05) • Abnormal EPS (conduction disease, SVT, VT) findings in 42% of pts with heart disease but 16% of pts w/o heart disease (p<0.01) • Syncope occurred in only 5% of treated pts with abnormal findings at EPS vs. 24% in the group not receiving any Rx (p<0.05) • No recurrent syncope in 27 pts treated with PPM vs. recurrent syncope in 20 of 84 pts (24%) not given PPM (p<0.05)	• Diagnostic yield of EPS is increased in pts with heart disease. • Pts with no heart disease had no mortality.

Data Supplement 8. RCTs Comparing Atropine to Placebo for Bradycardia (Section 5.3.2.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Smith I, et al. 1994 (76) 7906108	**Aim:** To compare the effectiveness in the treatment of intraoperative bradycardia of transesophageal atrial pacing, atropine, and glycopyrrolate **Study type:** RCT	**Inclusion criteria:** Men undergoing elective radical prostatectomy with sufentanil/N_2O/vecuronium anesthetic resulting in bradycardia (<50 bpm or <60 bpm and hypotension) **Exclusion criteria:** Pts not ASA status I–III.	**Intervention:** 15 patients were randomized to each group. **Comparator**: TAP vs. atropine vs. glycopyrrolate	**1° endpoint:** Time for heart rate to increase to >70 bpm was shortest in the temporary pacing group. There were no significant differences in postoperative course in the 3 groups. **Safety endpoint:** N/A	• N/A

	Size: N=64, of which 45 had treatment for bradycardia				
Sodeck GH et. al. 2007 (77) 17212976	**Study type:** Observational, retrospective, single center **Size:** N= 277	**Inclusion criteria:** Pts presenting to ED with symptomatic bradycardia of <60 bpm **Exclusion criteria:** Asymptomatic bradycardia	**1° endpoint:** 30 d mortality **Results:** 107 of 277 pts did well with flat positioning. Of 170 with persisting symptoms, 141 received atropine, 92 catecholamines (orciprenaline in 62, adrenaline in 24 and dopamine/dobutamine in 6), and 7 required transcutaneous pacing. Neither medical therapy nor cause-specific treatment could stabilize 54 of the 170 pts, who required temporary pacing.		• Initial stabilization with bedrest and intravenous atropine or catecholamines was effective in the majority of pts.
Aghamohammadi, H., et al. 2009 (78) 19472126	**Aim:** To determine the efficacy of pre-induction atropine in preventing bradycardia during laparoscopic urologic surgery **Study type:** RCT **Size:** N=64	**Inclusion criteria:** 15–50 y old undergoing elective urologic laparoscopic surgery **Exclusion criteria:** History of cardiac arrhythmia, drug induced bradycardia, cardiac disease, contraindication to general surgery.	**Intervention:** Atropine sulfate 0.6 mg IV **Comparator: Saline**	**1° endpoint:** Frequency of bradycardia was 28% in non-atropine group and 0 in the atropine group (p<0.01) **Safety endpoint (if relevant):** Mean systolic BP decrease was 15.7±10 mm Hg in atropine group and 23.5±9.8 mm Hg in controls (p<0.01)	• None of the pts treated with atropine had bradycardia, compared to 28.1% of pts in the saline group • Mean systolic and diastolic BP was more stable in the atropine group.

Data Supplement 9. Nonrandomized Trials, Observational Studies, and/or Registries of Atropine in SND and Hemodynamically Significant Bradycardia (Section 5.3.2.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Brady WJ, et al. 1999 (79) 10459592	**Study type:** Retrospective observational study of prehospital, emergency department, and hospital records **Size:** 172 pts met entry criteria, data were available for 131	**Inclusion criteria:** Prehospital pts with hemodynamically unstable bradycardia who received atropine by EMS. Hemodynamic instability was defined as the presence of any of the following: ischemic chest pain, dyspnea, syncope, altered mental status, and systolic BP less than 90 mm Hg. Bradycardia was defined as sinus bradycardia, junctional bradycardia, or idioventricular bradycardia (grouped as bradycardia) while AVB included first-, second- (types I and II), or third-degree (grouped as AVB). **Exclusion criteria:** N/A	**1° endpoint:** Heart rate response that occurred within one minute following each dose of atropine. **Results:** 45 pts with AVB, 86 bradycardia. 26 (19.8%)had a partial response, 36 (27.5%) complete, 65 (49.6%) none, and 4 (2.3%) had an adverse response	• One-half of pts had a complete or partial response to atropine and adverse reactions were uncommon. • Pts who presented with non-AVB bradycardia received less atropine and were more likely to arrive in the emergency department with SR.
Swart, G, et al. 1999 (80) 10597081	**Study type:** Retrospective observational study of	**Inclusion criteria:** Prehospital pts with hemodynamically	**1° endpoint:** Heart rate response that occurred within	• There were no differences in response to atropine in AMI vs. non-AMI pts with

	prehospital, emergency department, and hospital records **Size:** 172 pts met criteria, data available for 131; 45 presented with AMI	unstable bradycardia or AVB who received atropine by EMS. Hemodynamic instability was defined as the presence of any of the following: ischemic chest pain, dyspnea, syncope, altered mental status, and systolic BP less than 90 mm Hg. Bradycardia was defined as sinus bradycardia, junctional bradycardia, or idioventricular bradycardia (grouped as bradycardia), whereas AVB included first-, second- (types I and II), or third-degree (grouped as AVB). **Exclusion criteria:** N/A	1 min following each dose of atropine **Results:** No differences in AMI vs. non-AMI groups in the likelihood of achieving SR (40% vs. 18.6%; p=0.07), amount of atropine, or additional resuscitative therapies given.	hemodynamically unstable bradycardia or AVB. • Hemodynamically unstable AVB was associated with AMI in 55.6% of pts.
Warren JV, et al. 1976 (81) 1244735	**Study type:** Retrospective observational study of pts with AMI and bradycardia **Size:** N=70	**Inclusion criteria:** Pts in early phase of AMI with heart rate <60 bpm. **Exclusion criteria:** N/A	**1° endpoint:** Mortality **Results:** In pts with hypotension complicating presentation with AMI and hypotension, the mortality rate was 75% w/o atropine and 25% with atropine. In pt with normal BP, the mortality rate was 13 and 14% and did not differ between groups.	• The use of atropine to treat bradycardia with and w/o hypotension was effective and safe.

			Ventricular fibrillation occurred in 1/45 pts treated with atropine, and 2/45 pts not treated with atropine. Atropine at a dose of 0.5–1 mg was effective in increasing heart rate.	
Scheinman MM, et al. 1975 (82) 1157275	**Study type:** Observational, single center **Size:** N=56	**Inclusion criteria:** Pts with AMI and sinus bradycardia **Exclusion criteria:** Preterminal pts, during or after CPR, AMI and AVB, use of digitalis, propranolol, or pre-existing sinus bradycardia.	**1° endpoint:** Heart rate **Results:** Atropine increased heart rate and BP, abolished PVCs and accelerated idioventricular rhythm. 7 pts had serious adverse effects, including ventricular fibrillation and sinus tachycardia.	• Atropine had beneficial effects in pts with AMI complicated by sinus bradycardia, particularly at dosages of 0.5–0.6 mg. Higher doses were associated with a higher incidence of adverse effects.

Data Supplement 10. Nonrandomized Trials, Observational Studies, and/or Registries of Isoproterenol Effect in Electrophysiology Laboratory (Section 5.3.2.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR RR; & 95% CI)	Summary/Conclusion Comment(s)
Ogawa H, et. al. 1991 (83) 2010943	**Study type:** Single center study of IV isoproterenol, propranolol, atropine and methoxamine in electrophysiology lab **Size:** N=36	**Inclusion criteria:** SND and normal **Exclusion criteria:** N/A	**1° endpoint:** 28 pts with SND, 8 normal pts. Heart rate and recovery time before and after IV drug administration were measured. **Results:** 17 pts with SND w/o syncope had a normal heart rate response to isoproterenol compared to a significantly lower heart rate response in 11 pts with syncope	• Many pts with SND showed heart rate increases with isuprel similar to normal controls; this was seen less often in pts with SND and syncope
Mandel WJ, et al. 1972 (84) 5072776	**Study type:** Single center electrophysiology study **Size:** N=31	**Inclusion criteria:** Pts with ECG/monitor documented SND **Exclusion criteria:** N/A	**1° endpoint:** Response to autonomic, exercise and pacing maneuvers, isoproterenol infusion at 1–2 mcg/min. **Results:** 12 pts underwent Isoproterenol testing, all responded with an increase in heart rate to infusion (mean 52 bpm–mean 118 bpm). Comparatively, the response to atropine was less (52 bpm–64 bpm)	• In an SND population, response to exercise and isoproterenol was within the expected normal range. • Relative unresponsiveness of heart rate to atropine was noted in several pts. • The study concluded this small group of pts with SND are characterized by normal sympathetic reactivity and abnormal parasympathetic reactivity.
Strauss HC, et al. 1976 (85) 1260979	**Study type:** Single center electrophysiology study **Size:** N=20	**Inclusion criteria:** Pts with ECG documented SND **Exclusion criteria:** N/A	**1° endpoint:** Conduction times, response to atropine and isoproterenol infusion **Results:** Graded infusion of isoproterenol resulted in 19 pts, 4 required a dosage higher than 28.3 ng/kg/min to produce a 20% decrease in sinus cycle length. 19 pts received 1 mg of atropine, resulting in a mean reduction of sinus cycle length of 19%	• Heart rate increased in response to atropine and isuprel in pts with SND. • Higher doses of isoproterenol may be required.

Data Supplement 11. RCTs of Dopamine in Bradycardia (Section 5.3.2.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
• **'PrePACE'** Morrison LJ, et al. 2006 (86) 17933452	**Aim:** To evaluate the feasibility of a RCT of transcutaneous pacing vs. dopamine for atropine and fluid refractory bradycardia in the prehospital setting. **Study type:** RCT **Size:** 151 met criteria, 82 enrolled	**Inclusion criteria:** Unstable bradycardia unresponsive to fluid and atropine: heart rate <60/min and systolic BP (SBP) <80 mm Hg; or heart rate <60/min and SBP <100 mm Hg and at least one additional sign/symptom **Exclusion criteria:** Advance directives, trauma, hyperthermia, hypothermia or cardiac arrest, pts in whom it was not possible to start an intravenous line.	**Intervention:** All pts received 250 ml saline IV bolus. If nonresponse, pts received atropine 1 mg, repeated if improved. If pts failed to respond, they were randomized to transcutaneous pacing (with midazolam) vs. dopamine **Comparator:** Dopamine starting at 5 mcg/kg/min, increasing the dose by 5 mcg/kg min every 2 min until an improvement in signs and symptoms was observed, maximum dose of 20 mcg/kg/min	**1° endpoint:** Survival to hospital discharge **Safety endpoint (if relevant):** Ventricular arrhythmia, cutaneous burns, chest wall discomfort, cardiac arrest, TCP failure.	• Survival to hospital discharge was similar in both groups (70% vs. 69%; p=0.93), as were 2° outcomes.

Data Supplement 12. Nonrandomized Trials, Observational Studies, and/or Registries of Calcium, Glucagon and High Dose Insulin Therapy to treat Beta-Blocker and Calcium Channel Blocker Toxicity (CCB) (Section 5.3.2.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Howarth DM, et al. 1994 (87) 7909677	**Study type:** Multi-center observational study of CCB	**Inclusion criteria:** Admission for CCB overdose **Exclusion criteria:** N/A	**1° endpoint:** Clinical outcome	• Atropine was only effective after IV calcium was administered • Calcium often reversed hypotension and bradycardia, but

	overdose in an Australian population **Size:** N=15		**Results:** All pts treated with oral activated charcoal, most required calcium, atropine, and inotropic support. 4 pts died.	atropine and inotropic support were frequently required
Ramoska EA, et al. 1993 (88) 8427431	**Study type:** Retrospective, observational, 3 poison control centers **Size:** N= 138	**Inclusion criteria:** Hospitalized pts with CCB ingestion **Exclusion criteria:** N/A	**1° endpoint:** Clinical outcomes **Results:** There were no deaths. Ipecac (26%), lavage (40%), and activated charcoal (81%)were administered. Calcium was administered to 23 pts with sinus node suppression; 64% responded with an increased heart rate. Dopamine had no effect on bradycardia. Atropine was used in 7 pts with SND, 29% responded with an increased heart rate. Transvenous pacing was used in 4 pts. Isoproterenol increased heart rate in 2 pts with SND, but not the pt with AVB. Glucagon increased BP w/o effect on heart rate.	• Hypotension, dysrhythmias, and depression of the sinus node occurred with equal frequency in verapamil, nifedipine, and diltiazem overdose. AVB was more common and severe with verapamil. • Although IV calcium was not universally effective, its use was associated with clinical improvement in hemodynamic parameters in the majority. • No dose response relationship for either calcium gluconate or calcium chloride was noted
St-Onge M, et al. 2014 (89) 25283255	**Study type:** Systematic review **Size:** 216 studies	**Inclusion criteria:** Studies examining effects of various treatments for CCB poisoning for efficacy. **Exclusion criteria:** N/A	**1° endpoint:** Efficacy of treatments for CCB poisoning with primary outcomes of mortality and hemodynamic parameters **Results:** 117 case reports of 216 studies. 7 animal studies showing hemodynamic and mortality improvement with calcium. In humans, 11 case series and 21 case reports were inconsistent in demonstrating benefit.	• Evidence to support IV calcium in CCB overdose is of low quality, but animal studies and human case reports and series often demonstrate improved hemodynamic parameters, and adverse effects (hypercalcemia) are rare.
GLUCAGON				
Love JN, et al. 1998 (90) 9674488	**Study type:** Retrospective, observational, single center **Size:** N=9	**Inclusion criteria:** Pts presenting with symptomatic bradycardia who received glucagon therapy. **Exclusion criteria:** Clinical response to atropine	**1° endpoint:** Clinical improvement in heart rate and perfusion. **Results:** 9 pts were receiving BB, CCB, or digoxin therapy. Heart rate and BP increased significantly in all but one pt who received glucagon.	• 8/9 pts presenting with symptomatic bradycardia, that may have been caused or exacerbated by chronic BB, CCB, or digoxin therapy demonstrated clinical improvement with glucagon after failing atropine therapy.

Bailey B 2003 (91) 14514004	**Study type:** Systematic review **Size:** N=30 (all animal)	**Inclusion criteria:** Studies evaluating glucagon use in BB and CCB overdose. **Exclusion criteria:** Case report or case series.	**1° endpoint:** Effect of glucagon on heart rate, arterial pressure, contractility, cardiac output and survival in BB or CCB overdose. **Results:** 5 animal studies of BB overdose, glucagon increased heart rate, but effect on survival was unclear. In 6 animal studies of CCB overdose, glucagon transiently increased heart rate and reversed AVB w/o effect on survival.	• Evidence supporting the use of glucagon in the management of pts with BB or CCB overdose is limited, but demonstrates transient improvement in heart rate and conduction.
St-Onge M, et al. 2014 (89) 25283255	**Study type:** Systematic review **Size:** 216 studies	**Inclusion criteria:** Studies examining effects of various treatments for CCB poisoning for efficacy. **Exclusion criteria:** N/A	**1° endpoint:** Efficacy of treatments for CCB poisoning with primary outcomes of mortality and hemodynamic parameters **Results:** 2 of 3 animal studies, and 1 of 3 human case series showed improvement in heart rate with glucagon.	• Evidence to support the use of glucagon in CCB overdose is scant. Hyperglycemia and vomiting were side effects seen in case reports.
HIGH DOSE INSULIN THERAPY				
Engebretsen KM, et al. 2011 (92) 21563902	**Study type:** Systematic review **Size:** 72 studies	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** Efficacy **Results:** Clinical data are limited; animal studies and case reports demonstrate safety and survival in BB and CCB poisoning is superior when treated with HDIT compared with calcium, glucagon, epinephrine, and vasopressin.	• Evidence to support HDIT is of low quality, but validates safety and efficacy in the treatment of BB and CCB toxicity.
St-Onge M, et al. 2014 (89) 25283255	**Study type:** Systematic review **Size:** 216 studies	**Inclusion criteria:** Studies examining effects of various treatments for CCB poisoning for efficacy. **Exclusion criteria:** N/A	**1° endpoint:** Efficacy of treatments for CCB poisoning with primary outcomes of mortality and hemodynamic parameters **Results:** One observational study in humans of HDIT showed improved hemodynamic parameters and decreased mortality with risk of hypoglycemia and hypokalemia.	• Evidence to support HDIT in CCB overdose is of low quality, but observational data demonstrate improved hemodynamics and survival.
Greene SL, et al. 2007 (93) 17622512	**Study type:** Prospective, single center, observational	**Inclusion criteria:** Pts with CCB toxicity and hypotension treated with HDIT	**1° endpoint:** Safety of HDIT in CCB overdose. **Results:** 6/7 pts survived.	• HDIT in the setting of hemodynamically significant CCB overdose was safe in a critical care setting. Systolic BP was

	Size: N=7	**Exclusion criteria:** N/A		increased by insulin loading. Mild hypoglycemia and hypokalemia were noted.

Data Supplement 13. RCTs Comparing Anti-Digoxin Fab to placebo (Section 5.3.2.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Eddleston M, et al. 2000 (94) 10768435	**Aim:** To determine effectiveness of anti-digoxin Fab fragments in reversing oleander induced arrhythmias **Study type:** RCT **Size:** N=66	**Inclusion criteria:** Pts with Hx of yellow oleander ingestion with sinus bradycardia <40 bpm, sinus arrest or block, atrial tachyarrhythmias, or 2nd or 3rd degree heart block. **Exclusion criteria:** Hypotension (SBP < 80 mm Hg), ventricular tachycardia with shock	**Intervention:** 1200 mg of anti-digoxin antibodies **Comparator:** Saline placebo	**1° endpoint:** Reversal of original arrhythmia in 15/24 treated pts vs. 2/32 controls. Heart rate increased from 49.1 bpm to 66.8 bpm in 2 h in treated pts, did not change in controls (p<0.001). Serum potassium decreased from 4.9 mmol/L to 4.1 mmol/L at 2 h in cases, not in controls (p< 0.001). **Safety endpoint (if relevant):** N/A	• Anti-digoxin Fab antibody therapy increased heart rate and improved time to reversal of bradycardia.

Data Supplement 14. Nonrandomized Trials, Observational Studies, and/or Registries of Digoxin Fab Antibody Fragments (Section 5.3.2.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Lapostolle F, et al. 2008 (95) 18824911	**Study type:** Retrospective, single center, observational **Size:** N=141	**Inclusion criteria:** Pts admitted with digitalis poisoning **Exclusion criteria:** N/A	**1° endpoint:** Survival **Results:** 66/141 pts received Digoxin Fab. 5 pts died. No adverse effects were noted.	• Therapy of digitalis overdose with digoxin Fab was associated with a mortality rate of 7.6%
Lapostolle F, et al. 2008 (96) 18389220	**Study type:** Retrospective, observational, multi-center (20) **Size:** N=838	**Inclusion criteria:** Pts presenting with elevated digitalis concentration. **Exclusion criteria:** N/A	**1° endpoint:** Use and efficacy of digoxin antibody. **Results:** 67/838 pts received digoxin antibody. Mortality was significantly lower in Fab treated pts (6% vs. 15%)	• Digoxin antibody therapy may be underused, and is associated with improved mortality.
Chan BS and Buckley NA, 2014 (97) 25089630	**Study type:** Systematic Review **Size:** N= 140 studies	**Inclusion criteria:** N/A **Exclusion criteria:** Case reports w/o pharmacologic data.	**1° endpoint:** Effectiveness, pharmacology, safety and dosage of digoxin-Fab in pts with digoxin overdose. **Results:** There were no RCT of digoxin Fab for the treatment of digoxin toxicity. 10 case series with 2080 pts were evaluated. Clinical response occurs in 50–90% of pts within 30–45 min. Exacerbation of HF, tachycardia, hypokalemia, and allergic reactions happen in <10%.	• Digoxin Fab is safe and indicated in pts with life-threatening arrhythmias and an elevated digoxin concentration. • Full neutralizing dosages may not be required. In acute toxicity, 80 mg, repeated as required, is likely to be effective. In chronic toxicity, 40 mg with repeat in 60 min (or sooner if pt is unstable) is likely to be beneficial.
Smith TW, et al. 1982 (98) 6752715	**Study type:** Observational, single center **Size:** N=26	**Inclusion criteria:** Pts with digitalis toxicity and arrhythmia or hyperkalemia refractory to initial therapy **Exclusion criteria:** N/A	**1° endpoint:** Morality **Results:** 21/26 pts survived. Arrhythmia and hyperkalemia were rapidly reversed by digoxin Fab, and no adverse reactions were seen.	• Digoxin Fab is an effective and safe therapy for digitalis toxicity associated with arrhythmias or hyperkalemia
Wenger TL, et al. 1985 (99) 3886748	**Study type:** Observational multi-center (20)	**Inclusion criteria:** Pts with life-threatening digitalis toxicity.	**1° endpoint:** Clinical outcome	• Life-threatening digoxin toxicity can be safely and effectively treated with digoxin Fab.

	Size: N=63	**Exclusion criteria:** N/A	**Results:** Reversal of clinical toxicity within 30 min of administration. Digoxin concentration decreased to undetectable. No adverse reactions.	
Antman EM, et al. 1990 (100) 2188752	**Study type:** Observational multi-center (21) **Size:** N=150	**Inclusion criteria:** Pts with digitalis toxicity and life-threatening cardiac rhythm disturbances or hyperkalemia refractory or likely to be refractory to conventional therapy. **Exclusion criteria:** N/A	**1° endpoint:** Response to therapy. **Results:** 119/148 resolved all clinical evidence of toxicity, 14 improved, 15 showed no response. 5 pts were on hemodialysis and improved.	• Digoxin Fab is an effective antidote to digitalis toxicity.
Hickey AR, et al. 1991 (101) 1993775	**Study type:** Observational, retrospective. **Size:** N=717	**Inclusion criteria:** Adults who received digoxin Fab for digitalis intoxication. **Exclusion criteria:** N/A	**1° endpoint:** Clinical response **Results:** 50% complete, 24% partial, and 12% had no response. 0.8% had an allergic reaction.2.8% developed recurrent toxicity, which was associated with inadequate dosing.	• Digoxin Fab was well tolerated and effective in pts with digitalis toxicity.
Wenger TL, 1991 (102) 1997017	**Study type:** observational, retrospective **Size:** N/A	**Inclusion criteria:** Pts in multicenter study of digoxin Fab, a postmarket surveillance study, and any reports in the literature of pts treated with digoxin Fab with renal dysfunction. **Exclusion criteria:** N/A	**1° endpoint:** Clinical response **Results:** No evidence of decreased safety or efficacy with respect to response or recurrence. 28 subjects were anephric, one of these pts possibly had recrudescent toxicity with AVB.	• Digoxin Fab was effective and safe in pts with digitalis toxicity and renal dysfunction.

Data Supplement 15. Nonrandomized Trials, Observational Studies, and/or Registries of Dialysis for Digoxin Toxicity (Section 5.3.2.3 – Patton)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
EXTRIP Mowry JB, et al. 2016 (103) 26795743	**Study type:** Systematic review **Size:** N= 77 articles	**Inclusion criteria:** Use of dialysis in digitalis toxicity **Exclusion criteria:** N/A	**1° endpoint:** Clinical outcome and toxicokinetic data. **Results:** Only in vitro, animal studies, case reports, and case series were identified, with a total of 84 pts. Digoxin is slightly dialyzable, and dialysis is unlikely to improve the outcome of digoxin toxicity.	• The workgroup suggested against the use of dialysis in cases of digoxin toxicity, whether or not digoxin Fab was available.

Data Supplement 16. RCTs Comparing Methylxanthines in Bradycardic Arrest (Section 5.3.2.4)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Abu-Laban RB, et al. 2006 (104) 16698410	**Aim:** To determine if administration of aminophylline increases ROSC in bradycardic cardiac arrest **Study type:** RCT **Size:** N= 971	**Inclusion criteria:** Asystole, or PEA <60 bpm, unresponsive to epinephrine and atropine **Exclusion criteria:** Age <16 y, pregnancy, DNR, evidence of hemorrhage, trauma or hypothermia, dialysis, theophylline sensitivity or use.	**Intervention:** 250 mg aminophylline IV x2. **Comparator:** Placebo	**1° endpoint:** ROSC **Safety endpoint (if relevant):** N/A	• There was no difference in ROSC in the group that received aminophylline adjunctive therapy. Use of aminophylline was associated with an increase in non-sinus tachycardias
Hurley KF, et al. 2015 (105) 26593309	**Study type:** Systematic Review of effects of aminophylline in the treatment of	**Inclusion criteria:** All randomized trials of aminophylline vs. placebo in adults with		**1° endpoint:** Survival to hospital discharge.	• Prehospital administration of aminophylline in

	bradycardic cardiac arrest **Size:** 5 trials, N=1254 pts	nontraumatic bradycardic cardiac arrest treated with ACLS		**Results:** There was no survival benefit of aminophylline (RR: 0.58; 95% CI: 0.12–1.39); or on survival to hospital admission (RR: 0.92; 95% CI: 0.61–1.39); or ROSC (RR: 1.15; 95% CI: 0.89–1.49).	bradyasystolic arrest is not associated with improved survival, ROSC, or survival to hospital admission.

Data Supplement 17. Nonrandomized Trials, Observational Studies, and/or Registries of Methylxanthines for acute therapy of bradycardia due to spinal cord injury or post-heart transplant (Section 5.3.2.4)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Post-heart Transplant				
Redmond JM, et al. 2005 (106) 8443190	**Study type:** Nonrandomized trial of oral theophylline **Size:** N=15	**Inclusion criteria:** Sinus or nodal bradycardia or sinus arrest post-heart transplant **Exclusion criteria:** N/A	**1° endpoint:** restoration of normal SR **Results:** Normal SR was restored with a rate >90 bpm in 93.3% given theophylline • Therapy was initiated 3–24 d after transplantation • Mean duration of treatment was 57.4 d	• Oral theophylline was effective at restoring SR at a desirable heart rate. • Compared to historical controls, placement of a PPM was reduced from 16.1% to 2.6%
Bertolet BD, et al. 1996 (107) 8800116	**Study type:** Nonrandomized trial of oral theophylline **Size:** N=29	**Inclusion criteria:** Bradyarrhythmia (heart rate <70 bpm) in in heart transplant recipients **Exclusion criteria:** N/A	**1° endpoint:** Mean heart rate, length of stay **Results:** Mean heart rate increased from 62± 7 to 89±10 after administration of theophylline. Length of stay did not differ.	• Theophylline was effective at increasing heart rate post-transplant
Rothman SA, et al. 1995 (108) 7654727	**Study type:** Observational study	**Inclusion criteria:** Post-heart transplant pts **Exclusion criteria:** N/A	**1° endpoint:** Effects of IV aminophylline on heart transplant recipients	• Both groups had abnormal sinus node recovery times. Aminophylline did not correct this in transplant recipients with or w/o SND.

	Size: N=26 (13 with and 13 w/o sinus node dysfunction)		**Results:** Sinus node testing was performed in electrophysiology lab before and after infusion of 6 mg/kg of aminophylline.	
Heinz G, et al. 1993 (109) 8427182	**Study type:** observational single center. **Size:** N=9	**Inclusion criteria:** Pts with and w/o SND after heart transplant **Exclusion criteria:** N/A	**1° endpoint:** Changes in sinus node recovery time from baseline after aminophylline infusion **Results:** Normalization of sinus node function was seen after aminophylline 0.48 gm IV in all 3 pts with abnormal sinus node function.	• Aminophylline can improve sinus node function in heart transplant recipients with SND
Spinal Cord Injury				
Pasnoori VR, et al. 2004 (110) 14766019	**Study type:** Case series **Size:** N=2	**Inclusion criteria:** Pts with severe bradycardia and spinal cord injury **Exclusion criteria:** N/A	**1° endpoint:** Effects of aminophylline **Results:** Increased heart rate and BP with 300 mg IV aminophylline and 5 mg/kg/h infusion, changed to theophylline after 2 d	• Use of aminophylline, followed by theophylline in atropine resistant bradycardia was associated with increased heart rate and avoidance of PM placement
Sadaka F, et al. 2010 (111) 20878263	**Study type:** Observational case series **Size:** N=6	**Inclusion criteria:** Pts with severe bradycardia due to spinal cord injury **Exclusion criteria:** N/A	**1° endpoint:** Heart rate response to theophylline **Results:** Heart rates improved in all 6 pts with severe bradycardias and hypotension. Theophylline was used as a second-line agent (after atropine and/or dopamine) in 4/6, and first-line in 2/6	• Theophylline was effective and safe as a second-line agent, and potentially a first-line agent for treatment of hemodynamically unstable bradycardia in pts with acute spinal cord injury. • Effective dosages resulted in serum levels below the therapeutic range of 10–20 mcg/ml. • No pt required a PM.
Schulz-Stübner S, 2005 (112) 16301263	**Study type:** Case series **Size:** N=3	**Inclusion criteria:** Pts with severe bradycardia due to spinal cord injury **Exclusion criteria:** N/A	**1° endpoint:** Heart rate response to theophylline **Results:** Heart rates increased from 30–40 with pauses to 60–70 after theophylline. Increased respiratory drive was seen in one pt.	• Improved heart rate was seen in all 3 pts after IV theophylline, and maintained with oral theophylline • Dosages were 200 mg IV theophylline and 50–100 mg po every 8 h

Data Supplement 18. Trials of Temporary Transesophageal or Transvenous Pacing (Section 5.3.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Smith I, et al. 1994 (76) 7906108	**Aim:** To compare the effectiveness in the treatment of intraoperative bradycardia of transesophageal atrial pacing, atropine, and glycopyrrolate **Study type:** RCT **Size:** N=64, of which 45 had treatment for bradycardia	**Inclusion criteria:** Men undergoing elective radical prostatectomy with sufentanil/N_2O/vecuronium anesthetic resulting in bradycardia (<50 bpm or <60 bpm and hypotension) **Exclusion criteria:** Pts not ASA status I-IFII.	**Intervention:** 15 pts were randomized to each group. **Comparator**: TAP vs. atropine vs. glycopyrrolate	**1° endpoint:** Time for heart rate to increase to >70 bpm was shortest in the temporary pacing group. There were no significant differences in postoperative course in the 3 groups. **Safety endpoint:** N/A	• Transesophageal pacing route is relevant to SND.
Ferguson JD, et.al. 1997 (113) 9217762	**Aim:** To compare effectiveness of conventional TTVP with balloon floatation pacing catheters. **Study type:** Randomized, parallel-group trial **Size:** N= 40	**Inclusion criteria:** Pts needing TTVP. **Exclusion criteria:** N/A	**Intervention:** Balloon flotation pacing catheter. **Comparator:** Conventional TTVP.	**1° endpoint:** Procedural outcomes **Safety endpoint:** Complications	• Only 1/40 pts had sinus arrest. • Satisfactory TTVP positions were more frequently achieved with a reduction in procedure and fluoroscopy time using the balloon catheter. • Adverse event rates (crossover, dislodgement) were similar, but death and perforation did not occur in the balloon catheter group.

Data Supplement 19. Nonrandomized Trials, Observational Studies, and/or Registries of Temporary Transvenous Pacing (TTVP) (Section 5.3.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)

Lopez Ayerbe J, et al. 2004 (114) 15544753	**Study type:** Retrospective, observational, single-center **Size:** N=530	**Inclusion criteria:** Pts who underwent TTVP for symptomatic bradycardia. **Exclusion criteria:** N/A	**1° endpoint:** Clinical outcomes **Results:** Indications induced symptomatic SSS in 7.5% of implants, use in generator replacement in 14.7%, bradycardic drug toxicity in 12.2%. Femoral access was used in 99%, and duration was 4.2 d. 69.6% of pts required a PPM. 6.4% of pts died, 3 deaths were attributable to temporary pacing. There were complications in 22%, including dislodgement in 9%.	• TTVP is effective, yet has a complication rate of 22%, including an associated 6% mortality rate. • Use of TTVP for treatment of SND is comparatively rare.
Hynes JK, et al. 1983 (115) 6823157	**Study type:** Retrospective, observational, single-center **Size:** N=1022	**Inclusion criteria:** Pts in the coronary care unit with TTVP. **Exclusion criteria:** N/A	**1° endpoint:** Clinical outcomes **Results:** Access was antecubital in 59%, subclavian in 17%, right internal jugular in 11%, and femoral in 5%. Complications occurred in 13.7% with no deaths. The right internal jugular approach was associated with a decreased risk of complications.	• TTVP was associated with an overall risk of complications in approximately 14% of pts.
Murphy JJ, 1996 (116) 8620131	**Study type:** Retrospective, observational, multicenter (18) **Size:** N=194	**Inclusion criteria:** Pts undergoing TTVP. **Exclusion criteria:** N/A	**1° endpoint:** Clinical outcomes **Results:** 129/194 TTVP were implanted for CHB. Immediate or delayed complications occurred in 68 pts.	• TTVP was associated with complications in 35% of pts, including vascular access difficulties, dislodgement, infection, and sepsis.
Austin JL, et al. 1982 (117) 7058746	**Study type:** Retrospective, observational. Single center **Size:** N=100	**Inclusion criteria:** Pts who received TTVP. **Exclusion criteria:** N/A	**1° endpoint:** Complications and malfunction **Results:** 113 TTVPs were placed in 100 pts. Failure to capture or sense occurred in 37% and complications in 20%. These included ventricular arrhythmia, fever, pulmonary emboli, perforation, sepsis and phlebitis. There were no deaths.	• TTVP was associated with a 20% complication rate, and a high rate of malfunction. • 21/100 subjects underwent TTVP for SND; 18 for PM failure not otherwise specified
Munoz Bono JM, et al. 2011 (118) 21640435	**Study type:** Prospective, observational	**Inclusion criteria:** Pts in cardiac intensive care	**1° endpoint:** Clinical indications, morbidity, mortality.	• TTVP was associated with a risk of complications in 40%.

	Size: N=182	unit who underwent TTVP. **Exclusion criteria:** N/A	**Results:** Indication for TTVP was CHB in 77%, access was via the femoral vein in 92%, and complications occurred in 40.11%. Predictors of complications were restlessness, CV risk factors, and jugular or subclavian access.	• TTVP was indicated for SND in 9.3%, and bradycardia from drug intoxication in 12.1%
Betts TR, 2003 (119) 12954959	**Study type:** Prospective, observational, multi-center (5). **Size:** N=111	**Inclusion criteria:** Pts requiring TTVP **Exclusion criteria:** N/A	**1° endpoint:** Procedural and pt characteristics, outcomes. **Results:** 144 procedures in 111 pts. Venous access was subclavian in 47%, jugular in 33%, and femoral in 20%. There were procedural complications in 32% of the procedures; risk was decreased for experienced operators. Infection risk increased with dwell time >48 h. Complications delayed permanent implant in 23% of pts.	• TTVP was associated with a high risk of complications. • Infectious risk is increased with longer time of implant. • Immediate complication risk was lower for experienced operators. • Pacing indication was not described.
Jowett NI, et al. 1989 (120) 2594596	**Study type:** Retrospective, observational, single center **Size:** N=162	**Inclusion criteria:** Pts admitted to coronary care unit who underwent TTVP. **Exclusion criteria:** N/A	**1° endpoint:** Clinical outcomes. **Results:** The majority of TTVP was for CHB and MI (84.6%). 15.4% of TTVPs were placed for symptomatic bradycardia, including SND. Complications occurred in 19.8%, including arrhythmias during insertion, dislodgement, pneumothorax, and perforation.	• TTVP was associated with a 19.8% complication rate. Some TTVP was prophylactic, and may not have been indicated. • A minority of TTVP was performed for SND (15%)
Weinstein J, et al. 1973 (121) 4697639	**Study type:** Prospective, observational, single center **Size:** N=100	**Inclusion criteria:** Pts with bradycardia and conduction disease in the acute setting **Exclusion criteria:** N/A	**1° endpoint:** Clinical response and stability. **Results:** 17% of placements required repositioning, 2 instances of ventricular tachycardia, 2 perforations, 2 infections. Placement and stability was improved compared with prior historical series of 100 pts with jugular and subclavian approach.	• TTVP via the femoral approach was found to be reliable, and rapid with a reasonable complication rate in critically ill pts. • Pts were restricted to bedrest after dislodgements were noted to be associated with activity. • 10% of TTVP were placed for sinus bradycardia

Garcia Guerrero JJ, et al. 2010 (122) 20667893	**Study type:** Prospective, observational, single center **Size:** N=47	**Inclusion criteria:** Pts requiring TTVP who underwent novel active fixation femoral TTVP. **Exclusion criteria:** N/A	**1° endpoint:** Rate of deep venous thrombosis **Results:** Asymptomatic thrombosis was seen in 6.4%, compared with 25–39% in other observational reports. No pulmonary emboli were noted on lung scan.	• Mobility afforded by an active fixation TTVP is associated with a decreased risk of deep venous thrombosis. • Pacing indications were not reported.
Nolewajka AJ, et al. 1980 (123) 7398027	**Study type:** Prospective, observational **Size:** N=29	**Inclusion criteria:** Pts requiring TTVP. **Exclusion criteria:** N/A	**1° endpoint:** Femoral vein thrombosis and pulmonary emboli **Results:** 34% of pts had femoral vein thrombosis, and 60% had lung scan evidence of pulmonary emboli.	• TTVP via femoral vein access is associated with a high rate of thromboembolic complications, despite low-dose heparin. • 2/29 pts received TTVP for SND.
Sodeck GH, et al. 2006 (77) 17212976	**Study type:** Observational, retrospective, single center **Size:** N=277	**Inclusion criteria:** Pts presenting to ED with compromising bradycardia **Exclusion criteria:** Asymptomatic bradycardia	**1° endpoint:** 30 d mortality **Results:** 48% AVB, 17% SB/AVB, Sinus arrest 15%, AF 14%, PM failure 6%. 20% required transvenous pacing for stabilization, 50% permanent pacing	• Not all pts with bradycardia required temporary pacing
Jou YL, et al. 2010 (124) 20946290	**Study type:** Observational, retrospective, single-center **Size:** N=509	**Inclusion criteria:** Pts presenting with bradycardia requiring temporary pacing **Exclusion criteria:** N/A	**1° endpoint:** Clinical characteristics and underlying etiologies **Results:** 64% of temporary pacers were for AVB. AAD use correlated with SND in 38%. Increasing AVB seen over time	• Idiopathic degeneration was related to AVB, whereas extrinsic etiologies were related to SND.
McCann P, 2006 (125) 17235372	**Study type:** Systematic review of temporary cardiac pacing **Size:** N=15 studies, 3817 subjects	**Inclusion criteria:** Studies of temporary pacing wires **Exclusion criteria:** N/A	**1° endpoint:** Complication by access site, outcomes **Results:** The most common indication was AVB. Mean complication rate was 26.5% (10–59.9%), including access failure, lead malposition, sepsis, arterial puncture, lung or myocardial puncture, or arrhythmia	• Internal jugular vein access was associated with a lower complication rate compared with subclavian and femoral veins • Complications appear to be lower if operator is specialized

				• Antibiotics and ultrasound access reduced the risk of complications. • Methodologic limitations
Bjornstad CC, et al. 2012 (126) 22390277	**Study type:** Observational, prospective, 5 center study **Size:** N = 50	**Inclusion criteria:** All pts with temporary cardiac pacing wires **Exclusion criteria:** N/A	**1° endpoint:** Complications, outcomes **Results:** 30% with SND. Permanent pacing required in 60%, repeat procedures in 12%, mortality 18%, bacteremia 6%.	• High rates of subsequent PPM implantation • High rates of complications.

Data Supplement 20. RCTs of Transcutaneous Pacing (Section 5.3.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
PrePACE Morrison LJ, et al. 2006 (86) 17933452	**Aim:** To evaluate the feasibility of a RCT of transcutaneous pacing vs. dopamine for atropine and fluid refractory bradycardia in the prehospital setting. **Study type:** RCT **Size:** 151 met criteria, 82 enrolled	**Inclusion criteria:** Unstable bradycardia unresponsive to fluid and atropine: heart rate <60 per minute and systolic BP (SBP) <80 mm Hg; or heart rate <60/min and SBP <100 mm Hg and at least one additional sign/symptom **Exclusion criteria:** Advance directives, trauma, hyperthermia, hypothermia or cardiac arrest, pts in whom it was not possible to start an intravenous line.	**Intervention:** All pts received 250 ml saline IV bolus. If nonresponse, pts received atropine 1 mg, repeated if improved. If pts failed to respond, they were randomized to transcutaneous pacing (with midazolam) vs. comparator. **Comparator:** Dopamine starting at 5 mcg/kg min, increasing the dose by 5 mcg/kg min every 2 min until an improvement in signs and symptoms was observed, maximum dose of 20 mcg/kg min	**1° endpoint:** Survival to hospital discharge **Safety endpoint (if relevant):** Ventricular arrhythmia, cutaneous burns, chest wall discomfort, cardiac arrest, TCP failure.	• Survival to hospital discharge was similar in both groups (70% vs. 69%; p=0.93), as were 2° outcomes. • Paramedics chose not to enroll 20 pts due to pain concerns. 71% of TCP pts experienced chest discomfort during pacing.
Barthell E, et al. 1988 (127) 3056132	**Aim:** To determine if prehospital cardiac pacing affects mortality **Study type:** RCT) **Size:** N=239; 226 pulseless (asystole and EMD); 13 with hemodynamically significant bradycardia	**Inclusion criteria:** Pts with hemodynamically significant bradycardia **Exclusion criteria:** N/A	**Intervention:** Transcutaneous pacing **Comparator:** ACLS	**1° endpoint:** Survival to hospital admission (21.4% in pacing group vs. 20.6%) and survival to discharge (6.8% vs. 4.4%) **Safety endpoint:** None	• Randomization by day • No difference in rhythm subgroups of asystole vs. EMD • Improved survival in hypotensive bradycardic group (6/6 resuscitated, 5/6 survived, vs. 2/7 and 1/7 controls)

Data Supplement 21. Nonrandomized Trials, Observational Studies, and/or Registries of Transcutaneous Pacing (Section 5.3.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)

Sherbino J, et al. 2006 (128) 16814446	**Study type:** Systematic review of the efficacy of transcutaneous pacing in the management of symptomatic bradycardia and bradyasystolic arrest in the prehospital setting **Size:** 7 studies	**Inclusion criteria:** Case series, RCTs, and one subgroup analysis of transcutaneous pacing in symptomatic bradycardia or bradyasystolic arrest. inclusion criteria were euthermic, nontraumatized adults, who experienced prehospital hemodynamically symptomatic bradycardia or bradyasystolic cardiac arrest. Symptomatic bradycardia was defined a priori as a heart rate less than 60 bpm and at least one of the following: systolic BP less than 80 mm Hg; a change in mental status; angina pectoris; or acute pulmonary oedema.8 Bradyasystolic cardiac arrest was defined as the absence of a palpable pulse in the presence of an electrocardiographic bradycardic or asystolic rhythm. **Exclusion criteria:** N/A	**1° endpoint:** Survival to hospital discharge **Results:** No difference in survival to hospital discharge was noted in bradyasystolic cardiac arrest. A subgroup analysis in symptomatic bradycardia study showed borderline improved survival to discharge.	• Evidence to support the use of transcutaneous pacing in the prehospital setting for symptomatic bradycardia is insufficient. • Symptomatic bradycardia was defined as a heart rate less than 60 bpm and at least one of: systolic BP <80 mm Hg, change in mental status, angina, or pulmonary edema; the relevance to acute SND is therefore unclear.
Hedges JR, et al. 1991 (129) 1721129	**Aim:** To determine the importance of hemodynamic status and effect of prehospital transcutaneous pacing in pts with symptomatic bradycardia **Study type:** Observational	**Inclusion criteria:** Witnessed CV decompensation and initial bradycardia **Exclusion criteria:**	**1° endpoint:** Survival to hospital discharge. **Safety endpoint:** N/A	• Survival to hospital discharge showed a trend towards improvement in the pacing group (15% vs. 0%; p=0.07)

	Intervention: Transcutaneous pacing **Comparator**: No pacing **Size:** N=51			• Pts with a palpable pulse on EMS arrival had better survival (80% in paced group vs. 0%; p= 0.02)
Zoll PM, et al., 1985 (130) 3886190	**Aim:** To evaluate the effectiveness of external noninvasive TCP **Study type:** Prospective, observational, multicenter (3) **Size:** N=134	**Inclusion criteria:** Pts requiring or likely to require temporary pacing. **Exclusion criteria:** N/A	**1° endpoint:** Clinical outcomes **Results:** TCP was well tolerated in 73/82 awake pts, and successfully evoked response in 105/134.	• TCP was clinically useful. • Over 25% of enrolled subjects had SND as an indication for pacing.
Clinton JE, et al. 1985 (131) 3914511	**Study type:** Observational, single center **Size:** N=37	**Inclusion criteria:** Emergency room pts with hypotension and bradycardia **Exclusion criteria:** N/A	**1° endpoint:** Successful pacing capture and hemodynamic pacing response. **Results:** 8/37 pts were successfully treated with TCP. Surviving responders were more likely to present with sinus bradycardia, AF with bradycardia, or CHB, compared to asystole.	• TCP can effectively treat hemodynamically significant bradycardia, but does not appear to be useful in asystole. • 2/37 pts had SND as an indication for pacing.

Data Supplement 22. RCTs of General Principles of Chronic Therapy/Management of Bradycardia due to Sinus Node Dysfunction (Section 5.4.1)

Study Acronym; Author; Year Published; PMID	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
ADEPT Lamas GA, et al. 2007 (132) 17765608	**Aim:** To determine whether DDDR pacing improves QOL when	**Inclusion criteria:** Age ≥21 y, Class I or 2A indication for pacing, demonstrated chronotropic incompetence,	**Intervention:** MDT Kappa 400 DDDR pacemaker programmed to DDDR (N=443)	• Total exercise time (6 mo): 7.3 vs. 7.1 min (p=0.98) • Specific Activity Scale (SAS) at 1 y: 1.5 vs. 1.6 (p=0.96)	• No differences in other 2° QOL endpoints • CHF hospitalizations in DDDR group vs. DDD

	compared to DDD pacing alone **Study type:** Multi-center single-blind RCT **Size:** 872 pts	cannot exceed 80% of MPHR (220-age) at peak exercise **Exclusion criteria:** AF for >1 mo, overt CHF, serious chronic illness, score of <17 on MMSE, inability to tolerate high-rate pacing, severe limitations of functional capacity	**Comparator:** MDT Kappa 400 DDDR pacemaker programmed to DDD (N=429) Mean follow-up 1 y 64% had SND Vp% >90 in both groups		group: 7.3% vs. 3.5%; p=0.01 • No differences in other clinical endpoints
THEOPACE Alboni P, et al. 1997 (133) 9236443	**Aim:** To prospectively assess the effects of PPMs and theophylline in pts with SSS **Study type:** Randomized controlled trial **Size:** 107 pts	**Inclusion criteria:** Age ≥45 y, mean resting sinus rate <50 bpm and/or intermittent SA block, symptoms attributable to SND **Exclusion criteria:** very severe SSS, refractory HF, recent MI or stroke, life expectancy <2 y, significant renal or hepatic disease, Hx of VT, prior usage of theophylline, need for BB or CCB	**Intervention 1:** oral theophylline 550 mg/d (N=36) **Intervention 2:** DDDR PPM programmed to lower rate of 60–70 ppm and prolonged AV delay (N=36) **Comparator:** No treatment (N=35) Mean follow-up 19±14 mo	• Syncope: 6 (17%) theophylline, 2(6%) PPM, 8 (23%) control arm: p=0.02 (PPM vs. control); p=0.07 (theophylline vs. control) • HF: 1(3%) theophylline, 1(3%) PPM, 6(17%) control arm: p=0.05 (lower HF in PPM and theophylline vs. control arm • Permanent AF: 2(6%) theophylline, 3(9%) PPM, 4(11%) control arm: no difference (p=NS)	• Thromboembolism: 3(9%) theophylline, 3(9%) PPM, 1(3%) control arm: no difference (p=NS)

Data Supplement 23. Nonrandomized Trials, Observational Studies, and/or Registries of General Principles of Chronic Therapy/Management of Bradycardia due to Sinus Node Dysfunction (Section 5.4.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Sasaki Y, et al. 1988 (134) 2462243	Long-term follow-up of pts with SSS **Study type:** Prospective cohort **Size:** 49 pts	**Inclusion criteria:** Pts with SSS who underwent EPS and were symptomatic from bradycardia and requiring pacing, sinus pause >3 s during EPS **Exclusion criteria:** N/A	**Results:** • VVI pacing – 25 pts; atrial/DC pacing – 24 pts • Chronic AF: VVI vs. physiologic pacing group (36% vs. 0%; p<0.01) • Thromboembolism: VVI vs. physiologic pacing group (20% vs. 0%; p<0.05)	• In this group of pts with SSS requiring PPM, mode of pacing did not influence the survival rate; however, CV deaths were fewer in the physiologic pacing group. • There were significantly higher incidences of chronic AF and thromboembolism in

			• No difference in HF occurrence	the VVI group although this group was followed for a significantly longer period of time than the physiologic pacing group (35.1 vs. 19.7 mo; p<0.01)
Goldberger JJ, et al. 2011 (135) 21757182	Significance of asx bradycardia for subsequent PM implantation and mortality in pts age >60 y **Study type:** Retrospective cohort **Size:** 2,560 pts	**Inclusion criteria:** Age >60 y, resting heart rate <55 bpm (bradycardia group, N=470) or heart rate between 60–70 bpm (control group, N=2,090) **Exclusion criteria:** PPM implantation within 2 wk of initial EKG, heart rate outside the above range Mean follow-up 7.2 ± 2.9 y	**Results:** • Incidence of PPM placement: 9% in bradycardia cohort vs. 5% in control group; p<0.001 • Protection against mortality in the bradycardia group (HR: 0.78; 95% CI: 0.65–0.94; p=0.010)	• Higher incidence of PPM implantation in the bradycardia group did not appear until after the first 4 y. • Older outpatients with bradycardia not requiring urgent PPM implantation have very low rate (<1%/y) of subsequent PPM implantation. • Asymptomatic bradycardia has no adverse impact on all-cause mortality and may even be protective.
Denniss AR, et al. 1992 (75) 1572741	Electrophysiologic studies in pts with unexplained syncope **Study type:** Prospective cohort **Size:** 111 pts	**Inclusion criteria:** Unexplained syncope, prior general medical evaluation (H&P, CXR, echo, LHC, neuro exam, heart monitor, etc) **Exclusion criteria:** Documented tachy or bradyarrhythmia, Dx of vasovagal syncope, postural hypotension, AS, HOCM or prolonged QT interval Mean follow-up 20 mo	**Results:** • No mortality within 30 d of EPS • Pts with heart disease (CAD, HTN, MVP, CMP) had higher incidence of conduction disease (26%) than those w/o heart disease (8%; p<0.05) • Abnormal EPS (conduction disease, SVT, VT) findings in 42% of pts with heart disease but 16% of pts w/o heart disease (p<0.01) • Syncope occurred in only 5% of treated pts with abnormal findings at EPS vs. 24% in the group not receiving any Rx (p<0.05) • No recurrent syncope in 27 pts treated with PPM vs. recurrent syncope in 20 of 84 pts (24%) not given PPM (p<0.05)	• Diagnostic yield of EPS is increased in pts with heart disease. • Pts with no heart disease had no mortality.
Teichman SL, et al. 1985 (136) 4025122	The value of EPS in syncope of undetermined origin: Report of 150 cases	**Inclusion criteria:** Pts with syncopal and near-syncopal events (SUO) unexplained after general	• EP abnormality that could explain SUO was demonstrated in 36% of pts	• Presence of organic heart disease increased the incidence of positive EPS finding.

	Study type: Prospective cohort **Size:** 150 pts	medical evaluation, neuro evaluation, CXR, orthostatic, CSM, continuous rhythm monitoring for at least 24 h **Exclusion criteria:** Heart block, bradycardia, pauses >2.5 s, PVCs, VT, SVT, orthostasis Mean follow-up 31 mo	• Presence of organic heart disease was associated with increase in the incidence of EP findings (85% with vs. 64% w/o organic heart disease; p<0.005) • Pts with LBBB were more likely to have abnormal EPS than pts with RBBB (p<0.02)	• Pts who had EPS abnormalities detected and treated had had fewer recurrence of SUO than those with negative EPS. • SUO pts overall had low mortality rates during follow-up (±EPS)
Seidl K, et al. 2000 (137) 11227598	Diagnostic assessment of recurrent unexplained syncope with a new subcutaneously ILR **Study type:** Prospective cohort **Size:** 133 pts	**Inclusion criteria:** Recurrent unexplained syncope with initial nondiagnostic investigations (resting EKG, echo, ambulatory monitor, etc) **Exclusion criteria:** None Mean follow-up 10.8 mo	• Device-related complications in 9% • Definite determination of whether arrhythmia was the cause or not in 54% of pts. • 87% diagnostic yield (72 out of 83 pts) • Arrhythmic cause of syncope found in 44% of pts.	• ILR is useful for establishing a Dx when symptoms are recurrent but too infrequent for conventional noninvasive monitoring.

Data Supplement 24. RCTs of Clinical Presentation of Bradycardia due to Sinus Node Dysfunction (Section 5.3)

Study Acronym; Author; Year Published; PMID	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
DANPACE Nielsen JC, et al. 2011 (138) 21300730	**Aim:** To compare the efficacy of AAIR vs. DDDR pacing in pts with SSS and bradycardia **Study type:** RCT **Size:** 1,415 pts	**Inclusion criteria:** SA block or sinus arrest with pauses >2 s, PR ≤260 ms, QRS <120 ms, heart rate <40 while awake **Exclusion criteria:** AVB, BBB, long-standing PerAF, and	**Intervention:** Bipolar atrial lead only (AAIR pacing programmed to LR of 60 ppm) – must have 1:1 AV conduction at paced rate of 100 bpm (N=707) **Comparator:** DDDR pacing programmed to	• Mortality: 29.6% (AAIR) vs. 27.3% (DDDR) (adjusted HR: 0.94; 95% CI: 0.77–1.14; p=0.52)	• PAF: 28.4% (AAIR) vs. 23.0% (DDDR) (adjusted HR: 1.24; 95% CI: 1.01–1.52; p=0.042) • Chronic AF: 11.2% (AAIR) vs. 10.7% (DDDR) (adjusted HR: 1.01; 95% CI: 0.74–1.39; p=0.93) • Stroke: 5.5% (AAIR) vs. 4.8% (DDDR) (adjusted HR: 1.11; 95% CI: 0.70–1.77; p=0.65)

		carotid sinus hypersensitivity, planned cardiac surgery, life expectancy <1 y	LR of 60 ppm AND to minimize V pacing (N=708) [mean Vp%=65]		• HFH: 27 pts (AAIR) vs. 28 pts (DDDR) (p=0.90) • PPM reoperation: 22.1% (AAIR) vs. 11.9% (DDDR) (adjusted HR: 2.00; 95% CI: 1.54–2.61; p<0.001)

Data Supplement 25. RCTs of Permanent Pacing for Chronic Therapy/Management of Bradycardia due to Sinus Node Dysfunction (Section 5.4.4)

Study Acronym; Author; Year Published: PMID	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
DANISH Andersen HR, et al. 1997 (139) 9652562	**Aim:** Long-term follow-up of pts from a randomized trial of atrial vs. ventricular pacing for sick-sinus syndrome. To examine whether the beneficial effect of atrial pacing is maintained during extended follow-up of up to 8 y **Study type:** RCT **Size:** 225 pts	**Inclusion criteria:** Symptomatic bradycardia <50 bpm or pause >2 s **Exclusion criteria:** AVB, chronic AF, BBB, age <50, planned cardiac surgery, cancer, cerebral disease, CVA within 3 mo, major surgery, etc.	**Intervention:** Single chamber atrial pacing (only if 1:1 AV conduction at atrial pacing rate of 100 bpm) (N=110) **Comparator:** Single chamber ventricular pacing (N=115) Mean follow-up 5.5 y	• All-cause mortality: 39 atrial vs. 57 ventricular (RR: 0.66; 95% CI: 0.44–0.99; p=0.045) • CV mortality: 19 atrial vs. 39 ventricular (RR: 0.47; 95% CI: 0.27–0.82; p=0.0065) • AF: 26 atrial vs. 40 ventricular (RR: 0.54; 95% CI: 0.33–0.89; p=0.012) • Thromboembolism: 13 atrial vs. 26 ventricular (RR: 0.47; 95% CI: 0.24–0.92; p=0.023)	• Use of diuretics: significantly higher in the atrial group (p<0.05)
PASE Lamas GA, et al. 1998 (140) 9545357	**Aim:** To compare DC vs. ventricular only pacing for pts with symptomatic bradycardia **Study type:** RCT **Size:** 407 pts	**Inclusion criteria:** ≥65 y old, in SR, required PPM for prevention or treatment of bradycardia **Exclusion criteria:** Overt CHF, AF with no documentation of SR within 6 mo, serious noncardiac illnesses, cannot participate in quality-of-life assessments	**Intervention:** Dual chamber PPM programmed VVIR and programmed to LR limit of ≥50 bpm (N=204) **Comparator:** Dual chamber PPM programmed DDDR and programmed to LR limit of ≥50 bpm (N=203)	• PPM indications: AVB 49%, SND 43% • 26% (53) of VVIR group crossed over to DDDR group due to PM syndrome • QOL (as measured by SF-36 survey) improved significantly after PPM implantation (p<0.001) but NO difference between 2 pacing modes in QOL • In SND group (but not in AVB group), DC pacing resulted in significantly better QOL and CV functional status	• No significant differences in the rates of death from all causes, stroke or death, stroke or death or hospitalization for HF, and development of AF • Risk of AF development was higher in VVIR compared to DDDR group but was not statistically significant (28% vs. 19%; p=0.06)

MOST Lamas GA, et al. 2002 (141) 12063369	**Aim:** To compare DC vs. ventricular only pacing to treat pt with clinically significant bradycardia due to SND **Study type:** RCT **Size:** 2,010 pts	**Inclusion criteria:** ≥21 y old, in SR, undergoing DC PPM implant for symptomatic SND **Exclusion criteria:** Serious concurrent illnesses	**Intervention:** Dual chamber PPM programmed DDDR and programmed to LR limit of ≥60 bpm (N=1,014) **Comparator:** Dual chamber PPM programmed VVIR and programmed to LR limit of ≥60 bpm (N=996)	• Death or nonfatal stroke occurred in 21.5% of DDDR pts vs. 23.0% of VVIR pts (p=0.48) • 31.4% (313) of pts in the VVIR group was crossed over to DDDR group	• Incidence of AF was 21.4% in DDDR group vs. 27.1% in VVIR group (adjusted HR:0.77; 95% CI: 0.64–0.92; p=0.004) • Hospitalization for HF was 10.3% in DDDR group vs. 12.3% in VVIR group (adjusted HR:0.73; 95% CI: 0.56–0.95; p=0.02) • Combined clinical endpoint (death, stroke or HFH) was 27.6% in DDDR group vs. 29.9% in VVIR group (adjusted HR:0.85; 95% CI: 0.72–1.00; p=0.05) • DDDR pacing resulted in better improvement in QOL as compared with VVIR pacing. • **Adverse events:** Total 30 d rate of complication 4.8% (1.8% A-lead issue, 1.5% pneumothorax, 1.1% V-lead issue)
CTOPP Connolly SJ, et al. 2000 (142) 10805823	**Aim:** To assess whether physiologic pacing or ventricular pacing is better for pts with symptomatic bradycardia **Study type**: RCT **Size:** 2,568 pts	**Inclusion criteria:** ≥18 y old **Exclusion criteria:** Chronic AF, s/p AV nodal ablation, life expectancy <2 y	**Intervention:** Atrial-only pacing can be considered (if evidence of 1:1 AV conduction at paced rate of up to 130 bpm), o/w DC pacing (only 5.2% received atrial-only pacing) (N=1,094) **Comparator:** VVI pacing (N=1,474)	• PPM indications: 60% AVB, 42% SND • Annual rate of stroke or death was 5.5% for VVI pacing vs. 4.9% for physiologic pacing (95% CI: 10.5–25.7; p=0.33) • Subgroup analysis showed that pt with SND received no particular benefit from physiologic pacing compared to VVI pacing	• Annual rate of AF was 6.6% for VVI pacing vs. 5.3% for physiologic pacing (18% RR reduction; 95% CI: 0.3–32.6; p=0.05) • Annual rate of hospitalization for HF was 3.5% for VVI pacing vs. 3.1% for physiologic pacing (95% CI: -18.5–28.3%; p=0.52) • Annual rate of stroke was 1.1% for VVI pacing vs. 1.0% for physiologic pacing

					• **Adverse events:** More common in physiologic pacing group primarily due to atrial lead complications
SAVE PACe Sweeney MO, et al. 2007 (143) 17804844	**Aim:** To compare DC minimal ventricular pacing vs. DC pacing only in pts with sinus node disease **Study type:** RCT **Size:** 1,065 pts	**Inclusion criteria:** Symptomatic bradycardia due to SND, >18 y old, QRSd ≤120, AV conduction of 1:1 at 100 ppm **Exclusion criteria:** Persistent AF, ≥2 DCCV for AF within 6 mo, 2° or 3° AVB, life expectancy <2 y	**Intervention:** DC-minimal ventricular pacing (N=530) **Comparator:** DC pacing only (N=535)	• Median % of Vp (DC-minimal ventricular pacing 9.1% vs. DC only 99.0%; p<0.001) • Development of persistent AF (DC-minimal ventricular pacing 7.9% vs. DC only 12.7%; p=0.004); thus, 40% RR reduction for development of persistent AF (HR: 0.60; 95% CI: 0.41–0.88; p=0.009) • Time to 1st DCCV, AV node ablation or PVI favored DC-minimal ventricular pacing (HR: 0.62; 95% CI: 0.37–1.03; p=0.06)	• No significant difference in mortality (4.9% vs. 5.4%; HR: 0.85; 95% CI: 0.50–1.44; p=0.54) or rate of hospitalization for HF (2.8% vs. 3.1%; HR: 0.84; 95% CI: 0.42–1.68; p=0.62) • **Adverse events:** 4.0% lead problems, 0.3% device infections requiring removal, 1 intra-op death
DANPACE Nielsen JC, et al. 2011 (138) 21300730	**Aim:** To compare the efficacy of AAIR vs. DDDR pacing in pts with SSS and bradycardia **Study type:** RCT **Size:** 1,415 pts	**Inclusion criteria:** SA block or sinus arrest with pauses >2 s, PR ≤260 ms, QRS <120 ms, heart rate <40 while awake **Exclusion criteria:** AVB, BBB, LS PerAF, +carotid sinus hypersensitivity, planned cardiac surgery, life expectancy <1 y	**Intervention:** Bipolar atrial lead only (AAIR pacing programmed to LR of 60 ppm) – must have 1:1 AV conduction at paced rate of 100 bpm (N=707) **Comparator:** DDDR pacing programmed to LR of 60 ppm AND to minimize V pacing (N=708) (mean Vp%=65)	• Mortality: 29.6% (AAIR) vs. 27.3% (DDDR) (adjusted HR: 0.94; 95% CI: 0.77–1.14; p=0.52)	• PAF: 28.4% (AAIR) vs. 23.0% (DDDR) (adjusted HR: 1.24; 95% CI: 1.01–1.52; p=0.042) • Chronic AF: 11.2% (AAIR) vs. 10.7% (DDDR) (adjusted HR: 1.01; 95% CI: 0.74–1.39; p=0.93) • Stroke: 5.5% (AAIR) vs. 4.8% (DDDR) (adjusted HR: 1.11; 95% CI: 0.70–1.77; p=0.65) • HFH: 27 pts (AAIR) vs. 28 pts (DDDR) (p=0.90) • PPM reoperation: 22.1% (AAIR) vs. 11.9% (DDDR) (adjusted HR 2.00; 95% CI: 1.54–2.61; p<0.001)

Healey JS, et al. 2006 (144) 16801463	**Aim:** To determine whether atrial-based pacing (AAI or DDD) prevents MACE as compared to VVI pacing in pts with bradycardia **Study type:** Meta-analysis **Size:** 7,231 pts	**Inclusion criteria:** Publications since 1980, randomized controlled parallel design, have pt level data on outcomes **Exclusion criteria:** Post cardiac surgery or AV node ablation pts, multi-site A or V pacing, follow-up <6 mo	**Intervention:** Studies including pts who were AAI or DDD paced (atrial-based) pacing **Comparator:** Studies including pts who were VVI paced (ventricular-based) pacing	SND subgroup: • Overall mortality: ABP vs. VVI pacing (HR 0.92; 95% CI 0.81–1.05; p=NS Entire group: • AF: ABP vs. VVI pacing (HR: 0.80; 95% CI: 0.72–0.89; p=0.00003) • Stroke: ABP vs. VVI pacing (HR: 0.81; 95% CI: 0.67–0.99; p=0.035) • Implant complication rate: ABP 6.2% vs. VVI pacing 3.2%	SND subgroup: • Composite of stroke or CV death: ABP vs. VVI pacing (HR: 0.83; 95% CI: 0.72–0.97; p=0.04) • AF: ABP vs. VVI pacing (HR: 0.76; 95% CI: 0.67–0.86; p<0.0001) • Stroke: ABP vs. VVI pacing (HR: 0.84; 95% CI: 0.64–1.11; p=NS) • HFH: ABP vs. VVI pacing (HR: 0.92; 95% CI: 0.75–1.13; p=NS)
DANISH Andersen HR, et al. 1994 (145) 7983951	**Aim:** Prospective randomized trial of atrial vs. ventricular pacing in sick-sinus syndrome. To determine whether single chamber atrial or ventricular pacing is better in pts with SSS **Study type:** Prospective randomized **Size:** 225 pts	**Inclusion criteria:** Symptomatic bradycardia <50 bpm or pause >2 s **Exclusion criteria:** AVB, chronic AF, BBB, age <50 y, planned cardiac surgery, cancer, cerebral disease, CVA within 3 mo, major surgery, etc.	**Intervention:** Single chamber atrial pacing (only if 1:1 AV conduction at atrial pacing rate of 100bpm) (N=110) **Comparator:** Single chamber ventricular pacing (N=115) Mean follow-up 40±18 mo	• Death: 21 (atrial) vs. 25 (ventricular) (p=0.74) • CV death: 11 (atrial) vs. 20 (ventricular) (p=0.16) • AF: higher frequency in the ventricular group at follow-up • Thromboembolism: 6 (atrial) vs. 20 (ventricular) (p=0.0083) • HF did not differ between 2 groups	• LA diameter increased by more in the ventricular (p=0.0001) group vs. the atrial group (p=0.037) compared with preop values • 2 pts in the atrial group developed AVB **Adverse events:** • More common in atrial group (most common, lead dislodgement) than ventricular group (most common, PPM syndrome)
MOST sub-study Sweeney MO, et al. 2003 (146) 12782566	**Aim:** To examine the effect of pacing-induced ventricular desynchronization in pts with SND and normal QRSd	**Inclusion criteria:** SND, SR at the time of assignment, baseline QRSd <120 ms	**Intervention:** DDDR pacing (N=707) **Comparator:** VVIR pacing (N=632)	• Cum%VP: DDDR 90% vs. VVIR 58%; p=0.001 • HFH: In DDDR mode, the risk increased with increased Cum VP% from 0% up to ~40% pacing then leveled out. Vp >40% of time as	• AF: Risk increased by 1% for each 1% increase in Cum%VP up to 85%; p=0.012 (DDDR). Risk increased by 0.7% increase in Cum%VP up to 80%; p=0.039 (VVIR).

	Study type: Post-hoc analysis of RCT **Size:** 1,339 pts	**Exclusion criteria:** Baseline QRSd >120 ms	Median follow-up 33.1 mo	compared to <40% of time was associated with HR: 2.60 (p=0.040). In VVIR mode, the risk was level between 0–80% and increased from 80–100%. Vp >80% of time as compared to <80% of time was associated HR: 2.50 (p=0.0012)	
Nielsen JC, et al. 2003 (147) 12932590	**Aim:** A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with SSS. To compare AAI and DDD pacing in pts with SSS **Study type:** RCT **Size:** 177 pts	**Inclusion criteria:** SSS, normal AV conduction, symptomatic bradycardia <40 b symptomatic QRS pause of >2 s, age>18 y **Exclusion criteria:** BBB, AVB, chronic AF, cerebral disease, planned cardiac or major surgery, cancer	**Intervention 1:** AAIR (N=54) **Intervention 2:** DDDR with short AV delay (<150 ms) (DDDR-s) (N=60) **Intervention 3:** DDDR with fixed long AV delay (300 ms) (DDDR-l) (N=63) Mean follow-up 2.9 y	• LA diameter increased significantly in both DDDR groups (p<0.05) • LVES diameter increased significantly in both DDDR groups (p<0.05) • LVED diameter increased significantly in DDDR-l group (p<0.01) • LVFS decreased significantly in DDDR-s group (p<0.01) • Percent Vp: 90% in DDDR-s vs. 17% in DDDR-l	• AF incidence at follow-up: AAIR 7.4%, DDDR-s 23.3%, DDDR-l 17.5% (p=0.03) • Stroke: AAIR 5.6%, DDDR-s 11.7%, DDDR-l 6.3% (p=0.32) • Death: AAIR 16.7%, DDDR-s 23.3%, DDDR-l 22.2% (p=0.51) • CV death: AAIR 7.4%, DDDR-s 11.7%, DDDR-l 14.3% (p=0.43)
DANPACE Brandt NH, et al. 2016 (148) 28039212	**Aim:** To present a long-term outcome of initial DANPACE trial **Study type:** Long-term follow-up of RCT **Size:** 1,384 pts	**Inclusion criteria:** SA block or sinus arrest with pauses >2 s, PR ≤260 ms, QRS <120 ms, heart rate <40 while awake **Exclusion criteria:** AVB, BBB, long-standing PerAF, with carotid sinus hypersensitivity, planned cardiac surgery, life expectancy <1 y	**Intervention:** Bipolar atrial lead only (AAIR pacing programmed to LR of 60 ppm) – must have 1:1 AV conduction at paced rate of 100 bpm (N=696) **Comparator:** DDDR pacing programmed to LR of 60 ppm AND to minimize V pacing (N=688) Mean follow-up 8.9 y	• All-cause mortality: 59.3% AAIR vs. 53.3% DDDR (HR: 1.03; 95% CI: 0.90–1.19; p=0.65)	• AF: 28.6% AAIR vs. 29.1% DDDR (aHR: 0.98; 95% CI: 0.80–1.19; p=0.82) • Ischemic stroke: 9.0% AAIR vs. 8.6% DDDR (Ahr: 1.00; 95% CI: 0.69–1.43; p=0.99) • HFH: 12.0% AAIR vs. 11.5% DDDR (aHR: 1.01; 95% CI: 0.74–1.38; p=0.95) • Annual rate of pacing mode change from AAIR to DDDR 4.5%

ADEPT Lamas GA, et al. 2007 (132) 17765608	**Aim:** To determine whether DDDR pacing improves QOL when compared to DDD pacing alone **Study type:** Multi-center single-blind RCT **Size:** 872 pts	**Inclusion criteria:** Age ≥21 y, Class I or 2A indication for pacing, demonstrated chronotropic incompetence, cannot exceed 80% of MPHR (220-age) at peak exercise **Exclusion criteria:** AF for >1 mo, overt CHF, serious chronic illness, score of <17 on MMSE, inability to tolerate high-rate pacing, severe limitations of functional capacity	**Intervention:** MDT Kappa 400 DDDR pacemaker programmed to DDDR (N=443) **Comparator:** MDT Kappa 400 DDDR pacemaker programmed to DDD (N=429) Mean follow-up 1 y 64% had SND Vp% >90% in both groups	• Total exercise time (6 mo): 7.3 vs. 7.1 min (p=0.98) • Specific Activity Scale (SAS) at 1 y: 1.5 vs. 1.6 (p=0.96)	• No differences in other 2° QOL endpoints • CHF hospitalizations in DDDR group vs. DDD group: 7.3% vs. 3.5%; p=0.01 • No differences in other clinical endpoints
RAST Krahn AD, et al. 2001 (72) 11435336	**Aim:** To find out whether prolonged monitoring strategy is better than conventional strategy in the evaluation of recurrent syncope **Study type:** Prospective randomized trial **Size:** 60 pts	**Inclusion criteria:** Recurrent unexplained syncope or syncope X 1 associated with injury **Exclusion criteria:** LVEF <35%, <1 y expected survival, unable to provide follow-up or consent, clear NMS	**Intervention:** ILR (MDT Reveal) monitoring for 1 y (N=27) **Comparator:** Conventional testing – 2 to 4 wk of external loop recorder, TTT and EP testing (SNRT, SACT, antegrade/retrograde conduction, programmed electrical stimulation) (N=30) Crossover was allowed if Dx was unable to be made.	• Dx obtained in 14 of 27 pts (ILR group) vs. 6 of 30 pts (conventional group) (52% vs. 20%; p=0.012)	N/A
EaSyAS Farwell DJ, et al. 2004 (73)	**Aim:** Investigate the impact of ILRs on unselected	**Inclusion criteria:** Recurrent syncope but no definitive Dx	**Interventions:** CSM + TTT + implantation of loop recorder (N=103)	• EKG Dx made: 34 (33%) in ILR group vs. 4 (4%) in	• Total medical costs: £406 in ILR group vs. £1210 in

15246645	population of syncopal pts presenting to one institution **Study type:** Randomized trial **Size:** 201 pts	following initial clinical w/u (including CSM and TTT) **Exclusion criteria:** Structural heart disease	**Comparator:** CSM + TTT + conventional investigation (N=98) Mean follow-up 276 d	conventional group (HR: 8.93; 95% CI: 3.17–25; p<0.0001)	conventional group (mean difference £809; 95% CI: 123–2730)
FRESH Podoleanu C, et al. 2014 (74) 25241220	**Aim:** To compare conventional evaluation vs. early use of ILR in low-risk pts with syncope in France **Study type:** Prospective open-label randomized multicenter study **Size:** 78 pts	**Inclusion criteria:** Any recent unexplained syncope (after basic clinical exam) **Exclusion criteria:** Significant heart disease, EF <40%, Hx of MI or unstable CAD, Hx of arrhythmia, family Hx of SCD, conduction disturbance on EKG, HOCM, AS, potentially arrhythmogenic drug use	**Intervention:** ILR group (N=39) **Comparator:** Conventional evaluation strategy group (N=39) F/u 14 mo	• Identification of cause: 18 (46.2%) pts in ILR group vs. 2 (5%) pts in conventional group (p<0.001) • Days of hospitalization: 5.7 d in ILR group vs. 8.0 d in conventional group (p=0.55) • Number of advanced cardiac tests needed: 0.03/pt in ILR group vs. 0.2/pt in conventional group (p=0.05)	• Quality of life was no different between the 2 groups
THEOPACE Alboni P, et al. 1997 (133) 9236443	**Aim:** To prospectively assess the effects of PPMs and theophylline in pts with SSS **Study type:** Randomized controlled trial **Size:** 107 pts	**Inclusion criteria:** Age ≥45 y, mean resting sinus rate <50 bpm and/or intermittent SA block, symptoms attributable to SND **Exclusion criteria:** Very severe SSS, refractory HF, recent MI or stroke, life expectancy <2 y, significant renal or hepatic disease, Hx of	**Intervention 1:** oral theophylline 550 mg/d (N=36) **Intervention 2:** DDDR PPM programmed to lower rate of 60–70 ppm and prolonged AV delay (N=36) **Comparator:** No treatment (N=35)	• Syncope: 6(17%) theophylline, 2(6%) PPM, 8(23%) control arm: p=0.02 (PPM vs. control); p=0.07 (theophylline vs. control) • HF: 1(3%) theophylline, 1(3%) PPM, 6(17%) control arm: p=0.05 (lower HF in PPM and theophylline vs. control arm • Permanent AF: 2(6%) theophylline, 3(9%) PPM,	• Thromboembolism: 3(9%) theophylline, 3(9%) PPM, 1(3%) control arm: no difference (p=NS)

		VT, prior usage of theophylline, need for BB or CCB	Mean follow-up 19±14 mo	4(11%) control arm: no difference (p=NS)	

Data Supplement 26. Nonrandomized Trials, Observational Studies, and/or Registries of Reversible Causes of AV block (Section 6.3.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Kenneback G, et al. 2007 (149) 17255148	**Study type:** Single-center, prospective cohort (Sweden) **Size:** N=17 (53% men), mean age 77 y	**Inclusion criteria:** Pts admitted with high-degree AVB on antiarrhythmic therapy (88% beta blocker) who received PPM, who then had AAD withdrawn with return of AV conduction. **Exclusion criteria:** Valve surgery in past year, permanent AF	**1° endpoint:** Recurrence of AVB detected by PM algorithm over 2 y **Results:** 9/12 pts (75%) with QRS ≥120 ms and 1/5 pts (20%) developed recurrent AVB. 6/17 pts (35%) developed atrial tachyarrhythmias requiring AAD tx	• Appropriate to place PPM in pts with AVB and QRS ≥120 ms w/o further delay or evaluation.
Knudsen MB, et al. 2013 (150) 23869746	**Study type:** Single-center, retrospective cohort (Denmark) **Size:** N=55 (55% male, mean age 77 y)	**Inclusion criteria:** Pts admitted with 2/3 AVB, had temporary wire, were on class II-IV AADs or digoxin. **Exclusion criteria:** No ECG documentation, AVB due to other identified cause, prior PPM explant, died within several days	**1° endpoint:** Need for PPM; complications of TPM **Results:** 47/55 (85%) required PPM in hospital. 2/55 had recurrent AVB and required PPM. 11% of pts had complication of TPM (infection/ dislodgment), also prolonged hospital stay	• Pts with AVB on AADs /digoxin do not benefit from TPM and drug washout. Should proceed to PPM w/o delay. • "In the elderly, the drug is virtually never the sole culprit; rather, it just exposes the underlying weakness of the aging conduction system"
Osmonov D, et al. 2012 (151) 22530749	**Study type:** Single-center retrospective cohort (Turkey) **Size:** N=108 (16% of all 668 pts admit with 2/3 AVB). 30/108 (28%) had AF with SVR	**Inclusion criteria:** All pts admitted with 2/3 AVB who were on AV nodal blocking drugs 2008–9 **Exclusion criteria:** MI, electrolyte disturbances, digoxin toxicity, vasovagal syncope	**1° endpoint:** Resolution/ recurrence AVB, need for PPM **Results:** Resolution of AVB with 72 h in 78/108 (72%). 21/78 (27%) had recurrence of AVB. Overall 51/108 (48%) had persistent of recurrent AVB despite drug withdrawal.	• Half of pts with AVB on nodal-blocking drugs require PPM before discharge despite drug withdrawal. • Limited follow-up – other pts may have required PPM at later date

Zeltser D, et al. 2004 (152) 15234417	**Study type:** Single-center retrospective cohort (Israel) **Size:** N=169 (60% male, mean age 78 y). 92/169 (54%) receiving AV nodal blockers	**Inclusion criteria:** All pts admitted with 2/3 AVB 1999–2003. **Exclusion criteria:** MI, digoxin toxicity, vasovagal syncope	**1° endpoint:** Resolution/ recurrence AVB, need for PPM **Results:** 79/92 (86%) had drug discontinued. 32/79(41%) had resolution of AVB. 18/32 had relapse of AVB within 3 wk	• Overall, only 15% of pts with AVB on nodal blocking drugs had AVB "caused by drugs" • F-u limited to 3 wk
Risgaard B, et al. 2012 (153) 22333242	**Study type:** Retrospective single-center/region cohort study (Denmark) **Size:** N=259 (mean age 78 y, 46% male). 49.7% had 2/3 AVB. 15% had AF-slow ventricular response	**Inclusion criteria:** All pts referred for urgent PPM in 2009 **Exclusion criteria:** Discharged from hospital before implant, referred from outpatient department	**1° endpoint:** d to implant, complications during wait **Results:** Mean 8.3 d hospitalization to implant (3.2 d to Dx; 5.1 d waiting for PPM). 83/259 pts (32%) had complications while waiting – Infection (11%), asystole (20%), NSVT (5%), cardiac arrest (3%), death (1%)	• Pt harm results from delay to PPM for capacity issues.
Farre N, et al. 2014 (154) 24491864	**Study type:** Retrospective single-center cohort (Spain) **Size:** N=79; mean age 72 y, 50% male	**Inclusion criteria:** Consecutive pts with "reversible" 3rd degree AVB not undergoing initial PPM implant **Exclusion criteria:** None stated	**1° endpoint:** Persistence/recurrence of AVB, PPM implant **Results:** 39% of pts w/o ischemic/infarction developed recurrent AVB, had PPM	• Outside setting of MI/ischemia, high proportion of pts with 3rd degree AVB and "reversible causes" develop recurrent AVB. • Close f-u warranted • Study was research letter with little data presented
Antman EM, et al. 1990 (100) 2188752	**Study type:** Open-label, 21-center prospective cohort study 1974–86 **Size:** N=150 pts (79=53% with high-degree AVB). 46% male, mean age 65 y	**Inclusion criteria:** Pts who received digoxin-specific Fab fragments in trial 1974–86. **Exclusion criteria:** None stated	**1° endpoint:** Clinical "response" **Results:** 80% complete resolution of signs/sx. 10% partial response, 10% complete response.	• AVB pts not separately analyzed
Hickey AR, et al. 1991 (101) 1993775	**Study type:** Multi-center US national prospective cohort	**Inclusion criteria:** All pts in US receiving anti-digoxin Fab fragments **Exclusion criteria:** None stated	**1° endpoint:** Resolution of symptoms of digoxin toxicity	• No separate analysis of AVB pts

	Size: N=717; 40% men, mean age 74 y		**Results:** 50% complete response, 24% partial response; 12 % no response. 3% recurrence rate. 1% allergy to therapy	
Sadek MM, et al. 2013 (155) 23623644	**Study type:** Systematic review **Size:** 10 publications; 299 pts	**Inclusion criteria:** English language, original outcome data on pts with cardiac sarcoidosis tx with steroids. **Exclusion criteria:** Reports less than 5 subjects or less than 3-mo follow-up	**1° endpoint:** Reversal or improvement in AVB **Results:** 27/57 (47%) cases treated with steroids had improved or recovered AV conduction vs. 0/16 pts. w/o steroid treatment.	• Considerable study heterogeneity • "Improvement" in AV conduction not defined • Outcome not defined in terms of need for PM
Kandolin R, et al. 2011 (156) 21427276	**Study type:** Single-center retrospective cohort (Finland) **Size:** N=133; 72 pts with unexplained AVB	**Inclusion criteria:** Pts. 18–55 y who had PPM implant for unexplained $2^{nd}/3^{rd}$-degree AVB **Exclusion criteria:** None described	**1° endpoint:** Dx of cardiac sarcoidosis; reversal of AVB with treatment. **Results:** 18/72 (25%) had probable (4) or definite (14) cardiac sarcoidosis AVB reversed in only 2/16 pts (13%) treated with steroids	• Selected population, tertiary referral center • Little data about AVB described • Overall suggests low chance of reversing AVB with steroid treatment
Ozcan KS, et al. 2012 (157) 22738687	**Study type:** Single-center retrospective cohort (Turkey) **Size:** N=50 (29 hypothyroid, 21 hyperthyroid)	**Inclusion criteria:** All pts. with $2^{nd}/3^{rd}$ degree AVB who had hyper- or hypothyroidism **Exclusion criteria:** MI, electrolytes abnormalities, digoxin toxicity, vasovagal syncope, on AADs	**1° endpoint:** Persistent AVB despite treatment of thyroid abnormalities **Results:** 46/50 (92%) pts required PPM; 2 additional pts had persistent AVB. 22/29 (76%) with hypothyroidism and 18/21 (86%) with hyperthyroidism had irreversible AVB.	• Thyroid abnormalities are rarely a cause of reversible AVB.
Forrester JD, et al. 2014 (158) 24879781	**Study type:** Systematic review of case reports and case series **Size:** 34 manuscripts reporting 45 cases	**Inclusion criteria:** English language case reports or series in peer-reviewed journal of pts with Lyme disease and ECG-documented 3^{rd} degree AVB **Exclusion criteria:** Not in English, pt not US, no pt variables reported	**1° endpoint:** Outcomes, need for PPM, persistence of AVB **Results:** 18/45 (40%) required TPM, 2/45 (4%) had PPM, both in 1980s. All other cases resolved, median time to resolution 6 d (range 1–42 d).	• AVB with Lyme carditis almost always resolves with treatment
Van der Linde, MR, 1991 (159) 1947815	**Study type:** Review of published case reports in Europe and North	**Inclusion criteria:** Published case reports 1977–90,	**1° endpoint:** Outcome, resolution of AVB, need for PPM	• PPM rarely needed after episode of Lyme carditis

	America, European questionnaire, personal communication, observations **Size:** 105 cases	questionnaire, personal communication, observations **Exclusion criteria:** None	**Results:** 49% had 3rd degree AVB, 16% had 2nd degree AVB. 35% required TPM, 94% with complete recovery of AV conduction, only 1 pt (1%) had persistent 3rd degree AVB	

Data Supplement 27. RCTs Comparing Medical treatment for AV block (Section 6.3.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Abu-Laban RB, et al. 2006 (104) 16698410	**Aim:** To determine whether aminophylline increases rate of ROSC after out of hospital cardiac arrest **Study type:** RCT **Size:** N=971	**Inclusion criteria:** Pts over 16 y in British Columbia 2001–3 with brady-asystolic arrest refractory to intubation, atropine and epinephrine **Exclusion criteria:** Do-not-resuscitate order, pregnancy, hemorrhage/trauma or hypothermia, end-stage renal disease, on theophylline	**Intervention:** 500 mg IV aminophylline bolus **Comparator:** Matching placebo	**1° endpoint:** ROSC: 24.5% I vs. 23.7% C (0.8%, -4.6–6.2; p=0.778) Survival to hospital admission: 6.6% I vs. 7.6% C (-1.0%, -4.3–2.2; p=0.527) Survival to hosp. discharge: 0.4% I vs. 0.6% C (-0.2%, -1.1–0.7%; p=0.653) **Safety endpoint (if relevant):** None	• Did not call out pt with AVB • Prehospital setting only
PrePACE Morrison, LJ, et al. 2008 (86) 17933452	**Aim:** To compare outcome of pts with prehospital unstable bradycardia with TCP vs. dopamine **Study type:** RCT **Size:** N=82; mean age 71 y; 57% male	**In Inclusion criteria:** Pts ≥18 y presenting to Toronto EMS with hemodynamically unstable bradycardia unresponsive to fluids and atropine **Exclusion criteria:** Trauma, hyperthermia, hypothermia, cardiac arrest	**Intervention:** TCP 80 bpm **Comparator:** Dopamine 5–20 mcg/kg/min	**1° endpoint:** Survival to hospital discharge 69% I vs. 70% C (p=NS) **Safety endpoint:** VT/VF/cardiac arrest/burn: 7.1% C vs. 7.5% C (p=NS)	• Half of eligible pts not randomized • This was a pilot study for potential larger RCT • Dopamine equivalent to TCP in this small pilot study

Data Supplement 28. Nonrandomized Trials, Observational Studies, and/or Registries of Medical Treatment for AV block (Section 6.3.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Brady WJ, et al. 1999 (79) 10459592	**Study type:** Single-EMS system retrospective cohort in US **Size:** N=131; 45 with AVB; Mean age 69 y; 53% male	**Inclusion criteria:** All nontraumatized pts from 1990–1993 who experienced bradycardia with associated hemodynamic instability who received atropine in field. **Exclusion criteria:** Not stated, but presumably cardiac arrest. Also excluded pre-hospital deaths (N=16)	**1° endpoint:** "Response" in 4 categories – adverse, none, partial, complete **Results:** Mean dose 1.1 mg. Of 37 pts with 3rd degree AVB in field, 21 arrived in ED with 3rd degree AVB and only 9 left ED with 3rd degree AVB. Of all pts, 27% had complete response, 20% partial, 50% none; 3% adverse	• Limited methodology, results poorly described
Feigl D, et al. 1984 (160) 6736451	**Study type:** Single center retrospective cohort study in Israel 1978–1982 **Size:** N=34; mean age 62 y; 82% male	**Inclusion criteria:** 2nd or 3rd degree AVB developing in course of IMI who survived >72 h **Exclusion criteria:** None	**1° endpoint:** Outcomes, response to atropine **Results:** Of 15 pts with early AVB (<6 h). Atropine normalized conduction in 20%, increased V rate in others. 5 had normalization with isoproterenol. 14 pts had late AVB – less response to atropine (mean 16 bpm). 50% required TPM	• Descriptive, uncontrolled study • No adverse events to drug therapy reported
Sclarovsky S, 1984 (161) 6731277	**Study type:** Single center retrospective cohort study in Israel 1972–1982 **Size:** N=76	**Inclusion criteria:** All pts with acute inferior MI who developed 2nd or 3rd degree AVB in hospital **Exclusion criteria:** Combined AMI and IMI	**1° endpoint:** Description of outcomes, response to atropine and isoproterenol **Results:** 6/14 (36%) of pts with early AVB improved vs. 13/17 (77%) pts with late AVB (p<0.05). 2/8 (25%) of pts with early block and 2/6 (33%). 50% of pts had TPM	• Descriptive uncontrolled study • No adverse events to drug therapy reported
Chihrin SM, et al. 2008 (162) 18308011	**Study type:** Single center prospective cohort in Canada **Size:** N=100; mean age 75 y; 56% male	**Inclusion criteria:** Consecutive pts from 2003–2006 undergoing PPM generator change who were PM dependent **Exclusion criteria:** None	**1° endpoint:** Elicitation of escape rhythm with PM stepdown to 30 bpm or isoproterenol 1–2 mcg/min **Results:** 59% demonstrated intrinsic rhythm with stepdown alone. Of remaining 41 pts, 28 (68%) demonstrated	• Suggests that isoproterenol can be used to elicit faster escape rate in pts with AVB

			intrinsic rhythm with isoproterenol. No adverse events.	
Hurley KF, et al. 2015 (105) 26593309	**Study type:** Systematic review of 5 RCTs **Size:** N=1254	**Inclusion criteria:** RCTs of aminophylline used for pre-hospital resuscitate of bradyasystolic cardiac arrest **Exclusion criteria:** N/A	**1° endpoint:** Survival to discharge/admission, ROSC **Results:** No improvement in outcome by any measure with aminophylline. Overall survival extremely low	• Aminophylline not useful in out of hospital bradyasystolic arrest
Sodeck GH, et al. 2007 (77) 17212976	**Study type:** Retrospective analysis of single ED registry from tertiary center in Austria **Size:** N=277; mean age 68 y; 62% male; about 50% AVB	**Inclusion criteria:** Consecutive pts admitted to ED 1994–2004 with symptomatic, hemodynamically significant bradycardia **Exclusion criteria:** Asymptomatic and terminally ill pts	**1° endpoint:** Use of drugs for bradycardia, use of pacing **Results:** IV medications given to 170 pts (61%) – Atropine in 141 (51%), orciprenaline 62 (22%), epi 24 (9%), dopamine 6 (2%). 7 pts had TCP (4 successful); 54 (20%) had temporary TVP. 137/277 (50%) received PPM	• Descriptive study with no control group • Pts with AVB not separately reported or analyzed • Minimal information on clinical effects of intervention given
Bertolet BD, et al. 1995 (163) 7661495	**Study type:** Single-center observational cohort in US **Size:** N=8; 3 with complete AVB	**Inclusion criteria:** Pts with significant AVB developing within 4 h of admission for acute inferior MI, resistant to atropine, given IV theophylline up to 250 mg **Exclusion criteria:** Pts who received BBs or CCBs prior	**1° endpoint:** Restoration of 1-1 AV conduction **Results:** All 8 pts had restoration of 1-1 AV conduction within 3 min lasting at least 24 h	• No controls • Very small, single-center experience
Altun A, et al. 1998 (164) 9789698	**Study type:** Single-center observational cohort in Turkey **Size:** N=8; 6 with complete AVB; mean age 68 y	**Inclusion criteria:** Pts with 2nd or 3rd degree AVB after IMI for at least 1 h, resistant to atropine. Given 2 doses of aminophylline 240 mg 1 h apart **Exclusion criteria:** Pts in hyperacute phase of MI, received AV nodal blocking drugs	**1° endpoint:** Restoration of AV conduction **Results:** Aminophylline restored 1-1 AV conduction in 7 pts and Mobitz I AVB in 1. No adverse effects. AVB relapsed in 1 pt only	• No controls • Very small, single-center experience

Goodfellow J, et al. 1995 (165) 7588933	**Study type:** Single-center case series in United Kingdom **Size:** N=3	**Inclusion criteria:** Pts with atropine-resistant AVB with acute inferior MI treated with streptokinase. All had hypotension **Exclusion criteria:** None	**1° endpoint:** Restoration of 1-1 AV conduction **Results:** 1-1 AV conduction restored promptly with resolution of hypotension in all	• No controls • Very small case series
Love, JN, et al. 1998 (90) 9674488	**Study type:** Single center case series in US **Size:** N=9	**Inclusion criteria:** Pts presenting with symptomatic bradycardia resistant to atropine 1 mg who received IV glucagon 1–7 mg then 3–5 mg/h **Exclusion criteria:** None	**1° endpoint:** Improvement in bradycardia and hemodynamics **Results:** All pts improved at least transiently	• Most pts had BBs and/or CCBs as significant co-factors • Unknown how many had AVB
Dhingra RC, et al. 1973 (166) 4744693	**Study type:** Single center cohort undergoing invasive EP study in US **Size:** N=42; 8 with 3rd degree AVB, 3 with 2nd degree AVB	**Inclusion criteria:** 42 pts with heart disease undergoing invasive EPS w/o and with isoproterenol **Exclusion criteria:** None	**1° endpoint:** Improvement in AV conduction and change in ventricular rate **Results:** 2/8 pts with 3rd degree AVB had improved conduction with isoproterenol, as did 3/3 pts with 3rd degree AVB. Ventricular rate improved in all subjects from mean of 45 bpm to 62 bpm, regardless of site of block	• Very small study • Bias in reflects those able to undergo EPS • Hemodynamics/ BP not measured • Suggests isoproterenol useful to augment heart rate in 2nd and 3rd degree AVB
Hatle L, et al. 1971 (167) 5557475	**Study type:** Single center prospective cohort from Norway **Size:** N=105 pts with 2nd or 3rd degree AVB in setting of acute MI	**Inclusion criteria:** Pts with acute MI treated 1966–1970 with 2nd or 3rd degree AVB treated with isoproterenol, generally 1–3 mcg/min **Exclusion criteria:** None stated	**1° endpoint:** Improvement in heart rate **Results:** In hospital mortality 48%. 60 pts received isoproterenol: 38 (63%) had increase in heart rate and BP; 12 (20%) had increased in heart rate but minimal change in BP; 8 (13%) had minimal change; 2 (3%) isoproterenol terminated due to ventricular ectopy. 3 pts had ventricular fibrillation on isoproterenol, 1 of which died. 14 pts treated with TVP, 3 of whom died from ventricular fibrillation	• Very early cohort when there was minimal treatment for acute MI • Extremely high mortality • In this group, isoproterenol appeared safe compared with TVP • Uncontrolled cohort study

Data Supplement 29. RCTs Comparing Temporary Pacing (Section 6.3.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Ferguson JD, et al. 1997 (113) 9217762	**Aim:** Compare 2 types of TVP catheters for success and complication rates **Study type:** Unblinded RCT **Size:** 40 pts, mean age 72 y. 85% with AVB	**Inclusion criteria:** Undergoing temporary VVI pacing (85% with AVB) guided by fluoroscopy **Exclusion criteria:** None stated	**Intervention:** Use of balloon-tipped electrode (N=20) **Comparator:** Use of semi-rigid electrode (N=20)	**1° endpoint:** Procedure duration (264 vs. 540 s; p<0.002), fluoroscopy time (87 vs. 189 s; p<0.01), suitability of final position (0 unacceptable vs. 7; p<0.0001). Thresholds similar **Safety endpoint (if relevant):** Dislodgement (1 vs. 3) Death (0 vs. 2)	• When guided by fluoroscopy, balloon-tipped catheters are easier to place successfully than semi-rigid catheters • Use of balloon-tipped catheter associated with trend toward lower complication rate
Barthell E, 1988 (127) 3056132	**Aim:** Compared TCP added to ACLS vs. ACLS alone for pre-hospital pts with asystole, EMD, or hypotensive bradycardia **Study type:** Unblinded RCT (alternate d randomization) **Size:** N=239; 142 with asystole; 84 with EMD; 13 with hypotensive bradycardia	**Inclusion criteria:** All adult, nontraumatic bradyasystolic episodes or arrests treated by Milwaukee County Paramedic System Oct 1986–May 1987 **Exclusion criteria:** None stated	**Intervention:** TCP + ACLS **Comparator:** ACLS alone	**1° endpoint:** Survival to hospital admission: Asystole/EMD 17% I vs. 20% C (p=NS) Hypo-brady 100% I vs. 29% C (p=0.01) Survival to hospital discharge: Asystole/EMD 2% I vs. 4% C (p=NS) Hypo-brady 83% I vs. 14% C (p=0.01) **Safety endpoint:** None	• Limited form of randomization • Overall, no effect of TCP for pre-hospital use for asystole/EMD arrest • Possible benefit for hypotensive bradycardia, but number of pts very small

Cummins RO, et al. 1993 (168) 8474514	**Aim:** Determine efficacy of TCP of asystolic out of hospital cardiac arrest **Study type:** Modified RCT by center **Size:** N=1056 cardiac arrests; N=537 with asystole as first rhythm; N=305 with asystole after VF	**Inclusion criteria:** All cardiac arrests in Seattle area over 3 y period; Primary group was those with asystole as first rhythm **Exclusion criteria:** None	**Intervention:** 16 EMS/fire districts given TCP and trained in use **Comparator:** 23 EMS/fire districts given TCP and trained in use	**1° endpoint:** Survival to hospital admission/ primary asystole: 8% I vs. 8% C (p=NS) Survival to discharge: 4% I vs. 2% C (OR: 2.05; p=NS) **Safety endpoint:** None	• No improvement for pts with initial VF • Limited form of randomization
Hedges JR, et al. 1987 (169) 3315295	**Aim:** Determine efficacy of TCP added to ACLS for prehospital hemodynamically significant bradycardia or asystole **Study type**: RCT (alternate day) **Size:** N=202	**Inclusion criteria:** All pts over 14 y treated by Thurston County, EMS for hemodynamically-significant bradycardia with decreased mental status (Glasgow coma score ≤12) **Exclusion criteria:** None stated	**Intervention:** On odd calendar days, EMS used TCP 100 bpm at max output for pts **Comparator:** On even calendar days, TCP was not used	**1° endpoint:** Survival to hospital admission: 17% I vs. 17% C (p=NS) Survival to hospital discharge: 6% I vs. 4% C (p=NS) **Safety endpoint:** None	• Limited form of randomization • No improvement with TCP
PrePACE Morrison, LJ, et al. 2008 (86) 17933452	**Aim:** To compare outcome of pts with prehospital unstable bradycardia with TCP vs. dopamine **Study type:** RCT **Size:** N=82; mean age 71 y; 57% male	**Inclusion criteria:** Pts 18 y or older presenting to Toronto EMS with hemodynamically unstable bradycardia unresponsive to fluids and atropine **Exclusion criteria:** Trauma, hyperthermia, hypothermia, cardiac arrest	**Intervention:** TCP 80 bpm **Comparator:** Dopamine 5–20 mcg/kg/min	**1° endpoint:** Survival to hospital discharge 69% I vs. 70% C (p=NS) **Safety endpoint:** VT/VF/cardiac arrest/burn: 7.1% C vs. 7.5% C (p=NS)	• Half of eligible pts not randomized • This was a pilot study for potential larger RCT • No benefit to TCP seen

Data Supplement 30. Nonrandomized Trials, Observational Studies, and/or Registries of Temporary Pacing (Section 6.3.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Sodeck GH, et al. 2006 (77) 17212976	**Study type:** Single center retrospective cohort in Austria **Size:** 277 pts (62% male, 48% AVB)	**Inclusion criteria:** Pts >18 y presenting to ED with "compromising bradycardia from 1994–2004; mean heart rate 33 bpm **Exclusion criteria:** Asymptomatic bradycardia, terminal illness	**1° endpoint:** 30 d mortality **Results:** 5% mortality at 30 d. 20% of pts treated with temporary TVP. 50% of those pts went on to have permanent pacing	• Temporary TVP required in about 20% of pts presenting to ED with symptomatic bradycardia • Half of those pts go on to PPM
Brikhahn RH, et al. 2004 (170) 15039689	**Study type:** Single-center retrospective cohort in US **Size:** 154 pts, 117 meeting inclusion/ exclusion criteria. Mean age 78 y, 38% male, 51% AVB)	**Inclusion criteria:** All pts with temporary TVP placed in ED, intensive care unit, or ward 1999–2002. Only 3% placed under fluoroscopy **Exclusion criteria:** Indication asystole, TVP placed in cath or EP lab, no attending supervision	**1° endpoint:** Successful temporary TVP placement. Complication rate. **Results:** 88% success on first attempt. 17% serious complication rate. 96% placed by cephalic approach. 67% had PPM. 23% in-hospital mortality	• Similar success rates between ED physicians and cardiologists • High overall success rate of implantation of TVP • Cephalic route rarely used in general practice today
Betts TR, 2003 (119) 12954959	**Study type:** Prospective registry in 5 regional hospitals in England in 1999 **Size:** 144 procedures in 111 pts; mean age 75 y.; 63% male; 51% AVB	**Inclusion criteria:** All TVPs placed over 9 mo period in 1999 **Exclusion criteria:** None cited	**1° endpoint:** General overview of procedure technique, outcomes, complications **Results:** Procedure times shorter for cardiologists, 28% complication rate. Immediate complication rates lower with experience (1/81) vs. inexperienced (5/59) operators. Infection occurred more in wires left in >48 h (17/86) than <48 h (2/55). 23% of comps resulted in delayed PPM	• Suggests benefit to TVP implant by cardiologists/ experienced operators • Greater infection risk for TVP wires left in >48 h • High rate of overall complications seen • 23% of comps delayed PPM implantation

Mahapatra S, et al. 2005 (171) 16171740	**Study type:** Case-control derived from prospective database 1995–2003 at Mayo Clinic **Size:** 50 pts with cardiac perforation after PPM vs. 100 controls	**Inclusion criteria:** Pts undergoing PPM 1995–2003 with perforation and new effusion. **Exclusion criteria:** Age <18 y, prior effusion or cardiac surgery within 4 wk of PPM	**1° endpoint:** Risk factors for perforation after PPM **Results:** 1.2% of all pts had perforation. Predictors of perforation in multivariate analysis included prior TVP (HR: 2.7; 95% CI: 1.4–3.9], helical screw leads (HR: 2.5), steroid use (HR: 3.2)	• Suggests benefit to avoiding TVP prior to permanent pacing unless essential
Lang R, et al. 1981 (172) 6169032	**Study type:** Single-center nonrandomized controlled study comparing balloon-tipped, flow-guided TVP vs. standard semi-rigid catheter **Size:** 111 consecutive pts (67 flow-guided, 44 semi-rigid)	**Inclusion criteria:** Consecutive pts requiring emergency or semi-urgent temporary TVP at a single Israeli center **Exclusion criteria:** None stated	**1° endpoint:** Successful implant, procedure time, threshold, multiple safety endpoints **Results:** Flow-guided TVP had 1) shorter insertion time (7 min vs. 14 min); less dislodgement (13% vs. 32%), lower incidence of serious ventricular arrhythmia (1.5 vs. 20.4%) Thresholds similar.	• Superiority of balloon-tipped, flow guided electrode catheter for temporary TVP demonstrated.
Hynes JK, et al. 1983 (115) 6823157	**Study type:** Retrospective single-center cohort at Mayo Clinic **Size:** 1022 pts, mean age 68 y, (65% male)	**Inclusion criteria:** Consecutive pts undergoing temporary TVP wire in Mayo Clinic coronary care unit 1976–81. **Exclusion criteria:** None stated	**1° endpoint:** Complications **Results:** Implanted mean 3.1 d, 64% placed antecubital route, 19% subclavian vein, 12 % internal jugular vein. 13.7% complication rate, increasing with duration of TVP. Lowest comp rate with internal jugular vein 5.3% pericarditis. PPM implanted in 58% of pts.	• Preference for internal jugular rand subclavian vein access sites confirmed
Winner S and Boon N, 1989 (173) 2769615	**Study type:** Retrospective single region cohort study	**Inclusion criteria:** Consecutive pts referred to regional center for PPM **Exclusion criteria:** Missing records	**1° endpoint:** Complications, defined as "major problems": dislodgement, infection, pericarditis/perforation, thrombosis, wire in left ventricle	• Advise avoiding TVP before PPM unless absolutely necessary

	Size: 266 pts/ 158 (59%) had temporary TVP		**Results:** 36% rate of major problems, much higher rate at smaller referral hospitals. 6% infection; 30% failure to pace, 4% pericarditis	
López Ayerbe J, et al. 2004 (114) 15544753	**Study type:** Retrospective single center cohort in Barcelona, Spain **Size:** N=530; mean age 74 y, 54% male; 51% AVB.	**Inclusion criteria:** Pts receiving TVP 1997–2003. All via femoral route (99%) with fluoroscopic guidance **Exclusion criteria:** Pts transferred out with no available f-u (N=38)	**1° endpoint:** Complications, outcomes **Results:** Mean duration 4.2 d. 22% complication rate: 1% death (3 tamponade, 1 asystole, 1 PE, 1 sepsis). 9% migration/dislodgement' 9% other (VTE, effusion, infection)	• Complication rates improved compared with series from 1980s and 1990s (18–43%) • Lower use in pts with acute MI seen
Bjornstad CC, et al. 2012 (126) 22390277	**Study type:** Prospective regional 5 hospital study in Norway 2010–11. **Size:** N=50; 45% AVB; mean age 79 y, 62% male	**Inclusion criteria:** All pts with TVP in 5 hospitals March 2010–March 2011. All with fluoroscopy **Exclusion criteria:** None stated	**1° endpoint:** Complications, outcomes **Results:** 96% TVP; 4% TCP. 60% received PPM; 14% died. 30% rate of "serious complications" including 6% death from sepsis	• Fewer TVPs being performed by more physicians with less experience • Lower complication rate with more experienced implanters
McCann P, 2006 (125) 17235372	**Study type:** Systematic review 1973–2004 **Size:** 15 studies; N=3737; mean age 71 y	**Inclusion criteria:** Cohort studies of TVP published 1973–2004 **Exclusion criteria:** None stated	**1° endpoint:** Complications, outcomes **Results:** Overall complication rate 26.5%: 15% failed access, 10% failed placement, 9% sepsis, 4% arterial puncture, 2% lung/myocardium puncture	• Methodologically limited systematic review • Higher complication rate in older pts • Lower complication rate when implanted by specialists • Trend toward greater use of right internal jugular access over time
Jou YL, et al. 2010 (124) 20946290	**Study type:** Single center retrospective cohort in Taiwan 2002–8 **Size:** N=509; mean age 77 y, 74% male; 64% AVB	**Inclusion criteria:** All pts with TVP 2002 8 at single center **Exclusion criteria:** None stated	**1° endpoint:** Trends in use **Results:** Greater use for AVB with intrinsic disease, less for sinus node dysfunction and MI over time. 48% had PPM implant within 30 d (mean 6 d) with increasing rate over time.	• High rate of PPM for degenerative AVB

Knudsen MB, et al. 2013 (150) 23869746	**Study type:** Retrospective single-center cohort at academic medical center in Denmark 2000–11. **Size:** N=575 with TVP. N=55 with AVB and potential culprit drug. Mean age 77 y, 56% male	**Inclusion criteria:** Pts getting TVP wire 2000–11 who had AVB and potential culprit drug discontinued **Exclusion criteria:** No ECG documentation; other etiology of bradycardia documented; PPM infection; in hospital death	**1° endpoint:** Indication for PPM despite drug discontinuation; complications and outcomes **Results:** 49/55 (89%) ultimately required PPM, including 26/27 (96%) on BBs. 11% comp rate from TVP. PPM postponed mean of 7 d for drug withdrawal	• Authors conclude that: "Primary PPM implantation should be considered in pts with high-degree AVB and concomitant AV blocking therapy, unless other reversible causes…exist." • "In the elderly, the drug is virtually never the sole culprit; rather, it just exposes the underlying weakness of the aging conduction system
Murphy JJ, 1996 (116) 8620131	**Study type**: Prospective cohort in 18 hospitals in Northern England over 6 mo **Size:** N=194. Mean age 71 y; AVB (67%). Acute MI in 53%	**Inclusion criteria:** All TVP implants in 18 hospitals. **Exclusion criteria:** None stated	**1° endpoint:** Complications **Results:** Immediate complications in 12/194 (6%) – VT/VF in 6, arterial puncture (3), pneumothorax (2), brachial plexus injury (1). Late comps in 22/194 (11%) – VT/VF 10, definite/possible sepsis in 10 (5.2%) – almost all had TVP>48 h. 38/194 (20%) needed repositioning. Total comps 35%. 11/194 (5.5%) died within 1 h of procedure. 56/194 (29%) had PPM	• High rate of implant by junior staff (residents) • Continued high rate of complications in British medical system in 1990s
Pinneri F, et al. 2013 (174) 22240748	**Study type:** Single-center nonrandomized controlled study. **Size:** N=106; mean age 77 y, 51% male; 75% had AVB; 59% ultimately required PPM	**Inclusion criteria:** Consecutive pts requiring TVP 2003–2010. Pts underwent TVP guided by echo (N=53) or fluoroscopy (N=53) based on operator preference. **Exclusion criteria:** Incomplete follow-up (N=4)	**1° endpoint:** The primary efficacy endpoints were time to pacing, pacing threshold, changes in threshold and need for catheter replacement. The primary safety endpoints were overall complications and death related to TVP implant. **Results:** Successful in all but 1 in each group (98%). Time to pacing and 24 h threshold better in echo-guided group. TVP repositioned in 6% of echo-guided and 22% of fluoroscopy-	• Echo-guided TVP was safer and more effective in this single center cohort with cardiologists comfortable with technique. • Not clear why dislodgment rate and thresholds would be worse in fluoroscopy group.

			guided groups (p<0.001), Comp rate lower in echo (11%) than fluoroscopy (41%) group; p<0.001).	
Braun MU, et al. 2006 (175) 16923004	**Study type:** Non-randomized prospective controlled study comparing externalized active-fixation lead vs. standard temporary TVP wire) **Size:** 49 pts, mean age 72 y, 63% male	**Inclusion criteria:** Pts with systemic infection requiring VVI pacing >48 h **Exclusion criteria:** None stated	**1° endpoint:** Implant success, pacing thresholds, acute complications, dislodgement rate **Results:** 100% implant success in both groups, paced median 8 d, similar procedure time, acute comps, pacing threshold. There were 24 dislodgments in 12 pts in control group, only 1 in active-fixation lead group (p<0.01)	• Externalized active fixation TVP lead associated with much lower dislodgment rate than standard TVP wire. Equally safe to implant • Externalized active fixation TVP preferred if pacing >48 h is anticipated.
de Cock CC, et al. 2003 (176) 12765453	**Study type:** Non-randomized single-center comparison of TVP by femoral route with active vs. passive fixation wire in Netherlands 1998–2001 **Size:** N=72 pts; mean age 70 y, 51% male	**Inclusion criteria:** Consecutive pts requiring TVP at single center requiring prolonged temporary pacing (>48 h) – mean 6 d **Exclusion criteria:** None stated	**1° endpoint:** Implant parameters, dislodgments, other adverse events **Results:** Threshold higher in active (1.38V) than passive (0.7V). Dislodgement lower in active (2/36) than passive (12/36) groups (p<0.001). Other comps similar	• Fewer dislodgments using an active fixation lead using femoral approach
Kawata H, et al. 2013 (177) 23482613	**Study type:** Single center retrospective cohort study of temp active fix lead (TPPM) after lead extraction at UCSD **Size:** N=23; mean age 72 y, 70% male; 87% AVB	**Inclusion criteria:** 23/47 pts undergoing extraction for CIED infection who were PM-dependent 2010–12 **Exclusion criteria:** None stated	**1° endpoint:** Duration of TPPM, complications **Results:** Duration of TPPM mean 12 d. 12/23 discharged to home or SNF. 1 pt died of sepsis from primary infection; 1 pt developed vegetation on TPPM lead – removed and replaced. No dislodgements. One pts had late pocket infection after reimplant.	• TPPM is a safe and effective option for PM-dependent pts awaiting reimplant after CIED infection • Allows earlier mobilization and potential discharge to home/nursing facility to await CIED reimplant

Chihrin SM, et al. 2006 (178) 17145220	**Study type:** Single center retrospective cohort in Canada 2001–5 **Size:** N=20 pts; median 2 d; mean age 62 y; 75% male	**Inclusion criteria:** Pts implanted with TPPM via left subclavian vein or right internal jugular vein over 5 y period **Exclusion criteria:** None stated	**1° endpoint:** Pacing duration, complications, costs **Results:** Duration median 2 d (1–83 d); 1 dislodgement requiring repositioning (5%). Using economic modeling, costs lower with TPPM than conventional TVP at 48 h	• Despite higher lead cost, TPPM cost-effective after 24 h due to lower complications and less intensive bed use
Lever N, et al. 2003 (179) 12527682	**Study type:** Single center cohort in United Kingdom **Size:** N=20; mean age 66 y, 85% male	**Inclusion criteria:** Consecutive pts requiring prolonged temp pacing due to infection or drug washout who had tunneled TPPM **Exclusion criteria:** None stated	**1° endpoint:** Pacing duration, outcome, complications **Results:** Duration median 28 d (9–81 d); no dislodgments or repositioning; 2 minor local site infections, no systemic infection. One pt died from sepsis unrelated to TPPM	• TPPM safe and effective, allows early mobility for pts requiring prolonged temporary pacing
Kornberger A, et al. 2013 (180) 23718817	**Study type:** Single center cohort in Germany **Size:** N=60; mean age 73 y, 73% male	**Inclusion criteria:** Consecutive pts implanted with TPPM for CIED infection (70%) or other reasons (30%) 2000–2009 **Exclusion criteria:** None stated	**1° endpoint:** Duration of pacing, outcomes, complications at 30 d **Results:** Successful in 98% - VVI in 56, DDD in 3) Duration mean 15 d. Intraoperative comps in 2 pts (3.3% - one venous thromboembolism and tamponade, one dislodgement during lead extraction). 4 late comps (6.7%) – 3 possible lead infections, 1 dislodgement.	• TPPM safe and effective option for prolonged temporary pacing
Zei P, et al. 2006 (181) 16580542	**Study type:** Single-center cohort in Boston MA **Size:** N=62 pts; mean age 68 y; 60% male	**Inclusion criteria:** All pts getting TPPM for prolonged temp pacing at BWH 2000–2004 **Exclusion criteria:** None stated	**1° endpoint:** Duration of pacing, outcomes, complications **Results:** Median duration 7.5 d. 66% went on to have PPM. No deaths from arrhythmia, no complications from TPPM, no dislodgements	• TPPM safe and effective option for prolonged temporary pacing. • Allows management in lower cost less intensive setting

Zoll PM, et al. 1985 (130) 3886190	**Study type:** Prospective 5-center cohort study in US **Size:** 134 pts; mean age 70 y; 65% men	**Inclusion criteria:** All ED and hospital pts in whom TCP applied **Exclusion criteria:** None stated	**1° endpoint:** Stimulation effectiveness, clinical usefulness, survival in-hospital **Results:** QRS response to TCP in 78%, deemed clinically useful in 61%, survival in 62%	• Methodology for data collection not described • No controls • Endpoints not well described or documented • "This extensive experience with 134 pts treated by several investigators in 5 institutions under varied circumstances confirms the safety and efficacy of this new technique of noninvasive temporary pacing."
Sherbino J, et al. 2006 (128) 16814446	**Study type:** Systematic review of 7 studies of TCP for prehospital bradyasystole **Size:**7 studies, N= 1487	**Inclusion criteria:** Euthermic, nontraumatized adults who experience prehospital hemodynamically symptomatic bradycardia or bradyasystolic cardiac arrest **Exclusion criteria:** None stated	**1° endpoint:** Survival to hospital discharge **Results:** No benefits to TCP for bradyasystolic cardiac arrest. Data inadequate to determine efficacy of TCP for SB	• Limited systematic review: Heterogeneity of study designs precluded statistical analysis
Hedges JR, et al. 1991 (129) 1721129	**Study type:** Single EMS-system cohort in US **Size:** N=51; mean age 73 y, 67% male;	**Inclusion criteria:** Pt >17 y with hemodynamically compromised bradycardia with witness collapse **Exclusion criteria:** Trauma, hypothermia, initial rhythm asystole, VT, VF	**1° endpoint:** Arrival to ED with palpable pulse: 26% paced group vs. 13% control Survival to hospital discharge: 15% paced group vs. 0% control **Results:** Above	• Non-randomized • Potential for confounding by indication

Data Supplement 31. RCTs of clinical presentation of bradycardia due to AV block (Section 6.3)

Study Acronym; Author; Year Published PMID	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events

PRESS Santini M, et al. 2013 (182) 23390123	**Aim:** Assess whether PM in pts with bifascicular block+syncope reduces symptoms **Study type:** RCT **Size:** N=101	**Inclusion criteria:** LBBB or RBBB+LPFB/LAFB and syncope. Negative EKG, Holter, TTT, EPS **Exclusion criteria:** Known PM indication	**Intervention:** All pts got PM; DDD 60 or DDI 30 **Comparator:** DDI 30 pts	**1° combined endpoint**: Syncope, presyncope, or other symptoms due to AVB occurred in 23%. **Results**: Reduction in combined events (HR: 0.32; p=0.042) but syncope alone not reduced.	• 5% developed a new PM indication with AVB

Data Supplement 32. Nonrandomized data of Clinical Presentation of Bradycardia due to AV block (Section 6.3)

Study Acronym; Author; Year Published PMID	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)
Guerrero-Marquez FJ, et al. 2016 (183) 28496928	**Aim:** To write a featured review of paroxysmal AVB **Study type:** Review **Size:** N/A	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**Intervention:** N/A **Comparator:** N/A	• Idiopathic AVB is paroxysmal 3rd degree heart block (sudden CHB) with no other rhythm abnormal pre or post in pts with NL heart and EKG • Etiology unknown • Intrinsic AVB occurs in pts with underlying HD due to phase 3 or phase 4 block, degeneration of HP or valve disease, ACS (infant MI) • Other causes of AVB; extrinsic vagal effect, Lev-Lenegre disease, SLE, bacterial endocarditis with abscess, sarcoid, Lyme disease, sickle cell
Brignole M, et al. 2011; (184) 21570228	**Aim:** Follow 18 pts with unexplained syncope	**Inclusion criteria:** Normal EKG, no SHD , parox CHB per monitoring	**Intervention:** EPS, Adenosine plasma level, ATP test, TTT, CSM	PPM relieved symptoms in all pts None progressed to perm AVB
ISSUE Brignole M, et al. 2001 (185) 11673344	**Aim:** Determine mechanism of syncope in pts with BBB and neg EPS **Study type:** Single arm prospective	**Inclusion criteria:** 52 pts with syncope, BBB, QRS >100, neg EPS	**Intervention:** ILR	**Results**: Most frequent cause of recurrent finding was sudden onset AVB with pauses (63%); CHB typically lasts 2–10 d

	Size: N=52			
Carano N, et al. 2012 (186) 23110777	**Aim:** Case report and review of RHD and CHB **Size**: N=1	**Inclusion criteria:** Case report and PubMed search	**Intervention:** Amoxicillin	**Results:** Resolution of CHB
Ando G, et al. 2005 (187) 16091145	**Aim:** Assess hemodynamic of long AVD	**Inclusion criteria:** Case report	**Intervention:** PPM	**Results:** AVD from 290 to 150 and improved symptoms
Koehler U, et al. 1998 (67) 9551750	**Aim:** Assess effect of OSA Rx on brady **Size:** N=651	**Inclusion criteria:** Mod- sec OSA, neg EPS, echo, EKG, stress test	**Intervention:** CPAP	**Results:** 651 brady episodes in 16 pts- 73% were 2nd and 3rd AVB; reduced to 72 episodes post CPAP, 3 got PPM for >5 s pauses despite good Rx
Maeno K, et al. 2009 (188) 19466526	**Aim:** Report the interaction of hypoxia and bradyarrhythmia **Study type:** Case report, literature review **Size**: N=1	**Inclusion criteria:** N/A	**Intervention:** CPAP	**Results:** Profound AVB resolved
Moya A, et al. 2011 (189) 21444367	**Aim:** Ability of protocol to Dx etiology of syncope **Study type:** Prospective nonrandomized study using 3 phases; EKG/echo/Holter, EPS/CSM, ILR **Size**: N=323	**Inclusion criteria:** Syncope +BBB, preserved EF	Prospective nonrandomized study using 3 phases; EKG/echo/Holter, EPS/CSM, ILR	**Results:** 158 (about 50%) were due to paroxysmal AVB or infraHisian abnormalities on EPS
Panic G, et al. 2011 (190) 20226549	**Aim:** Case report	N/A	N/A	**Results:** • Presented with high-grade AVB, resolution after 12 d abx

				• 5% of pts with Lyme will have cardiac involvement, typically AVB
Carroz P, et al. 2010 (191) 19946114	**Aim:** Discuss pseudo PM syndrome	**Inclusion criteria:** **C**ase report	Case report	**Results:** PR was 480 ms, had intermittent cannon A waves, symptoms of fatigue due to atrial contraction before complete A filling, increase PCWP, decrease CO, improved with PPM
Marti-Almor J, et al. 2009 (192) 19578058	**Aim:** N=259 with BFB, 82% had syncope or presyncope, 18% no symptoms; 61% on EPS had conduction abnormal and received PPM **Study type**: Observational **Size**; N=259	**Inclusion criteria:** LBBB or RBBB+LAFB or RBBB+LPFB 82% had syncope	Prospective consecutive observational study	**Results:** 82% had symptoms (syncope, presyncope) 61% had pos. EPS (HV >70 if sx, HV>100 if asx, or infraHisian with RAP) and almost all got PPM, 2/3 had progression of AVB
Barold SS, et al. 1996 (193) 8734740	**Aim:** Editorial **Study type:** N/A **Size:** N=N/A	**Inclusion criteria:** N/A		**Opinion:** PMs can be used especially in pts with normal LVEF
Barold SS, et al. 2006 (194) 17334913	**Aim:** Describe clinical manifestations of 1st AVB **Study type:** Review paper **Size:** N=N/A	**Inclusion criteria:** N/A	**Intervention:** PM, CRT	**Results**: Pacing addresses symptoms, CRT response is less than in those with normal PR
Barra SN, et al. 2012 (195) 22897386	**Aim:** Review the more common and rarer causes of AVB in young adults	**Inclusion criteria:** N/A	**Recommendations:** Work up for underlying cause based on family Hx and symptoms and risk factors for CAD	**Results:** More common causes in young adults: CAD, degenerative diseases, cardiomyopathies, infection, rheumatic, autoimmune, infiltrative, vagally induced, drugs

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Kenneback G, et al. 2007 (149) 17255148	**Study type:** Single-center, prospective cohort (Sweden) **Size:** N=17 (53% men), mean age 77 y	**Inclusion criteria:** Pts admitted with high-degree AVB on antiarrhythmic therapy (88% beta blocker) who received PPM, who then had AAD withdrawn with return of AV conduction. **Exclusion criteria:** Valve surgery in past year, permanent AF	**1° endpoint:** Recurrence of AVB detected by PM algorithm over 2 y **Results:** 9/12 pts (75%) with QRS ≥120 ms and 1/5 pts (20%) developed recurrent AVB. 6/17 pts (35%) developed atrial tachyarrhythmias requiring AAD tx	• Appropriate to place PPM in pts with AVB and QRS ≥120 ms w/o further delay or evaluation.
Knudsen MB, et al. 2013 (150) 23869746	**Study type:** Single-center, retrospective cohort (Denmark) **Size:** N=55 (55% male, mean age 77 y)	**Inclusion criteria:** Pts admitted with 2/3 AVB, had temporary wire, were on class II-IV AADs or digoxin. **Exclusion criteria:** No ECG documentation, AVB due to other identified cause, prior PPM explant, died within several days	**1° endpoint:** Need for PPM; complications of TPM **Results:** 47/55 (85%) required PPM in hospital. 2/55 had recurrent AVB and required PPM. 11% of pts had complication of TPM (infection/ dislodgment), also prolonged hospital stay	• Pts with AVB on AADs /digoxin do not benefit from TPM and drug washout. Should proceed to PPM w/o delay. • "In the elderly, the drug is virtually never the sole culprit; rather, it just exposes the underlying weakness of the aging conduction system"
Osmonov D, et al. 2012 (151) 22530749	**Study type:** Single-center retrospective cohort (Turkey) **Size:** N=108 (16% of all 668 pts admit with 2/3 AVB). 30/108 (28%) had AF with SVR	**Inclusion criteria:** All pts admitted with 2/3 AVB who were on AV nodal blocking drugs 2008–9 **Exclusion criteria:** MI, electrolyte disturbances, digoxin toxicity, vasovagal syncope	**1° endpoint:** Resolution/ recurrence AVB, need for PPM **Results:** Resolution of AVB with 72 h in 78/108 (72%). 21/78 (27%) had recurrence of AVB. Overall 51/108 (48%) had persistent of recurrent AVB despite drug withdrawal.	• Half of pts with AVB on nodal-blocking drugs require PPM before discharge despite drug withdrawal. • Limited follow-up – other pts may have required PPM at later date
Zeltser D, et al. 2004 (152) 15234417	**Study type:** Single-center retrospective cohort (Israel)	**Inclusion criteria:** All pts admitted with 2/3 AVB 1999–2003.	**1° endpoint:** Resolution/ recurrence AVB, need for PPM **Results:** 79/92 (86%) had drug discontinued. 32/79(41%) had	• Overall, only 15% of pts with AVB on nodal blocking drugs had AVB "caused by drugs" • F-u limited to 3 wk

	Size: N=169 (60% male, mean age 78 y). 92/169 (54%) receiving AV nodal blockers	**Exclusion criteria:** MI, digoxin toxicity, vasovagal syncope	resolution of AVB. 18/32 had relapse of AVB within 3 wk	
Risgaard B, et al. 2012 (153) 22333242	**Study type:** Retrospective single-center/region cohort study (Denmark) **Size:** N=259 (mean age 78 y, 46% male). 49.7% had 2/3 AVB. 15% had AF-slow ventricular response	**Inclusion criteria:** All pts referred for urgent PPM in 2009 **Exclusion criteria:** Discharged from hospital before implant, referred from outpatient department	**1° endpoint:** d to implant, complications during wait **Results:** Mean 8.3 d hospitalization to implant (3.2 d to Dx; 5.1 d waiting for PPM). 83/259 pts (32%) had complications while waiting – Infection (11%), asystole (20%), NSVT (5%), cardiac arrest (3%), death (1%)	• Pt harm results from delay to PPM for capacity issues.
Farre N, et al. 2014 (154) 24491864	**Study type:** Retrospective single-center cohort (Spain) **Size:** N=79; mean age 72 y, 50% male	**Inclusion criteria:** Consecutive pts with "reversible" 3rd degree AVB not undergoing initial PPM implant **Exclusion criteria:** None stated	**1° endpoint:** Persistence/recurrence of AVB, PPM implant **Results:** 39% of pts w/o ischemic/infarction developed recurrent AVB, had PPM	• Outside setting of MI/ischemia, high proportion of pts with 3rd degree AVB and "reversible causes" develop recurrent AVB. • Close f-u warranted • Study was research letter with little data presented
Antman EM, et al. 1990 (100) 2188752	**Study type:** Open-label, 21-center prospective cohort study 1974–86 **Size:** N=150 pts (79=53% with high-degree AVB). 46% male, mean age 65 y	**Inclusion criteria:** Pts who received digoxin-specific Fab fragments in trial 1974–86. **Exclusion criteria:** None stated	**1° endpoint:** Clinical "response" **Results:** 80% complete resolution of signs/sx. 10% partial response, 10% complete response.	• AVB pts not separately analyzed
Hickey AR, et al. 1991 (101) 1993775	**Study type:** Multi-center US national prospective cohort **Size:** N=717; 40% men, mean age 74 y	**Inclusion criteria:** All pts in US receiving anti-digoxin Fab fragments **Exclusion criteria:** None stated	**1° endpoint:** Resolution of symptoms of digoxin toxicity **Results:** 50% complete response, 24% partial response; 12 % no response. 3% recurrence rate. 1% allergy to therapy	• No separate analysis of AVB pts
Sadek MM, et al. 2013 (155) 23623644	**Study type:** Systematic review	**Inclusion criteria:** English language, original outcome data	**1° endpoint:** Reversal or improvement in AVB	• Considerable study heterogeneity

	Size: 10 publications; 299 pts	on pts with cardiac sarcoidosis tx with steroids. **Exclusion criteria:** Reports less than 5 subjects or less than 3-mo follow-up	**Results:** 27/57 (47%) cases treated with steroids had improved or recovered AV conduction vs. 0/16 pts. w/o steroid treatment.	• "Improvement" in AV conduction not defined • Outcome not defined in terms of need for PM
Kandolin R, et al. 2011 (156) 21427276	**Study type:** Single-center retrospective cohort (Finland) **Size:** N=133; 72 pts with unexplained AVB	**Inclusion criteria:** Pts. 18–55 y who had PPM implant for unexplained 2nd/3rd-degree AVB **Exclusion criteria:** None described	**1° endpoint:** Dx of cardiac sarcoidosis; reversal of AVB with treatment. **Results:** 18/72 (25%) had probable (4) or definite (14) cardiac sarcoidosis AVB reversed in only 2/16 pts (13%) treated with steroids	• Selected population, tertiary referral center • Little data about AVB described • Overall suggests low chance of reversing AVB with steroid treatment
Ozcan KS, et al. 2012 (157) 22738687	**Study type:** Single-center retrospective cohort (Turkey) **Size:** N=50 (29 hypothyroid, 21 hyperthyroid)	**Inclusion criteria:** All pts. with 2nd/3rd degree AVB who had hyper- or hypothyroidism **Exclusion criteria:** MI, electrolytes abnormalities, digoxin toxicity, vasovagal syncope, on AADs	**1° endpoint:** Persistent AVB despite treatment of thyroid abnormalities **Results:** 46/50 (92%) pts required PPM; 2 additional pts had persistent AVB. 22/29 (76%) with hypothyroidism and 18/21 (86%) with hyperthyroidism had irreversible AVB.	• Thyroid abnormalities are rarely a cause of reversible AVB.
Forrester JD, et al. 2014 (158) 24879781	**Study type:** Systematic review of case reports and case series **Size:** 34 manuscripts reporting 45 cases	**Inclusion criteria:** English language case reports or series in peer-reviewed journal of pts with Lyme disease and ECG-documented 3rd degree AVB **Exclusion criteria:** Not in English, pt not US, no pt variables reported	**1° endpoint:** Outcomes, need for PPM, persistence of AVB **Results:** 18/45 (40%) required TPM, 2/45 (4%) had PPM, both in 1980s. All other cases resolved, median time to resolution 6 d (range 1–42 d).	• AVB with Lyme carditis almost always resolves with treatment
Van der Linde, MR, 1991 (159) 1947815	**Study type:** Review of published case reports in Europe and North America, European questionnaire, personal communication, observations	**Inclusion criteria:** Published case reports 1977–90, questionnaire, personal communication, observations **Exclusion criteria:** None	**1° endpoint:** Outcome, resolution of AVB, need for PPM **Results:** 49% had 3rd degree AVB, 16% had 2nd degree AVB. 35% required TPM, 94% with complete recovery of AV conduction, only 1 pt (1%) had persistent 3rd degree AVB	• PPM rarely needed after episode of Lyme carditis

	Size: 105 cases			

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Abu-Laban RB, et al. 2006 (104) 16698410	**Aim:** To determine whether aminophylline increases rate of ROSC after out of hospital cardiac arrest **Study type:** RCT **Size:** N=971	**Inclusion criteria:** Pts over 16 y in British Columbia 2001–3 with brady-asystolic arrest refractory to intubation, atropine and epinephrine **Exclusion criteria:** Do-not-resuscitate order, pregnancy, hemorrhage/trauma or hypothermia, end-stage renal disease, on theophylline	**Intervention:** 500 mg IV aminophylline bolus **Comparator:** Matching placebo	**1° endpoint:** ROSC: 24.5% I vs. 23.7% C (0.8%, -4.6–6.2; p=0.778) Survival to hospital admission: 6.6% I vs. 7.6% C (-1.0%, -4.3–2.2; p=0.527) Survival to hosp. discharge: 0.4% I vs. 0.6% C (-0.2%, -1.1–0.7%; p=0.653) **Safety endpoint (if relevant):** None	• Did not call out pt with AVB • Prehospital setting only
PrePACE Morrison, LJ, et al. 2008 (86) 17933452	**Aim:** To compare outcome of pts with prehospital unstable bradycardia with TCP vs. dopamine **Study type:** RCT **Size:** N=82; mean age 71 y; 57% male	**In Inclusion criteria:** Pts ≥18 y presenting to Toronto EMS with hemodynamically unstable bradycardia unresponsive to fluids and atropine **Exclusion criteria:** Trauma, hyperthermia, hypothermia, cardiac arrest	**Intervention:** TCP 80 bpm **Comparator:** Dopamine 5–20 mcg/kg/min	**1° endpoint:** Survival to hospital discharge 69% I vs. 70% C (p=NS) **Safety endpoint:** VT/VF/cardiac arrest/burn: 7.1% C vs. 7.5% C (p=NS)	• Half of eligible pts not randomized • This was a pilot study for potential larger RCT • Dopamine equivalent to TCP in this small pilot study

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)

Brady WJ, et al. 1999 (79) 10459592	**Study type:** Single-EMS system retrospective cohort in US **Size:** N=131; 45 with AVB; Mean age 69 y; 53% male	**Inclusion criteria:** All nontraumatized pts from 1990–1993 who experienced bradycardia with associated hemodynamic instability who received atropine in field. **Exclusion criteria:** Not stated, but presumably cardiac arrest. Also excluded pre-hospital deaths (N=16)	**1° endpoint:** "Response" in 4 categories – adverse, none, partial, complete **Results:** Mean dose 1.1 mg. Of 37 pts with 3rd degree AVB in field, 21 arrived in ED with 3rd degree AVB and only 9 left ED with 3rd degree AVB. Of all pts, 27% had complete response, 20% partial, 50% none; 3% adverse	• Limited methodology, results poorly described
Feigl D, et al. 1984 (160) 6736451	**Study type:** Single center retrospective cohort study in Israel 1978–1982 **Size:** N=34; mean age 62 y; 82% male	**Inclusion criteria:** 2nd or 3rd degree AVB developing in course of IMI who survived >72 h **Exclusion criteria:** None	**1° endpoint:** Outcomes, response to atropine **Results:** Of 15 pts with early AVB (<6 h). Atropine normalized conduction in 20%, increased V rate in others. 5 had normalization with isoproterenol. 14 pts had late AVB – less response to atropine (mean 16 bpm). 50% required TPM	• Descriptive, uncontrolled study • No adverse events to drug therapy reported
Sclarovsky S, 1984 (161) 6731277	**Study type:** Single center retrospective cohort study in Israel 1972–1982 **Size:** N=76	**Inclusion criteria:** All pts with acute inferior MI who developed 2nd or 3rd degree AVB in hospital **Exclusion criteria:** Combined AMI and IMI	**1° endpoint:** Description of outcomes, response to atropine and isoproterenol **Results:** 6/14 (36%) of pts with early AVB improved vs. 13/17 (77%) pts with late AVB ($p<0.05$). 2/8 (25%) of pts with early block and 2/6 (33%). 50% of pts had TPM	• Descriptive uncontrolled study • No adverse events to drug therapy reported
Chihrin SM, et al. 2008 (162) 18308011	**Study type:** Single center prospective cohort in Canada **Size:** N=100; mean age 75 y; 56% male	**Inclusion criteria:** Consecutive pts from 2003–2006 undergoing PPM generator change who were PM dependent **Exclusion criteria:** None	**1° endpoint:** Elicitation of escape rhythm with PM stepdown to 30 bpm or isoproterenol 1–2 mcg/min **Results:** 59% demonstrated intrinsic rhythm with stepdown alone. Of remaining 41 pts, 28 (68%) demonstrated intrinsic rhythm with isoproterenol. No adverse events.	• Suggests that isoproterenol can be used to elicit faster escape rate in pts with AVB

Hurley KF, et al. 2015 (105) 26593309	**Study type:** Systematic review of 5 RCTs **Size:** N=1254	**Inclusion criteria:** RCTs of aminophylline used for pre-hospital resuscitate of bradyasystolic cardiac arrest **Exclusion criteria:** N/A	**1° endpoint:** Survival to discharge/admission, ROSC **Results:** No improvement in outcome by any measure with aminophylline. Overall survival extremely low	• Aminophylline not useful in out of hospital bradyasystolic arrest
Sodeck GH, et al. 2007 (77) 17212976	**Study type:** Retrospective analysis of single ED registry from tertiary center in Austria **Size:** N=277; mean age 68 y; 62% male; about 50% AVB	**Inclusion criteria:** Consecutive pts admitted to ED 1994–2004 with symptomatic, hemodynamically significant bradycardia **Exclusion criteria:** Asymptomatic and terminally ill pts	**1° endpoint:** Use of drugs for bradycardia, use of pacing **Results:** IV medications given to 170 pts (61%) – Atropine in 141 (51%), orciprenaline 62 (22%), epi 24 (9%), dopamine 6 (2%). 7 pts had TCP (4 successful); 54 (20%) had temporary TVP. 137/277 (50%) received PPM	• Descriptive study with no control group • Pts with AVB not separately reported or analyzed • Minimal information on clinical effects of intervention given
Bertolet BD, et al. 1995 (163) 7661495	**Study type:** Single-center observational cohort in US **Size:** N=8; 3 with complete AVB	**Inclusion criteria:** Pts with significant AVB developing within 4 h of admission for acute inferior MI, resistant to atropine, given IV theophylline up to 250 mg **Exclusion criteria:** Pts who received BBs or CCBs prior	**1° endpoint:** Restoration of 1-1 AV conduction **Results:** All 8 pts had restoration of 1-1 AV conduction within 3 min lasting at least 24 h	• No controls • Very small, single-center experience
Altun A, et al. 1998 (164) 9789698	**Study type:** Single-center observational cohort in Turkey **Size:** N=8; 6 with complete AVB; mean age 68 y	**Inclusion criteria:** Pts with 2nd or 3rd degree AVB after IMI for at least 1 h, resistant to atropine. Given 2 doses of aminophylline 240 mg 1 h apart **Exclusion criteria:** Pts in hyperacute phase of MI, received AV nodal blocking drugs	**1° endpoint:** Restoration of AV conduction **Results:** Aminophylline restored 1-1 AV conduction in 7 pts and Mobitz I AVB in 1. No adverse effects. AVB relapsed in 1 pt only	• No controls • Very small, single-center experience
Goodfellow J, et al. 1995 (165) 7588933	**Study type:** Single-center case series in United Kingdom	**Inclusion criteria:** Pts with atropine-resistant AVB with acute inferior MI treated with	**1° endpoint:** Restoration of 1-1 AV conduction	• No controls • Very small case series

	Size: N=3	streptokinase. All had hypotension **Exclusion criteria:** None	**Results:** 1-1 AV conduction restored promptly with resolution of hypotension in all	
Love, JN, et al. 1998 (90) 9674488	**Study type:** Single center case series in US **Size:** N=9	**Inclusion criteria:** Pts presenting with symptomatic bradycardia resistant to atropine 1 mg who received IV glucagon 1–7 mg then 3–5 mg/h **Exclusion criteria:** None	**1° endpoint:** Improvement in bradycardia and hemodynamics **Results:** All pts improved at least transiently	• Most pts had BBs and/or CCBs as significant co-factors • Unknown how many had AVB
Dhingra RC, et al. 1973 (166) 4744693	**Study type:** Single center cohort undergoing invasive EP study in US **Size:** N=42; 8 with 3rd degree AVB, 3 with 2nd degree AVB	**Inclusion criteria:** 42 pts with heart disease undergoing invasive EPS w/o and with isoproterenol **Exclusion criteria:** None	**1° endpoint:** Improvement in AV conduction and change in ventricular rate **Results:** 2/8 pts with 3rd degree AVB had improved conduction with isoproterenol, as did 3/3 pts with 3rd degree AVB. Ventricular rate improved in all subjects from mean of 45 bpm to 62 bpm, regardless of site of block	• Very small study • Bias in reflects those able to undergo EPS • Hemodynamics/ BP not measured • Suggests isoproterenol useful to augment heart rate in 2nd and 3rd degree AVB
Hatle L, et al. 1971 (167) 5557475	**Study type:** Single center prospective cohort from Norway **Size:** N=105 pts with 2nd or 3rd degree AVB in setting of acute MI	**Inclusion criteria:** Pts with acute MI treated 1966–1970 with 2nd or 3rd degree AVB treated with isoproterenol, generally 1–3 mcg/min **Exclusion criteria:** None stated	**1° endpoint:** Improvement in heart rate **Results:** In hospital mortality 48%. 60 pts received isoproterenol: 38 (63%) had increase in heart rate and BP; 12 (20%) had increased in heart rate but minimal change in BP; 8 (13%) had minimal change; 2 (3%) isoproterenol terminated due to ventricular ectopy. 3 pts had ventricular fibrillation on isoproterenol, 1 of which died. 14 pts treated with TVP, 3 of whom died from ventricular fibrillation	• Very early cohort when there was minimal treatment for acute MI • Extremely high mortality • In this group, isoproterenol appeared safe compared with TVP • Uncontrolled cohort study

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events

Ferguson JD, et al. 1997 (113) 9217762	**Aim:** Compare 2 types of TVP catheters for success and complication rates **Study type:** Unblinded RCT **Size:** 40 pts, mean age 72 y. 85% with AVB	**Inclusion criteria:** Undergoing temporary VVI pacing (85% with AVB) guided by fluoroscopy **Exclusion criteria:** None stated	**Intervention:** Use of balloon-tipped electrode (N=20) **Comparator:** Use of semi-rigid electrode (N=20)	**1° endpoint:** Procedure duration (264 vs. 540 s; p<0.002), fluoroscopy time (87 vs. 189 s; p<0.01), suitability of final position (0 unacceptable vs. 7; p<0.0001). Thresholds similar **Safety endpoint (if relevant):** Dislodgement (1 vs. 3) Death (0 vs. 2)	• When guided by fluoroscopy, balloon-tipped catheters are easier to place successfully than semi-rigid catheters • Use of balloon-tipped catheter associated with trend toward lower complication rate
Barthell E, 1988 (127) 3056132	**Aim:** Compared TCP added to ACLS vs. ACLS alone for pre-hospital pts with asystole, EMD, or hypotensive bradycardia **Study type:** Unblinded RCT (alternate d randomization) **Size:** N=239; 142 with asystole; 84 with EMD; 13 with hypotensive bradycardia	**Inclusion criteria:** All adult, nontraumatic bradyasystolic episodes or arrests treated by Milwaukee County Paramedic System Oct 1986–May 1987 **Exclusion criteria:** None stated	**Intervention:** TCP + ACLS **Comparator:** ACLS alone	**1° endpoint:** Survival to hospital admission: Asystole/EMD 17% I vs. 20% C (p=NS) Hypo-brady 100% I vs. 29% C (p=0.01) Survival to hospital discharge: Asystole/EMD 2% I vs. 4% C (p=NS) Hypo-brady 83% I vs. 14% C (p=0.01) **Safety endpoint:** None	• Limited form of randomization • Overall, no effect of TCP for pre-hospital use for asystole/EMD arrest • Possible benefit for hypotensive bradycardia, but number of pts very small
Cummins RO, et al. 1993 (168) 8474514	**Aim:** Determine efficacy of TCP of asystolic out of hospital cardiac arrest **Study type:** Modified RCT by center **Size:** N=1056 cardiac arrests; N=537 with asystole as first rhythm; N=305 with asystole after VF	**Inclusion criteria:** All cardiac arrests in Seattle area over 3 y period; Primary group was those with asystole as first rhythm **Exclusion criteria:** None	**Intervention:** 16 EMS/fire districts given TCP and trained in use **Comparator:** 23 EMS/fire districts given TCP and trained in use	**1° endpoint:** Survival to hospital admission/ primary asystole: 8% I vs. 8% C (p=NS) Survival to discharge: 4% I vs. 2% C (OR: 2.05; p=NS) **Safety endpoint:** None	• No improvement for pts with initial VF • Limited form of randomization

Hedges JR, et al. 1987 (169) 3315295	**Aim:** Determine efficacy of TCP added to ACLS for prehospital hemodynamically significant bradycardia or asystole **Study type**: RCT (alternate day) **Size:** N=202	**Inclusion criteria:** All pts over 14 y treated by Thurston County, EMS for hemodynamically-significant bradycardia with decreased mental status (Glasgow coma score ≤12) **Exclusion criteria:** None stated	**Intervention:** On odd calendar days, EMS used TCP 100 bpm at max output for pts **Comparator:** On even calendar days, TCP was not used	**1° endpoint:** Survival to hospital admission: 17% I vs. 17% C (p=NS) Survival to hospital discharge: 6% I vs. 4% C (p=NS) **Safety endpoint:** None	• Limited form of randomization • No improvement with TCP
PrePACE Morrison, LJ, et al. 2008 (86) 17933452	**Aim:** To compare outcome of pts with prehospital unstable bradycardia with TCP vs. dopamine **Study type:** RCT **Size:** N=82; mean age 71 y; 57% male	**Inclusion criteria:** Pts 18 y or older presenting to Toronto EMS with hemodynamically unstable bradycardia unresponsive to fluids and atropine **Exclusion criteria:** Trauma, hyperthermia, hypothermia, cardiac arrest	**Intervention:** TCP 80 bpm **Comparator:** Dopamine 5–20 mcg/kg/min	**1° endpoint:** Survival to hospital discharge 69% I vs. 70% C (p=NS) **Safety endpoint:** VT/VF/cardiac arrest/burn: 7.1% C vs. 7.5% C (p=NS)	• Half of eligible pts not randomized • This was a pilot study for potential larger RCT • No benefit to TCP seen

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Sodeck GH, et al. 2006 (77) 17212976	**Study type:** Single center retrospective cohort in Austria **Size:** 277 pts (62% male, 48% AVB)	**Inclusion criteria:** Pts >18 y presenting to ED with "compromising bradycardia from 1994–2004; mean heart rate 33 bpm **Exclusion criteria:** Asymptomatic bradycardia, terminal illness	**1° endpoint:** 30 d mortality **Results:** 5% mortality at 30 d. 20% of pts treated with temporary TVP. 50% of those pts went on to have permanent pacing	• Temporary TVP required in about 20% of pts presenting to ED with symptomatic bradycardia • Half of those pts go on to PPM

Brikhahn RH, et al. 2004 (170) 15039689	**Study type:** Single-center retrospective cohort in US **Size:** 154 pts, 117 meeting inclusion/ exclusion criteria. Mean age 78 y, 38% male, 51% AVB)	**Inclusion criteria:** All pts with temporary TVP placed in ED, intensive care unit, or ward 1999–2002. Only 3% placed under fluoroscopy **Exclusion criteria:** Indication asystole, TVP placed in cath or EP lab, no attending supervision	**1° endpoint:** Successful temporary TVP placement. Complication rate. **Results:** 88% success on first attempt. 17% serious complication rate. 96% placed by cephalic approach. 67% had PPM. 23% in-hospital mortality	• Similar success rates between ED physicians and cardiologists • High overall success rate of implantation of TVP • Cephalic route rarely used in general practice today
Betts TR, 2003 (119) 12954959	**Study type:** Prospective registry in 5 regional hospitals in England in 1999 **Size:** 144 procedures in 111 pts; mean age 75 y.; 63% male; 51% AVB	**Inclusion criteria:** All TVPs placed over 9 mo period in 1999 **Exclusion criteria:** None cited	**1° endpoint:** General overview of procedure technique, outcomes, complications **Results:** Procedure times shorter for cardiologists, 28% complication rate. Immediate complication rates lower with experience (1/81) vs. inexperienced (5/59) operators. Infection occurred more in wires left in >48 h (17/86) than <48 h (2/55). 23% of comps resulted in delayed PPM	• Suggests benefit to TVP implant by cardiologists/ experienced operators • Greater infection risk for TVP wires left in >48 h • High rate of overall complications seen • 23% of comps delayed PPM implantation
Mahapatra S, et al. 2005 (171) 16171740	**Study type:** Case-control derived from prospective database 1995–2003 at Mayo Clinic **Size:** 50 pts with cardiac perforation after PPM vs. 100 controls	**Inclusion criteria:** Pts undergoing PPM 1995–2003 with perforation and new effusion. **Exclusion criteria:** Age <18 y, prior effusion or cardiac surgery within 4 wk of PPM	**1° endpoint:** Risk factors for perforation after PPM **Results:** 1.2% of all pts had perforation. Predictors of perforation in multivariate analysis included prior TVP (HR: 2.7; 95% CI: 1.4–3.9], helical screw leads (HR: 2.5), steroid use (HR: 3.2)	• Suggests benefit to avoiding TVP prior to permanent pacing unless essential
Lang R, et al. 1981 (172) 6169032	**Study type:** Single-center nonrandomized controlled study	**Inclusion criteria:** Consecutive pts requiring emergency or semi-urgent temporary TVP at a single Israeli center	**1° endpoint:** Successful implant, procedure time, threshold, multiple safety endpoints	• Superiority of balloon-tipped, flow guided electrode catheter for temporary TVP demonstrated.

	comparing balloon-tipped, flow-guided TVP vs. standard semi-rigid catheter **Size:** 111 consecutive pts (67 flow-guided, 44 semi-rigid)	**Exclusion criteria:** None stated	**Results:** Flow-guided TVP had 1) shorter insertion time (7 min vs. 14 min); less dislodgement (13% vs. 32%), lower incidence of serious ventricular arrhythmia (1.5 vs. 20.4%) Thresholds similar.	
Hynes JK, et al. 1983 (115) 6823157	**Study type:** Retrospective single-center cohort at Mayo Clinic **Size:** 1022 pts, mean age 68 y, (65% male)	**Inclusion criteria:** Consecutive pts undergoing temporary TVP wire in Mayo Clinic coronary care unit 1976–81. **Exclusion criteria:** None stated	**1° endpoint:** Complications **Results:** Implanted mean 3.1 d, 64% placed antecubital route, 19% subclavian vein, 12 % internal jugular vein. 13.7% complication rate, increasing with duration of TVP. Lowest comp rate with internal jugular vein 5.3% pericarditis. PPM implanted in 58% of pts.	• Preference for internal jugular rand subclavian vein access sites confirmed
Winner S and Boon N, 1989 (173) 2769615	**Study type:** Retrospective single region cohort study **Size:** 266 pts/ 158 (59%) had temporary TVP	**Inclusion criteria:** Consecutive pts referred to regional center for PPM **Exclusion criteria:** Missing records	**1° endpoint:** Complications, defined as "major problems": dislodgement, infection, pericarditis/perforation, thrombosis, wire in left ventricle **Results:** 36% rate of major problems, much higher rate at smaller referral hospitals. 6% infection; 30% failure to pace, 4% pericarditis	• Advise avoiding TVP before PPM unless absolutely necessary
López Ayerbe J, et al. 2004 (114) 15544753	**Study type:** Retrospective single center cohort in Barcelona, Spain **Size:** N=530; mean age 74 y, 54% male; 51% AVB.	**Inclusion criteria:** Pts receiving TVP 1997–2003. All via femoral route (99%) with fluoroscopic guidance **Exclusion criteria:** Pts transferred out with no available f-u (N=38)	**1° endpoint:** Complications, outcomes **Results:** Mean duration 4.2 d. 22% complication rate: 1% death (3 tamponade, 1 asystole, 1 PE, 1 sepsis). 9% migration/dislodgement' 9% other (VTE, effusion, infection)	• Complication rates improved compared with series from 1980s and 1990s (18–43%) • Lower use in pts with acute MI seen

Bjornstad CC, et al. 2012 (126) 22390277	**Study type:** Prospective regional 5 hospital study in Norway 2010–11. **Size:** N=50; 45% AVB; mean age 79 y, 62% male	**Inclusion criteria:** All pts with TVP in 5 hospitals March 2010–March 2011. All with fluoroscopy **Exclusion criteria:** None stated	**1° endpoint:** Complications, outcomes **Results:** 96% TVP; 4% TCP. 60% received PPM; 14% died. 30% rate of "serious complications" including 6% death from sepsis	• Fewer TVPs being performed by more physicians with less experience • Lower complication rate with more experienced implanters
McCann P, 2006 (125) 17235372	**Study type:** Systematic review 1973–2004 **Size:** 15 studies; N=3737; mean age 71 y	**Inclusion criteria:** Cohort studies of TVP published 1973–2004 **Exclusion criteria:** None stated	**1° endpoint:** Complications, outcomes **Results:** Overall complication rate 26.5%: 15% failed access, 10% failed placement, 9% sepsis, 4% arterial puncture, 2% lung/myocardium puncture	• Methodologically limited systematic review • Higher complication rate in older pts • Lower complication rate when implanted by specialists • Trend toward greater use of right internal jugular access over time
Jou YL, et al. 2010 (124) 20946290	**Study type:** Single center retrospective cohort in Taiwan 2002–8 **Size:** N=509; mean age 77 y, 74% male; 64% AVB	**Inclusion criteria:** All pts with TVP 2002 8 at single center **Exclusion criteria:** None stated	**1° endpoint:** Trends in use **Results:** Greater use for AVB with intrinsic disease, less for sinus node dysfunction and MI over time. 48% had PPM implant within 30 d (mean 6 d) with increasing rate over time.	• High rate of PPM for degenerative AVB
Knudsen MB, et al. 2013 (150) 23869746	**Study type:** Retrospective single-center cohort at academic medical center in Denmark 2000–11. **Size:** N=575 with TVP. N=55 with AVB and potential culprit drug. Mean age 77 y, 56% male	**Inclusion criteria:** Pts getting TVP wire 2000–11 who had AVB and potential culprit drug discontinued **Exclusion criteria:** No ECG documentation; other etiology of bradycardia documented; PPM infection; in hospital death	**1° endpoint:** Indication for PPM despite drug discontinuation; complications and outcomes **Results:** 49/55 (89%) ultimately required PPM, including 26/27 (96%) on BBs. 11% comp rate from TVP. PPM postponed mean of 7 d for drug withdrawal	• Authors conclude that: "Primary PPM implantation should be considered in pts with high-degree AVB and concomitant AV blocking therapy, unless other reversible causes…exist." • "In the elderly, the drug is virtually never the sole culprit; rather, it just exposes the underlying weakness of the aging conduction system

Murphy JJ, 1996 (116) 8620131	**Study type**: Prospective cohort in 18 hospitals in Northern England over 6 mo **Size:** N=194. Mean age 71 y; AVB (67%). Acute MI in 53%	**Inclusion criteria:** All TVP implants in 18 hospitals. **Exclusion criteria:** None stated	**1° endpoint:** Complications **Results:** Immediate complications in 12/194 (6%) – VT/VF in 6, arterial puncture (3), pneumothorax (2), brachial plexus injury (1). Late comps in 22/194 (11%) – VT/VF 10, definite/possible sepsis in 10 (5.2%) – almost all had TVP>48 h. 38/194 (20%) needed repositioning. Total comps 35%. 11/194 (5.5%) died within 1 h of procedure. 56/194 (29%) had PPM	• High rate of implant by junior staff (residents) • Continued high rate of complications in British medical system in 1990s
Pinneri F, et al. 2013 (174) 22240748	**Study type:** Single-center nonrandomized controlled study. **Size:** N=106; mean age 77 y, 51% male; 75% had AVB; 59% ultimately required PPM	**Inclusion criteria:** Consecutive pts requiring TVP 2003–2010. Pts underwent TVP guided by echo (N=53) or fluoroscopy (N=53) based on operator preference. **Exclusion criteria:** Incomplete follow-up (N=4)	**1° endpoint:** The primary efficacy endpoints were time to pacing, pacing threshold, changes in threshold and need for catheter replacement. The primary safety endpoints were overall complications and death related to TVP implant. **Results:** Successful in all but 1 in each group (98%). Time to pacing and 24 h threshold better in echo-guided group. TVP repositioned in 6% of echo-guided and 22% of fluoroscopy-guided groups (p<0.001), Comp rate lower in echo (11%) than fluoroscopy (41%) group; p<0.001).	• Echo-guided TVP was safer and more effective in this single center cohort with cardiologists comfortable with technique. • Not clear why dislodgment rate and thresholds would be worse in fluoroscopy group.
Braun MU, et al. 2006 (175) 16923004	**Study type:** Non-randomized prospective controlled study comparing externalized active-fixation lead vs. standard temporary TVP wire)	**Inclusion criteria:** Pts with systemic infection requiring VVI pacing >48 h **Exclusion criteria:** None stated	**1° endpoint:** Implant success, pacing thresholds, acute complications, dislodgement rate **Results:** 100% implant success in both groups, paced median 8 d, similar procedure time, acute comps, pacing threshold. There were 24 dislodgments in 12 pts in control	• Externalized active fixation TVP lead associated with much lower dislodgment rate than standard TVP wire. Equally safe to implant • Externalized active fixation TVP preferred if pacing >48 h is anticipated.

	Size: 49 pts, mean age 72 y, 63% male		group, only 1 in active-fixation lead group (p<0.01)	
de Cock CC, et al. 2003 (176) 12765453	**Study type:** Non-randomized single-center comparison of TVP by femoral route with active vs. passive fixation wire in Netherlands 1998–2001 **Size:** N=72 pts; mean age 70 y, 51% male	**Inclusion criteria:** Consecutive pts requiring TVP at single center requiring prolonged temporary pacing (>48 h) – mean 6 d **Exclusion criteria:** None stated	**1° endpoint:** Implant parameters, dislodgments, other adverse events **Results:** Threshold higher in active (1.38V) than passive (0.7V). Dislodgement lower in active (2/36) than passive (12/36) groups (p<0.001). Other comps similar	• Fewer dislodgments using an active fixation lead using femoral approach
Kawata H, et al. 2013 (177) 23482613	**Study type:** Single center retrospective cohort study of temp active fix lead (TPPM) after lead extraction at UCSD **Size:** N=23; mean age 72 y, 70% male; 87% AVB	**Inclusion criteria:** 23/47 pts undergoing extraction for CIED infection who were PM-dependent 2010–12 **Exclusion criteria:** None stated	**1° endpoint:** Duration of TPPM, complications **Results:** Duration of TPPM mean 12 d. 12/23 discharged to home or SNF. 1 pt died of sepsis from primary infection; 1 pt developed vegetation on TPPM lead – removed and replaced. No dislodgements. One pts had late pocket infection after reimplant.	• TPPM is a safe and effective option for PM-dependent pts awaiting reimplant after CIED infection • Allows earlier mobilization and potential discharge to home/nursing facility to await CIED reimplant
Chihrin SM, et al. 2006 (178) 17145220	**Study type:** Single center retrospective cohort in Canada 2001–5 **Size:** N=20 pts; median 2 d; mean age 62 y; 75% male	**Inclusion criteria:** Pts implanted with TPPM via left subclavian vein or right internal jugular vein over 5 y period **Exclusion criteria:** None stated	**1° endpoint:** Pacing duration, complications, costs **Results:** Duration median 2 d (1–83 d); 1 dislodgement requiring repositioning (5%). Using economic modeling, costs lower with TPPM than conventional TVP at 48 h	• Despite higher lead cost, TPPM cost-effective after 24 h due to lower complications and less intensive bed use

Lever N, et al. 2003 (179) 12527682	**Study type:** Single center cohort in United Kingdom **Size:** N=20; mean age 66 y, 85% male	**Inclusion criteria:** Consecutive pts requiring prolonged temp pacing due to infection or drug washout who had tunneled TPPM **Exclusion criteria:** None stated	**1° endpoint:** Pacing duration, outcome, complications **Results:** Duration median 28 d (9–81 d); no dislodgments or repositioning; 2 minor local site infections, no systemic infection. One pt died from sepsis unrelated to TPPM	• TPPM safe and effective, allows early mobility for pts requiring prolonged temporary pacing
Kornberger A, et al. 2013 (180) 23718817	**Study type:** Single center cohort in Germany **Size:** N=60; mean age 73 y, 73% male	**Inclusion criteria:** Consecutive pts implanted with TPPM for CIED infection (70%) or other reasons (30%) 2000–2009 **Exclusion criteria:** None stated	**1° endpoint:** Duration of pacing, outcomes, complications at 30 d **Results:** Successful in 98% - VVI in 56, DDD in 3) Duration mean 15 d. Intraoperative comps in 2 pts (3.3% - one venous thromboembolism and tamponade, one dislodgement during lead extraction). 4 late comps (6.7%) – 3 possible lead infections, 1 dislodgement.	• TPPM safe and effective option for prolonged temporary pacing
Zei P, et al. 2006 (181) 16580542	**Study type:** Single-center cohort in Boston MA **Size:** N=62 pts; mean age 68 y; 60% male	**Inclusion criteria:** All pts getting TPPM for prolonged temp pacing at BWH 2000–2004 **Exclusion criteria:** None stated	**1° endpoint:** Duration of pacing, outcomes, complications **Results:** Median duration 7.5 d. 66% went on to have PPM. No deaths from arrhythmia, no complications from TPPM, no dislodgements	• TPPM safe and effective option for prolonged temporary pacing. • Allows management in lower cost less intensive setting
Zoll PM, et al. 1985 (130) 3886190	**Study type:** Prospective 5-center cohort study in US **Size:** 134 pts; mean age 70 y; 65% men	**Inclusion criteria:** All ED and hospital pts in whom TCP applied **Exclusion criteria:** None stated	**1° endpoint:** Stimulation effectiveness, clinical usefulness, survival in-hospital **Results:** QRS response to TCP in 78%, deemed clinically useful in 61%, survival in 62%	• Methodology for data collection not described • No controls • Endpoints not well described or documented • "This extensive experience with 134 pts treated by several investigators in 5 institutions under varied circumstances confirms the safety and efficacy of this new technique of noninvasive temporary pacing."

Sherbino J, et al. 2006 (128) 16814446	**Study type:** Systematic review of 7 studies of TCP for prehospital bradyasystole **Size:**7 studies, N= 1487	**Inclusion criteria:** Euthermic, nontraumatized adults who experience prehospital hemodynamically symptomatic bradycardia or bradyasystolic cardiac arrest **Exclusion criteria:** None stated	**1° endpoint:** Survival to hospital discharge **Results:** No benefits to TCP for bradyasystolic cardiac arrest. Data inadequate to determine efficacy of TCP for SB	• Limited systematic review: Heterogeneity of study designs precluded statistical analysis
Hedges JR, et al. 1991 (129) 1721129	**Study type:** Single EMS-system cohort in US **Size:** N=51; mean age 73 y, 67% male;	**Inclusion criteria:** Pt >17 y with hemodynamically compromised bradycardia with witness collapse **Exclusion criteria:** Trauma, hypothermia, initial rhythm asystole, VT, VF	**1° endpoint:** Arrival to ED with palpable pulse: 26% paced group vs. 13% control Survival to hospital discharge: 15% paced group vs. 0% control **Results:** Above	• Non-randomized • Potential for confounding by indication

Data Supplement 33. RCTs of General Principles of Chronic Therapy/Management of Bradycardia due to AV block (Section 6.4.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2^0 Endpoint (if any); Study Limitations; Adverse Events
THEOPACE Alboni P et al. 1997 (133) 9236443	**Aim:** Compare the effects of PM to oral theophylline and to control **Study type**: RCT (3 arms) **Size:** 107	**Inclusion criteria:** Pts with SND **Exclusion criteria:** Heart rate <30 bpm, pauses >3 s.	**Intervention:** PM or theophylline **Comparator:** Control	**Results:** Syncope reduced in PM group but not in theophylline group compared to control (p=0.02 and 0.07 respectively)	• PM and theophylline groups had lower incidence of HF compared to control (p=0.05) • Theophylline stopped for side effects in 11%

Data Supplement 34. Nonrandomized data of General Principles of Chronic Therapy/Management of Bradycardia due to AV block (Section 6.4)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Dhingra RC, et al. 1974 (196) 4817704	**Aim:** Describe natural Hx of 2nd AVB+ BBB **Study type:** Prospective observational **Size:** 15	**Inclusion criteria:** BBB+ 2nd degree AVB **Exclusion criteria:** Acute MI	**Intervention:** EPS **Comparator:** N/A	**Results:** At EPS, type I (Wenckebach) block pts had block proximal to the His and those with type II block or 2:1 block had block distal to the His	• Syncope more common in those with block distal to the His • All 9 pts with infra-His block implanted with PM for syncope, CHF LBBB, but not RBBB, was associated with block distal to the His
Shaw DB and Eraut D 1970 (197) 5413952	**Aim:** Follow 2nd and 3rd degree HB pts for symptoms and mortality **Study type:** Observational **Size:** 100	**Inclusion criteria:** 2nd 3rd degree HB **Exclusion criteria:** Digoxin or propranolol use, acute MI	**Intervention:** None	**Results:** Prevalence of heart block increases with age.	• About 50% had syncopal events • About 10% had CHF No reported deaths
Simon AB, et al. 1978 (198) 626128	**Aim:** Follow natural Hx of AVB pts with PMs **Study type:** Observational **Size:** 246	**Inclusion criteria:** 2nd or 3rd degree AVB **Exclusion criteria:** SND	**Intervention:** PM implant	**Results: S**urvival at 1 and 5 y was 88% and 61% mostly due to underlying cardiac disease and age	• Using historical data (50% mortality in first year), authors conclude large mortality benefit with PM • Most common mode of death was SCD 3 deaths clearly attributable to PM failure
Strasberg B, et al. 1981 (199) 7471363	**Aim:** Assess natural Hx of 2nd AVB **Study type:** Prospective observational **Size:** 56	**Inclusion criteria**: 2nd AVB that is chronic, and shown by EPS **Exclusion criteria:** Acute AVB in setting of MI	**Intervention:** None	**Results:** 2/3 had Hx of heart disease which conferred worse survival. Causes of death were CHF, MI, and SCD	• All ECGs showed type I AVB. • None progressed to CHB • 3 deaths were attributed to PM failure

Edhag O, et al. 1976 (200) 1015354	**Aim:** Report natural Hx of pts with CHB or arrhythmic syncope **Study type:** Retrospective **Size:** 101	**Inclusion criteria:** PM not implanted **Exclusion criteria:** PM implantation	**Intervention:** None	**Results:** CHB with Adams-Stokes had worse survival than asx CHB	• Survival at 1 y=68%, at 5 y=37%
Shaw DB, et al. 1985 (201) 4005079	**Aim:** Compare outcomes in pts with type I and type II 2nd degree AVB **Study type:** Observational **Size:** 214 (77 Mobitz I, 86 Mobitz II, 51 2:1)	**Inclusion criteria:** 2nd degree AVB	**Intervention:** PM **Comparator:** No PM	**Results:** 5-y survival for pts with PM=78%; survival for those w/o a PM=41%	• Pts with Mobitz I and Mobitz II had similar prognosis
Wahbi K, et al. 2012 (202) 22453570	**Aim:** Determine whether EPS+ prophylactic PM improves survival in MD **Study type:** Retrospective study using DM1 Heart Registry **Size:** 486	**Inclusion criteria:** PR >200, QRS >100, or both **Exclusion criteria:** High-grade AVB or already have PM	**Intervention:** EPS and implant PM if HV >70 ms **Comparator:** Noninvasive strategy	**Results:** Overall survival 74.4% (95% CI: 69.2–79.9%) The EPS+PM group survival was 76.7% and the noninvasive group was 69.2%; when adjusted for clinical variables the HR=0.61 (95% CI: 0.38–0.98; p=0.04)	• The HR of dying suddenly was 75% lower in the invasive group • The noninvasive group had an incidence if SCD of 18% (95% CI: 10.2–27.4%)
Buckley AE, et al. 1999 (203) 10377322	**Aim:** Describe cardiac involvement in Emery Dreifuss **Study type:** Small case series	**Inclusion criteria:** Pts with Emery Dreifuss and cardiac involvement	**Intervention:** PM	**Results:** The pts exhibited atrial tachycardia, AF, and atrial standstill with junctional bradycardia.	• N/A

	Size: 3				
Kitaguchi T, et al. 2001 (204) 11525883	**Aim:** Describe a proband and his family **Study type:** Observational **Size:** 14	**Inclusion criteria:** Family members with limb girdle MD	**Intervention:** PM	**Results:** All family members had AVB and arrhythmias requiring PM	• N/A
Finsterer J, et al. 2016 (205) 27014341	**Aim:** Thorough review of all neuromuscular disease and cardiac involvement **Study type:** Comprehensive literature search **Size:** 224 papers	**Inclusion criteria:** Comprehensive list of search terms and manual searches **Exclusion criteria:** Abstracts	**Intervention:** N/A	**Results:** Several aspects of cardiac involvement were including hypertrophic CM, DCM, CHF, SCD, arrhythmias	• N/A
Ha AH, et al. 2012 (206) 22385162	**Aim:** Determine predictors of AVB in MD pts **Study type:** Observational single center **Size:** 236	**Inclusion criteria:** MD type I and II	**Intervention:** PM and ICD **Comparator:** No device	**Results:** 23.8% of DM I and 16.7% of DM II pts had a severe ECG abnormality (defined as PR ≥240 ms or QRS ≥120 ms). PMs and ICDs were implanted in 14% overall but in 65% of those with severe ECG abnormality	• Over 44 months of follow-up mean rates of ventricular pacing in device pts was 24% and 13% developed CHB 3 pts died of SCD, 2 of whom had functioning PMs (1.3%)
Lazarus A, et al. 2002 (207) 12427418	**Aim:** Document incidence of AVB in MD pts with HV>70 but no symptoms **Study type:** Single arm, prospective	**Inclusion criteria:** MD pts with HV >70 regardless of symptoms	**Intervention:** PM	**Results:** 43% developed CHB, 51% had atrial tachyarrhythmias and 26.5% had VA.	• No deaths due to AVB • 4 sudden deaths; 2 of which did not have arrhythmia cause per PM interrogation

	Size: 49				
Facenda-Lorenzo M, et al. 2013 (208) 24775453	**Aim:** Document frequency of arrhythmias in MD type I pts **Study type:** Retrospective observational study **Size:** 81	**Inclusion criteria:** Pts with genetic tested Dx of type I MD pts referred to cardiology	**Intervention:** EPS, PM, ICD per physician discretion	**Results:** At baseline visit, 71.6% had a normal ECG. At follow-up, 48.8% had sinus bradycardia and 31.3% had PR ≥220 ms	• 8.6% developed 2nd or 3rd degree AVB during follow-up • Holter found 2nd or 3rd AVB in 9 pts 2 pts required an ICD
Bhakta D, et al. 2011 (209) 22035077	**Aim:** Assess implantation of PM and ICD rates in type I MD pts **Study type:** Prospective multicenter registry **Size:** 406	**Inclusion criteria:** Pts seen at 23 different neuromuscular clinics in US	**Intervention:** PM or ICD per physician discretion	**Results:** • 11.3% implanted with a PM, 5.2% with an ICD • 52% of PM pts died in follow-up. PM pts often died of respiratory failure or sudden death • None of pts implanted for isolated 1st AVB progressed to CHB	• PR interval ≥240 or QRSd ≥120 ms appear to predict 2nd or 3rd degree AVB (NPV 99.6% and PPV of 10.3%) • Almost 1/3 of PM pts were PM dependent by last follow-up
Groh WJ, et al. 2008 (210) 18565861	**Aim:** Assess if ECG can predict SCD in MD type I pts **Study type:** Prospective multicenter registry **Size:** 406; of which 96 had severe ECG abnormality	**Inclusion criteria:** Pts seen at 23 different neuromuscular clinics in US; including those with either non-SR, PR ≥240 ms, QRS ≥120 ms, 2nd/3rd degree AVB (termed "severe ECG abnormality") **Exclusion criteria:** N/A	**Intervention:** PM or ICD per physician discretion	**Results:** 20% died; 33% were sudden death. 41 received PM; 27 were prophylactic • Severe EKG abnormality had sensitivity =74.1%, specificity =61.7% for prediction of SCD	• Atrial tachyarrhythmias were common (30%) • Risk factors for sudden death were severe ECG abnormalities and atrial tachyarrhythmias
Groh WJ, 2012 (211) 22760083	**Aim:** Contemporary review and expert opinion	**Inclusion criteria:** N/A	**Intervention:** N/A	• Reviews role of PM and ICD • Conduction abnormalities are frequent	• N/A

	Study type: N/A **Size:** N/A			• ICDs are often needed to treat VA and SCD	
Kabunga P, et al. 2015 (212) 25540845	**Aim:** Systematic review of arrhythmias in Kearns-Sayre pts **Study type:** Literature review **Size:** 54 studies	**Inclusion criteria:** Specific search terms	**Intervention:** PM or ICD	**Results:** • 57% of Kearns Sayre pts develop cardiac disease SCD has been reported in up to 20% • Most common is conduction disease which can progress to CHB, or PMVT/torsade	• Most common ECG abnormality is LAFB +/-RBBB • Progression to high-grade AVB can be sudden • VA are often bradycardia related
Saxon LA, et al. 1990 (213) 1695352	**Aim:** Look at Holter and correlate to cerebral symptoms **Study type:** Retrospective **Size:** 411	**Inclusion criteria:** All Holters with persistent AF	**Intervention:** N/A	**Results:** • There was no difference between the group with symptoms and 2-s pauses and the group with no symptoms and 2-s pauses • Many pts had resolution of symptoms w/o PM implant	• 2 s did not appear to correlate to cerebral symptoms
Hilgard J, et al. 1985 (214) 3984858	**Aim:** Look at 3 s pauses on Holter and correlate clinical outcomes **Study type:** Retrospective **Size:** 52	**Inclusion criteria:** 6470 Holters screened; 52 had pauses ≥3 s.	**Intervention:** Per the physician discretion to implant PM	**Results:** Of 52 Holters with pauses, 18 showed AF with slow ventricular response, and 12 had AVB.	• 26 of 52 received a PM • 5 out of 52 pts had symptoms during the pause
Ector H, et al. 1983 (215) 6191291	**Aim:** Assess etiology of pauses and indications for PM **Study type**: Retrospective	**Inclusion criteria:** Consecutive Holters, 53 had a pause ≥3 s.	**Intervention:** None	**Results:** Of the 53 Holters with pauses, 5 had AVB and 29 had slow AF. Symptoms were reported in 45 of 53	Authors propose pauses of 3 s as the cutoff for PM

	Size: 2350 Holters; 53 had pauses				
Michaelsson M, et al. 1995 (216) 7634461	**Aim:** Assess long-term outcome of adults with CCHB **Study type**: Prospective observational **Size:** 102	**Inclusion criteria:** Isolated CCHB diagnosed in pts 15 y or younger; mean age at follow-up was 38 y	**Intervention:** 54 implanted with a PM	**Results:** • Stokes Adams attacks occurred in 27, 8 of whom died • 24 women w/o PM gave birth, 6 had syncope during pregnancy	• There were 11 deaths; 2 died of PM failure and 6 died suddenly 2 pts required an ICD • 8 had BBB, QRS not a predictor of syncope/death
Sholler GF, et al. 1989 (217) 2480059	**Aim:** Identify factors that predict need for PM in congenital CHB pts **Study type:** Retrospective chart review **Size:** 43	**Inclusion criteria:** Children with isolated CCHB 1955–1985 at Boston Children's Hospital	**Intervention:** PM for symptoms only, not EKG or Holter findings	**Results:** • 29 remained free of symptoms • 14 had symptoms (near syncope, exercise intolerance), 1 had CHF at birth, 1 had cardiac arrest	• Heart rate on ECG or Holter did not predict need for PM
Ando G, et al. 2005 (187) 16091145	**Aim:** Assess hemodynamics of long AV delay **Study type:** Case report **Size:** 1	**Inclusion criteria:** Case report	**Intervention:** PM	**Results:** During a hemodynamic assessment, atrial contraction was seen to occur while AV valves are closed, similar to PM syndrome	• AV delay decreased from 290 to 150 with PM improved symptoms
Carroz P, et al. 2010 (191) 19946114	**Aim:** Report pseudo PM syndrome **Study type:** Case report **Size:** 1	**Inclusion criteria:** Case report of pt with marked 1st degree AV block	**Intervention:** Rapid atrial pacing and atropine injection	**Results:** At baseline, pt had PR= 480 ms, intermittent cannon A waves. Symptoms of dizziness and dyspnea improved with PM	• N/A

Kim YH, et al. 1993 (218) 8269289	**Aim:** Describe symptoms of pseudo-PM syndrome **Study type**: Case report **Size:** 1	**Inclusion criteria:** Case report of pseudo-PM syndrome after fast PW ablation and resultant long PR	**Intervention:** Fast PW ablation	**Results:** Marked 1st degree AVB, very symptomatic. Symptoms improved with PM	• N/A
Barold SS, 1996 (193) 8734740	**Aim:** Editorial to discuss role of PM in 1st degree AVB **Study type:** N/A **Size:** N/A	**Inclusion criteria:** N/A	**Intervention:** PM implant	**Opinion:** PMs can be used especially in pts with normal LVEF	• N/A
Alboni P, et al. 2013 (219) 23286970	**Aim:** Describe vagally mediated AVB **Study type:** N/A **Size:** N/A	**Inclusion criteria:** N/A	**Intervention:** None	• PMs are not warranted in asx pts with vagally mediated AVB • Typically, these pts have normal AV conduction	• N/A
Massie B, et al. 1978 (220) 668079	**Aim:** Describe EPS findings in pts with Mobitz II AVB **Study type:** Case series **Size:** 13	**Inclusion criteria:** Mobitz type II with concomitant sinus slowing **Exclusion criteria:** No associated sinus slowing	**Intervention:** EPS; PM for persistent symptoms	**Results:** Mobitz type II with sinus slowing appears related to vagal tone	• These episodes of bradycardia were responsive to atropine • Dx of Mobitz type II best when sinus rate is stable
Mosqueda-Garcia, R et al. 2000 (221) 11104751	**Aim:** Attempt to explain the pathophysiology of neurally mediated syncope	**Inclusion criteria:** N/A	**Intervention:** N/A	**Conclusions:** neurally mediated syncope is not a uniform syndrome in all pts and involves baroreceptor reflex abnormalities and neurohumoral mechanisms	• N/A

	Study type: Comprehensive review **Size:** N/A				
Guerrero-Marquez FJ, et al. 2016 (183) 28496928	**Aim:** To write a featured review of paroxysmal AVB **Study type:** Review **Size:** N/A	**Inclusion criteria:** N/A	**Intervention:** N/A	**Conclusions:** Idiopathic AVB is paroxysmal 3rd degree heart block with no other rhythm abnormalities pre or post in pts with normal heart and EKG	Other causes of AVB include; extrinsic vagal effect, Lev-Lenegre disease, SLE, bacterial endocarditis with abscess, sarcoid, Lyme disease, sickle cell
Kato Y, et al. 2003 (222) 12870723	**Aim:** Assess efficacy of steroids for resolution of AVB in sarcoidosis **Study type:** retrospective **Size:** 20	**Inclusion criteria:** Pts with cardiac sarcoid, AVB and normal EF	**Intervention: S**teroids per physician discretion	• **Results:** Of the 7 treated with steroids 4 had resolution of AVB, 6 had steroid side effects	• None of the 13 untreated pts resolved the AVB
Takaya Y, et al. 2015 (223) 25529542	**Aim:** Assess outcomes of sarcoid pts with AVB as initial manifestation **Study type:** Retrospective observational study **Size:** 53	**Inclusion criteria:** Consecutive cardiac sarcoid pts with either AVB or VT or CHF	**Intervention:** PM or ICD per physician	• in general pts presenting with AVB have fewer cardiac adverse events than those with VT/HF (mostly HFH) however cardiac mortality is about the same • Of the 17 with high-grade AVB treated with steroids, 7 responded	• Of the 17 pts with AVB, 7 died of fatal SCD including 3 who responded to steroids for AVB
Padala SK, et al. 2017 (224) 27836297	**Aim:** Assess impact of steroids given early on AVB, VA, and LVEF **Study type:** retrospective	**Inclusion criteria:** Cardiac sarcoid pts given steroids early after Dx	**Intervention:** Steroids	**Results:** Only those where steroids started within 30 d had improvement in LVEF • Some with early steroid treatment had no VT or AVB recurrence	• Pts who did not receive early steroid treatment did not have any improvement

	Size: 30				
Birnie DH, et al. 2016 (225) 27443438	**Aim:** Review literature on cardiac sarcoid **Study type:** N/A **Size:** N/A	**Inclusion criteria:** N/A	**Intervention:** N/A	• **Results:** RBBB is more common than LBBB. Epsilon waves are rare.	• Sarcoidosis with cardiac involvement portends a worse prognosis
Sadek MM, et al. 2013 (155) 23623644	**Aim:** Systematic review and meta-analysis of cardiac sarcoidosis and steroids **Study type:** N/A **Size:** 10 studies	**Inclusion criteria:** Published studies on steroids for cardiac sarcoidosis	**Intervention:** Steroids	• **Results:** Overall steroids beneficial for recovery of AVB with 47.4% of pts improved	• There are no RCT looking at steroid use in cardiac sarcoid
Zhou Y, et al. 2017 (226) 27614001	**Aim:** Determine outcome of cardiac sarcoidosis in a single institution **Study type:** Retrospective **Size:** 73	**Inclusion criteria:** All pts who met criteria for sarcoid	**Intervention:** Per physician discretion	• **Results:** Heart block was present in 19.2% of pts. 5-y survival overall was 95.5%.	• Lack of ICD or PM predicted increased mortality
Sayed RH, et al. 2015 (227) 25549725	**Aim:** Characterize the bradyarrhythmias in cardiac AL amyloid pts **Study type:** Single arm prospective **Size:** 20	**Inclusion criteria:** AL amyloidosis + (pre) syncope symptoms	**Intervention:** All pts received ILR	**Results:** 13 of the 20 died with median survival 60 d • 8 of the 13 had bradycardia (heart rate <35 bpm) preceding PEA	Baseline ECG showed 1st degree AVB in 45% and 1 pt had Mobitz type I at baseline

Reisinger J, et al. 1997 (228) 9316537	**Aim:** Assess spectrum of EP abnormalities in AL amyloid **Study type:** Case series **Size:** 25	**Inclusion criteria:** AL amyloid	**Intervention:** EPS. ICD or PM per physician discretion	**Results:** All 25 had abnormal EKG with conduction disease present • 23 of 25 had HV >55ms (most had narrow QRS)	• 23 died; 10 died of SCD (of which 2 had PM and 1 had ICD)
Panic G, et al. 2011 (190) 20226549	**Aim:** Case report of AVB due to Lyme disease **Study type:** Case report **Size:** 1	**Inclusion criteria:** Pt with Lyme disease and high-grade 2nd degree AVB	**Intervention:** Antibiotics	**Results:** Pt presented with high-grade AVB which resolved after 12 d of antibiotics	Pt presented for symptoms of fatigue and heart rate of 31 bpm
Maeno K, et al. 2009 (188) 19466526	**Aim:** Report the interaction of OSA and bradyarrhythmia **Study type**: Case report and literature review **Size:** 1	**Inclusion criteria:** N/A	**Intervention:** CPAP	• **Results**: Profound AVB resolved with CPAP	• In this case, AVB was seen prior to hypoxia and was not simultaneous
Benditt DG, et al. 1983 (229) 6359850	**Aim:** Assess EP effects of IV and PO theophylline **Study type:** Single arm **Size:** 10	**Inclusion criteria:** No significant structural heart disease and bradycardia with symptoms. All had prior syncope	**Intervention:** Acute IV theophylline, then chronic PO theophylline	• **Results:** Chronic treatment with level 9–12 tolerated in 8/10 (80%); suppression of symptoms achieved in 6 of the 8	• N/A
Nimura A, et al. 2011 (230) 21921376	**Aim:** Discuss possible mechanisms of AVB	**Inclusion criteria:** Case report	**Intervention:** Cilostazol	• **Results**: In an elderly pt with high-grade AVB, the AVB	• N/A

	resolution with cilostazol **Study type:** Case report **Size:**			resolved after cilostazol treatment	

Data Supplement 35. RCTs of meds/reversible/transient causes of bradycardia due to AVB (Section 6.4.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2^0 Endpoint (if any); Study Limitations; Adverse Events
Birmingham Trial Watson RD, et al. 1984 (231) 6475712	**Aim:** Determine if PM in post MI pts with conduction disease reduces mortality **Study type**: RCT **Size:** 50	**Inclusion criteria:** Survived 14 d post MI, have RBBB or RBBB+ left hemiblock **Exclusion criteria:** Prior conduction disease, PM	**Intervention:** Ventricular PM (27) **Comparator:** Control (23)	• **Results:** At 5-y follow-up, 61% of PM pts had died compared to 41% of control pts	• Over 5-y follow-up no progression of AVB • PM of no benefit • VT was an important cause of death

Data Supplement 36. Nonrandomized data of Medications/Reversible/Transient Causes of Bradycardia due to AVB (Section 6.4.2)

Study Acronym; Author; Year Published PMID	Study Type/Design; Study Size (N)	Patient Population	Primary Endpoint and Results	Summary/Conclusion; Comments
Tans AC, et al. 1980 (232) 7350750	**Aim:** Prognosis of acute inferior MI with heart block **Study type:** Observational **Size:** 144	**Inclusion criteria:** Acute inferior MI, 2nd and 3rd AVB, AF with rate <60, 2:1 AVB, AVB lasted >30 min	**1° endpoint:** AVB was associated with increased mortality (22% vs. 9%) **Results:** AVB developed between 1 and 5 d after MI	• 94 had CHB, 84 recovered 1:1 conduction, 10 died • Duration of AVB was 30 min–16 d • AVB after MI typically resolves

Ginks WR, et al. 1977 (233) 836733	**Aim:** Determine the need for permanent PM in pts with Anterior MI and temp. pacing for CHB **Study type**: Observational **Size:** 52	**Inclusion criteria:** Anterior MI, CHB 2 had CHB, narrow QRS 50 had QRS >120	**1° endpoint:** Of the 25 survivors, 4 required permanent pacing **Results:** 27 of the 52 died	• Of the surviving 25 pts, 1 remained in CHB and underwent PM before discharge and 2 pts developed CHB months later • Do not recommend PM if CHB resolves
Singh SM, et al. 2015 (234) 25205530	**Aim:** Determine incidence of high-grade AVB in ACS **Study type:** Global registry (GRACE) **Size:** 1701 (of 59,229 subjects in GRACE)	**Inclusion criteria:** GRACE Registry subject with high-grade AVB **Exclusion criteria:** Lack of high-grade AVB	**1° endpoint:** 2.9% of subjects had high-grade AVB **Results:** Rate of high-grade AVB decreased over time.	• 46% present initially with AVB and 54% developed in hospital • 23% of high-grade AVB pts died in the hospital (OR: 4.2; 95% CI: 3.6–4.9; p<0.001) • Of the 1701, 100 (5.9%) required permanent PM
Osmonov D, et al. 2012 (151) 22530749	**Study type:** Single-center retrospective cohort of pts with drug induced AVB **Size:** N=108 (16% of all 668 pts admit AVB).	**Inclusion criteria:** All pts admitted with Mobitz type II or 3rd degree AVB or 2:1 AVB who were on AV nodal blocking drugs **Exclusion criteria:** MI, electrolyte disturbances, digoxin toxicity	**1° endpoint:** Resolution/ recurrence AVB, need for PPM **Results:** Resolution of AVB within 72 h in 72%. 21/78 (27%) had recurrence of AVB. Overall 51/108 (48%) had persistent of recurrent AVB despite drug withdrawal.	• Half of pts with AVB on nodal-blocking drugs require PM before discharge despite drug withdrawal. • Limited follow-up – other pts may have required PPM at later date
Zeltser D, et al. 2004 (152) 15234417	**Study type:** Single-center retrospective cohort **Size:** N=169 (60% male, mean age 78 y).	**Inclusion criteria:** All pts admitted with 2nd or 3rd degree AVB 1999–2003. **Exclusion criteria:** MI, digoxin toxicity	**1° endpoint:** Resolution/ recurrence AVB, need for permanent PM **Results:** 92/169 (54%) were receiving AV nodal blockers; 79/92 (86%) had drug discontinued. 41% had resolution of AVB with stopping drug; 56% had relapse of AVB	• Overall, only 15% of pts with AVB on nodal blocking drugs had AVB "caused by drugs" • AVB may recur despite remaining off the drug
Knudsen MB, et al. 2013 (150) 23869746	**Study type:** Single-center, retrospective cohort	**Inclusion criteria:** Pts admitted with 2nd or 3rd degree AVB, had	**1° endpoint:** Need for permanent PM after drug discontinuation; complications of TPM	• Pts with AVB on AADs or digoxin do not benefit from temp. PM and

	Size: N=55	temporary pacing wire, were on class II-IV AADs or digoxin. **Exclusion criteria:** AVB due to other identified cause, prior PM explant, died within several days	**Results:** 47/55 (85%) required permanent PM in hospital. 2/55 had recurrent AVB and required PPM. 11% of pts had complication of temp. PM (infection/ dislodgment)	drug washout. Should proceed to PPM w/o delay.
Ozcan KS, et al. 2012 (157) 22738687	**Study type:** Single-center retrospective cohort **Size:** N=50 (29 hypothyroid, 21 hyperthyroid)	**Inclusion criteria:** All pts. with 2nd/3rd degree AVB who had hyper- or hypothyroidism **Exclusion criteria:** MI, electrolytes abnormalities, digoxin toxicity, on AADs	**1° endpoint:** Persistent AVB despite treatment of thyroid abnormalities **Results:** 46/50 (92%) pts required permanent PM; 2 additional pts had persistent AVB. 76% of hypothyroid and 86% of hyperthyroid had irreversible AVB.	Thyroid abnormalities are rarely a cause of reversible AVB.
Farre N, et al. 2014 (154) 24491864	**Aim:** Assess outcome of CHB due to ACS and other causes **Study type**: Retrospective **Size:** 79 pts with reversible AVB; grp A=ACS, N=52 Grp B=non-ACS, N=27	**Inclusion criteria:** reversible CHB, no indwelling PM **Exclusion criteria:** Felt not to be reversible	**Results:** For the ACS group 1/52 received a permanent PM. For the non-ACS, AVB was due to hyperkalemia, AVN blockers, acute infection, 1 PE; 9/27 had recurrent AVB and required permanent PM	• If ACS, syncope presenting symptom of CHB 6%; for non-ACS 33%. • 39% of reversible non-ACS pts had recurrent AVB requiring permanent PM • 2% of ACS had recurrent AVB • Many non-ACS had residual LBBB
Panic G, et al. 2011 (190) 20226549	**Aim:** Case report of AVB due to Lyme disease **Study type:** Case report **Size:** 1	**Inclusion criteria:** Pt with Lyme disease and high-grade 2nd degree AVB	**Results:** Pt presented with high-grade AVB which resolved after 12 d of antibiotics	• Pt presented with high-grade AVB, resolution after 12 d antibiotics • 5% of pts with Lyme will have cardiac involvement, typically AVB
Kostic T, et al. 2017 (235) 28082088	**Study type:** Review of Lyme carditis and clinical course	**Inclusion criteria:** N/A	**Results:** AVB is the most common conduction disorder with Lyme carditis	• Manifestations of AVB may progress rapidly in hours or days

Robinson ML, et al. 2015 (236) 25999222	**Study type:** Review **Size:** N/A	**Inclusion criteria:** N/A	**Results:** 1.1% of Lyme disease reported to CDC between 2000–2010 included cardiac manifestations	• N/A
Carano N, et al. 2012 (186) 23110777	**Aim:** Case report and review of rheumatic HD and CHB **Study type:** Literature review and case report **Size:** 1	**Inclusion criteria:** N/A	**Results:** Pt presented with acute rheumatic carditis and CHB; CHB resolved within 24 h of antibiotics	• Of the 25 cases found in the literature, the AVB lasted from minutes to several days • PM implant typically not needed (in 7 of 25 cases)
Koehler U, et al. 1998 (67) 9551750	**Aim:** Assess effect of OSA Rx on brady **Study type:** Prospective single arm **Size:** 16	**Inclusion criteria:** Pts with OSA, and negative EPS, echo, EKG, stress test	**1° endpoint:** Assess effect of CPAP or BiPAP on nocturnal AVB **Results:** CPAP and BiPAP reduced the number of AVB episodes from 651 to 72 ($p<0.01$)	• 4 pts received PM for continued pauses despite effective OSA therapy
Maeno K, et al. 2009 (188) 19466526	**Aim:** Report the interaction of hypoxia and AVB **Study type:** Case report, literature review **Size:** 1	**Inclusion criteria:** N/A	**1° endpoint:** Resolution of AVB with CPAP **Results:** AVB occurred prior to oxygen desaturation and resolved with CPAP	• AVB may be due to increased vagal tone
Becker H, et al. 1995 (66) 7812557	**Aim:** Assess effect of CPAP on AVB and bradycardia **Study type**: Prospective single arm observational **Size:** 17	**Inclusion criteria:** All referrals for sleep apnea and if 2nd or 3rd degree AVB or asystole >2 s. noted during sleep study	**1° endpoint:** CPAP reduced incidence of heart block **Results:** 12 of 17 had AVB eliminated with CPAP, 3 had substantial reduction in AVB, and 2 had persistent bradycardia	• 7.1% of sleep apnea pts referred for sleep study had AVB during sleep • Most had normal baseline EKG (1 RBBB, 1 1st AVB) • Mean duration of 3rd AVB was 8.4 s
Grimm W, et al. 2000 (68) 10980227	**Aim:** Assess outcomes of pts with OSA-related bradycardia **Study type**: Prospective single arm	**Inclusion criteria:** Negative EPS and Holter for AVB **Exclusion criteria:** Taking digoxin/BB/CCB	**1° endpoint:** Effect of CPAP **Results:** CPAP resolved >3 s pauses in 21/29	• 7 out of 8 with continued pauses received a PM • PM had no effect on outcomes (syncope) and prognosis is good

	Size: 29			
Unterberg C, et al. 2005 (237) 16126716	**Aim:** Compare CPAP to atrial overdrive pacing **Study type:** Prospective crossover **Size:** 10	**Inclusion criteria:** Pts on CPAP for OSA, no PM indication	**1° endpoint:** Assess if atrial overdrive pacing or CPAP is superior for reducing apneic episodes **Results:** The apneas were significantly reduced with CPAP but not with atrial pacing	• CPAP improved apneas but pacing did not despite elimination of bradycardia or asystole episodes
Garrigue S, et al. 2002 (238) 11832528	**Aim:** Assess utility of PM overdrive pacing for OSA and central sleep apnea **Study type**: Prospective crossover study **Size:** 15	**Inclusion criteria:** Pts with DC pacemakers with symptoms of OSA and had positive test for OSA	**1° endpoint:** Compare ventricular back up pacing to atrial overdrive pacing **Results:** The hypopnea index was reduced from 9 to 3 with atrial overdrive pacing (p<0.001)	• Atrial overdrive pacing reduced the number of apneic episodes >50% in majority of pts
Stegman SS, et al. 1996 (70) 8774819	**Aim:** Determine if asx bradycardia during sleep is due to OSA **Study type:** Prospective single arm **Size:** 8	**Inclusion criteria:** Pts with asx bradycardia referred for PM	**1° endpoint:** Determine incidence of OSA in these pts **Results:** 7 of 8 had a positive sleep study for OSA and did not receive PM	• Pts remained asx and improved sleep symptoms

Data Supplement 37. RCT data of additional testing for Bradycardia due to AV block (Section 6.4.3)

Study Acronym; Author; Year Published PMID	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Sivakumaran S, et al. 2003 (17) 12867227	**Aim**: Compare utility of loop recorder vs. Holter	**Inclusion criteria**: Syncope or presyncope	**Intervention:** 48 h Holter (n=51) vs. 30 d event (n=49)	Diagnostic yield was 63% for loop vs. 24 % for Holter (p<0.0001)	• 23% of loop recorder pts failed to activate during symptoms

	Study type: RCT **Size:** 100				
Kinlay S, et al. 1996 (239) 7503472	**Aim:** Compare 3-month event monitor to 48-h Holters **Study type:** Randomized Crossover trial **Size:** 43	**Inclusion criteria:** Pts with palpitations and no prior testing	**Intervention:** Received a 90-d Event monitor	**Results:** Event monitors were more likely to provide a Dx (67% vs. 35%; p<0.001). Holter not a good test for intermittent symptoms or events	• The event monitor is more cost effective due to higher yield ($213 per additional rhythm strip)
Giada F, et al. 2007 (240) 17498580	**Aim:** Compare Holter+event+ EPS to ILR for diagnostic yield **Study type:** RCT **Size:** 50	**Inclusion criteria**: Infrequent palpitations that last >1 min **Exclusion criteria:** Abnormal H&P, ECG, echo	**Intervention:** ILR **Control:** 24-h Holter, 4-wk external monitor, and if negative, an EPS	**Results:** ILR more effective in establishing etiology of palpitations (73% vs. 21%; p<0.001)	• The event monitor is more cost effective
FRESH Podoleanu C, et al. 2014 (74) 25241220	**Aim:** Role of ILR for syncope evaluation **Study type**: RCT **Size:** 78	**Inclusion criteria:** Syncope	**Intervention:** ILR **Control**: Standard of care, per physician discretion	**Results:** ILR yield is superior (cause of syncope identified in 46.2% vs. 5%; p<0.001)	• The ILR was more cost effective with fewer hospitalization days and fewer tests

Data Supplement 38. Nonrandomized data of additional testing for Bradycardia due to AV block (Section 6.4.3)

Study Acronym; Author; Year Published PMID	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)
Katritsis DG, et al. 2017 (241) 28507743	**Aim:** Review the role of EPS in bradycardia	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**Intervention:** N/A **Comparator:** N/A	• 30% of Mobitz II blocks have narrow QRS • 20% of 2:1 AVB is in the AV Node

	Study type: N/A **Size:** N/A			• HV >70 is nonspecific, HV >100 is specific but insensitive • Proposed indications for EPS of AV Block: • (1) Asymptomatic 2nd degree AVB with BBB (type I or not sure) (2) suspect phase 4 infranodal block (3) suspect type II but QRS narrow (4) symptomatic type I block and BBB
Mangiardi LM, et al. 1982 (242) 7064840	**Aim:** Assess utility of CSM and atropine **Study type:** Prospective, nonrandomized **Size:** 25 (15 with intraHis block and 10 with intranodal block)	**Inclusion criteria:** Documented AVB at EPS and narrow QRS	**Intervention:** Carotid sinus massage × 10 s., 2 mg atropine, EPS	• Atropine and carotid massage yielded a Dx in 22 (13/15 and in 9/10) pts • Atropine and carotid sinus did yield differing results at bedside vs. EPS in some pts
Twidale N, et al. 1988 (243) 2462213	**Aim:** Determine use for assessing AVB **Study type:** Prospective, nonrandomized **Size:** 89	**Inclusion criteria:** 51 with bifascicular block and syncope or transient high-grade AVB or tachyarrhythmia; 38 with no syncope and normal ECG (control group)	**Intervention:** EPS with IV procainamide	• In those with bifascicular block, procainamide prolonged HV, developed high-grade AVB; in control group HV only minimally prolonged and no AVB seen
Bogossian H, et al. 2017 (244) 28294370	**Aim:** Assess role of EPS in BBB pts **Study type:** Prospective single arm **Size:**30	**Inclusion criteria:** Symptomatic bifascicular block (RBBB+LAFB) and 1st AVB	**Intervention:** EPS	• All pts had long HV, mean 82 ms • 1st AVB in symptomatic pts with bifascicular block likely due to infraHisian delay
Kalscheur MM, et al. 2016 (245) • 27565449	**Aim:** Examine the IIa indication for PM for bifascicular block +syncope **Study type:** Retrospective **Size:** 43	**Inclusion criteria:** Pts with bifascicular block and syncope who underwent PM **Exclusion criteria:** vasovagal, orthostatic cause of syncope	**Intervention:** Negative EPS, and empiric PM Implant (n=26) **Comparator:** Positive EPS or ILR findings for AVB and PM implant (n=17)	• Primary endpoint: time to 1st recurrence of syncope • Syncope recurrence was 18%/5 y in empiric grp vs. 0% in pos. EPS/ILR group • Progression to high-grade AVB in 53% of the pos. EPS/ILR group vs. 27% of the empiric group (p=0.11)

Morady F, et al. 1984 (246) 6475778	**Aim:** Assess role of EPS in pts with BBB and syncope **Study type:** Prospective, nonrandomized **Size:** 32	**Inclusion criteria:** BBB and syncope **Exclusion criteria:** 2nd or 3rd degree AVB or SVT, SND	**Intervention:** EPS	• 12/32 had HV ≥70 ms • 44% had inducible VT
Click RL, et al. 1987 (247) 3825942	**Aim:** Assess role of EPS **Study type:** Retrospective **Size:** 112	**Inclusion criteria:** Chronic BBB, with symptoms	**Intervention:** EPS	• 34 received PM for long HV • 39 had ventricular arrhythmias induced and 21 had conduction disease and VT
Brignole M, et al. 1995 (248) 7618623	**Aim:** Look at role of EPS in syncope pts **Study type:** Prospective **Size:** 25	**Inclusion criteria:** Unexplained syncope who during monitoring had documented bradycardia causing syncope	**Intervention:** EPS, TTT, CSM	• EPS useful for AVB Dx • Carotid massage and TTT useful for neurally mediated Dx • These 3 tests are complimentary when done together; if all 3 are negative bradycardia unlikely as cause of syncope
Dhingra RC, et al. 1979 (249) 498473	**Aim:** Role of EPS in bifascicular block **Study type:** Prospective nonrandomized **Size:** 531	**Inclusion criteria:** Bifascicular block w/o 2nd or 3rd degree block	**Intervention:** EPS with atrial pacing	• Pacing induced infraHisian block during Wenckebach was functional but if occurred during normal AV conduction, was pathologic
Zipes DP, et al. 1979 (250) 378457	**Aim:** Physiology review of 2nd degree AVB **Study type:** N/A **Size:** N/A	**Inclusion criteria:** N/A	**Intervention:** N/A	• Described maneuvers to distinguish type I vs. type II 2nd degree AVB
Shetty RK, et al. 015 (251) 25819829	**Aim:** Describe worsening AVB with exercise **Study type:** Case report **Size:** 1	**Inclusion criteria:** Pt with RBBB, LAFB and 1st degree AVB	**Intervention:** Treadmill which induced complete AVB	• 1:1 AV conduction present at rest; CHB seen during treadmill testing

Toeda T, et al. 2000 (252) 10793447	**Aim:** Assess for exercise induced AVB **Study type:** Case report **Size:** 1	**Inclusion criteria:** Pt with exercise induced AVB	**Intervention:** EPS showed infranodal AVB	• EPS showed gap phenomenon with AV conduction
Chokshi SK, et al. 1990 (253) 2360528	**Aim:** Assess importance of exercise induced AVB **Study type:** Case series **Size:** 3	**Inclusion criteria:** AVB during exercise testing	**Intervention:** EPS showed prolonged HV and block distal to His	• All 3 had negative Holter monitoring • All 3 had prolonged HV interval and infraHisian block at EPS
Bakst A, et al. 1975 (254) 1191459	**Aim:** Assess exercise induced AVB **Study type**: Case report and discussion **Size:** 1	**Inclusion criteria:** Pt with exertional dyspnea and EKG with 1:1 conduction	**Intervention:** Treadmill and atropine	• Exercise improves Mobitz type I AVB and worsens AV conduction if underlying Mobitz type II AVB • Atropine similarly worsens AV conduction when underlying Mobitz type II
Egred M, et al. 2004 (255) 15561349	**Aim:** Assess importance of exercise induced AVB **Study type**: Case report **Size:** 1	**Inclusion criteria:** Syncope during walking	**Intervention:** Treadmill	• Treadmill testing can be an important diagnostic tool when evaluating exertional syncope
Fisher JD, 1981 (256) 7019962	**Aim:** Assess role of EPS **Study type:** Review of EPS, its role in SSS, AVN disease	**Inclusion criteria:** N/A	**Intervention:** Detailed account of how to do EPS	• Reviews role of CSM, exercise testing, breath holding

Data Supplement 39. RCTs for Permanent Pacing for AV block (Section 6.4.4)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events

UKPace Toff WD, et al. 2005 (257) 16014884	**Aim:** Assess mortality benefit from dual vs. ventricular pacing in pts with AVB **Study type**: RCT **Size:** 2,021	**Inclusion criteria**: Age >70 y, 2nd or 3rd degree AVB (73.3% had CHB) **Exclusion criteria:** AF, NYHA class IV	**Intervention:** Randomized to dual PM, or ventricular PM-fixed rate, or to ventricular PM-adaptive rate **Comparator:** Compare DC pacing to ventricular pacing	**1° endpoint:** No all-cause mortality benefit for DC pacing at 3 y (7.2% vs. 7.4%; p=NS; CI: 0.83–1.11)	• More procedural complications in the DC group Slightly higher risk of CVA/TIA/TE event in fixed rate ventricular pacing group (p=0.04) but not in the rate adaptive ventricular pacing group
PASE Lamas GA, et al. 1998 (140) 9545357	**Aim:** Determine difference in health related QOL in ventricular vs. DC pacing in pts >65 y **Study type:** RCT **Size:** 407	**Inclusion criteria:** >65 y, SR (49% had AVB at baseline) **Exclusion criteria:** AF	**Intervention:** Implanted with DC PM; randomized to ventricular or DC pacing **Comparator:** Ventricular pacing	**1° endpoint:** QOL improved for both groups compared to baseline (p<0.001) but no difference between pacing modes.	• No difference in death, stroke, AF rates • AVB subgroup did not experience better QOL or functional status
MOST Lamas GA, et al. 2002 (141) 12063369	**Aim:** Assess mortality and stroke benefit with DC pacing **Study type:** RCT **Size:** 2,010	**Inclusion criteria:** SND (21% with concomitant AVB) **Exclusion criteria:** Non-SR	**Intervention**: Implanted with DC PM, randomized to pacing mode **Comparator:** Ventricular pacing	**1° endpoint:** All-cause mortality+ nonfatal stroke in DC pacing (21.5%) vs. ventricular pacing (23%) was not significant (p=0.48)	No subgroup analysis of AVB group done
MOST Vp40% Sweeney MO, et al. 2003 (146) 12782566	**Aim:** Use MOST database to assess whether RV pacing increases HFH and AF **Study type:** Reanalysis of RCT data **Size:** 1,339	**Inclusion criteria:** MOST trial subjects with % ventricular pacing data **Exclusion criteria:** MOST trial subjects w/o ventricular pacing data	**Intervention**: Implanted DC PM, randomized to pacing mode **Comparator:**	**1° endpoint:** Ventricular pacing >40% of the time increases risk of a HFH (HR 2.56–2.99) and AF risk linearly increases as % ventricular pacing increases regardless of pacing mode	• The increasing risk of HFH with increasing ventricular pacing levels off after 40%

CTOPP Connolly SJ, et al. 2000 (142) 10805823	**Aim:** Assess for reduction in stroke and CV mortality with DC pacing vs. ventricular pacing **Study type:** RCT **Size:** 2,568	**Inclusion criteria:** Indicated for PM (60% had AVB) **Exclusion criteria:** AF	**Intervention:** Randomized to ventricular or DC PM **Comparator:** Ventricular pacing	**1° endpoint:** First occurrence of CVA or CV mortality over 3 y was 5.5% in the ventricular group and 4.9% in the DC group (p=0.33) • Less AF with DDD (p=0.05)	• All-cause mortality was 6.6% vs6.3% (p=0.92) • Annual AF rates were lower in the dual pacing group (5.3% vs. 6.6%; p=0.5) • No difference in HFH or stroke
CTOPP Extended Kerr CR, et al. 2004 (258) 14707022	**Aim:** Reassess primary endpoint of stroke and CV mortality at 6 y of follow-up **Study type**: RCT **Size**: 1995	**Inclusion criteria:** Undergoing PM for bradycardia (60% had AVB) **Exclusion criteria:** AF	**Intervention:** Randomized to ventricular or DC PM **Comparator:** Ventricular pacing	**1° endpoint**: No change from above (combined endpoint of CV mortality+ stroke 6.1% vs. 5.5%; p=0.26)	Annual risk of AF was less with DC pacing (4.5% vs. 5.7%; p=0.009)
BLOCK-HF Curtis AB, et al. 2013 (259) 23614585	**Aim:** Whether BiV pacing reduces mortality+ morbidity or LV remodeling in AVB pts **Study type:** RCT **Size:** 691	**Inclusion criteria:** Pts with AVB indicated for PM, LVEF ≤50% **Exclusion criteria:** Indicated for CRT	**Intervention:** BiV PM or ICD, randomized to RV or BiV pacing **Comparator:** Dual chamber pacing	**1° endpoint**: Composite of all-cause mortality, HF event, or 15% increase in LVESV was met (HR: 0.74; 95% CI: 0.6–0.9)	• **2° endpoint**: Composite of death or HFH was met (HR: 0.78; 95% CI: 0.61–0.99)
Gierula J, et al. 2013 (260) 23736807	**Aim:** Assess benefit of CRT upgrade in CHB PM pts **Study type**: RCT **Size:** 50	**Inclusion criteria:** PM dep pts (pacing >80%), LVEF <50% **Exclusion criteria:** Symptomatic HF or recent HFH	**Intervention:** Upgrade to BiV PM **Comparator:** DC pacing	**1° endpoint**: Change in LVEF at 6 months was significantly improved in the CRT group (9% vs. -1.5%; p<0.0001)	• **2° endpoints:** pVO_2, QOL, and NT-proBNP improved with CRT (p≤0.03 for all 3 outcomes) • Reduction in LVEDD did not reach statistical significance
HOBIPACE Kindermann M, et al. 2006 (261)	**Aim:** Assess benefit of CRT in pts with depressed LVEF who	**Inclusion criteria:** LVEF ≤40%, LVEDD	**Intervention:** CRT devices implanted	**1° endpoints**: (1) With CRT, LVESV decreased 17% (p<0.001), (2) LVEF	• NT-proBNP reduced 31% with CRT (p<0.002)

16697307	are indicated for pacing **Study type:** Prospective randomized crossover **Size:** 30	≥60 mm, PM indication with AVB **Exclusion criteria:** Not meeting inclusion criteria	**Comparator:** After 3-month run in period, 3 months of RV pacing compared to 3 months of CRT	increased 22% (p<0.0002), (3) pVO_2 increased 12% (p<0.0003)	
DAVID Wilkoff BL, et al. 2002 (262) 12495391	**Aim:** Compare DC pacing to VVI backup pacing in ICD indicated pts with no pacing indication **Study type:** RCT **Size:** 506	**Inclusion criteria:** ICD indicated, LVEF ≤40% **Exclusion criteria:** Any PM indication	**Intervention:** All pts were implanted with a DC ICD **Comparator:** Ventricular back up pacing vs. DC pacing	**1° endpoint**: Freedom from composite of time to death or 1st HFH at 1 y (83.9% for ventricular backup vs. 73.3% for DC pacing; HR: 1.61; 95% CI: 1.06–2.44)	HFH was 13.3% in the ventricular back up group vs. 22.6% (HR: 1.54; 95% CI: 0.97–2.46)
PAVE Doshi RN, et al. 2005 (263) 16302897	**Aim:** Compare RV to BiV pacing in pts with AVN ablation for AF **Study type:** RCT **Size:** 184	**Inclusion criteria:** Any LVEF, AF, AVN ablation, **Exclusion criteria:** NYHA class IV	**Intervention**: AVN ablation +dual or BiV PM **Comparator:** RV pacing	**1° endpoint**: BiV group had a greater improvement at 6 months in 6MHW (31% increase vs. 24%; p=0.04)	• No difference in QOL • No difference in LVEF The benefit of BiV with 6MHW more pronounced in those with LVEF <45%
APAF Brignole M, et al. 2011 (264) 21606084	**Aim:** Compare RV pacing to CRT in pts undergoing AV node ablation **Study type:** RCT **Size:** 186	**Inclusion criteria:** Permanent AF undergoing AV node ablation with or w/o refractory HF and reduced EF **Exclusion criteria:** NYHA class IV with systolic BP ≤80 mm Hg, prior PM	**Intervention:** All subjects implanted with CRT **Comparator:** RV pacing to CRT pacing 1:1 randomization	**1° endpoint**: Composite endpoint of death due to HF, HFH, worsening HF was lower with CRT (11% vs. 26% event rate p=0.005; 95% CI: 0.18–0.73)	• **2^0 endpoint:** CRT had lower rates of worsening HF (p=0.001; 95% CI: 0.12–0.58) and HFH (p=0.013; 95% CI: 0.06–0.72) • No mortality difference between groups • CRT benefit evident in LVEF >35% subgroup

OPSITE Brignole M, et al. 2005 (265) 15618036	**Aim:** Compare RV to LV and to BiV pacing in pts with permanent AF and AV node ablation **Study type:** Prospective randomized crossover **Size:** 56	**Inclusion criteria:** Permanent AF and AV node ablation **Exclusion criteria:** NYHA class IV, unsuccessful AV node ablation	**Intervention:** AV node ablation and CRT implant **Comparator:** Each subject paces RV, LV, and BiV	**1° endpoint:** QOL measures were minimally improved with BiV (MLHFQ up 10%, NYHA improved 11%, LVEF increased 5%; all with p<0.05) but exercise capacity at 3 months did not improve.	• Large interpatient variability present • LV only pacing did not confer as much benefit as BiV pacing

Data Supplement 40. Nonrandomized data for Permanent Pacing for AV block (Section 6.4.4)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)
Brignole M, et al. 2012 (266) 22095616	**Aim:** Identify predictors of improvement after AV node ablation **Study type:** Prospective observational study of RCT cohort **Size:** 171	**Inclusion criteria:** Subjects enrolled in APAF with 2-y follow-up **Exclusion criteria:** Inadequate follow-up	**Intervention:** CRT vs. RV pacing after AV node ablation **Comparator:** Compared responders and nonresponders	**1° endpoint:** RV 63% responder rate and 83% responder rate for CRT (p=0.003) • On multivariate Cox regression analysis, the only predictor of response was CRT mode and having CRT echo optimized
Dretzke J, et al. 2004 (267) 15106214	**Aim:** Cochrane review: compare clinical effectiveness of VVI and DC PMs in pts with SND or AVB **Study type:** Review of RCT and crossover **Size:** N= 31 studies	**Inclusion criteria:** RCT and crossover studies comparing DDD and VVI PMs **Exclusion criteria:** Atrial single chamber pacing	**Intervention:** N/A **Comparator:** N/A	• There is significantly less AF with DDD pacing • Dual chamber pacing is favored for PM syndrome • Trend (NS) for less stroke, HF, mortality and improved exercise capacity

Dhingra RC, et al. 1974 (196) 4817704	**Aim:** Natural Hx of 2^0 AVB+BBB **Study type:** Prospective observational **Size:** N=15	**Inclusion criteria:** BBB+ 2nd degree AVB **Exclusion criteria:** Acute MI	**Intervention:** EPS; follow-up **Comparator:** N/A	• Only 3 were asx at presentation • Permanent PM indicated for severe bradycardia, syncope, CHF • All 9 pts with infra-His block got PM for syncope, CHF • 2 of 4 with supra-Hisian block got PM for syncope, CHF, 1 developed interim CHB but refused PM, 1 asx
Shaw DB, et al. 1970 (197) 5413952	**Aim:** Determine prevalence of pts with 2nd and 3rd degree AVB pts and record their symptoms **Study type**: Observational **Size:** N=100	**Inclusion criteria:** 2nd 3rd degree AVB **Exclusion criteria:** Digoxin or propranolol use, acute MI	**Intervention:** None **Comparator:** N/A	• 48% had syncopal events • 9% had CHF • No reported deaths
Simon AB, et al. 1978 (198) 626128	**Aim:** Follow natural Hx and survival of AVB pts who underwent PM implant **Study type:** Retrospective **Size:** N=246	**Inclusion criteria:** 2nd or 3rd degree AVB **Exclusion criteria:** SND	**Intervention:** Ventricular PM **Comparator:** Historical reports of pts w/o a PM	• Natural Hx of CHB is 50% mortality in the first year based on prior historical literature • Survival improved to 61% at 5 y with a PM • Post PM, new CV events were common including MI, CHF, and stroke and SCD was the most common mode of death
Strasberg B, et al. 1981 (199) 7471363	**Aim:** Assess natural Hx of 2nd AVB **Study type**: Retrospective, observational **Size**: N=56	**Inclusion criteria:** Consecutive pts with chronic 2nd AVB and EPS positive for 2nd AVB **Exclusion criteria:** Acute AVB in setting of MI or digoxin toxicity	**Intervention:** None	• All had 2nd degree type I (Wenckebach) on baseline ECG (none had type II) • 34% did not have heart disease and had a normal HV interval; none died of cardiac cause • 66% had heart disease, some had prolonged HV; 25% received a PM • No one progressed to CHB

Vatankulu MA, et al. 2009 (268) 19406272	**Aim:** Assess LV remodeling in CHB PM pts after PM upgrade to CRT **Study type:** Prospective single arm **Size:** N=26	**Inclusion criteria:** CHB, upgraded PM to CRT, on optimal GDMT **Exclusion criteria:** Asymptomatic, medications stable <1 month	**Intervention:** BiV upgrade+/- defibrillator **Comparator:** None	• NYHA improved by one class in most subjects • Mean EF increased from 39% to 46% • 25% decrease in mean LVESV • 18% decrease in mean LVEDV • No clinical hard endpoints such as HFH or mortality
Kiehl EL, et al. 2016 (269) 27855853	**Aim:** Determine incidence of PM-induced CM, and identify predictors of RV-pacing induced CM **Study type:** Retrospective **Size**: N=823	**Inclusion criteria:** Consecutive pts receiving PM between 2000–2014 for CHB; LVEF >50%; many pts had procedural/surgical AVB **Exclusion criteria:** Generator change procedure, no echo within 6 months of implant	**Intervention:** CRT upgrade in some PM pts **Comparator:** Compared those with RV-induced CM and those w/o	• 12.3% developed PM-induced CM with mean EF 34% • Of the 25 CRT upgrades with post CRT echo, 84% were responders with mean LVEF increase 18%, LVESV decreased by 45% • RV pacing burden of 20% seemed to delineate increased risk of developing HF
MOST Ellenbogen KA, et al. 2003 (270) 12972124	**Aim:** Characterize complications from DC PM implants using the MOST database **Study type:** Retrospective analysis of RCT **Size:** N=2010	**Inclusion criteria:** DDDR PM implanted for SND; SR **Exclusion criteria:** Serious comorbidities	**Intervention:** Dual chamber PM **Comparator:** Ventricular single chamber PM	• Most common complication in the DC PM group was atrial lead dislodgement (1.7%) • Female sex seemed to predict risk of complication
FOLLOWPACE Udo EO, et al. 2012 (271) 22182495	**Aim:** Determine incidence and predictors of PM complications **Study type:** Prospective, multicenter **Size:** N=1517	**Inclusion criteria:** All pts undergoing initial PM implant **Exclusion criteria:** Generator change procedures;	**Intervention:** PM implant **Comparator:** None	• 69% of implanted PMs were DC • There were 5.54% lead related problems in the 1st 2 months • 12.4% of pts had a complication within 2 months of implant • Multivariate analysis showed a HR of 3.09 for DC devices compared to single chamber devices for complications within 2 months of implant

		investigational PM implanted		
Ellenbogen KA, et al. 2000 (272) 10867093	**Aim:** Determine predictors of PM syndrome in the PASE study **Study type:** Retrospective analysis of RCT **Size:** N= 407	**Inclusion criteria:** Indication for PM implant; in SR **Exclusion criteria:** Severe CHF; AF	**Intervention:** Randomized to single or DC PM **Comparator:** Compare the 2 arms	• Predictors of PM syndrome in a Cox multivariate regression model include: reduced systolic BP with VVI pacing, use of BB, DCM • 26% crossed over from ventricular to DC pacing
MOST Link MS, et al. 2004 (273) 15172414	**Aim:** Determine incidence and predictors of PM syndrome in SND pts treated with ventricular pacing using the MOST database **Study type:** Retrospective analysis of RCT **Size:** N= 996	**Inclusion criteria:** Randomized to ventricular pacing and meet criteria for PM syndrome **Exclusion criteria:** Not meeting pre-defined criteria for PM syndrome	**Intervention:** PM syndrome pts crossed over to DC pacing **Comparator:** Pts compared to themselves pre-crossover	• 18.3% met criteria for PM syndrome • Predictors of PM syndrome include lower sinus rate, higher paced rate, higher % paced beats
Arbustini E, et al. 2002 (274) 11897440	**Aim:** Assess prevalence of LMNA mutations in a DCM cohort **Study type:** Prospective **Size:** N=73 and 107 controls	**Inclusion criteria:** DCM (familial and sporadic) with and w/o AVB. Control group=29 with ischemic or valvular disease and 107 blood donors w/o known heart disease **Exclusion criteria:** DCM pts who do not meet WHO criteria	**Intervention:** Genetic testing (73) **Comparator:** **G**enetic testing (107)	• LMNA gene mutations accounted for 33% of the pts with DCM with AVB • AVB associated with DCM is a reason for LMNA gene molecular screening • None of the DCM pts with intact AV conduction had any LMNA defects

Anselme, F, et al. 2013 (275) 23811080	**Aim:** Assess utility of primary prevention ICD placement in pts with LMNA mutation and AVB **Study type:** Prospective, single arm **Size:** N=47	**Inclusion criteria:** Consecutive pts with LMNA mutation and either a (1) PM, or an (2) indication for PM, or (3) PR interval>240 ms and either LBBB or NSVT **Exclusion criteria:** LMNA pts w/o the 3 additional criteria were enrolled but did not receive an ICD	**Intervention:** ICD (n=21) **Comparator:** Standard of care w/o ICD (n=24); 2° prevention ICD (n=2)	• None of the ICD pts died of SCD over median follow-up of 62 months • 52% of primary prevention ICD recipients experienced sustained VAs requiring ICD therapy • Conduction disorders was a predictor of VA
Hasselberg, NE, et al. 2014 (276) 24058181	**Aim:** To look for predictors of VA in pts with lamin A/C mutation **Study type:** Prospective observational **Size:** N= 41	**Inclusion criteria:** LMNA mutation positive **Exclusion criteria:** Inability to consent	**Intervention:** ECG, Holter, echo, CMRI, genetic testing **Comparator:** N/A	• 7 of the 41 (27%) lamin A/C mutation positive subjects had AVB • 21 (51%) had VA • All 8 pts with sustained VT had AVB and markedly prolonged AVB (median 310 ms) • Prolonged PR interval and any type of AVB were the strongest predictors of sustained VA

Data Supplement 41. Nonrandomized Trials, Observational Studies, and/or Registries of Conduction Disorders (Section 7)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
The Framingham Study Schneider JF, et al. 1979 (27) 154870	**Aim:** Assess the clinical implications of LBBB **Study type:** Nested case-control in Framingham cohort **Size:** 55 pts who developed LBBB, 110 matched controls Mean age at study onset =50 y Mean age at onset of LBBB =62 y	**Inclusion criteria:** LBBB and age- and sex-matched control pts who did not develop LBBB from Framingham cohort **Exclusion criteria:** N/A	**1° endpoint:** Development of CV disease **Results:** 55/5209 people developed LBBB in 18 y of follow-up 48% of these develop CAD or HF for the 1st time with or following Dx of LBBB Only 11% remained free of clinically apparent CV abnormal In men, the appearance of LBBB contributed independently to an	• Comparison with age- and sex-matched control subjects free from LBBB suggests that newly acquired LBBB is most often a hallmark of advanced hypertensive or ischemic heart disease, or both

			increased risk of CV disease mortality	
Fahy GJ, et al. 1996 (31) 8651093	**Aim:** Determine the long-term outcome of pts with BBB and no clinical evidence of CV disease **Study type:** Nested case-control **Size:** 310 pts with BBB, 310 matched controls out of 110,000 participant screening program in Ireland	**Inclusion criteria:** BBB/age- and sex-matched controls **Exclusion criteria:** Suspected heart disease	**1° endpoint:** Long-term "outcome" of BBB pts **Results:** BBB did not impact overall mortality Cardiac mortality was significantly increased in the LBBB group compared to their controls LBBB, but not RBBB, was associated with an increased prevalence of CV disease at the follow-up (21% vs. 11%; p=0.04).	• Isolated left BBB is associated with an increased risk of developing overt CV disease and increased cardiac mortality.
Talreja D, et al. 2000 (43) 10689252	**Aim:** Assess ability to predict LV dysfunction on echo, by historic, clinical, radiographic, and ECG parameters **Study type:** Cross-sectional **Size:** 300	**Inclusion criteria:** Consecutive inpatients referred for the echocardiographic assessment of LV function	**1° endpoint:** LVER <45% **Results:** 124 (41%) had LVEF <45% Presence of LBBB, male sex, and CM on CXR were associated with presence of LV dysfunction Only 2 pts with LVSD had a normal ECG More than 50% of the predictive power of the model rested on the discriminatory ability of a normal ECG	• When ECG is normal, it is extremely unlikely to have LV systolic dysfunction. • It can be argued that such pts should not be referred for echocardiography.
Eriksson P, et al. 1998 (30) 9832497	**Aim:** Assess prevalence of BBB, its impact on mortality and coexisting CV conditions **Study type:** Prospective cohort **Size:** 855 men who were 50 y old in 1963 followed for 30 y 82 developed BBB 22 of those were LBBB	**Inclusion criteria:** Random sampling of Swedish men **Exclusion criteria:** N/A	**1° endpoint:** Mortality and CV disease **Results:** The prevalence of BBB increases from 1% at age 50 y to 17% at age 80 y, resulting in a cumulative incidence of 18%. BBB did not predict ischemic heart disease or mortality Men who developed BBB had bigger LV volume at baseline and greater incidence of DM and HF	• BBB correlates strongly to age and is common in elderly men. • BBB is a marker of a slowly progressing degenerative disease that affects the myocardium. • BBB is not associated with increased mortality • I could not find data broken down by LBBB vs. RBBB; vast majority were RBBB*

Mahmod M, et al. 2012 (277) 21805313	**Aim:** Evaluate the diagnostic value of CMR in asx pts with LBBB **Study type:** Cross-sectional **Size:** 54 pts	**Inclusion criteria:** Asymptomatic adults with complete LBBB referred for cardiac MR **Exclusion criteria:** Absence of echo	**1° endpoint:** Pathologic findings on MR **Results:** 9/29 (31%) had abnormal MR despite normal echo: 6 with DCM, 2 with LVH 19/25 (76%) with abnormal echo also had abnormal MR; in 13 of them (52%) the MR provided new "clinically relevant" findings: 8 DCM, 1 cardiac sarcoid	• CMR detects subclinical CMP in 1/3 of asx pts with LBBB and normal echo • CMR provides additional clinically relevant data in over 50% of pts • CMR is valuable adjuvant diagnostic tool for pt with asx LBBB
Brignole M, et al. 2001 (185) 11673344	**Study type:** Prospective Observational **Size:** 52 pts	**Inclusion criteria:** BBB and negative conventional workup	**1° endpoint:** Rhythm at syncope recurrence as assessed by ILR **Safety endpoint:** N/A	In pts with BBB and negative EPS, most syncopal recurrences result from prolonged asystolic pauses, mainly attributable to paroxysmal AVB.
Moya A, et al. 2011 (189) 21444367	**Aim:** To analyze the clinical outcomes of pts with syncope and BBB following a systematic diagnostic approach: 3-phase: clinical evaluation, EPS, ILR **Study type:** Multicentered prospective observational trial **Size:** 323 patients (after exclusions)	**Inclusion criteria:** ≥1 syncope in the last 6 mo. and BBB on EGG with a QRSd of ≥120 ms **Exclusion criteria**: Indication for prophylactic ICD due to low LVEF; pre-excitation; long QT syndrome; Brugada syndrome; acute MI; pregnancy; life expectancy <1 y due to noncardiac cause; geographically or otherwise inaccessible for follow-up; unwilling or unable to give informed consent	**1° endpoint:** Clinical Dx (established in 267 patients (82.7%) -recurrent syncope: in 15/215 (7%) after phase 1/2; 36 of 108 (33% after phase 3 -documented spontaneous arrhythmias -death due to any cause: no difference in mortality rate between pts diagnosed at Phase I or II, compared with those who had implanted ILR (6.0 vs. 6.5%) **Safety endpoint:** N/A	• In pts with syncope, BBB, and preserved LVEF, a systematic diagnostic strategy (ESC guidelines) achieves a high rate of Dx (82.6%) with a low rate of mortality (6%), allowing clinicians to institute etiology-specific treatment. • The most common cause of syncope was bradyarrhythmia, mostly due to paroxysmal A-V block. Other etiologies of syncope were recognized in 17.6% • initial clinical evaluation achieved a Dx in 25%; the most frequent Dx at EPS was a bradyarrhythmia (76%), VT or SVT was induced in 14%. • The study was not designed to determine whether this diagnostic strategy was better than implanting a PM in the majority of pts
McAnulty JH, et al. 1982 (278) 7088050	**Study type:** Prospective Observational	**Inclusion criteria:** Bifascicular or trifascicular block	**1° endpoint:** Major clinical events, death, heart block, need for PPM, syncope	• A higher percentage of pts with syncope were shown to develop CHB (17%) vs. those w/o syncope (2%)

	Size: 554 pts 351 had EPS and 203 refused it	**Exclusion criteria:** Terminal non-cardiac disease; symptoms already documented as due to bradycardia prior to study	**Safety endpoint:** N/A	• Heart block occurred in 4.9% of those with long HV compared to 1.9% with normal HV • A prolonged PR interval (found in 13%) was associated with and increased risk of all death, sudden death, major clinical events or HF, but not development of heart block. • Bundle branch block occurs in 1% of population, and requires no special evaluation in asx pts
Kwok CS, et al. 2016 (279) 26879241	**Aim:** Determine if prolonged PR interval is associated with adverse CV outcomes and mortality. **Study type:** Systemic review + meta-analysis **Size: 1**4 studies, 400,750 pts	**Inclusion criteria:** Studies that evaluated clinical outcomes associated with prolonged and normal PR intervals **Exclusion criteria:** From main analysis: Studies of pts with specific cardiac pathologies (such as AS, sinus nodal dysfunction and HF) or of pts who had received intervention (angiography or CRT)	**1° endpoint:** Mortality **Results:** Increased risk of mortality with prolonged PR interval risk ratio (RR: 1.24; 95% CI: 1.02–1.51, 5 studies. Prolonged PR interval was associated with significant risk of HF or LV dysfunction (RR: 1.39; 95% CI: 1.18–1.65, 3 studies) and AF (RR: 1.45; 95% CI: 1.23–1.71, 8 studies) but not CV mortality, coronary heart disease or MI or stroke or TIA.	• Possible association between prolonged PR interval and significant increases in AF, HF and mortality.
Boriani G, et al. 2003 (280) 12649505	**Size:** 18 pts (age 42.8±19.6 y) with genetically confirmed X-linked (N=10) or autosomal dominant (N=8) EDMD	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**Results:** Pacemakers were required by 10 of 18 (56%) pts for bradyarrhythmia	• >50% of pts with muscular dystrophy (EDMD) require PM implant. • Survival after PM implant is very reasonable
Mymin D, et al. 1986 (281) 3762641	**Study type:** Longitudinal, Observational **Size:** 3983 healthy men	**Inclusion criteria:** Healthy males **Exclusion criteria:** Females	**1° endpoint:** 1°AVB **Results:** 52 initial cases plus 124 new cases over 30 y. No difference in all-cause mortality	• Primary first-degree heart block with moderate PR prolongation is a benign condition • may not apply to more marked prolongation of the PR interval
Huhta JC, et al. 1983 (282) 6851033	**Study type:** Retrospective review	107 pts with ccTGA	23 of 107 (21%) developed naturally occurring AVB at a rate of 2% per yr. 12 of 49 (24%) developed AVB at VSD closure.	• Pts with ccTGA are at a constant and elevated risk of developing complete AVB throughout their lives.

Connelly MS, et al. 1996 (283) 8609349	**Study type:** Retrospective review	52 pts with ccTGA	9 or 52 (17.3%) developed spontaneous AVB; 9 of 52 (17.3%) developed postoperative AVB	• 17% of pts developed progressive AVB unrelated to surgery
Weindling SN, et al. 1998 (284) 9723647	**Study type:** Retrospective review	54 pts with postoperative heart block following congenital heart surgery	31 of 32 pts who recovered AV conduction did so by the 9th postoperative day.	• 43% did not recover conduction • 97% of those who recovered conduction – did so by d 9
Meune C, et al. 2006. (285) 16407522	**Study type:** Prospective observational	19 pts with lamin A mutations referred for pacing and receiving an ICD	9 pts (46%) received an appropriate shock for ventricular tachyarrhythmias	• The implantation of an ICD, rather than a PM, should be considered for these pts
van Rijsingen, IA, et al. 2012. (286) 22281253	**Study type:** Retrospective multicentered cohort	269 pts with LMNA mutations	Malignant ventricular arrhythmias occurred (5%/y) in pts with ≥2 of: NSVT, LVEF <45% at the first clinical contact, male sex, and non-missense mutations	• Specific risk factors portend a higher risk of ventricular arrhythmia in carriers of LMNA mutations
Maury P, et al. 2013. (287) 24011739	**Study type:** Retrospective review	325 pts	First degree AVB was independently associated with sudden death or implantable cardioverter-defibrillator appropriated therapies (OR: 2.41; 95% CI: 1.01–0.73; p=0.046)	• First degree AVB is independently linked to outcome and may be proposed to be used for individual risk stratification
O'Mahony C, et al. 2011. (288) 21856674	**Study type:** Observational, longitudinal, retrospective cohort study	204 pts; 12 had device implant during follow-up for bradyarrhythmias	Independent predictors of future antibradycardia pacing were (in a multivariable Cox model): QRSd and PR interval duration	• Pacing for AV and sinus node disease is common (±8%) • Pts with QRS ≥110 ms should be closely monitored for bradyarrhythmias
Polak PE, et al. 1989 (289) 2707275	**Study type:** Case series	2 pts	Pts with fascicular block progressed to PM-dependent complete block	• N/A
Khambatta S, et al. 2014 (290) 25061332	**Study type:** Retrospective review	35 pts	PM/ICD required in 31 % (11 pts) 4 pts (11%) in the series died, but all deaths were from sudden cardiac events.	• High incidence of device implantation implant and sudden death
Ali H, et al. 2017 (291) 28583850	**Study type:** Systematic Review	Case reports on CHB following blunt cardiac injury were available for 50 pts	PPM implantation was indicated in ~50% of early survivors because of recurrent or permanent CHB. BBB was present in >70% of pts A fatal outcome occurred in 20% of pts; structural damage of AV	• CHB secondary to blunt cardiac injury is associated with 20% mortality mainly occurring in the early post-traumatic period and most of the deaths are due to arrhythmia.

			conduction system in 50% of necropsies	• Recurrent or permanent CHB requiring PM implantation occurs in ~50% of survivors. • A structural damage of the AV conductive system can be found in 50% of victims

Data Supplement 42. Randomized Data for Predicting Perioperative Bradycardia (Section 8.1.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Chierichini A, et al. 2015 (292) 25953222	**Aim:** Evaluate the use of irrigation fluid using norepinephrine or epinephrine in pts undergoing arthroscopy for rotator cuff surgery **Study type:** Prospective randomized double blind controlled study **Size:** 120 pts	**Inclusion criteria:** ASA status 1 or 2, >18 y, scheduled for rotator cuff surgery with interscalene brachial plexus block **Exclusion criteria:** CAD, cardiac conduction defects, BB or ACEI:	**Intervention:** Norepinephrine (0.66 mg/L) to the irrigation bag **Comparator:** Epinephrine (0.33 mg/L) to the irrigation bag	**1° endpoint:** Development of hypotension or bradycardia (<30 bpm in ≤5 min or <50 bpm **Safety endpoint:** Timing and safety of events	• Hypotension and/or bradycardia ○ NE: 5/60 (8%) ○ E: 15/59 (25%) • Did not separate bradycardia events • Timing similar (30–35 min)

Data Supplement 43. RCTs of Conduction Disorders (Section 7)

Data Supplement 44. Nonrandomized Data for predicting perioperative bradycardia (Section 8.1.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Marrocco-Trischitta MM, et al. 2016 (293) 27177706	**Aim:** Evaluate use of temporary transvenous pacing (TTVP) for pts with	**Inclusion criteria:** Database searched for pts with CEA and TTVP	**1° endpoint:** 4/34 CEA surgeries with TTVP had PM activation	• Temporary transvenous pacing may be useful in pts undergoing CEA

	trifascicular block undergoing CEA **Study type:** Retrospective with historical controls (other pts with vascular surgery and TTVP **Size:** 31 CEAs compared to 37 other vascular surgery (68 total)	**Exclusion criteria:** None	**Results:** • Adverse events were • Defined as follows: PM activation, occurrence • Of block progression to 2nd degree AVB of Mobitz type II, or third-degree A-V block, • bradycardia 40 bpm with a minimum duration 10 s and/or a hemodynamic compromise (i.e., systolic BP <90 mm Hg), asystole with a duration >5 s • 4 pts with PM activation • In 2 pts procedure stopped due to asystole	
Cheung CC, et al. 2015 (294) 25541033	**Aim:** Evaluate prevalence of hypotension and bradycardia during elective noncardiac surgery **Study type:** Retrospective **Size:** 193 pts undergoing noncardiac elective surgery	**Inclusion criteria:** Post-hoc analysis of prospectively acquired data from a study evaluating withdrawal/management of a loop diuretic prior to surgery **Exclusion criteria:** None	**1° endpoint:** 67 pts developed intraoperative bradycardia (< 60 bpm for 2 sequential measurements >5 min apart) **Results:** Developed a HEART score for predicting hypotension or bradycardia based on baseline heart rate and BP, Age, Drug Rx, Cardiac complications score, and complexity of surgery (OR: 2.51; 95% CI: 1.79–3.53; C-statistic: 0.75)	• Surgical risk for hypotension and bradycardia can be assessed preoperatively
Bauer AM, et al. 2014 (295) 24651937	**Aim:** **Study type:** Case report **Size:**	**Inclusion criteria:** N/A **Exclusion criteria:** None	**1° endpoint:** N/A **Results:** Single pt with a carotid body tumor who became asystolic during surgery	Single pt with a carotid body tumor who became asystolic during surgery
Fritsch G, et al. 2012 (296) 22188223	**Aim:** Identify factors associated with surgical complications **Study type:** Retrospective analysis **Size:** 1,363 consecutive pts	**Inclusion criteria:** 1,363 consecutive pts in a 3 mo period scheduled for elective surgery **Exclusion criteria:** None	**1° endpoint:** 86 pts (6.3%) developed some complication. Hypotension most common but 20 pts (1.5%) developed hemodynamically relevant bradycardia	• Did not specifically analyze pts with bradycardia • Age, type of surgery and medical Hx were predictors for complications in general

Perreira ID, et al. 2011 (297) 21920207	**Aim:** Identify factors associated with intraoperative bradycardia
	
	Study type: Retrospective
	
	Size: 80,660 pts with neuraxial anesthesia from a single center
		Inclusion criteria: >18 y old
		
		Exclusion criteria: None
			1° endpoint: Sinus bradycardia
			
			Results:
			• Sinus bradycardia more common with age
			  • 18–40 y: 2.5%
			  • 41–60 y: 4.1%
			  • >61 y: 5.2%
			• Sinus bradycardia dependent on anesthesia
			  • SSA (single puncture subarachnoid): 3.4%
			  • CSA (continuous subarachnoid): 3.5%
			  • SE (single puncture epidural): 1.3%
			  • CE (continuous epidural): 3.4%
			  • DB (double block): 1.5%
			• Variables associated with sinus bradycardia:
			  • Age
			  • Gender (0.74 for women)
			  • Physical status (ASA III/IV 2.49/1.94)
			  • Type of surgery (Emergency 1.98)
				• Sinus bradycardia more common with age, sex, anesthesia, and physical status

Mitar MD, et al. 2015 (298) 25746023	**Aim:** Evaluate pacing requirement for rotational atherectomy **Study type:** Retrospective **Size:** 138 pts Temporary pacing in 67 No temporary pacing in 67	**Inclusion criteria:** Consecutive pts undergoing rotational atherectomy **Exclusion criteria:** None	**1° endpoint:** (2nd degree AVB or asystole >2 s in the no PM group **Results:** Pacemaker activated in PM group or AVB in no PM group: • LM: 1/19 (5%) • LAD: 2/38 (5%) • Cx: 10/25 (40%) • RCA: 28/51 (55%)	• Pacemaker activated in PM group or AVB in no PM group in pts with RCA or Cx PCI
Im SH, et al. 2008 (299) 18254669	**Aim:** Evaluate utility of transcutaneous pacing with carotid angioplasty and stenting **Study type:** Retrospective cohort **Size:** 30 pts and 31 procedures	**Inclusion criteria:** Consecutive pts who underwent elective carotid angioplasty and stenting and placement of a transcutaneous pacing system. **Exclusion criteria:** None	**1° endpoint:** Transcutaneous pacing use **Results:** • 24/31 required transcutaneous pacing (77%) • Continuous pacing for 10–30 min required in 5/31 pts (16%)	• Pacing support often required with elective carotid angioplasty and stenting

Bush RL, et al. 2004 (300) 15181504	**Aim:** Evaluate incidence of bradycardia with carotid stenting procedures **Study type:** Retrospective **Size:** 48 pts who underwent 51 procedures	**Inclusion criteria:** Carotid artery stenting procedures in consecutive pts who were thought to be of unacceptable risk for carotid artery endarterectomy. **Exclusion criteria:** None	**1° endpoint:** Clinically significant bradycardia or hypotension **Results:** • Access site hematomas in 2 pts (4%) • Significant bradycardia or asystole in 11/49 (22%) of procedures • Mean time of pacing was 6.6±1.2 min (range: 2.2–20.1 min) • No correlation between preprocedural cardiac status (History of MI or CABG) and development of bradycardia and hypotension	• Significant bradycardia or asystole in 11/49 in carotid stenting procedures
Harrop JS, et al. 2001 (301) 11564241	**Aim:** Evaluate hypotension and bradycardia associated with carotid artery interventional procedures **Study type:** Retrospective **Size:** 43 pts underwent 47 carotid artery angioplasty and stenting procedures	**Inclusion criteria:** All pts undergoing carotid artery procedures **Exclusion criteria:** 10 pts excluded; no reasons given	**1° endpoint:** Use of pacing for bradycardia and hypotension **Results:** • Pacemaker activation in 23/37 procedures (73%) • No correlation between PM activation and sex, etiology of stenosis, severity of stenosis, number of inflations	• Pacemaker activation common with CEA
Gauss A, et al. 1999 (302) 10456813	**Aim:** Evaluation of transcutaneous pacing in pts thought to be at risk for bradycardia (trifascicular block) **Study type:** Consecutive, prospective **Size:** 39 pts	**Inclusion criteria:** Consecutive pts with asx chronic 1st degree AVB and LBBB or bifascicular block. **Exclusion criteria:** None	**1° endpoint:** Progression of AVB, asystole >5 s or bradycardia <40 bpm >10 s) **Results:** • 37 of 39 pts could be paced transcutaneously • 0/39 had progression of AVB • 9 pts had bradycardia <40 bpm (6 intraoperatively and 3 postoperatively) • No pts absolutely required pacing for rate support	• No pts absolutely required pacing for rate support
Killeavey ES, et al. 1990 (303) 15227187	**Aim:** Evaluate the use of transvenous pacing during PCI	**Inclusion criteria:** Consecutive pts undergoing PCI	**1° endpoint:** Requirement for pacing **Results:**	• Requirement for pacing low

	Study type: Retrospective **Size:** 778 pts (398 w/o transvenous pacing and 379 with prophylactic pacing and 1 emergent pacing)	**Exclusion criteria:** None	• 2 pts developed ventricular arrhythmias associated with prophylactic pacing (0.5%) • 8/379 had pacing required (2%) • Overall incidence for pacing for hemodynamically significant bradycardia in prophylactic situations was 7/777 (0.8%)	
Chowdhury T, et al. 2015 (304) 26656339	**Aim:** Propofol boluses aborted the trigeminal cardiac reflex (TCR) induced severe bradycardia during dural manipulation. **Study type:** Case report **Size:** 1 pt	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** During dural stimulation, propofol 50 mg IV terminated sinus bradycardia	• Case report discussing that during dural stimulation, propofol 50 mg IV terminated sinus bradycardia
Yong J, et al. 2015 (305) 26424701	**Aim:** Evaluate development of cardiac arrest during laparoscopic surgery **Study type:** Retrospective analysis of the Australian Incident Monitoring Study (AIMS) database **Size:** 14 cases from >11,000 pt database	**Inclusion criteria:** Cardiac arrest pts **Exclusion criteria:** N/A	**1° endpoint:** Cardiac arrest (bradycardia) **Results:** • 9/14 bradycardia • 2 critical points for cardiac arrest: insufflation or establishment of pneumoperitoneum (12/14; 86%) Anesthesia induction (2/14; 14%)	• Bradycardia common during laparoscopy
Vimala S, et al. 2016 (306) 26114985	**Aim:** Case report of asystole during dural manipulation **Study type:** Case report **Size:** 1 pt	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** • Bradycardia and asystole during dural manipulation and excision of a temporal lobe meningioma (near the left insula)	• Case report of bradycardia during dural manipulation

Mohan S, et al. 1990 (307) 24788865	**Aim:** Evaluate the use of transvenous pacing during PCI **Study type:** Case report **Size:** 1	**Inclusion criteria:** 60 y undergoing maxillectomy for squamous cell cancer **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** • Asystole during posterior osteotomy • Bradycardia again during manipulation of the posterior maxillary tuberosity • Treatment by atropine and minimizing surgical manipulation	
Ishii D, et al. 1990 (308) 23834853	**Aim:** Evaluate the use of cilostazol for preventing bradycardia during carotid artery stenting **Study type:** Retrospective **Size:** 53 pts who underwent 54 carotid artery stenting procedures divided into procedures where pts received cilostazol (26) and those who did not (28)	**Inclusion criteria:** Pts who underwent carotid artery stenting at a single institution **Exclusion criteria:** None	**1° endpoint:** Bradycardia (<50 bpm or hypotension (<90 mm Hg) **Results:** • Intraprocedural bradycardia: ○ Cilostazol: 4/26 (15%) ○ No cilostazol: 15/28 (54%) • Postprocedure bradycardia ○ Cilostazol: 0/26 ○ No cilostazol: 3/28 (11%)	• Cilostazol reduced intraoperative bradycardia
Schipke JD, et al. 2013 (309) 23332411	**Aim:** 1 pt who developed asystole during paranasal sinus surgery **Study type:** Case report **Size:** 1	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** • 15 s of asystole with instrumenting the paranasal sinuses	• Asystole with instrumenting the paranasal sinuses
Haldar R, et al. 2013 (310) 23242253	**Aim:** 1 pt who developed bradycardia during skull pin fixation **Study type:** Case report **Size:** 1	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** • Heart rate decreased from 88 to 44 bpm with skull fixation pin tightening that stopped when instrumentation stopped and recurred with tightening again.	• Heart rate decreased with skull fixation pin tightening that stopped when instrumentation stopped and recurred with tightening again.

Seo KC, et al. 2010 (311) 20498810	**Aim:** Identify possible factors contributing to bradycardia and hypotension during shoulder surgery **Study type:** Retrospective **Size:** 63	**Inclusion criteria:** ASA I/II pts who received interscalene block for arthroscopic shoulder surgery in the sitting position **Exclusion criteria:** N/A	**1° endpoint:** Bradycardia (<50 bpm) and/or hypotension (<100 mm Hg or use of ephedrine) **Results:** • 13/63 with bradycardia and hypotension • Bradycardia and hypotension more likely with: Right sided procedures (R: 27% vs. L: 5%) Higher use of fentanyl (54% vs. 0.4%)	• Bradycardia and hypotension more common with tight sided procedures
Jeyabalan G, et al. 2010 (312) 20557186	**Aim:** Identify factors associated with bradycardia during pharmacomechanical thrombectomy for deep vein thrombosis **Study type:** Retrospective **Size:** 57 pts	**Inclusion criteria:** Consecutive pts who underwent pharmacomechanical (AngioJet) therapy for deep vein thrombosis **Exclusion criteria:** N/A	**1° endpoint:** Bradycardia **Safety endpoint:** • 7/57 (12.3%) had bradyarrhythmias asystole 2 sinus bradycardia: 5 More than 1 episode: 4 • Bradycardia resolved in 5/7 pts with cessation of therapy. 2 pts received atropine	• Bradycardia observed with AngioJet procedures
Usami K, et al. 2010 (313) 20448432	**Aim:** Describe 3 pts who developed bradycardia with surgery for cerebellopontine angle meningiomas **Study type:** Case series **Size:** 3	**Inclusion criteria:** Case series of pts with bradycardia during meningioma surgery **Exclusion criteria:** N/A	**1° endpoint:** Bradycardia **Results:** • Transient bradycardia/asystole and hypotension apparently due to activation of the trigeminocardiac reflex by direct stimulation of the trigeminal nerve or branches in the dura mater or cerebellar tentorium • Remifentanil suggested as a possible contributor	• Transient bradycardia/asystole and hypotension apparently due to activation of the trigeminocardiac reflex by direct stimulation of the trigeminal nerve or branches in the dura mater or cerebellar tentorium
Lubbers HT, et al. 2010 (314) 20347202	**Aim:** Describe 3 pts who developed bradycardia with craniomaxillofacial surgery. **Study type:** Case series **Size:** 3	**Inclusion criteria:** Case series, N/A **Exclusion criteria:** N/A	**1° endpoint:** Bradycardia **Results:** • Describe 3 pts identified from a single center surgical database with bradycardia during craniomaxillofacial surgery	• Purely descriptive with no specific recommendations or findings

Christensen RE, et al. 2010 (315) 19933174	**Aim:** Describe outcomes in pts with surgically corrected D transposition of the great arteries (D-TGA) undergoing noncardiac surgery **Study type:** Retrospective **Size:** 50 procedures (34 pts)	**Inclusion criteria:** Consecutive pts with surgically corrected D-TGA undergoing noncardiac surgery (43 pediatric and 7 adults) **Exclusion criteria:** N/A	**1° endpoint:** Adverse events including bradycardia **Results:** 4 adverse events. 1 pt with severe bradycardia during abdominal insufflation	• 4 adverse events observed in pts with congenital heart disease and noncardiac surgeries.
Jacques F, et al. 2009 (316) 18657390	**Aim:** Compare regional anesthesia and general anesthesia for CEA surgery **Study type:** Retrospective **Size:** 72 Regional anesthesia: 25 General anesthesia: 47	**Inclusion criteria:** Consecutive pts undergoing CEA from a single center **Exclusion criteria:** None	**1° endpoint:** Hypotension and bradycardia (<60 bpm) **Results:** Regional anesthesia associated with less intraoperative bradycardia (4%) when compared to general anesthesia (63%)	• Regional anesthesia associated with less intraoperative bradycardia
Hanss R, et al. 2008 (317) 18211442	**Aim:** Evaluate heart rate variability as a tool to identify pts who will have hypotension or bradycardia during surgery **Study type:** Retrospective model followed by a prospective study **Size:** 100	**Inclusion criteria:** High perioperative risk (ASA III/IV) undergoing major vascular or abdominal surgery **Exclusion criteria:** Not in SR, <18 y, emergency surgery	**1° endpoint:** Bradycardia and hypotension **Results:** • No specific data on bradycardia but those pts with lower heart rate variability (stratified by a total power <500 Ms^2Hz^{-1}) were more likely to develop hypotension and bradycardia • 4/50 pts in the retrospective model development group had bradycardia (<50 bpm)	• Small numbers of bradycardia (mostly hypotension)
Reddy MK, et al. 2008 (318) 18157036	**Aim:** Describe a pt who developed bradycardia during surgical positioning of an unstable cervical spine	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** Bradycardia **Results:** • Bradycardia (35 bpm) and hypotension (50 mm Hg) with initial skull positioning	• Case report of bradycardia with skull positioning

	Study type: Case report **Size:** 1		• Atropine and beta agonists not successful but surgical repositioning of the spine led to resolution and development of a heart rate 100 bpm	
Ardesch JJ, et al. 2007 (319) 17825483	**Aim:** Describe cardiac responses with vagal nerve stimulation **Study type:** Retrospective **Size:** 111	**Inclusion criteria:** Pts who received a vagal nerve stimulator for treatment of epilepsy **Exclusion criteria:** None	**1° endpoint:** Bradycardia **Results:** 3 cases of bradycardia during intraoperative testing. Not subsequently observed on postoperative testing.	• Transient bradycardia can be observed with vagal stimulation.
Jones PM and Soderman RM, 2007 (320) 17223834	**Aim:** Describe a pt on 2 cholinesterase inhibitors who developed intraoperative bradycardia **Study type:** Case report **Size:** 1	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** Bradycardia **Results:** Bradycardia (35 bpm) with induction of anesthesia	• Bradycardia (35 bpm) with induction of anesthesia
Wijeysundera DN, et al. 2014 (321) 25091545	**Aim:** ERC report on perioperative BB use **Study type:** Meta-analysis **Size:** N/A	**Inclusion criteria:** Varied among studies **Exclusion criteria:** Varied among studies	**1° endpoint:** Bradycardia **Results:** Perioperative beta blockade started within 1 d or less before noncardiac surgery increases risks of intraoperative bradycardia (RR: 2.61; 95% CI: 2.18– 3.12).	• Perioperative beta blockade started within 1 d or less before noncardiac surgery increases risks of intraoperative bradycardia

Data Supplement 45. Nonrandomized Data for predicting complete heart block with pulmonary artery catheter insertion (Section 8.1.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)

Morris D, et al. 1987 (322) 3675104	**Aim:** Evaluate the incidence of CHB in pts with LBBB undergoing PA catheter placement **Study type:** Retrospective **Size:** 47 pts who underwent 82 PA catheter placements	**Inclusion criteria:** All pts with LBBB who underwent PA catheter placement **Exclusion criteria:** None	**1° endpoint:** CHB **Results:** • 5 episodes of CHB in the setting of old LBBB but none temporally related to PA catheter placement • 2 episodes of CHB in the setting of new LBBB but none temporally related to PA catheter insertion-though occurred while the catheter was in place	• Authors do not recommend prophylactic temporary transvenous pacing
Elliott CG, et al. 1979 (323) 510002	**Aim:** Evaluate complications associated with PA catheter placement **Study type:** Prospective **Size:** 116 PA catheters	**Inclusion criteria:** Consecutive pts undergoing PA catheter placement **Exclusion criteria:** None	**1° endpoint:** Arrhythmias, ECG changes, or complications **Results:** Transient RBBB in 3% of pts	• Transient RBBB fairly rare
Unnikrishnan D, et al. 2003 (324) 14570803	**Aim:** Describe complications associated with PA catheter placement **Study type:** Case report **Size:** 1	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** Complete heart block with central venous line placement in a pt with LBBB	• Transient CHB may occur with placement of central venous catheter

Data Supplement 46. Nonrandomized data for Permanent Pacing for TAVI/valve surgery

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P value; OR or RR; & 95% CI)
Mouillet G, et al. 2013 (325) 22972678	**Aim:** Predict which pts need PPM after Core Valve	**Inclusion criteria:** Pts getting Core Valve	Follow for 2nd or 3rd degree AVB	• All pts got temp pacing x 72 h; of 90 pts, 11 had immediate AVB and PPM; 21 subsequently needed PPM, mostly in the first wk.

	Study type: Prospective Observational study of pts getting Core Valve **Size**: N=90			• Post TAVI QRSd <128 ms predicted no PM needed
Rabinovitz, E et al. 2016 (326) 26936468	**Aim**: Assess need for PM **Study type:** Observational **Size**: N=302	**Inclusion criteria:** Consecutive TAVI pts	**Intervention**: TAVI	• 20% required PPM
PARTNER Leon MB, et al. 2010 (327) 20961243	**Aim**: Assess TAVI in severe AS pts	**Inclusion criteria:** Severe AS N=358	TAVI vs. medical Rx	• 3.4% underwent PPM after TAVI
Kogan A, et al. 2015 (328) 25583151	**Aim:** Assess incidence of PPM with SAVR pre and post TAVI **Study type:** Retrospective **Size**: N=290	**Inclusion criteria:** SAVR pre and post 2008 and TAVI pts, single center	Retrospective observational study	• **Results**: 2.48% got PPM within 7 d, over half of these had CHB. Pre TAVI, was 3.79% and post TAVI was 1.47%. • **PARTNER trial:** SAVR had 3.6% PPM
Rivard L, et al. 2015 (329) 25446155	**Aim:** Determine if EPS helps predict PM post TAVI **Study type:** Retrospective **Size**: N=75	**Inclusion criteria:** 75 consecutive TAVI pts with no prior PM	EPS, assess HV interval	• Delta HC >13 ms (pre-post TAVI) and new LBBB with HV >65 were predictive of PM • 13 ms delta is 100% sensitivity and 84% specificity
Rene AG, et al. 2013 (330) 24028584	**Aim:** Assess recovery of AV conduction after valve surgery **Study type:** Observational **Size**: N=98	**Inclusion criteria:** S/P valve surgery and received PPM same hospital.	**Intervention:** PPM	• Of the 98 with CHB, 77% became PM dependent • 40% who received a PM had no evidence of high-grade AVB during PM follow-up • 26% of those who recovered AV conduction in 30 d had recurrent AVB
Steyers CM, et al. 2015 (331) 26470027	**Aim:** Comprehensive review of AVB post cardiac surgery **Study type:** Review	**Inclusion criteria:** AVR, MVR, CABG, CABG/valve	N/A	• PM dependency was highly variable • Recovery of AV conduction highly variable

	Size: N=10 studies, 780 pts			• Optimal timing for PM (how long to wait for recovery) not established
Dawkins S, et al. 2008 (332) 18154792	**Aim:** Identify incidence and predictors of AVB after AVR **Study type:** Retrospective observational **Size**: N=354	**Inclusion criteria:** Surgical AVR	**Intervention:** PM	• 7% needed PM in AS pts • 16% needed PM in AI pts
Viles-Gonzalez JF, et al. 2014 (333) 24526511	**Aim:** Observe natural Hx of AVB after MVR	**Inclusion criteria:** 290 MVR pts	Retrospective observational study	• **Results:** 2% got PPM mostly for AVB, 55% recovered conduction abnormal, some had residual 1st AVB; mean time to recover was 3 d. Predictors include RBBB
Merin O, et al. 2009 (334) 19140907	**Aim:** **Study type:** **Size**: N=4,999	**Inclusion criteria:** CABG, AVR, MVR	**Intervention:** PM	• 81% had a CABG • Predictor for PM=LBBB • 1.5% got a PM • 1/3 recovered AV conduction at late follow-up

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
The Birmingham Trial Watson RD, et al. 1984 (231) 6475712	**Aim:** To determine whether permanent pacing reduces mortality in pts with fascicular block ≥14 d post-MI, and whether measurement of intracardiac conduction times predicts later death. **Study type:** RCT	**Inclusion criteria:** Survived at least 14 d after AMI; RBBB alone or in combination with left anterior or left posterior hemiblock or left posterior hemiblock alone **Exclusion criteria:** Age ≥70 y; previous ECG evidence of conduction disorder (before infarction)	**Intervention:** Permanent pacing **Comparator:** No permanent pacing Resting intracardiac conduction times were measured in both groups prior to pacing	**1° endpoint:** No difference in mortality **Safety endpoint (if relevant):** N/A	• Progression of conduction disease was not observed • Measurement of infranodal conduction time (HV interval) did not predict outcome • Ventricular arrhythmia was an important cause of death

	Size: 50 pts	Pts with left bundle branch block were not included due to the difficulty in identifying the ECG features of AMI.			
PACE Petrac, D., et al. 1996 (335) 8734745	**Aim:** **Study type:** **Size:** 192 pts.	**Inclusion criteria:** **Exclusion criteria:**	**Intervention:** His bundle recording during atrial pacing **Comparator:** Nonfunctional infraHisian 2° AVB	**1° endpoint:** In pts with chronic BBB and syncope, a nonfunctional infraHisian AVB induced by incremental atrial pacing identified pts with particularly high risk of development of spontaneous infraHisian AVB. **Safety endpoint:** N/A	• Incremental atrial pacing identified pts at high risk of development of spontaneous infraHisian AVB
The PRESS Study Santini M, et al. 2013 (182) 23390123	**Aim:** To demonstrate a reduction in symptomatic events in pts with bifascicular block and syncope of undetermined origin implanted with PPM. **Study type:** Randomized **Size:** 100 pts	**Inclusion criteria:** **Exclusion criteria:**	**Intervention:** Permanent DDD pacing with a low rate of 60 bpm **Comparator:** Permanent DDI pacing with a low rate of 30 bpm	**1° endpoint:** (1) syncope, (2) symptomatic presyncopal episodes associated with a device intervention (ventricular pacing), and (3) symptomatic episodes associated with intermittent or permanent AVB (any degree).	• DDD60 led to a significant reduction of syncope or symptomatic events associated with a cardioinhibitory origin, compared with DDI30 programming

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
The Framingham Study Schneider JF, et al.	**Aim:** Assess the clinical implications of LBBB	**Inclusion criteria:** LBBB and age- and sex-matched control pts who did not	**1° endpoint:** Development of CV disease	• Comparison with age- and sex-matched control subjects free from LBBB suggests that newly acquired

1979 (27) 154870	**Study type:** Nested case-control in Framingham cohort **Size:** 55 pts who developed LBBB, 110 matched controls Mean age at study onset =50 y Mean age at onset of LBBB =62 y	develop LBBB from Framingham cohort **Exclusion criteria:** N/A	**Results:** 55/5209 people developed LBBB in 18 y of follow-up 48% of these develop CAD or HF for the 1st time with or following Dx of LBBB Only 11% remained free of clinically apparent CV abnormal In men, the appearance of LBBB contributed independently to an increased risk of CV disease mortality	LBBB is most often a hallmark of advanced hypertensive or ischemic heart disease, or both
Fahy GJ, et al. 1996 (31) 8651093	**Aim:** Determine the long-term outcome of pts with BBB and no clinical evidence of CV disease **Study type:** Nested case-control **Size:** 310 pts with BBB, 310 matched controls out of 110,000 participant screening program in Ireland	**Inclusion criteria:** BBB/age- and sex-matched controls **Exclusion criteria:** Suspected heart disease	**1° endpoint:** Long-term "outcome" of BBB pts **Results:** BBB did not impact overall mortality Cardiac mortality was significantly increased in the LBBB group compared to their controls LBBB, but not RBBB, was associated with an increased prevalence of CV disease at the follow-up (21% vs. 11%; p=0.04).	• Isolated left BBB is associated with an increased risk of developing overt CV disease and increased cardiac mortality.
Talreja D, et al. 2000 (43) 10689252	**Aim:** Assess ability to predict LV dysfunction on echo, by historic, clinical, radiographic, and ECG parameters **Study type:** Cross-sectional **Size:** 300	**Inclusion criteria:** Consecutive inpatients referred for the echocardiographic assessment of LV function	**1° endpoint:** LVER <45% **Results:** 124 (41%) had LVEF <45% Presence of LBBB, male sex, and CM on CXR were associated with presence of LV dysfunction Only 2 pts with LVSD had a normal ECG More than 50% of the predictive power of the model rested on the discriminatory ability of a normal ECG	• When ECG is normal, it is extremely unlikely to have LV systolic dysfunction. • It can be argued that such pts should not be referred for echocardiography.

Eriksson P, et al. 1998 (30) 9832497	**Aim:** Assess prevalence of BBB, its impact on mortality and coexisting CV conditions **Study type:** Prospective cohort **Size:** 855 men who were 50 y old in 1963 followed for 30 y 82 developed BBB 22 of those were LBBB	**Inclusion criteria:** Random sampling of Swedish men **Exclusion criteria:** N/A	**1° endpoint:** Mortality and CV disease **Results:** The prevalence of BBB increases from 1% at age 50 y to 17% at age 80 y, resulting in a cumulative incidence of 18%. BBB did not predict ischemic heart disease or mortality Men who developed BBB had bigger LV volume at baseline and greater incidence of DM and HF	• BBB correlates strongly to age and is common in elderly men. • BBB is a marker of a slowly progressing degenerative disease that affects the myocardium. • BBB is not associated with increased mortality • I could not find data broken down by LBBB vs. RBBB; vast majority were RBBB*
Mahmod M, et al. 2012 (277) 21805313	**Aim:** Evaluate the diagnostic value of CMR in asx pts with LBBB **Study type:** Cross-sectional **Size:** 54 pts	**Inclusion criteria:** Asymptomatic adults with complete LBBB referred for cardiac MR **Exclusion criteria:** Absence of echo	**1° endpoint:** Pathologic findings on MR **Results:** 9/29 (31%) had abnormal MR despite normal echo: 6 with DCM, 2 with LVH 19/25 (76%) with abnormal echo also had abnormal MR; in 13 of them (52%) the MR provided new "clinically relevant" findings: 8 DCM, 1 cardiac sarcoid	• CMR detects subclinical CMP in 1/3 of asx pts with LBBB and normal echo • CMR provides additional clinically relevant data in over 50% of pts • CMR is valuable adjuvant diagnostic tool for pt with asx LBBB
Brignole M, et al. 2001 (185) 11673344	**Study type:** Prospective Observational **Size:** 52 pts	**Inclusion criteria:** BBB and negative conventional workup	**1° endpoint:** Rhythm at syncope recurrence as assessed by ILR **Safety endpoint:** N/A	In pts with BBB and negative EPS, most syncopal recurrences result from prolonged asystolic pauses, mainly attributable to paroxysmal AVB.
Moya A, et al. 2011 (189) 21444367	**Aim:** To analyze the clinical outcomes of pts with syncope and BBB following a systematic diagnostic approach: 3-phase: clinical evaluation, EPS, ILR **Study type:** Multicentered prospective observational trial **Size:** 323 patients (after exclusions)	**Inclusion criteria:** ≥1 syncope in the last 6 mo. and BBB on EGG with a QRSd of ≥120 ms **Exclusion criteria**: Indication for prophylactic ICD due to low LVEF; pre-excitation; long QT syndrome; Brugada syndrome; acute MI; pregnancy; life expectancy	**1° endpoint:** Clinical Dx (established in 267 patients (82.7%) -recurrent syncope: in 15/215 (7%) after phase 1/2; 36 of 108 (33% after phase 3 -documented spontaneous arrhythmias -death due to any cause: no difference in mortality rate	• In pts with syncope, BBB, and preserved LVEF, a systematic diagnostic strategy (ESC guidelines) achieves a high rate of Dx (82.6%) with a low rate of mortality (6%), allowing clinicians to institute etiology-specific treatment. • The most common cause of syncope was bradyarrhythmia, mostly due to paroxysmal A-V block. Other

		<1 y due to noncardiac cause; geographically or otherwise inaccessible for follow-up; unwilling or unable to give informed consent	between pts diagnosed at Phase I or II, compared with those who had implanted ILR (6.0 vs. 6.5%) **Safety endpoint:** N/A	etiologies of syncope were recognized in 17.6% • initial clinical evaluation achieved a Dx in 25%; the most frequent Dx at EPS was a bradyarrhythmia (76%), VT or SVT was induced in 14%. • The study was not designed to determine whether this diagnostic strategy was better than implanting a PM in the majority of pts
McAnulty JH, et al. 1982 (278) 7088050	**Study type:** Prospective Observational **Size:** 554 pts 351 had EPS and 203 refused it	**Inclusion criteria:** Bifascicular or trifascicular block **Exclusion criteria:** Terminal non-cardiac disease; symptoms already documented as due to bradycardia prior to study	**1° endpoint:** Major clinical events, death, heart block, need for PPM, syncope **Safety endpoint:** N/A	• A higher percentage of pts with syncope were shown to develop CHB (17%) vs. those w/o syncope (2%) • Heart block occurred in 4.9% of those with long HV compared to 1.9% with normal HV • A prolonged PR interval (found in 13%) was associated with and increased risk of all death, sudden death, major clinical events or HF, but not development of heart block. • Bundle branch block occurs in 1% of population, and requires no special evaluation in asx pts
Kwok CS, et al. 2016 (279) 26879241	**Aim:** Determine if prolonged PR interval is associated with adverse CV outcomes and mortality. **Study type:** Systemic review + meta-analysis **Size: 1**4 studies, 400,750 pts	**Inclusion criteria:** Studies that evaluated clinical outcomes associated with prolonged and normal PR intervals **Exclusion criteria:** From main analysis: Studies of pts with specific cardiac pathologies (such as AS, sinus nodal dysfunction and HF) or of pts who had received intervention (angiography or CRT)	**1° endpoint:** Mortality **Results:** Increased risk of mortality with prolonged PR interval risk ratio (RR: 1.24; 95% CI: 1.02–1.51, 5 studies. Prolonged PR interval was associated with significant risk of HF or LV dysfunction (RR: 1.39; 95% CI: 1.18–1.65, 3 studies) and AF (RR: 1.45; 95% CI: 1.23–1.71, 8 studies) but not CV mortality, coronary heart disease or MI or stroke or TIA.	• Possible association between prolonged PR interval and significant increases in AF, HF and mortality.

Boriani G, et al. 2003 (280) 12649505	**Size:** 18 pts (age 42.8±19.6 y) with genetically confirmed X-linked (N=10) or autosomal dominant (N=8) EDMD	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**Results:** Pacemakers were required by 10 of 18 (56%) pts for bradyarrhythmia	• >50% of pts with muscular dystrophy (EDMD) require PM implant. • Survival after PM implant is very reasonable
Mymin D, et al. 1986 (281) 3762641	**Study type:** Longitudinal, Observational **Size:** 3983 healthy men	**Inclusion criteria:** Healthy males **Exclusion criteria:** Females	**1° endpoint:** 1°AVB **Results:** 52 initial cases plus 124 new cases over 30 y. No difference in all-cause mortality	• Primary first-degree heart block with moderate PR prolongation is a benign condition • may not apply to more marked prolongation of the PR interval
Huhta JC, et al. 1983 (282) 6851033	**Study type:** Retrospective review	107 pts with ccTGA	23 of 107 (21%) developed naturally occurring AVB at a rate of 2% per yr. 12 of 49 (24%) developed AVB at VSD closure.	• Pts with ccTGA are at a constant and elevated risk of developing complete AVB throughout their lives.
Connelly MS, et al. 1996 (283) 8609349	**Study type:** Retrospective review	52 pts with ccTGA	9 or 52 (17.3%) developed spontaneous AVB; 9 of 52 (17.3%) developed postoperative AVB	• 17% of pts developed progressive AVB unrelated to surgery
Weindling SN, et al. 1998 (284) 9723647	**Study type:** Retrospective review	54 pts with postoperative heart block following congenital heart surgery	31 of 32 pts who recovered AV conduction did so by the 9th postoperative day.	• 43% did not recover conduction • 97% of those who recovered conduction – did so by d 9
Meune C, et al. 2006. (285) 16407522	**Study type:** Prospective observational	19 pts with lamin A mutations referred for pacing and receiving an ICD	9 pts (46%) received an appropriate shock for ventricular tachyarrhythmias	• The implantation of an ICD, rather than a PM, should be considered for these pts
van Rijsingen, IA, et al. 2012. (286) 22281253	**Study type:** Retrospective multicentered cohort	269 pts with LMNA mutations	Malignant ventricular arrhythmias occurred (5%/y) in pts with ≥2 of: NSVT, LVEF <45% at the first clinical contact, male sex, and non-missense mutations	• Specific risk factors portend a higher risk of ventricular arrhythmia in carriers of LMNA mutations
Maury P, et al. 2013. (287) 24011739	**Study type:** Retrospective review	325 pts	First degree AVB was independently associated with sudden death or implantable cardioverter-defibrillator appropriated therapies (OR: 2.41; 95% CI: 1.01–0.73; p=0.046)	• First degree AVB is independently linked to outcome and may be proposed to be used for individual risk stratification
O'Mahony C, et al. 2011. (288) 21856674	**Study type:** Observational, longitudinal, retrospective cohort study	204 pts; 12 had device implant during follow-up for bradyarrhythmias	Independent predictors of future antibradycardia pacing were (in a multivariable Cox model): QRSd and PR interval duration	• Pacing for AV and sinus node disease is common (±8%) • Pts with QRS ≥110 ms should be closely monitored for bradyarrhythmias

Polak PE, et al. 1989 (289) 2707275	**Study type:** Case series	2 pts	Pts with fascicular block progressed to PM-dependent complete block	• N/A
Khambatta S, et al. 2014 (290) 25061332	**Study type:** Retrospective review	35 pts	PM/ICD required in 31 % (11 pts) 4 pts (11%) in the series died, but all deaths were from sudden cardiac events.	• High incidence of device implantation implant and sudden death
Ali H, et al. 2017 (291) 28583850	**Study type:** Systematic Review	Case reports on CHB following blunt cardiac injury were available for 50 pts	PPM implantation was indicated in ~50% of early survivors because of recurrent or permanent CHB. BBB was present in >70% of pts A fatal outcome occurred in 20% of pts; structural damage of AV conduction system in 50% of necropsies	• CHB secondary to blunt cardiac injury is associated with 20% mortality mainly occurring in the early post-traumatic period and most of the deaths are due to arrhythmia. • Recurrent or permanent CHB requiring PM implantation occurs in ~50% of survivors. • A structural damage of the AV conductive system can be found in 50% of victims

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
Chierichini A, et al. 2015 (292) 25953222	**Aim:** Evaluate the use of irrigation fluid using norepinephrine or epinephrine in pts undergoing arthroscopy for rotator cuff surgery **Study type:** Prospective randomized double blind controlled study	**Inclusion criteria:** ASA status 1 or 2, >18 y, scheduled for rotator cuff surgery with interscalene brachial plexus block **Exclusion criteria:** CAD, cardiac conduction defects, BB or ACEI:	**Intervention:** Norepinephrine (0.66 mg/L) to the irrigation bag **Comparator:** Epinephrine (0.33 mg/L) to the irrigation bag	**1° endpoint:** Development of hypotension or bradycardia (<30 bpm in ≤5 min or <50 bpm **Safety endpoint:** Timing and safety of events	• Hypotension and/or bradycardia ○ NE: 5/60 (8%) ○ E: 15/59 (25%) • Did not separate bradycardia events • Timing similar (30–35 min)

	Size: 120 pts				

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Marrocco-Trischitta MM, et al. 2016 (293) 27177706	**Aim:** Evaluate use of temporary transvenous pacing (TTVP) for pts with trifascicular block undergoing CEA **Study type:** Retrospective with historical controls (other pts with vascular surgery and TTVP **Size:** 31 CEAs compared to 37 other vascular surgery (68 total)	**Inclusion criteria:** Database searched for pts with CEA and TTVP **Exclusion criteria:** None	**1° endpoint:** 4/34 CEA surgeries with TTVP had PM activation **Results:** • Adverse events were • Defined as follows: PM activation, occurrence • Of block progression to 2nd degree AVB of Mobitz type II, or third-degree A-V block, • bradycardia 40 bpm with a minimum duration 10 s and/or a hemodynamic compromise (i.e., systolic BP <90 mm Hg), asystole with a duration >5 s • 4 pts with PM activation • In 2 pts procedure stopped due to asystole	• Temporary transvenous pacing may be useful in pts undergoing CEA
Cheung CC, et al. 2015 (294) 25541033	**Aim:** Evaluate prevalence of hypotension and bradycardia during elective noncardiac surgery **Study type:** Retrospective **Size:** 193 pts undergoing noncardiac elective surgery	**Inclusion criteria:** Post-hoc analysis of prospectively acquired data from a study evaluating withdrawal/management of a loop diuretic prior to surgery **Exclusion criteria:** None	**1° endpoint:** 67 pts developed intraoperative bradycardia (< 60 bpm for 2 sequential measurements >5 min apart) **Results:** Developed a HEART score for predicting hypotension or bradycardia based on baseline heart rate and BP, Age, Drug Rx, Cardiac complications score, and complexity of surgery (OR: 2.51; 95% CI: 1.79–3.53; C-statistic: 0.75)	• Surgical risk for hypotension and bradycardia can be assessed preoperatively

Bauer AM, et al. 2014 (295) 24651937	**Aim:** **Study type:** Case report **Size:**	**Inclusion criteria:** N/A **Exclusion criteria:** None	**1° endpoint:** N/A **Results:** Single pt with a carotid body tumor who became asystolic during surgery	Single pt with a carotid body tumor who became asystolic during surgery
Fritsch G, et al. 2012 (296) 22188223	**Aim:** Identify factors associated with surgical complications **Study type:** Retrospective analysis **Size:** 1,363 consecutive pts	**Inclusion criteria:** 1,363 consecutive pts in a 3 mo period scheduled for elective surgery **Exclusion criteria:** None	**1° endpoint:** 86 pts (6.3%) developed some complication. Hypotension most common but 20 pts (1.5%) developed hemodynamically relevant bradycardia	• Did not specifically analyze pts with bradycardia • Age, type of surgery and medical Hx were predictors for complications in general

Perreira ID, et al. 2011 (297)
21920207
	Aim: Identify factors associated with intraoperative bradycardia
	
	Study type: Retrospective
	
	Size: 80,660 pts with neuraxial anesthesia from a single center
		Inclusion criteria: >18 y old
		
		Exclusion criteria: None
			1° endpoint: Sinus bradycardia
			
			Results:
			• Sinus bradycardia more common with age
			  • 18–40 y: 2.5%
			  • 41–60 y: 4.1%
			  • >61 y: 5.2%
			• Sinus bradycardia dependent on anesthesia
			  • SSA (single puncture subarachnoid): 3.4%
			  • CSA (continuous subarachnoid): 3.5%
			  • SE (single puncture epidural): 1.3%
			  • CE (continuous epidural): 3.4%
			  • DB (double block): 1.5%
			• Variables associated with sinus bradycardia:
			  • Age
			  • Gender (0.74 for women)
			  • Physical status (ASA III/IV 2.49/1.94)
			  • Type of surgery (Emergency 1.98)
				• Sinus bradycardia more common with age, sex, anesthesia, and physical status

Mitar MD, et al. 2015 (298) 25746023	**Aim:** Evaluate pacing requirement for rotational atherectomy **Study type:** Retrospective	**Inclusion criteria:** Consecutive pts undergoing rotational atherectomy **Exclusion criteria:** None	**1° endpoint:** (2^{nd} degree AVB or asystole >2 s in the no PM group **Results:** Pacemaker activated in PM group or AVB in no PM group: • LM: 1/19 (5%)	• Pacemaker activated in PM group or AVB in no PM group in pts with RCA or Cx PCI

	Size: 138 pts Temporary pacing in 67 No temporary pacing in 67		• LAD: 2/38 (5%) • Cx: 10/25 (40%) • RCA: 28/51 (55%)	
Im SH, et al. 2008 (299) 18254669	**Aim:** Evaluate utility of transcutaneous pacing with carotid angioplasty and stenting **Study type:** Retrospective cohort **Size:** 30 pts and 31 procedures	**Inclusion criteria:** Consecutive pts who underwent elective carotid angioplasty and stenting and placement of a transcutaneous pacing system. **Exclusion criteria:** None	**1° endpoint:** Transcutaneous pacing use **Results:** • 24/31 required transcutaneous pacing (77%) • Continuous pacing for 10–30 min required in 5/31 pts (16%)	• Pacing support often required with elective carotid angioplasty and stenting
Bush RL, et al. 2004 (300) 15181504	**Aim:** Evaluate incidence of bradycardia with carotid stenting procedures **Study type:** Retrospective **Size:** 48 pts who underwent 51 procedures	**Inclusion criteria:** Carotid artery stenting procedures in consecutive pts who were thought to be of unacceptable risk for carotid artery endarterectomy. **Exclusion criteria:** None	**1° endpoint:** Clinically significant bradycardia or hypotension **Results:** • Access site hematomas in 2 pts (4%) • Significant bradycardia or asystole in 11/49 (22%) of procedures • Mean time of pacing was 6.6±1.2 min (range: 2.2–20.1 min) • No correlation between preprocedural cardiac status (History of MI or CABG) and development of bradycardia and hypotension	• Significant bradycardia or asystole in 11/49 in carotid stenting procedures
Harrop JS, et al. 2001 (301) 11564241	**Aim:** Evaluate hypotension and bradycardia associated with carotid artery interventional procedures **Study type:** Retrospective **Size:** 43 pts underwent 47 carotid artery angioplasty and stenting procedures	**Inclusion criteria:** All pts undergoing carotid artery procedures **Exclusion criteria:** 10 pts excluded; no reasons given	**1° endpoint:** Use of pacing for bradycardia and hypotension **Results:** • Pacemaker activation in 23/37 procedures (73%) • No correlation between PM activation and sex, etiology of stenosis, severity of stenosis, number of inflations	• Pacemaker activation common with CEA

Gauss A, et al. 1999 (302) 10456813	**Aim:** Evaluation of transcutaneous pacing in pts thought to be at risk for bradycardia (trifascicular block) **Study type:** Consecutive, prospective **Size:** 39 pts	**Inclusion criteria:** Consecutive pts with asx chronic 1st degree AVB and LBBB or bifascicular block. **Exclusion criteria:** None	**1° endpoint:** Progression of AVB, asystole >5 s or bradycardia <40 bpm >10 s) **Results:** • 37 of 39 pts could be paced transcutaneously • 0/39 had progression of AVB • 9 pts had bradycardia <40 bpm (6 intraoperatively and 3 postoperatively) • No pts absolutely required pacing for rate support	• No pts absolutely required pacing for rate support
Killeavey ES, et al. 1990 (303) 15227187	**Aim:** Evaluate the use of transvenous pacing during PCI **Study type:** Retrospective **Size:** 778 pts (398 w/o transvenous pacing and 379 with prophylactic pacing and 1 emergent pacing)	**Inclusion criteria:** Consecutive pts undergoing PCI **Exclusion criteria:** None	**1° endpoint:** Requirement for pacing **Results:** • 2 pts developed ventricular arrhythmias associated with prophylactic pacing (0.5%) • 8/379 had pacing required (2%) • Overall incidence for pacing for hemodynamically significant bradycardia in prophylactic situations was 7/777 (0.8%)	• Requirement for pacing low
Chowdhury T, et al. 2015 (304) 26656339	**Aim:** Propofol boluses aborted the trigeminal cardiac reflex (TCR) induced severe bradycardia during dural manipulation. **Study type:** Case report **Size:** 1 pt	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** During dural stimulation, propofol 50 mg IV terminated sinus bradycardia	• Case report discussing that during dural stimulation, propofol 50 mg IV terminated sinus bradycardia
Yong J, et al. 2015 (305) 26424701	**Aim:** Evaluate development of cardiac arrest during laparoscopic surgery	**Inclusion criteria:** Cardiac arrest pts **Exclusion criteria:** N/A	**1° endpoint:** Cardiac arrest (bradycardia) **Results:** • 9/14 bradycardia • 2 critical points for cardiac arrest:	• Bradycardia common during laparoscopy

	Study type: Retrospective analysis of the Australian Incident Monitoring Study (AIMS) database **Size:** 14 cases from >11,000 pt database		insufflation or establishment of pneumoperitoneum (12/14; 86%) Anesthesia induction (2/14; 14%)	
Vimala S, et al. 2016 (306) 26114985	**Aim:** Case report of asystole during dural manipulation **Study type:** Case report **Size:** 1 pt	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** • Bradycardia and asystole during dural manipulation and excision of a temporal lobe meningioma (near the left insula)	• Case report of bradycardia during dural manipulation
Mohan S, et al. 1990 (307) 24788865	**Aim:** Evaluate the use of transvenous pacing during PCI **Study type:** Case report **Size:** 1	**Inclusion criteria:** 60 y undergoing maxillectomy for squamous cell cancer **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** • Asystole during posterior osteotomy • Bradycardia again during manipulation of the posterior maxillary tuberosity • Treatment by atropine and minimizing surgical manipulation	
Ishii D, et al. 1990 (308) 23834853	**Aim:** Evaluate the use of cilostazol for preventing bradycardia during carotid artery stenting **Study type:** Retrospective **Size:** 53 pts who underwent 54 carotid artery stenting procedures divided into procedures where pts received cilostazol (26) and those who did not (28)	**Inclusion criteria:** Pts who underwent carotid artery stenting at a single institution **Exclusion criteria:** None	**1° endpoint:** Bradycardia (<50 bpm or hypotension (<90 mm Hg) **Results:** • Intraprocedural bradycardia: ○ Cilostazol: 4/26 (15%) ○ No cilostazol: 15/28 (54%) • Postprocedure bradycardia ○ Cilostazol: 0/26 ○ No cilostazol: 3/28 (11%)	• Cilostazol reduced intraoperative bradycardia

Schipke JD, et al. 2013 (309) 23332411	**Aim:** 1 pt who developed asystole during paranasal sinus surgery **Study type:** Case report **Size:** 1	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** • 15 s of asystole with instrumenting the paranasal sinuses	• Asystole with instrumenting the paranasal sinuses
Haldar R, et al. 2013 (310) 23242253	**Aim:** 1 pt who developed bradycardia during skull pin fixation **Study type:** Case report **Size:** 1	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** • Heart rate decreased from 88 to 44 bpm with skull fixation pin tightening that stopped when instrumentation stopped and recurred with tightening again.	• Heart rate decreased with skull fixation pin tightening that stopped when instrumentation stopped and recurred with tightening again.
Seo KC, et al. 2010 (311) 20498810	**Aim:** Identify possible factors contributing to bradycardia and hypotension during shoulder surgery **Study type:** Retrospective **Size:** 63	**Inclusion criteria:** ASA I/II pts who received interscalene block for arthroscopic shoulder surgery in the sitting position **Exclusion criteria:** N/A	**1° endpoint:** Bradycardia (<50 bpm) and/or hypotension (<100 mm Hg or use of ephedrine) **Results:** • 13/63 with bradycardia and hypotension • Bradycardia and hypotension more likely with: Right sided procedures (R: 27% vs. L: 5%) Higher use of fentanyl (54% vs. 0.4%)	• Bradycardia and hypotension more common with tight sided procedures
Jeyabalan G, et al. 2010 (312) 20557186	**Aim:** Identify factors associated with bradycardia during pharmacomechanical thrombectomy for deep vein thrombosis **Study type:** Retrospective **Size:** 57 pts	**Inclusion criteria:** Consecutive pts who underwent pharmacomechanical (AngioJet) therapy for deep vein thrombosis **Exclusion criteria:** N/A	**1° endpoint:** Bradycardia **Safety endpoint:** • 7/57 (12.3%) had bradyarrhythmias asystole 2 sinus bradycardia: 5 More than 1 episode: 4 • Bradycardia resolved in 5/7 pts with cessation of therapy. 2 pts received atropine	• Bradycardia observed with AngioJet procedures
Usami K, et al. 2010 (313) 20448432	**Aim:** Describe 3 pts who developed bradycardia with surgery for cerebellopontine angle meningiomas	**Inclusion criteria:** Case series of pts with bradycardia during meningioma surgery	**1° endpoint:** Bradycardia **Results:** • Transient bradycardia/asystole and hypotension apparently due to activation of the	• Transient bradycardia/asystole and hypotension apparently due to activation of the trigeminocardiac reflex

	Study type: Case series **Size:** 3	**Exclusion criteria:** N/A	trigeminocardiac reflex by direct stimulation of the trigeminal nerve or branches in the dura mater or cerebellar tentorium • Remifentanil suggested as a possible contributor	by direct stimulation of the trigeminal nerve or branches in the dura mater or cerebellar tentorium
Lubbers HT, et al. 2010 (314) 20347202	**Aim:** Describe 3 pts who developed bradycardia with craniomaxillofacial surgery. **Study type:** Case series **Size:** 3	**Inclusion criteria:** Case series, N/A **Exclusion criteria:** N/A	**1° endpoint:** Bradycardia **Results:** • Describe 3 pts identified from a single center surgical database with bradycardia during craniomaxillofacial surgery	• Purely descriptive with no specific recommendations or findings
Christensen RE, et al. 2010 (315) 19933174	**Aim:** Describe outcomes in pts with surgically corrected D transposition of the great arteries (D-TGA) undergoing noncardiac surgery **Study type:** Retrospective **Size:** 50 procedures (34 pts)	**Inclusion criteria:** Consecutive pts with surgically corrected D-TGA undergoing noncardiac surgery (43 pediatric and 7 adults) **Exclusion criteria:** N/A	**1° endpoint:** Adverse events including bradycardia **Results:** 4 adverse events. 1 pt with severe bradycardia during abdominal insufflation	• 4 adverse events observed in pts with congenital heart disease and noncardiac surgeries.
Jacques F, et al. 2009 (316) 18657390	**Aim:** Compare regional anesthesia and general anesthesia for CEA surgery **Study type:** Retrospective **Size:** 72 Regional anesthesia: 25 General anesthesia: 47	**Inclusion criteria:** Consecutive pts undergoing CEA from a single center **Exclusion criteria:** None	**1° endpoint:** Hypotension and bradycardia (<60 bpm) **Results:** Regional anesthesia associated with less intraoperative bradycardia (4%) when compared to general anesthesia (63%)	• Regional anesthesia associated with less intraoperative bradycardia

Hanss R, et al. 2008 (317) 18211442	**Aim:** Evaluate heart rate variability as a tool to identify pts who will have hypotension or bradycardia during surgery **Study type:** Retrospective model followed by a prospective study **Size:** 100	**Inclusion criteria:** High perioperative risk (ASA III/IV) undergoing major vascular or abdominal surgery **Exclusion criteria:** Not in SR, <18 y, emergency surgery	**1° endpoint:** Bradycardia and hypotension **Results:** • No specific data on bradycardia but those pts with lower heart rate variability (stratified by a total power <500 Ms^2Hz^{-1}) were more likely to develop hypotension and bradycardia • 4/50 pts in the retrospective model development group had bradycardia (<50 bpm)	• Small numbers of bradycardia (mostly hypotension)
Reddy MK, et al. 2008 (318) 18157036	**Aim:** Describe a pt who developed bradycardia during surgical positioning of an unstable cervical spine **Study type:** Case report **Size:** 1	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** Bradycardia **Results:** • Bradycardia (35 bpm) and hypotension (50 mm Hg) with initial skull positioning • Atropine and beta agonists not successful but surgical repositioning of the spine led to resolution and development of a heart rate 100 bpm	• Case report of bradycardia with skull positioning
Ardesch JJ, et al. 2007 (319) 17825483	**Aim:** Describe cardiac responses with vagal nerve stimulation **Study type:** Retrospective **Size:** 111	**Inclusion criteria:** Pts who received a vagal nerve stimulator for treatment of epilepsy **Exclusion criteria:** None	**1° endpoint:** Bradycardia **Results:** 3 cases of bradycardia during intraoperative testing. Not subsequently observed on postoperative testing.	• Transient bradycardia can be observed with vagal stimulation.
Jones PM and Soderman RM, 2007 (320) 17223834	**Aim:** Describe a pt on 2 cholinesterase inhibitors who developed intraoperative bradycardia **Study type:** Case report **Size:** 1	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** Bradycardia **Results:** Bradycardia (35 bpm) with induction of anesthesia	• Bradycardia (35 bpm) with induction of anesthesia

Wijeysundera DN, et al. 2014 (321) 25091545	**Aim:** ERC report on perioperative BB use **Study type:** Meta-analysis **Size:** N/A	**Inclusion criteria:** Varied among studies **Exclusion criteria:** Varied among studies	**1° endpoint:** Bradycardia **Results:** Perioperative beta blockade started within 1 d or less before noncardiac surgery increases risks of intraoperative bradycardia (RR: 2.61; 95% CI: 2.18– 3.12).	• Perioperative beta blockade started within 1 d or less before noncardiac surgery increases risks of intraoperative bradycardia

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Morris D, et al. 1987 (322) 3675104	**Aim:** Evaluate the incidence of CHB in pts with LBBB undergoing PA catheter placement **Study type:** Retrospective **Size:** 47 pts who underwent 82 PA catheter placements	**Inclusion criteria:** All pts with LBBB who underwent PA catheter placement **Exclusion criteria:** None	**1° endpoint:** CHB **Results:** • 5 episodes of CHB in the setting of old LBBB but none temporally related to PA catheter placement • 2 episodes of CHB in the setting of new LBBB but none temporally related to PA catheter insertion- though occurred while the catheter was in place	• Authors do not recommend prophylactic temporary transvenous pacing
Elliott CG, et al. 1979 (323) 510002	**Aim:** Evaluate complications associated with PA catheter placement **Study type:** Prospective **Size:** 116 PA catheters	**Inclusion criteria:** Consecutive pts undergoing PA catheter placement **Exclusion criteria:** None	**1° endpoint:** Arrhythmias, ECG changes, or complications **Results:** Transient RBBB in 3% of pts	• Transient RBBB fairly rare
Unnikrishnan D, et al. 2003 (324) 14570803	**Aim:** Describe complications associated with PA catheter placement **Study type:** Case report	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** Complete heart block with central venous line placement in a pt with LBBB	• Transient CHB may occur with placement of central venous catheter

	Size: 1			

Data Supplement 47. Nonrandomized Trials, Observational Studies, and/or Registries of CABG (Section 8.1.2.1)

Study Acronym; Author; Year Published' PMID	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Bougioukas I, et al. 2017 (336) 28122567	**Aim:** Correlation of temporary pacing wire removal and bleeding **Study type:** Observational **Size:** 4244	**Inclusion criteria:** Pts undergoing cardiac surgery	**Intervention:** Cardiac surgery **Comparator:** Pts who underwent re-exploration unrelated to pacer removal **1° endpoint:** 0.18% bleeding after temporary pacing wire removal **Safety endpoint:** 2 pts died after removal from tamponade	• Retrospective review • Not clear of decision to leave in and cut wires instead of removal
Bethea BT, et al. 2005 (337) 15620924	**Aim:** Determine need for temporary pacing **Study type:** Observational **Size:** 222	**Inclusion criteria:** CABG **Exclusion criteria:** OP-CABG	**Intervention:** CABG **1° endpoint:** 3 risk factors related to need for pacing: DM, need for pacing at CPB separation, preop arrhythmia	• Small, retrospective • Even after risk factors eliminated 2.6% still needed wires.
Puskas JD, et al. 2003 (338) 14721993	**Aim:** Compare off-pump vs. on pump CABG **Study type:** RCT sub-analysis **Size:** 200	**Inclusion criteria:** Pts undergoing CABG **Exclusion criteria:** Addition of valve surgery recognized at time of operation	**Intervention:** Temporary pacing wires only placed if needed before chest closure **1° endpoint:** Only 17% of pts need wires **Safety endpoint:** No adverse event in the non-pacing wire group	• Not intervention randomized • Small, retrospective • Does not discuss any need for pacing Swann • No adverse event reported from pulling wires

Caspi Y, et al. 1987 (339) 3493391	**Aim:** Identify incidence of conduction block after CABB **Study type:** Observational **Size:** 316	**Inclusion criteria:** Pts undergoing CABG	**Intervention:** CABG **Comparator:** Pts who did not have conduction block **1° endpoint:** 17% had new bundle branch block associated with preop MI, low cardiac output and death	• Small. retrospective • Potentially dated due to changes in surgical technique
Zeldis SM, et al. 1978 (340) 306190	**Aim:** Identify frequency of new fascicular conduction disturbances after CABG **Study type:** Observational	**Inclusion criteria:** Isolated CABG	**Intervention:** CABG **Comparator:** Pts who did not have conduction block **1° endpoint:** 20% new disturbances, 6% RBBB, 6% LAH. Pts with transient or persistent LBB or L anterior hemiblock had increased late mortality and MI	• Small, retrospective • Potentially dated due to changes in surgical technique
Cook DJ, et al. 2005 (341) 16242447	**Aim:** Assess incidence of **n**ew conduction defects over time after isolated CABG **Study type:** Observational **Size:** 800	**Inclusion criteria:** Isolated CABG pts **Exclusion criteria:** Pre-existing conduction defect, PM, peri-op AF	**Intervention:** CABG **Comparator:** Pts whose operations were performed in 1991 vs. 2001 **1° endpoint:** Decline in conduction defects from 19% to 6%. Associated with year of operation, age, IABP use, number of vessels bypassed and crystalloid cardioplegia	• Small, retrospective
Tuzcu EM, et al. 1990 (342) 2387933	**Aim:** Identify incidence and significance of new conduction defects after CABG **Study type:** Observational, matched	**Inclusion criteria:** Isolated elective CABG	**Intervention:** CABG **Comparator:** Matched pts w/o conduction defects **1° endpoint:** 5.5% new conduction block, 85% RBBB, 4% LBBB. No difference in late mortality or need for PM with matched group	• Small, retrospective

	Size: 2,000			
Ngaage DL, et al. 2007 (343) 17198809	**Aim**: Influence of preop AF on outcomes after CABG **Study type:** observational, matched **Size:** 526	**Inclusion criteria:** Pts undergoing CABG with preop AF	**Intervention:** CABG **Comparator**: Matched pts **1° endpoint:** AF pts: higher MACE, late mortality and late PM implantation (RR: 2.1)	• Small, retrospective
Yesil M, et al. 2008 (344) 18855876	**Aim:** Determine effect of revascularization on present conduction disturbances **Study type:** Observational **Size:** 53	**Inclusion criteria:** Pts with CAD and 3rd degree block **Exclusion criteria:** Acute coronary syndrome	**Intervention:** Revascularization **Comparator**: Medical management of CAD **1° endpoint:** 81% in medical arm vs. 73% in revascularized arm still in 3 degree heart block	• Small, retrospective
Satinsky JD, et al. 1974 (345) 4843620	**Study type:** Retrospective case series **Size:** 280 pts	**Inclusion criteria:** Pts undergoing cardiac surgery	**1° endpoint:** New conduction defects after cardiac surgery **Results:** 6% of all pts had new conduction defects, 12% after valve surgery-only 0.7% of total, both valve pts required PM	• Small, retrospective, mixed group

Data Supplement 48. Nonrandomized Trials, Observational Studies, and/or Registries of Open Surgery for Atrial Fibrillation or Valvular Surgery (Section 8.1.2.2. and 8.1.2.3)

Study Acronym; Author; Year Published' PMID	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Dawkins S, et al. 2008 (332) 18154792	**Aim:** Determine incidence and predictors of PPM after AVR **Study type:** Observational **Size:** 354	**Inclusion criteria:** Pts undergoing AVR **Exclusion criteria:** Pts with preop pacer	**Intervention:** PM placement **Comparator**: No pacer required **1° endpoint:** 8.5% required permanent pacer. Only predictor: preop conduction system disease (RR: 2.88).	• Small, retrospective
Limongelli G, et al. 2003 (346) 12860869	**Aim:** Identify incidence and predictors of PPM after AVR **Study type:** Observational cohort **Size:** 276	**Inclusion criteria:** Pts undergoing AVR	**Intervention:** PPM **Comparator:** No PPM **1° endpoint:** 3.2% required PPM. Risk factors: preop AI, MI, PHTN, and postop electrolyte abnormalities.	• Small, retrospective • Did not control for preop conduction abnormalities
Bagur R, et al. 2011 (347) 21828221	**Aim:** Identify incidence and predictors of PPM after AVR in elderly **Study type:** Observational cohort **Size:** 780	**Inclusion criteria:** Pts ≥70 y undergoing isolated AVR **Exclusion criteria:** Age <70 y, preop PPM/AICD, ascending aortic replacement	**Intervention:** PPM **Comparator:** NO PPM **1° endpoint:** 3.2% needed PPM, predicted by preop LBB or RBB. PPM associated with longer hospital stay but no survival difference at 30d or 5 y.	• Small, retrospective
Baraki H, et al. 2013 (348) 23300203	**Aim:** Determine if AVN function recovers after PPM post AVR **Study type:** Observational cohort **Size:** 138/2,106	**Inclusion criteria:** PPM post AVR **Exclusion criteria:** Death	**Intervention:** PM interrogation **1° endpoint:** only 10% of survivors were no longer pacer-dependent	• Small, retrospective

Greason KL, et al. 2017 (349) 28433222	**Aim:** Determine if PPM after AVR effects survival **Study type:** Observational cohort **Size:** 5,482	**Inclusion criteria:** Pts undergoing AVR	**Intervention:** PPM within 30 d of surgery (N=146) **Comparator:** No PPM **1° endpoint:** PPM associated with increased mortality (HR: 1.49).	• Small, retrospective
Berdajs D, et al. 2008 (350) 18482844	**Aim:** Identify cause of conduction block after MV surgery **Study type:** Observational cohort, autopsy **Size:** 391/92/55	**Inclusion criteria:** 2 populations: (1) those undergoing MV operations and (2) cadaver dissection	**Intervention:** (1) MVR +/- PPM: (2) dissection **1° endpoint:** (1) 23% AVB, 4% needed PPM. (2) 23% of cadavers had AV nodal artery running near MV annulus	• Amiodarone, sotalol, cross-clamp time risk factors for PPM; digoxin protective • AV nodal artery injury possible mechanism for block • Small, retrospective, dissections not on surgical pts.
Goldstein D, et al. 2016 (351) 26550689	**Aim:** Compare outcomes between chordal-sparing mitral replacement and mitral repair **Study type:** RCT sub-analysis **Size:** 256	N/A	**Intervention:** Mitral valve repair or replacement **1° endpoint:** Readmission higher in MV repair group largely due to higher rate of PPM/AICD placement (59 vs. 38)	• Small • Not designed to answer question
Saint LL, et al. 2013 (352) 23998785	**Aim:** Identify incremental risk of adding a maze operation in MV surgery **Study type:** Observational cohort **Size:** 213	N/A	**Intervention:** MV surgery plus Maze **Comparator**: MV surgery w/o Maze **1° endpoint:** No difference in mortality, no difference in PM **Safety endpoint:** Pts not offered a Maze had more	• Small, retrospective • PPM 11% in Maze vs. 6% w/o-study likely not powered to show difference • Pts not offered a Maze had more serious comorbidities

Gammie JS, et al. 2008 (353) 18291169	**Aim:** Identify if AF surgery increased risk in pts undergoing mitral surgery **Study type:** STS Database sub-analysis **Size:** 12,235	**Inclusion criteria:** All pts in database **Exclusion criteria:** Non-mitral surgery	**Intervention:** MV surgery + preop AF + AF correction **Comparator:** MV surgery + preop AF - AF correction **1° endpoint:** Mortality same: PPM higher in Maze group (AOR: 1.26)	• Non-randomized, no propensity match, probable selection bias
Gillinov AM, et al. 2015 (354) 25853744	**Aim:** Determine if the addition of AF surgery to MV surgery is effective **Study type:** RCT **Size:** 260	**Inclusion criteria:** Pre-op AF + MV surgery	**Intervention:** MV+ AF surgery **Comparator:** MV – AF surgery **1° endpoint:** Lower rate of AF post maze (63% vs. 24%), Higher need for PPM (21 vs. 8 per 100 pt y) **Safety endpoint:** No difference in mortality	• Not standardized AF surgery • No analysis of repair vs. replace • Unclear if powered for PPM endpoint
Phan K, et al. 2014 (355) 24650881	**Aim:** Determine efficacy of AF surgery **Study type:** Meta-analysis of 16 RCT **Size:** 1,082	**Inclusion criteria:** RCT **Exclusion criteria:** RCT that did not include sinus restoration or AF-free survival	**Intervention:** AF surgery **Comparator:** No AF surgery **1° endpoint:** No difference in mortality, no difference in PPM, higher prevalence of SR in Maze group	• Not standardized lesion set • Subgroup analysis on cardiac surgery type not available • Follow-up ECG or 24 h Holter
Chikwe J, et al. 2015 (356) 25936265	**Aim:** To assess long-term effect of TV repair **Study type:** Observational cohort **Size:** 645	**Inclusion criteria:** Mitral surgery **Exclusion criteria:** 3 V CAD, AV surgery	**Intervention:** Tricuspid repair **Comparator:** No TV repair **1° endpoint:** No difference in morbidity, mortality or PPM (2.4% vs. 1.3%)	• Selection Bias • 99% MV repair, likely avoided anterior leaflet • Likely not powered for difference in PPM
Scully HE, et al. 1995 (357) 7776666	**Aim:** Describe early and late results after tricuspid valve replacement **Study type:** Observational cohort **Size:** 60	**Inclusion criteria:** Pts undergoing tricuspid valve surgery	**Intervention:** Tricuspid replacement **Comparator:** **1° endpoint:** 22% required permanent epicardial lead placement	• Small, retrospective • Potentially outdated surgical technique

Jokinen JJ, et al. 2009 (358) 19463599	**Aim:** Need for PPM after TV surgery and implications on morbidity **Study type:** Observational cohort **Size:** 136	**Inclusion criteria:** Pts undergoing tricuspid valve surgery-94% repaired	**Intervention:** PPM placement **Comparator:** TV surgery w/o PPM placement **1° endpoint:** 21% needed PPM, PPM pts had better 5 y survival, MORE TIA and worse CHF and QOL	• Small, retrospective • Potentially outdated surgical technique
McCarthy PM, et al. 2004 (359) 15001895	**Aim:** Assess durability of TV repair **Study type:** Observational cohort **Size:** 790	**Inclusion criteria:** Tricuspid repair	**Intervention:** Tricuspid repair **Comparator:** Use of Ring vs. No ring **1° endpoint:** Freedom from TR. In pts who need PPM after repair, Incidence of TR ≥3 is 42%	• Small, retrospective • Potentially outdated surgical technique

Data Supplement 49. Nonrandomized Trials, Observational Studies, and/or Registries of Conduction Abnormalities After TAVR (Section 8.1.2.4)

Study Acronym; Author; Year Published' PMID	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Incidence of Conduction Abnormality and PPM				
Piazza N, et al. 2008 (360) 19463319	**Study type:** Retrospective **Size:** 40	**Inclusion criteria:** CoreValve TAVR 11/2005 3/2008	**1° endpoint:** Conduction abnormalities and the need for pacing **Results:** • LBBB: 15% pre, 55% post (p<0.001) • 18% required PPM 2 pts with RBBB required PPM (100%)	• Significant increase in LBBB • Pts with RBBB may be at risk for CHB
Roten L, et al. 2010 (361) 21059439	**Study type:** Observational **Size:** 67	**Inclusion criteria:** MDT or Edwards TAVI Follow-up: >30 d **Exclusion criteria:** Pre-existing PPM	**1° endpoint:** AV conduction abnormality and/or need for PPM **Results:** PPM in 34%, 3°HB in 22% 2° HB in 6%, new LBBB in 22%, 3°HB resolved in 64%, RBBB only predictor of CHB (OR: 7.3; 2.4–22.2)	• TAVI associated with AV conduction impairment • 3°HB resolves in over half pts • Preexisting RBBB at risk for 3°HB

van der Boon, RM, et al. 2013 (362) 23295037	**Study type:** Observational **Size**: 167 pts from 11/2005–2/2011	**Inclusion criteria:** 36 who received new PPM after TAVR **Exclusion criteria:** Existing PPM or no new PPM	**1° endpoint:** Number pacer dependent at median follow-up 11.5 mo (IQR 5–18) **Results** (number dependent): 16 of 30 (53.3%) with HDAVB Overall 20 of 36 (55.6%)	• Improvement in AV conduction occurs in over half of pts
Siontis, GC, et al. 2014 (363) 25011716	**Study type:** Meta-analysis **Size:** 41 studies encompassing 11,210 pts	**Inclusion criteria:** Studies reporting incidence of PPM after TAVR **Exclusion criteria:** 194 of 235 studies	**1° endpoint:** PPM post TAVR **Results:** Increased risk of PPM Men- RR: 1.23; p<0.01 1°block- RR: 1.52; p<0.01 L ant hemiblock-RR: 2.89; p<0.01 RBBB- RR: 2.89; p<0.01 AVB- RR: 3.49; p<0.01	• Male, baseline conduction disturbance, and intraprocedural AVB are predictors of PPM
Boerlage-Van Dijk K, 2014 (364) 25040838	**Study type:** Observational **Size:** 121	**Inclusion criteria:** Single center TAVR 10/2007–6/2011 Follow-up 1, 3 and 12 mo **Exclusion criteria:** Valve in valve	**1° endpoint:** Conduction abnormalities and new PPM **Results:** 38.8% new LBBB, half of which were temporary New PPM in 23 pts (19%) Predictors of new PPM: MAC (OR: 1.3, 1.05–1.56; p=0.02), RBBB (OR: 8.8, 1.61–44.91; p=0.01) At follow-up: 52% pacer dependent, 22% not paced, 26% intermittent	• MAC and RBBB predictors of new PPM • Prosthesis size is a predictor of LBBB
Mortality and new PPM after TAVR				
Nazif TM, et al. 2015 (365) 25616819	**Study type:** Registry **Size:** 1973	**Inclusion criteria:** In PARTNER Registry **Exclusion criteria:** Pre-procedure PPM	**1° endpoint:** New PPM **Results:** 8% new PPM Predictors: RBBB (OR: 7.03, 4.92–10.06; p<0.0001), prosthesis/outflow tract diameter ratio (OR: 1.29, 1.10–1.51; p=0.002), New PPM not associated with increased 1 y mortality. EF at 1 y same in PPM vs. no PPM	• 8.8% required new PPM • New PPM associated with: longer LOS, more re-hospitalization • New PPM not associated with increased mortality or decreased EF at 1 y
FRANCE 2 Mouillet G, et al. 2015 (366)	**Study type:** Registry **Size:** 833	**Inclusion criteria:** 29 centers in FRANCE 2 registry	**1° endpoint:** Incidence of new PPM or Mortality at 242±179 d	• All-cause mortality same in PPM vs. no PPM at mean follow-up of 8 mo

25573445	1/2010–10/2011	**Exclusion criteria:** Pre-existing PPM	**Results:** 30% rate of new PPM Mortality PPM vs.no PPM: 16.3 vs. 16.9; p=0.83	
Impact of Mitral Annular Calcification (MAC)				
Abramowitz Y, et al. 2017 (367) 28039339	**Study type:** Observational **Size:** 761 pts: 49.3% MAC Mild MAC 30.4% Mod MAC 9.5% Severe MAC 9.5%	**Inclusion criteria:** 3 y series of TAVR at Cedars-Sinai **Exclusion criteria:** N/A	**1° endpoint:** 30 d mortality ± MAC **Results**: Severe MAC is a predictor of: overall mortality HR: 1.95 (1.24–3.07; p=0.004) Cardiovascular mortality HR: 2.35 (1.99–4.66; p=0.01) New PPM HR: 2.83 (1.08–7.47; p=0.03)	• Severe MAC is associated with increased all-cause and cardiac mortality and with conduction abnormalities after TAVR • Mild and moderate MAC are not predictors of adverse outcomes
Predictors and impact of new LBBB after TAVR				
Franzoni I, et al. 2013 (368) 23726173	**Study type:** Observational **Size**: 238 (2007–2011) San Raffaele, Milan MCRS N=87 ESV N=151	**Inclusion criteria:** TAVR **Exclusion criteria:** Previous: PPM, RBBB, LBBB	**1° endpoint:** New LBBB **Results:** New LBBB in 26.5% (ESV 13.5%, MCVS 50%) Persistent LBBB at discharge= 17.2% New PPM=12.7% (2° CHB, bradycardia)	• LBBB was NOT a predictor of: PPM, overall mort, cardiac mort, at 1 y
Urena M, et al. 2012 (369) 23040577	**Study type:** Observational **Size:** 202, median follow-up 12 mo	**Inclusion criteria:** TAVR **Exclusion criteria:** No baseline conduction disturbances	**1° endpoint** New onset LBBB **Results:** 30.2% new LBBB LBBB resolved in 37.7% at discharge LBBB resolved in 57.3% at 6–12 mo LBBB at discharge associated with: Higher rate of syncope (16.0% vs. 0.7%; p=0.001) CHB needing PPI (20 vs. 0.7%; p<0.001 no increase in global or cardiac mortality	• Pts with new LBBB at discharge are at 20% risk of receiving a new PPM but do not have increased all-cause or cardiac mortality • LBBB persistent at discharge is associated with increased syncope, CHB
Testa L, et al. 2013 (370) 23443735	**Study type:** Observational **Size:** 818 10/2007 to 4/2011	**Inclusion criteria:** CoreValve TAVR **Exclusion criteria:** Baseline PPM or LBBB Received new PPM <48 h postop	**1° endpoint:** New LBBB **Results:** 27.4% new LBBB At 30 d and 1 y, LBBB not associated with higher all-cause or cardiac mortality At 30 d LBBB had higher rate of PPI (4.9% vs. 2%; p=0.02)	• new LBBB post TAVR not associated with higher all-cause or cardiac mortality • New LBBB at discharge is associated with a higher rate of PPI at 30 d
Egger F, et al. 2014 (371)	**Study type:** Single center prospective	**Inclusion criteria:** TAVR	**1° endpoint:** Development of high degree AVB	• In pts with LBBB after TAVR, intensified

25034184	**Size:** 50	10 with pre-existing LBBB and 7 with new LBBB received new DDD PMI	**Results:** 10 of 17 with LBBB developed episode of high degree AVB. In 5/17 (29.4%) the first episode of high degree AVB occurred after discharge (mean follow-up 578 d)	monitoring may be reasonable
Schymik G, et al. 2015 (372) 25388650	**Study type:** Observational 10/2008–4/2012 **Size:** 197	**Inclusion criteria:** New onset LBBB after TAVR **Exclusion criteria:** N/A	**1° endpoint:** Mortality **Results:** 31% new LBBB New LBBB independent predictor of all-cause mortality at 1 y (HR: 1.84; 1.35–2.02) At 1-y survival with PPM not different than survival w/o PPM (81.2% vs. 85.0%; p=0.377)	• New onset LBBB is a predictor of increased 1 y all-cause mortality, but mortality is not altered by PPI
Regueiro A, et al. 2016 (373) 27169577	**Study type:** Meta-analysis **Size:** 17 studies 4,756 pts w/new LBBB 7,032 pts w/new LBBB&PPI	**Inclusion criteria:** New LBBB post TAVR **Exclusion criteria:** N/A	**1° endpoint:** PPI or mortality at 1 y **Results:** New onset LBBB associated with: PPI (RR: 2.18, 1.28–3.70) Cardiac death (RR: 1.39, 1.04–1.86) No increase in all-cause mort (RR: 1.21, 0.98–1.50) Peri-procedural PPI post TAVR -> NO protective effect on cardiac death (RR: 0.78, 0.6–1.03)	• New onset LBBB post TAVR is associated with increased cardiac death and need for PPI at 1 y • Peri-procedural PPI post TAVR did not decrease the risk of cardiac death at 1 y.
RBBB as predictor of PPI post TAVR				
Mauri V, et al. 2016 (374) 27832845	**Study type:** Observational **Size**: 229 8/2013–1/2016	**Inclusion criteria:** TAVR with Edwards SAPIEN 3 **Exclusion criteria:** N/A	**1° endpoint:** PPI **Results:** Among other preprocedure nonconduction factors, RBBB is an independent predictor of 30 d PPI	• Confusing and self-contradictory paper. • Abstract says that RBBB is a predictor of PPI • Body of the paper just says that prior conduction abnormalities are predictive.
OCEAN-TAVI Wantanabe, Y, et al. 2016 (375) 27832846	**Study type**: Registry **Size**: 749, 102 with RBBB 10/2013–8/2015	**Inclusion criteria**: TAVR at 8 Japanese centers **Exclusion criteria**: N/A	**1° endpoint**: Incidence of PPI and death with pre-existent RBBB **Results:** • New PPI higher in RBBB (17.6% vs. 2.9%; p<.01) • Early survival RBBB vs. no RBBB (96% vs. 98.6; p=0.09) • Overall survival at 24mo lower in RBBB, log rank p=0.03	• Pts with RBBB with and w/o PPM at higher risk of cardiac death early after discharge • Pts with RBBB should be carefully monitored

			• Cardiac survival lower in RBBB, log rank p<.01 • RBBB is a predictor of cardiac death: HR: 2.59 (1.15–5.86; p=0.021)	
Nazif TM, et al. 2015 (365) 25616819	**Study type:** Analysis of PARTNER Trial and Registry post hoc **Size:** 2559	**Inclusion criteria:** TAVR **Exclusion criteria:** N/A	**1° endpoint:** Requiring ppm **Results:** New PPM RBBB vs. no RBBB: 47.6% vs. 12.8%; p<0.001	• Pre-existing RBBB is a predictor of PPI after TAVR
Auffret V, et al 2017 (376) 28734885	**Study type:** Multicenter **Size:** 3,527 pts, 362 with preexisting RBBB	**Inclusion criteria:** TAVR	**1° endpoint:** Complications and death **Results:** Preexisting RBBB associated with increased all-cause mortality (HR: 1.31) and CV mortality (HR: 1.45). Baseline RBBB associated with a higher 30-d rate of PPM implant (40% vs. 13.5%; p<0.001)	• Preexisting RBBB associated with poorer outcomes in pts undergoing TAVR
Rampat R, et al. 2017 (377) 28641846	**Study type:** Retrospective multicenter **Size:** 228 pts	**Inclusion criteria:** LOTUS TAVR	**1° endpoint:** PPM **Results:** PPM in 64 pts for AVB or LBBB and first degree AVB. Preprocedural conduction abnormality associated with higher likelihood for PPM	• Pts with preprocedural conduction disturbance and noncalcified AV more likely to require PPM after LOTUS TAVR
Predictors of readmission post TAVR				
Nombela-Franco L, et al. 2015 (378) 26476610	**Study type:** Observational **Size:** 720 consecutive pts at 2 centers, follow-up 23 mo	**Inclusion criteria:** TAVR **Exclusion criteria:** N/A	**1° endpoint:** Early readmission <30 d Late readmission 30–365 d **Results:** 4.9% readmitted Average 1.6 readmits /pt Noncardiac 59% vs. cardiac 41% BBB not a predictor of readmission but AF was (p=0.012)	• Although rhythm disturbances cause 21.2% of readmissions, BBB is not a predictor.
Predictors of Late Death after TAVR				
Urena, M, et al. 2015 (379) 25660921	**Study type:** Observational **Size:** 3726	**Inclusion criteria:** TAVR at 18 centers **Exclusion criteria:** N/A	**1° endpoint:** Death from HF and SCD post TAVR mean follow-up 22 mo **Results:**	• New onset persistent LBBB is a predictor of SCD post TAVR • PPI in LBBB is not protective against SCD

			4% died of HF (15% of total deaths, 46.1% cardiac deaths) 15% died of SCD (5.6% of all deaths, 16.9% of cardiac) Predictors of SCD: new LBBB HR: 2.26 (1.23–4.14; p=0.009) new LBBB and QRS >160 ms HR: 4.78 (1.56–14.63; p=0.006) NO difference in SCD between LBBB w/o ppm (N=471) and LBBB with PPI (N=92): HR: 3.13 (0.38–25.63; p=0.287)	
Dizon JM, et al. 2015 (380) 26261157	**Study type:** Series of pts in PARTNER Trial and Registry- post hoc analysis **Size:** Prior ppm:586 New ppm:173 No ppm: 1612 LBBB& no ppm: 160	**Inclusion criteria:** Trial and registry, 1-y follow-up **Exclusion criteria:** N/A	**1° endpoint:** 1 y mortality and re-hospitalization **Results** Prior PPM (p=0.001), new PPM (p=0.05) and LBBB/no ppm (p=0.02) all had higher mort than no PPM LBBB not a predictor of mortality new ppm HR: 1.38(1.0–1.89; p=0.05) and prior ppm HR: 1.31 (1.08–1.6; p=0.006) predict 1 y mort	• LBBB/no ppm was not compared to LBBB/new ppm • LBBB associated with worse outcomes but not an independent predictor of mort • Any PPM: higher 1 y mortality

Data Supplement 50. Nonrandomized Trials, Observational Studies, and/or Registries of Pacing after Heart Transplant (Section 8.1.2.5.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Mallidi HR, et al. 2017 (381) 28331443	**Study type:** Retrospective single center study **Size:** 1,450 transplants	**Inclusion criteria:** Heart transplant at Stanford **Exclusion criteria:** None	**1° endpoint:** Pacemaker implant **Results:** • 84/1,450 pts (5.8%) had a PPM placed • Of these 55 (65%) had the PPM placed within 30 d • Early PPM implant with shorter survival compared to late PPM (6.4 y vs. 7.7 y) • Incidence of PPM was 2% for bicaval and 9.1% for biatrial transplant • More rejection episodes with PPM	• Decreased PPM need with bicaval transplant • PPM more likely with older donor grafts
Wellmann P, et al. 2017 (382) 28101990	**Study type:** Retrospective single center study **Size:** 1,179 transplants	**Inclusion criteria:** Transplant **Exclusion criteria:** None	**1° endpoint:** PPM **Results:** • 135/1,179 pts (11.5%) required a PPM • PPM more likely with prolonged operation and biatrial transplant (9.4% vs. 4.4 %) • Approximately 85% with SND and 15% with AVB • No survival differences	• PPM mainly for SND • Requirement for PPM has decreased with bicaval transplant
Lee W, et al. 2016 (383) 26847073	**Study type:** Retrospective single center **Size:** 33 (2 pacing dependent)	**Inclusion criteria:** Requirement for pacing after transplant **Exclusion criteria:** None	**1° endpoint:** Clinical HF or LVEF <35% **Results:** 2 pts were PM dependent and developed HF 31 pts with a PPM but did not pace continuously did not have HF	• AVB with high RV pacing burden associated with HF • Numbers small
El-Assaad I, et al. 2015 (384) 25956965	**Study type:** Retrospective UNOS database **Size:** 6,156	**Inclusion criteria:** Transplant UNOS <18 y old **Exclusion criteria:** None	**1° endpoint:** Acute PPM placement **Results:** 69/6,156 pts required a PPM acutely PPM use decreased over time	• PPM recipients with higher risk of infection and dialysis but similar survival

			PPM more likely with a biatrial anastomosis, higher donor age PPM pts more likely to have post-transplant infection (48% vs. 26%)	
Knight CS, et al. 2010 (385) 19144548	**Study type:** Case series **Size:** 6 (2 with autopsy)	**Inclusion criteria:** Pts identified from a transplant database with syncope due to bradycardia **Exclusion criteria:** None	**1° endpoint:** Pathologic evaluation **Results:** Autopsy revealed preferential severe rejection in the cardiac conduction system	• Rejection can preferentially affect the conduction system
Braith RW, et al. 2000 (386) 11144044	**Study type:** Prospective treadmill testing **Size:** 8 pts with PPM	**Inclusion criteria:** Transplant with PPM **Exclusion criteria:** None	**1° endpoint:** Treadmill performance **Results:** Chronotropic support improves treadmill times (14.6 min vs. 12.4 min) and peak VO_2 (18.9 vs. 15.4 mL/kg/min)	• Rate adaption helpful
Bacal F, et al. 2000 (387) 10904516	**Study type:** Single center retrospective **Size:** 114 pts	**Inclusion criteria:** Transplant **Exclusion criteria:** None	**1° endpoint:** Temporary or permanent pacing **Results:** 14/114 (12%) required temporary pacing mainly for SND (78.5%), 4 pts required PPM, 3 for SND Rejection with AF	• SND main reason for PPM or temporary pacing after transplant
Nagele H, et al. 1998 1998 (388) 9773864	**Study type:** Single center retrospective **Size:** 112 pts	**Inclusion criteria:** Transplant and placement of epicardial biatrial pacing **Exclusion criteria:** None	**1° endpoint:** NYHA class, hemodynamic parameters **Results:** Modest improvement with biatrial pacing	• Biatrial pacing may be beneficial
Jones DG, et al. 2011 (389) 21783383	**Study type:** Single center retrospective **Size:** 48 pts	**Inclusion criteria:** PPM after transplant **Exclusion criteria:** None	**1° endpoint:** Prognosis **Results:** 48/309 pts required PPM after transplant (12.3%) 30 with PPM during hospitalization and 18 with late PPM (3 y after transplant) SND more common early and AVB later.	• Late pacing not associated with rejection

			Late pacing not associated with rejection	
Cantillon DJ, et al. 2010 (390) 20601151	**Study type:** UNOS **Size:** 35,998 pts	**Inclusion criteria:** Transplant and PPM **Exclusion criteria:** None	**1° endpoint:** Outcomes **Results:** • 3,940/35,987 (10.9%) required PPM • PPM recipients with improved survival (8 y vs.5.2 y) • Bicaval implant with less PPM (OR: 0.33; 95% CI: 0.29–0.36) • PPM associated with increasing donor age (OR: 1.04; 95% CI: 1.00–1.09; p<0.001) and recipient age (OR: 1.09; 95% CI: 1.0–1.12; p<0.001) • Transplant CAD (OR: • 2.12; 95% CI: 0.92–2.33; p=0.409), donor heart ischemic time (OR: 1.03; 95% CI: 0.97–1.04; p=0.880), and graft rejection requiring treatment (OR: 0.95; 95% CI: 0.84–1.07, P.367) were not associated with PPM requirement.	• PPM less common with bicaval • PPM not associated with rejection

Data Supplement 51. Nonrandomized Studies for Alcohol Septal Ablation/Septal Myectomy (Section 8.1.2.5.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)

Liebregts M, et al. 2017 (391) 28595881	**Aim:** Evaluate use of ASA particularly in younger pts **Study type:** Retrospective analysis of 3 registries **Size:** 1,197 pts who underwent ASA	**Inclusion criteria:** International multicenter study of pts who underwent ASA (National registries of Germany, Netherlands, Denmark) **Exclusion criteria:** None	**1° endpoint:** All-cause mortality Adverse arrhythmic event (VT, VF, appropriate ICD shocks) **2° endpoint:** Periprocedural AVB (<30 d) PPM **Results** • Mean follow-up 5.4 y • Complete Heart block ○ <50: 119/369 (32%) ○ 51–64: 161/423 (39%) ○ >65: 169/405 (42%) • PPM ○ <50: 29/369 (8%) ○ 51–64: 53/423 (13%) ○ >65: 65/405 (16%) • ICD (rate support?) ○ <50: 21/369 (6%) ○ 51–64: 18/423 (4%) ○ >65: 11/405 (3%)	• Heart block more common in older pts • Authors conclude ASA safe in younger pts • Do not discuss PPM use 30 d after the procedure • Note that outcomes are better with lower dose alcohol use
Poon SS, et al. 2017 (392) 28329292	**Aim:** Evaluate outcomes between ASA and myectomy **Study type:** Systematic search **Size:** 15 articles-14 observational and 1 meta-analysis	**Inclusion criteria:** Systematic search-keywords: Cardiomyopathy and myectomy and ablation 218 studies **Exclusion criteria:** 15 studies chosen as best nonoverlapping studies	**1° endpoint:** Multiple depending on study **Results** PPM implant: • ASA: 1.7–22% • Myectomy: 2.4%–12.5%	• Authors conclude both procedures reduce LVOT gradient
Axelsson A, et al. 2014 (393) 24662414	**Aim:** Evaluate AV conduction over time after ASA **Study type:**	**Inclusion criteria:** Pts who underwent ASA **Exclusion criteria:** Baseline CIED	**1° endpoint:** Pacing and AV conduction over time **Results:**	• Late PPM in 3 pts at variable times after ASA • About 40% of pts who need PPM will have recurrent 1:1 AV

	Single center retrospective study **Size:** 87 pts		• 24/87 (28%) pts had PPM paced after ASA • 10 lost to follow-up • 6/14 remaining pts had recovery of AV conduction at follow-up 6.2 y (2.1–9.4 y) • Pts with persistent AVB after ASA had longer PR intervals at baseline • Permanent AV conduction abnormalities in pts with baseline 1st degree AVB and persistent CHB • 3 pts who initially did not need a PPM later had a PPM implanted (8 mo, 9 y, and 9 y after the index ASA)	conduction at extended follow-up
Veselka J, et al. 2014 (394) 24360153	**Aim:** Evaluate outcomes in pts with PPM for AVB after ASA **Study type:** Retrospective analysis **Size:** 167 pts	**Inclusion criteria:** 167 consecutive pts with HCM who underwent ASA for LVOT gradients **Exclusion criteria:** Baseline CIED	**1° endpoint:** 17 pts (10%) required PPM placed 3–15 d after ASA **Results:** • At follow-up 11/17 (65%) had recovery of AV conduction at 6 mo. • In the nonpaced group 3/150 pts (2%) had PPM placed • Similar outcomes between the paced and nonpaced groups	• Recovery of AV conduction was high at 6 mo. • Pacemakers placed if conduction block >24 h • In the nonpaced group 3/150 pts (2%) had PPM placed 12–53 mo after ASA • Pacing vs. nonpacing does not change clinical outcomes

El-Jack SS, et al. 2007 (395) 17300408	**Aim:** Evaluate ECG changes after ASA
	
	Study type: Retrospective
	
	Size: 50 pts who underwent ASA
		Inclusion criteria: 50 pts who underwent ASA
		
		Exclusion criteria: N/A
			1° endpoint: ECG changes
			
			Results:
			• ECG changes
			  • New RBBB (57%)
			  • Transient CHB with recovery <24 h: 10 pts (20%)
			  • Persistent CHB (>24 h) requiring PPM: 9 pts (18%)
			• PPM more likely with baseline LBBB
				• PPM placed if CHB >24 h
				• PPM more likely with baseline LBBB
				• 7/9 were still PPM dependent at 14 d
				• New RBBB common (57%)

McCann, GP et al. 2007 (396) 17293204	**Aim:** Evaluate scarring after ASA **Study type:** Retrospective	**Inclusion criteria:** Consecutive pts undergoing ASA **Exclusion criteria:** None	**1° endpoint:** ECG changes **Results:** • ECG after ASA • 2 with persistent RBBB	• New RBBB suggestive of more extensive septal infarct • At 6-mo follow-up no new PPM

	Size: 27 pts evaluated with MRI at baseline and at 1 mo. 25 pts with baseline, 1 mo, 6 mo		• 30 with normal QRS • 17 with new RBBB (1/17 required PPM) • 9 normal • 1 LBBB • New RBBB associated with >CPK and larger scar by MRI • No change in status at 6 mo (1 PPM in new RBBB pt)	
Faber L, et al. 2007 (397) 17067708	**Aim:** Evaluate post ASA AV conduction abnormalities **Study type:** Retrospective cohort **Size:** 155 pts	**Inclusion criteria:** 155 Consecutive pts who underwent ASA **Exclusion criteria:** N/A	**1° endpoint:** ECG changes **Results:** • Transient AVB: 71/155 pts (46%) • Permanent pacing in 11/155 pts (7%) • 4/11 pt who required PPM had baseline LBBB • AV conduction returned in 4/11 pts who had PPM placed • No late development of AVB	• Used a point score for identifying whether to put in a PPM rather than a prescribed time. Point score used AVB recovery but also baseline ECG and LVOT characteristics • Pt assessed at 48 h for whether PPM should be implanted

Talreja DR, et al. 2004 (398) 15607394	**Aim:** Evaluate effect of septal reduction therapies on conduction tissue
	
	Study type: Retrospective
	
	Size: 58 pts who underwent ASA; 117 pts who underwent myectomy
		Inclusion criteria: Myectomy or ASA for HCM
		
		Exclusion criteria: None
			1° endpoint: ECG changes
			
			Results:
			• ASA:
			  • RBBB: 21/58 (36%)
			  • CHB requiring PPM: 6/58 (12%); 3 of these pts with baseline LBBB
			• Myectomy
			  • New LBBB: 47/117 (40%)
			  • CHB requiring PPM: 4/117 pts (3%)
				• Can use baseline conduction abnormalities to predict whether CHB will develop.
				• No specific protocol listed on when PPM implanted

Wang S, et al. 2013 (399) 22761504	**Aim:** Evaluate pts after myectomy
	
	Study type: Retrospective
	
	Size: 93 pts underwent myectomy
		Inclusion criteria: Consecutive pts undergoing myectomy
		
		Exclusion criteria: N/A
			1° endpoint: ECG changes
			
			Results:
			• ECG changes
			  • New LBBB: 44/93 (40%)
			  • CHB requiring PPM: 3/93 (3%)
			  • RBBB: 2/93 pts (2%)
				• No late PPM identified-though follow-up only to 1 y.

			• During follow-up (10.7 mo), no progression of AV conduction abnormalities or PPM	
Agarwal S, et al. 2013 (400) 20170823	**Aim:** Meta-analysis of myectomy vs. ASA **Study type:** Meta-analysis **Size:** 12 studies	**Inclusion criteria:** All observational studies that compared ASA with myectomy **Exclusion criteria:** 288 abstracts, 177 excluded for lack of a control/comparison group, 39 excluded because case report/case series	**1° endpoint:** 30 d all-cause mortality **Results:** • No significant difference in mortality (long-term or short-term), postintervention functional class, postintervention ventricular arrhythmias • ASA associated with increased risk for new RBBB (OR: 56.3; 95% CI: 11.6–273.9) • ASA associated with increased risk for PPM (OR: 2.6; 95% CI: 1.7–3.9)	• No significant difference in mortality (long-term or short-term), postintervention functional class, postintervention ventricular arrhythmias • ASA associated with increased risk for new RBBB and PPM

Schuller JL, et al. 2015 (401) 25689552	**Aim:** Evaluate predictors of late CHB after ASA
	
	Study type: Retrospective
	
	Size: 145 pts followed for 3.2±2.3 y
		Inclusion criteria: 145 pts who underwent ASA
		
		Exclusion criteria: N/A
			1° endpoint: Late CHB (First identified >48 h after ASA)
			
			Safety endpoint:
			• Late CHB in 15/168 pts (8.9%)
			• Late CHB more likely:
			  • Multiple ASA procedures (OR: 4.14; 95% CI:1.24–13.9)
			  • High resting or provocable LVOT (OR for each 10 mm Hg: 1.14; 95% CI:1.00–1.20)
			• High provocable LVOT gradient after Multivariate analysis
			• 3 unexplained deaths: new RBBB, found dead 5 mo after 2nd ASA, new LBBB, found dead 3 d after discharge, no change in QRS, found dead after 5 mo
				• Late CHB can be seen in almost 10% of pts
				• Authors suggest post discharge ECG surveillance

Veselka J, et al. 2013 (402) 23927866	**Aim:** Evaluate predictors of complications after ASA
	
	Study type: Retrospective multicenter
	
	Size: 421 pts from 8 European Centers
		Inclusion criteria: 421 pts who underwent ASA
		
		Exclusion criteria: If outside 2003–5 (to include only "low dose" era)
			1° endpoint: CHB >10 s Early <24 h, late >24 h
			
			Results:
			• Transient CHB in 70/421 pts (17%),
			  • Intraprocedural: 51 (12%)
			  • Transient: 33 (8%)
			  • Late: 12 (3%)
			  • Recurrent: 9 (2%)
			• 97% CHB up to 5th d after ASA
			• PPM in 35% of pts
			• 6 pts required resuscitation, one 10 d after ASA
				• Authors suggest close post procedural monitoring and 5 d hospitalizations after ASA

Kim LK, et al. 2016 (403) 27438114	**Aim:** Evaluate effect of hospital volume on complications after ASA or myectomy
	
	Study type: Retrospective evaluation of the Nationwide Inpatient Sample from 2003 to 2011
	
	Size: 11,248 patients underwent septal reduction procedures
		Inclusion criteria: All pts who underwent septal reduction procedures
		
		Exclusion criteria: N/A
			1° endpoint: Mortality, PPM, bleeding
			
			Results:
			• PPM: myectomy
			  • Total: 9.8%
			  • First tertile: 10%
			  • Second tertile: 13.8%
			  • Third tertile: 8.9%
			• PPM: ASA
			  • Total: 11.9 %
			  • First tertile: 14.2 %
			  • Second tertile: 12.4 %
			  • Third tertile: 11.5 %
				• PPM common in both myectomy and ASA at discharge
				• No data on post discharge outcomes after myectomy and ASA.

Liebregts M, et al. 2015 (404) 26454847	**Aim:** Evaluate ASA or myectomy **Study type:** Systematic review **Size:** 16 myectomy cohorts and 15 ASA cohorts	**Inclusion criteria:** Studies of myectomy of ASA **Exclusion criteria:** N/A	**1° endpoint:** Mortality, PPM, SCD **Results:** • PPM: • ASA: 10 % • Myectomy: 4.4%	• ASA with similar mortality compared to septal myectomy but with higher PPM rate and higher likelihood of repeat procedures

Balt JC, et al. 2015 (405) 25073885	**Aim:** Evaluate use of continuous ECG monitoring after ASA **Study type:** Retrospective **Size:** 44 pts	**Inclusion criteria:** Pts undergoing ASA with PPM or ILR **Exclusion criteria:** N/A	**1° endpoint:** VT/VF or other events recorded on the ILR **Results:** • Pts with VT/VF often had associated CHB (during hospitalization) • No late AVB identified	• ILR did not identify any arrhythmias with 3 y monitoring after ASA

Qin JX, et al. 2004 (406) 14715342	**Aim:** Evaluate conduction tissue after ASA or myectomy
	
	Study type: Retrospective
	
	Size: 70 pts ASA; 134 myectomy
		Inclusion criteria: Pts undergoing ASA or myectomy
		
		Exclusion criteria: N/A
			1° endpoint: ECG
			
			Results:
			• 146 pts with normal QRS preprocedure had prolongation of the QRS (72%)
			  • RBBB in 62% of pts after ASA
			  • LBBB in 93 % of pts after myectomy
			• 174 pts w/o a preexisting CIED
			• ASA: 22% required PPM
			• Myectomy: 10%
				• In pts with preexisting BBB, PPM more likely-approximately 60% (7/12)
				• Although PPM in 25 pts in the entire cohort-33% PPM dependent at follow-up

Chang SM, et al. 2003 (407) 12875767	**Aim:** Evaluate conduction tissue after ASA
	
	Study type: Retrospective
	
	Size: 261 pts ASA, 224 w/o a CIED
		Inclusion criteria: Pts undergoing ASA
		
		Exclusion criteria: N/A
			1° endpoint: ECG/PPM
			
			Results:
			• Independent predictors for CHB:
			  • Women (OR: 4.33)
			  • Bolus injection (OR: 51)
			  • >1septal (OR: 4.6)
			  • Baseline LBBB (OR: 39)
			  • Baseline 1st degree AVB (OR: 14)
			• Describe 1 pt who developed AVB 5 d after DC
			• 31/224 (14%) required new PPM:
			• At 2-y follow-up 25/31 PPM dependent
				• Similar hemodynamic benefit regardless of whether a PPM required or not

Chen AA, et al. 2006 (408) 16442376	**Aim:** Evaluate conduction tissue after ASA **Study type:** Retrospective	**Inclusion criteria:** Pts undergoing ASA **Exclusion criteria:** N/A	**1° endpoint:** ECG/PPM **Results:** • Acute CHB in 62% of pts; all normalized within 24 h	• Authors conclude temporary pacing for 48 h ASA or after resolution of CHB • Authors conclude that pts w/o acute CHB or new IVCD are at low risk for subacute CHB

	Size: 52 pts ASA, 224 w/o a CIED		• Recurrent CHB in 13 pts (25%), 36±22 h)	
Lawrenz T, et al. 2007 (409) 17572252	**Aim:** Evaluate conduction tissue after ASA **Study type:** Retrospective **Size:** 172 pts underwent simultaneous ASA and EPS	**Inclusion criteria:** Pts undergoing ASA **Exclusion criteria:** N/A	**1° endpoint:** ECG/PPM **Results:** • Intraprocedural AVB • Delayed AVB occurred in 15 pts (8.7%) 1–6 d after ASA. All of these pts showed lack of VA conduction • No pt with intact VA conduction after ASA developed delayed CHB • Risk factors for delayed AVB were advanced age, intraprocedural CHB, and prolonged QRSd before or after ASA • PPM in 20 pts	• Intact VA conduction a helpful sign for determining whether a PPM will be required

Data Supplement 52. Nonrandomized Studies for ICDs for Alcohol Septal Ablation/Septal Myectomy (Section 8.1.2.5.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Wang W, et al. 2017 (410) 28314849	**Aim:** Evaluate NSVT as a predictor for appropriate ICD therapy **Study type:** Retrospective analysis **Size:** 160 pts who underwent ICD implant	**Inclusion criteria:** Single center **Exclusion criteria:** None	**1° endpoint:** ICD treated VT/VF **Results:** NSVT associated with appropriate ICD therapy: No NSVT: 10.2% NSVT: 47.4%	• NSVT confirmed to be a risk factor in pts with ICDs
Thavilkulwat AC, et al. 2016 (411) 27138377	**Aim:** Evaluate appropriate ICD use in HCM **Study type:** Retrospective **Size:** 135 pts with ICD	**Inclusion criteria:** Single center review of pts with HCM receiving an ICD **Exclusion criteria:** NR	**1° endpoint:** ICD treated VT/VF **Results:** Appropriate ICD therapy in 25 pts Primary prevention: 2.6%/y Secondary prevention: 9.8%/y	• Appropriate ICD therapy lower than previously reported

Maron BJ, et al. 2007 (412) 17652294	**Aim:** Evaluate appropriate ICD use in HCM **Study type:** Retrospective **Size:** 506 pts with ICD	**Inclusion criteria:** Multicenter Registry of pts with HCM receiving an ICD **Exclusion criteria:** NR	**1° endpoint:** ICD treated VT/VF **Results:** Appropriate ICD therapy: Primary prevention: 3.6%/y Secondary prevention: 10.6%/y. Similar event rates for 1,2, or 3 risk factors for SCD	• Presence of any risk factor sufficient to confer risk

Data Supplement 53. Nonrandomized Trials, Observational Studies, and/or Registries of Adult Congenital Heart Disease (ACHD) (Section 8.2)

Study Acronym; Author; Year	Aim of Study Study Type Study Size (N) Patient population	Primary endpoint results (p values OR or RR; & 95% CI)	Relevant 2° Endpoint (if any) Study limitations Adverse events	Outcomes
Gelatt M, et al. 1997 (413) 8996314	**Aim**: Examination of mortality after Mustard **Study type**: Retrospective observational; 534 pts – single center	Pacemaker implantation is required in 11% of these pts over 35-y follow-up.	No PM implant	• Loss of SR is associated with higher mortality • Late SND and PM implantation is common
Helbing WA, et al. 1994 (414) 8041184	**Aim**: Assess long-term results of atrial switch **Study type**: Retrospective observational; 122 atrial switch pts followed for a median duration of 16 y	Loss of SR occurred in 50–80% of pts depending on type of surgery	Sinus rhythm maintained	Loss of sinus node function is especially common in this group
Anand N, et al. 2006 (415) 16762984	**Aim**: Evaluate the association of bradycardia with atrial flutter **Study type**: Retrospective case-control; 84 pts; CHD and with or w/o atrial arrhythmias	Development of atrial arrhythmias	Pacemaker implant	Late postop atrial flutter is associated with chronotropic incompetence in CHD pts.
Diller G, et al. 2006 (416) 16979014	**Aim**: Assess the long-term outcomes in atrial switch pts	Heart rate reserve predicted mortality independently of	Pts who did not develop CHB	Blunted heart rate with exercise predicts an enhanced mortality risk

	Study type: Retrospective observational; 727 consecutive pts with CHD; longitudinal follow-up	antiarrhythmic therapy, functional class, and peak VO_2		independently of antiarrhythmic medication
Janousek J, et al. 1994 (417) 7846933	**Aim**: Determine the natural history for pts with an atrial switch **Study type**: Retrospective observational; 359 pts with transposition and atrial switch; longitudinal follow-up	SND	N/A	SND occurred in 51% of pts
Fishberger S, et al. 1997 (418) 9011705	**Aim**: Identify factors that influence the development of atrial flutter after Fontan operation **Study type**: Retrospective observational; 334 pts with prior Fontan surgery; longitudinal follow-up	Development of atrial arrhythmias	N/A	The presence of SND was associated with a higher incidence of atrial flutter ($p<0.001$).
Michaëlsson M, et al. 1995 (216) 7634461	**Aim**: Longitudinal study of isolated congenital complete AVB in adult life **Study type**: Prospective follow-up 102 pts	• Mean age at death: 38 y • SA attacks in 27 pts, (8 fatal) • 6 was first event • PM reduced the risk of death	N/A	High incidence of unpredictable SA attacks
Dewey RC, et al. 1987 (419) 3821827	**Aim**: Define long-term natural Hx of congenital CHB **Study type**: 27 pts prospectively followed with frequent Holters for a mean of 8 y; longitudinal follow-up	No pts with a mean daytime heart rate of 50 bpm or more had an adverse clinical outcome	N/A	Mean daytime junctional rate below 50 bpm may represent a manifestation of junctional instability and should be viewed as a risk factor for sudden death or eventual need for a PPM
Lundtsrom U, et al. 1990 (420) 2337032	**Aim**: Natural Hx of ccTGA **Study type**: 111 pts with ccTGA 20-y follow-up	Major risk factor for early death: heart block	N/A	N/A
Connelly MS, et al. 1996 (283) 8609349	**Aim**: Clinical outcome of ccTGA **Study type**: Retrospective observational; 52 pts	40% required PPM	N/A	High rate of AVB

Graham TP, et al. 2000 (421) 10898443	**Aim**: Long-term outcome in ccTGA **Study type**: Multicenter retrospective 182 pts from 19 institutions	41% required PPM	N/A	PM implantation common. Also associated with systemic ventricular dysfunction
Khairy P, et al. 2006 (422) 16702467	**Aim**: Assess risk of thromboemboli in pts with transvenous pacing leads and intracardiac shunts **Study type**: Multicenter, retrospective cohort study of 202 pts with intracardiac shunts	Transvenous leads an independent predictor of systemic thromboemboli (HR: 2.6; p=0.0265)	N/A	Transvenous leads incur a >2-fold increased risk of systemic thromboemboli in pts with intracardiac shunts
DeSimone CV, et al. 2013 (423) 23946264	**Aim**: Stroke or TIA in pts with endocardial leads and a PFO **Study type**: Retrospective observational; 6,075 pts (364 with PFO)	**1° endpoint:** Stroke/TIA: 30/364 (8.2%) PFO vs 117/5711 (2.0%) non-PFO (HR: 3.49; 95% CI: 2.33–5.25; p<0.0001)	N/A	Presence of a PFO is associated with a substantially increased risk of embolic stroke/TIA
Kim MH, et al. 2001 (424) 11230857	**Aim**: Assess prevalence and natural history of complete AVB after valvular heart surgery. Assess the optimal timing of PM implantation **Study type**: Retrospective observational; 155 pts with valvular surgery; 17 (11%) pts had complete AVB in the postop period	• At 1-y follow-up: • 5 of 9 pts (56%) remained in complete AVB • 2 of 9 pts (22%) had resolution of AVB • 2 of 9 (22%) lost to follow-up	N/A	If complete AVB is present after aortic and mitral valve surgery within the first 24 h postop and persists for >48 h, it is unlikely to resolve within the next 1–2 wk
Glikson M, et al. 1997 (425) 9388104	**Aim**: Define long-term dependency in permanent pacing after cardiac surgery **Study type**: Retrospective observational; 120 adults post-cardiac surgery who received PPM	Postop complete AVB is the most important predictor of PM dependency	N/A	In pts with complete AVB, an early decision to implant a permanent PM is probably justified
Edwards W, et al. 1978 (426) 625125	**Aim**: Examination of postmortem findings of the sinus nodal tissue in pts with an atrial switch procedure	Sinus nodal artery damage	N/A	• The sinus node showed acute necrosis or compression in 77% of cases

	Study type: 32 pts; atrial switch pts; postmortem pathological analyses			• Para-nodal areas were damaged in 100% of pts
Sanders P, et al. 2004 (427) 15007004	**Aim**: Atrial mapping in pts with SND **Study type**: 32 pts, 16 pts with SND, 16 controls; case control comparative analysis	SND	Normal hearts with no evidence of SND	SND is associated with diffuse atrial remodeling characterized by structural change, conduction abnormalities, and increased right atrial refractoriness. Also associated with caudal shift of PM
Bolens M and Friedli B 1984 (428) 6720586	**Aim**: EP mapping of sinus and AV nodal function in pts with secundum ASD **Study type**: Case control comparative analysis; 18 pts studied before and after surgical closure	Prior to surgery	Following ASD repair	• Sinus nodal, atrial conduction, atrial refractory and AV nodal refractory times improved following surgery • Ectopic atrial rhythms developed postop in a third of pts
Gillette PC, et al. 1974 (429) 4818151	**Aim**: Electrophysiological examination of atrial, sinus and AV nodal function **Study type**: Prospective observational 16 pts studied following atrial switch surgery (Mustard)		N/A	SND was the primary abnormality detected
Garson A, et al. 1985 (430) 4031302	**Aim**: Identify predictors of death in younger pts (predominantly CHD) and atrial flutter **Study type**: Longitudinal retrospective observational; 380 pts followed long-term for morbidity and mortality		N/A	• Effective control of atrial flutter was associated with improved outcomes • Surgical repair in CHD pts with atrial flutter results in a marked improvement in outcomes
Albin G, et al. 1985 (431) 4033231	**Aim**: SND in young adult pts: treatment by implantation of a PPM **Study type**: Retrospective observational; 39 pts, mean age 23 y; most commonly TGA; mean follow-up of 50.5 mo	No PM-related deaths	N/A	• Permanent pacing is an effective therapeutic modality • Prognosis seems to be excellent • Mortality unrelated to pacing

McLeod CJ, et al. 2010 (432) 20563634	**Aim**: Epicardial versus endocardial permanent pacing in adults with congenital heart disease **Study type**: Retrospective observational; 106 pts and 259 PM procedures: SND in 20%, heart block (25%); followed for 11.6±14 y	Re-intervention was driven primarily by lead failure (49%)	N/A	Epicardial systems were most likely to develop lead failure, predominantly in the ventricular lead
Walker F, et al. 2004 (433) 15145118	**Aim**: Long-term outcomes of cardiac pacing in adults with congenital heart disease **Study type**: Retrospective observational; 168 adults with CHD, and with PMs; mean age at implant was 28 y; mean pacing duration 11 y at follow-up		N/A	Lead complications were not significantly different for epicardial vs. endocardial improved lead survival in pts with endocardial leads
Bink-Boelkens M, et al. 1983 (434) 6869177	**Aim**: Identification of surgical factors which affect the development of bradycardia and arrhythmias **Study type**: Retrospective observational; 204 pts with secundum ASD repair, 50 pts with atrial switch (Mustard)		N/A	Postop atrial flutter is common occurring in 20–40% of the group Damage to the sinus node at surgery was considered a major predictor of SND
Stephenson E, et al. 2003 (435) 14516898	**Aim**: Efficacy of atrial ATP in treating atrial flutter in ACHD pts **Study type:** 5 pts with atrial arrhythmias	AT was appropriately detected and ATP was enabled for 167 treatable episodes, successfully converting 90 (54%)	N/A	Atrial tachycardias in congenital heart disease are amenable to ATP algorithms
Rhodes LA, et al. 1995 (436) 7659551	**Aim**: Atrial ATP in ACHD after repair of congenital heart disease **Study type**: Prospective cohort 18 pts (2–32 y with a variety of antitachycardia congenital heart lesions underwent atrial PM	Over 4–30 mo, 6 pts had 189 episodes of tachycardia successfully converted with atrial ATP	N/A	In selected cases, atrial ATP is a useful tool in the management of pts with congenital heart disease and atrial arrhythmias

	placement for recurrent atrial tachycardia			
Weindling SN, et al. 1998 (284) 9723647	**Study type**: Out of 2,698 cardiac surgeries 54 (2%) were complicated by CHB	Recovery of AV conduction occurred by postoperative d 9 in 97% of pts with transient heart block	The greatest risk for CHB occurred in surgery for: • LVOT • ccTGA • VSD • Tetralogy of Fallot Majority were children	Heart block following surgery for congenital heart disease resolves in 2/3 of pts, usually by the 9th postop day
Ayyildiz P, et al. 2015 (437) 26517970	**Aim**: Evaluation for AVB following pediatric cardiac surgery for CHD **Study type**: Retrospective observational; 1,550 pts with CHD surgery between 2010–2015; median age 0.5–1 y	• Complete AVB occurred (6.2%) in the early postop period • 97% of transient AVB recovered by d 10; 84% at 1 wk	Tetralogy of Fallot and complete AV septal defect are at highest risk	Transient AVB occurred in 12%, and complete AVB in 6% Transient AVB recovered almost entirely by 10 d
Aziz PF, et al. 2013 (438) 23179430	**Aim**: Evaluation for AVB following pediatric cardiac surgery for CHD **Study type**: Retrospective, observational, single center, cohort; pediatric not adult group; 44 pts in this study who experienced TCHB - 37 recovered completely	All 37 subjects with transient heart block recovered AV conduction within 12 d	N/A	Delayed recovery of conduction after transient AVB (≥7 d) is a predictor of late block
Lin A, et al. 2010 (439) 20381087	**Aim**: Evaluation for AVB following pediatric cardiac surgery for CHD **Study type**: Retrospective, observational, single center; 922 pts, median age 6 mo	Postop AVB developed in 2.3% transient, with recovery at mean of 3 d in 1.4% permanent, with PPM implanted at mean 10 d 0.9%	N/A	By 10 d minimal recovery of transient AVB is present

Data Supplement 54. RCTs, Nonrandomized Trials, Observational Studies, and/or Registries of Bradycardia and Pacemaker Implantation in Patients with an Acute MI (Section 8.3)

Study Acronym; Author; Year	Aim of Study; Study Type	Patient Population	Study Intervention / Study Comparator	Primary endpoint results (p values OR or RR; & 95% CI)	Summary/Conclusion Comments
Domenghetti G, et al. 1980 (440) 7363920	**Aim:** Examine impact of acute intraventricular conduction abnormalities on survival following acute MI **Study type:** Retrospective observational	59 pts admitted to CCU – single center	N/A	• IV conduction disturbances • Mortality 13% if AVB present	• Higher mortality in the context of intraventricular conduction abnormalities following an MI. • This was evident short term and long term. • Mortality rate twice the comparator group
Col JJ and Weinberg SL 1972 (441) 5060806	**Aim:** Assess incidence and mortality of conduction defects following AMI **Study type:** Retrospective observational	212 consecutive pts admitted to CCU with MI	N/A	• IV conduction disturbances	• Most common defect was LAH • Mortality rate among those with IV conduction abnormal – 47% vs. 21%
Ritter WS, et al. 1976 (442) 952264	**Aim:** Evaluate prognosis following permanent pacing in pts with trifascicular block following AMI **Study type:** Retrospective observational	18 pts with RBBB, LAH and transient CHB during AMI	Pts who received a PPM	• 5/6 pts w/o PPM died within 2.4 mo of discharge • 6/12 pts with a PPM survived (mean survival 18 mo)	• Prophylactic permanent pacing significantly improves the prognosis after MI in this select subgroup
Lamas GA, et al. 1986 (443) 3717016	**Aim:** Development of a method to predict CHB following AMI **Study type:** Retrospective observational	698 pts with AMI.	N/A	• Pts who developed CHB	• CHB risk score can predict risk of CHB development based on ECG findings.
Shaw, DB et al. 1980 (444) 7357290	**Aim:** Determine the natural Hx for pts with sick-sinus syndrome **Study type:** Prospective survey	381 pts with sinoatrial disease	N/A	• Longitudinal study of pts with sinus node disease	• Sinoatrial dysfunction has a benign prognosis, and PPM implantation did not affect mortality – yet did improve symptoms • Acute MI during this follow-up did not affect

					mortality in a significant manner.
Hindman MC, et al. 1978 (445, 446) 688580 688579	**Aim:** To identify determinants of SCD or recurrent high degree AVB in pts following MI with BBB **Study type:** Retrospective observational	432 pts with AMI and BBB.	N/A	• Mortality	• Pts with progression to 2nd or 3rd degree AV have increased mortality • Pts with transient high degree AVB during MI had a 28% incidence of sudden death or recurrent high degree block during the first year of follow-up • At highest risk were those pts with RBBB and left fascicular block
Ginks WR, et al. 1977 (233) 836733	**Aim:** Assess long-term prognosis of AMI with AVB **Study type:** Retrospective observational	52 pts with CHB and AMI	21 hospital survivors w/o PPM followed for 49 months	• 10 /14 survived w/o PPM • PPM failed to prevent sudden death in 2/4	• Recommendation: PPM implant is not justified in pts with partial bilateral bundle-branch block following AMI
The Birmingham Trial Watson RD, et al. 1984 (231) 6475712	**Aim:** To determine whether permanent pacing reduces mortality in pts with fascicular block ≥14 d post-MI, and whether measurement of intracardiac conduction times predicts later death. **Study type:** RCT **Size:** 50 pts	**Inclusion criteria**: Survived at least 14 d after AMI; RBBB alone or in combination with left anterior or left posterior hemiblock or left posterior hemiblock alone **Exclusion criteria**: Age ≥70 y; previous ECG evidence of conduction disorder, LBBB	**Intervention**: Permanent pacing **Comparator**: No permanent pacing Resting intracardiac conduction times were measured in both groups prior to pacing	**1° endpoint**: No difference in mortality **Safety endpoint**: N/A	• Progression of conduction disease was not observed • Measurement of infranodal conduction time (HV interval) did not predict outcome • Ventricular arrhythmia was an important cause of death
Meine TJ, et al. 2005 (447)	**Aim:** Incidence, predictors, and outcomes of high-	70,742 pts with STEMI compared	N/A	• Incidence of AVB was 6.9%	In the thrombolytic era:

15990751	degree AVB AMI treated with thrombolytics **Study type:** Meta-analysis from 4 studies	with 5,251 pts with STEMI and AVB		• AVB and inferior MI, mortality OR: 2.2 (95% CI: 1.7–2.7) • AVB and anterior MI, mortality OR: 3.0 (95% CI: 2.2–4.1)	• AVB in the setting of STEMI is common • It is associated with higher mortality
Gang UJ, et al. 2012 (448) 22645234	**Aim:** High-grade AVB in STEMI pts treated with PCI **Study type:** Retrospective observational	2073 STEMI pts with primary PCI from Danish National Registry	All-cause mortality was the primary endpoint	• High-grade AVB: 3.2% • Early mortality higher • Yet equal mortality at 30 d compared with pts w/o AVB	In primary PCI era: • incidence of AVB in STEMI pts treated with PCI has been reduced • If pts survive to 30 d: mortality is equal to non-AVB pts
Auffret V, et al. 2016 (449) 26660871	**Aim:** High-grade AVB complicating STEMI (2006–2013) **Study type:** Large prospective registry	6,662 pts with STEMI	N/A	• AVB in 3.5% • AVB at admission or in first 24 h had higher mortality rates (18.1% and 28.6%)	Combine thrombolytic and primary PCI: • HAVB was not independently associated with in-hospital mortality
Kim HL, et al. 2014 (450) 25304975	**Aim:** High-grade AVB on 30-d outcome following AMI in the drug-eluting stent era **Study type:** Retrospective observational	13,862 pts with AMI, registered in the nation-wide AMI database from 2005–2013	N/A	• Heart block occurred in 2.7% • Pts with heart block showed worse clinical parameters at admission, • presence of AVB associated with 30 d MACE in univariate but not multivariate after adjustment	STEMI treated with DES: • Heart block was not an independent risk factor for 30-d MACE in adjusted analyses • LAD culprit was an independent risk factor for 30-d MACE among pts with heart block
Singh SM, et al. 2015 (234) 25205530	**Aim:** High-grade AVB in acute coronary syndromes **Study type:** GRACE registry	59,229 pts with ACS between 1999 and 2007	N/A	• 2.9% of pts had HAVB • High in-hospital death (23%) • Pts with AVB surviving to discharge had similar adjusted survival at 6 mo compared with those w/o AVB	• AVB is continues to decrease • Mortality dictated by type of MI and time to reperfusion
Ranganathan N, et al. 1972 (451) 5009474	**Aim:** Determine the validity of His bundle recordings in managing BBB	20 pts with BBB and 13 pts w/o BBB	EPS	• Abnormal His-Purkinje conduction	• BBB may be associated with infra-nodal conduction abnormalities as evidenced by an abnormal His recording

	Study type: Prospective observational				
Scheinman MM, et al. 1975 (82) 1157275	**Aim:** Use of atropine in pts with acute MI and sinus bradycardia **Study type:** Retrospective observational	56pts with AMI and sinus brady	N/A	• Atropine improved AV conduction in 11 of 13 pts (85%) acute inferior MIs (with 2nd or 3rd degree AVB	• Atropine recommended as drug of choice for sinus brady and AMI • 7 pts developed 10 side effects: VT/VF, ventricular ectopy
Swart G, et al. 1999 (80) 10597081	**Aim:** Use of atropine in acute MI in prehospital setting **Study type:** Retrospective Observational	131 pts with acute MI and associated bradycardia	Atropine	N/A	• No difference in response to atropine between AMI vs. non-AMI pts • MI pts are more likely to recover conduction in hospital
Feigl D, et al. 1984 (160) 6736451	**Aim:** Early and late AVB in acute inferior MI **Study type:** Single center retrospective cohort	34 pts with 2nd or 3rd degree AVB developing in course of AMI who survived >72 h	Atropine	• Of 15 pts with early AVB (<6 h). Atropine normalized conduction in 20%, increased V-rate in others. 5 had normalization with isoproterenol. 14 pts had late AVB – less response to atropine (mean 16 bpm). 50% required TPM	• No adverse events to drug therapy reported
Bertolet BD, et al. 1995 (163) 7661495	**Aim:** Theophylline for the treatment of AVB after MI **Study type:** Single center retrospective cohort	8 pts with significant AVB developing within 4 h of admission for acute inferior MI, resistant to atropine, given IV theophylline up to 250 mg	Aminophylline	• All 8 pts had restoration of 1–1 AV conduction within 3 min lasting at least 24 h	• Potentially safe • Efficacy in very small study
Altun A, et al. 1998 (164) 9789698	**Aim:** Effect of aminophylline in pts with atropine-resistant later advanced AVB during acute inferior MI	8 pts with 2nd or 3rd degree AVB after IMI for at least 1 h, resistant to atropine.	Given 2 doses of aminophylline 240 mg 1 h apart	• Aminophylline restored 1-1 AV conduction in 7 pts and Mobitz I AVB in 1. No adverse effects. AVB relapsed in 1 pt only	• Very small, single-center experience

	Study type: Retrospective observational				
Hatle L, et al. 1971 (167) 5557475	**Aim:** Conservative treatment of AVB in AMI **Study type:** Results in 105 consecutive pts	Pts with acute MI treated with 2nd or 3rd degree AVB	Treated with isoproterenol, generally 1–3 mcg/min	• In hospital mortality 48%. 60 pts received isoproterenol: 38 (63%) had increase in heart rate and BP; 12 (20%) had increased in heart rate but minimal change in BP; 8 (13%) had minimal change; 2 (3%) isoproterenol terminated due to ventricular ectopy. 3 pts had ventricular fibrillation on isoproterenol, 1 of which died. 14 pts treated with TVP, 3 of whom died from ventricular fibrillation	• Extremely high mortality • In this group, isoproterenol appeared safe compared with TVP
Hynes JK, et al. 1983 (115) 6823157	**Aim:** 5-y experience with TPM therapy in the coronary care unit. **Study type:** Retrospective, observational, single-center **Size**: N = 1,022	1,022 pts in the coronary care unit with TTVP.	Temporary transvenous pacing	**1° endpoint:** Clinical outcomes **Results:** Access was antecubital in 59%, subclavian in 17%, right internal jugular in 11%, and femoral in 5%. Complications occurred in 13.7% with no deaths. The right internal jugular approach was associated with a decreased risk of complications.	• TTVP was associated with an overall risk of complications in approximately 14% of pts.
Jowett NI, et al. 1989 (120) 2594596	**Aim:** Temporary transvenous cardiac pacing: 6 y experience in 1 coronary care unit **Study type**: Retrospective, observational, single-center	162 pts admitted to coronary care unit who underwent TTVP.	Temporary transvenous pacing	• The majority of TTVP was for CHB and MI (84.6%). 15.4% of TTVPs were placed for symptomatic bradycardia, including SND. Complications occurred in 19.8%, including arrhythmias during insertion, dislodgement, pneumothorax, and perforation.	• TTVP was associated with a 19.8% complication rate. Some TTVP was prophylactic and may not have been indicated. • A minority of TTVP was performed for SND (15%)
Rotman M, et al. 1972 (452) 4551931	**Aim:** Bradyarrhythmias in AMI	539 pts with acute MI (prethrombolytic and pre-PCI)	Short- and long-term outcomes	• Incidence of sinus bradycardia 26% • 3-fold more frequent in the setting of inferior infarction	• Sinus brady is common • Sinus bradycardia not associated with worse outcomes

	Study type: Retrospective, observational, single-center			• Overall mortality of 539 pts was 20%. • In those pts with sinus bradycardia the mortality was 10%.	

Data Supplement 55. Nonrandomized Data for Predicting Bradycardia Associated with Seizures (Section 8.4.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Bestawros M, et al. 2015 (453) 25391254	**Aim:** Evaluate incidence of ictal asystole **Study type:** Retrospective evaluation of an epilepsy database **Size:** 10 ictal asystole events from 5,312 video-EEG/ECG studies	**Inclusion criteria:** Database searched for pts with ictal asystole defined as RR interval >3s and >2-fold lengthening over the prior RR interval **Exclusion criteria:** None	**1° endpoint:** Ictal asystole **Results:** • 10 pts with 76 seizures with 26 ictal asystole events, 15 of which had associated syncope • Seizure with asystole duration >6 s associated with syncope • All with temporal lobe seizure • 8 pts received a PPM with resolution of syncope	• Permanent pacing can be considered if seizure poorly controlled by drug or surgery
Lanz M, et al. 2011 (454) 21183363	**Aim:** Evaluate incidence of ictal asystole **Study type:** Retrospective **Size:** 2,003 pts undergoing video EEG/ECG studies	**Inclusion criteria:** >3 s **Exclusion criteria:** None	**1° endpoint:** >3 s pause **Results:** • 7/2,003 pts with bradycardia • 1 pt with insular seizure prolonged, the rest were self-limited though durations of 5, 6, 25, 29, 34, 35, and 77 s and from the temporal lobe • Sinus arrest in 3. CHB in 4 • Pacemakers in 6	• No cases of sudden unexpected death in epilepsy with a mean follow-up of 5.6 y
Schuele SU, et al. 2007 (455) 17664402	**Aim:** Evaluate incidence of ictal asystole **Study type:** Retrospective **Size:** 6,825 pts undergoing video EEG/ECG studies	**Inclusion criteria:** >3 s and >2-fold lengthening over the prior RR interval **Exclusion criteria:** None	**1° endpoint:** >3 s pause **Results:** • 10 pts with ictal asystole • 8 temporal • Pacemakers in 6 of 8 pts	• No specific data on response to pacing

Tenyi D, et al. 2017 (456) 27988965	**Aim:** Evaluate incidence of ictal asystole using a systematic review **Study type:** Systematic review **Size:** 157 cases of ictal asystole pts undergoing video EEG/ECG studies	**Inclusion criteria:** >3 s and >2-fold lengthening over the prior RR interval **Exclusion criteria:** None	**1° endpoint:** >3 s pause **Results:** • Localization: ○ Temporal: 80–82% ○ Frontal: 6–10% ○ Insular: 3–5% ○ Other 3–11% • Duration ○ <30 s: 90% ○ >30 s: 10% • Rx: • Pacemaker: 35/68 • Adjusted AED: 25/33 pts who did not receive a PPM • Surgery: 8/33 ○ Rx response: ○ Pacemaker: no asystole falls,14/33 with recurrent seizures, 19/33 w/o recurrent seizures ○ Adjusted AED: 5/23 with recurring asystolic falls, 6/23 with recurrent seizures (w/o asystole), 12/23 w/o recurrent seizures ○ Surgery: ○ No asystolic falls, 2/8 with recurring nonasystolic seizures, 6/8 w/o recurrent seizures	• No specific data on response to pacing

Data Supplement 56. Nonrandomized Data for Device Type (Section 9)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)

Ogunbayo GO, et al. 2017 (457) 28735733	**Aim:** Evaluate incidence of pneumothorax associated with CIED implant **Study type:** Retrospective evaluation of National Inpatient Sample **Size:** 3.7 million people underwent CIED implant	**Inclusion criteria:** Database searched for pts with primary implantation of a CIED with at least 1 vascular access **Exclusion criteria:** None	**1° endpoint:** Pneumothorax **Results:** • Pneumothorax occurred in 1.6% of cases • Pneumothorax associated with increased length of stay and increased mortality (1.2% vs. 0.7%) • Pneumothorax associated with older age, female sex, chronic obstructive lung disease, DC device	• Pneumothorax remains an important complication
Sochala M, et al. 2017 (458) 28598855	**Aim:** Evaluate risk of complication after CIED implant for myotonic dystrophy **Study type:** Retrospective **Size:** 914 pts with myotonic dystrophy Type 1–23 with an ICD and 46 with a PPM	**Inclusion criteria:** Myotonic dystrophy type 1 and CIED placement **Exclusion criteria:** None	**1° endpoint:** Complications **Results:** • After 6-y follow-up device related complications in 9 ICD pts (Inappropriate shocks 5, lead dysfunction 5, infection 2) and 3 PPM pts (lead dysfunction)	• Increased risk of complications with ICD though small numbers
Bai Y, et al. 2017 (459) 28587353	**Aim:** Evaluate incidence of hematoma after CIED **Study type:** Retrospective **Size:** 339 pts from a single center undergoing CIED placement	**Inclusion criteria:** Pts undergoing CIED placement **Exclusion criteria:** None	**1° endpoint:** Hematoma **Results:** • History of allergy associated with hematoma • Hematoma more common with larger devices (ICD and CRT): 30% vs. 8%)	• Larger devices type though do not address vascular access • Only 27 pts with larger device
Hosseini SM, et al. 2017 (460) 28329322	**Aim:** Evaluate complications associated with CRT **Study type:** Retrospective **Size:** 439,010 pts from National Inpatient Sample undergoing CRT	**Inclusion criteria:** CRT device **Exclusion criteria:** None	**1° endpoint:** In-hospital complications **Results:** • 6.1% of pts with at least one complication • Complications more likely in older pts, women, elective admission,	• Increased complication rate over time • No difference between CRT-P and CRT-D

			and increased comorbidities (Charlson)	
Gupta N, et al. 2016 (461) 26961369	**Aim:** Evaluate complications associated different CIED **Study type:** Retrospective-Kaiser database **Size:** 11,924 ICDs, 33,519 PPMs, 4,472 CRT	**Inclusion criteria:** CIED implant **Exclusion criteria:** None	**1° endpoint:** In-hospital complications, 30 d failure rates, outcomes **Results:** • CIED failure ○ PM: 0.85% ○ ICD: 2.17% ○ CRT: 4.93%	• Increased complication rate over time • No difference between CRT-P and CRT-D
Friedman DJ, et al. 2015 (462) 26670062	**Aim:** Evaluate complications associated CRT in pts with moderate renal dysfunction **Study type:** Retrospective-NCDR and matched to Medicare **Size:** 9.525 CRT-D vs. propensity matched ICD only (1,421)	**Inclusion criteria:** CRT eligible pts with stage 3–5 CKD **Exclusion criteria:** None	**1° endpoint:** Mortality, HFH **Results:** • HFH or death: 0.84; 95% CI: 0.78–0.91 • Death: 0.85; 95% CI: 0.77–0.93	• CRT associated with improved outcomes
Witt CT, et al. 2016 (463) 26378089	**Aim:** Evaluate complications associated ICD Rx with CRT **Study type:** Retrospective-single center **Size:** 917 HF pts-427 with NICM and 490 with ICM	**Inclusion criteria:** CRT and HF **Exclusion criteria:** None	**1° endpoint:** Mortality **Results:** • Median follow-up 4 y • Mortality: ○ NICM: 0.96; 95% CI: 0.60–1.51; p=0.85 ○ ICM: 0.74; 95% CI: 0.56–0.97; p=0.03	• ICD associated with better outcomes in ICM but not NICM
Gadler F, et al. 2015 (464) 25336667	**Aim:** Evaluate complications associated with CIED implant **Study type:** Retrospective-multicenter registry (Sweden) **Size:** 6,617 PPM. 1,298 ICD	**Inclusion criteria:** First CIED implant **Exclusion criteria:** None	**1° endpoint:** Complications **Results:** Complications (1 y) • PM: 5.3% • ICD: 10.1%	• ICD associated with higher complication rate

Essebag V, et al. 2015 (465) 25417892	**Aim:** Evaluate complications associated with CRT upgrade vs. de novo implant **Study type:** Subgroup analysis of the Canadian cohort **Size:** Pts with CRT: 644 de Novo and 80 upgrade	**Inclusion criteria:** Randomized to CRT-D **Exclusion criteria:** None	**1° endpoint:** Complications **Results:** Success rate • de Novo: 95% • Upgrade: 96%	• Similar results for CRT-D whether de Novo or as an upgrade
Chung MK, et al. 2014 (466) 25221331	**Aim:** Evaluate mortality associated with different cardiac procedures **Study type:** Retrospective subanalysis **Size:** 1,744 pts with CIED replacement	**Inclusion criteria:** CIED replacement **Exclusion criteria:** None	**1° endpoint:** Complications/mortality **Results:** Mortality due to comorbidities and not device type	• Complications, mortality due to comorbidities
Adelstein E, et al. 2014 (467) 24657426	**Aim:** Evaluate risks and benefits with device upgrades **Study type:** Retrospective subanalysis **Size:** 157 pts	**Inclusion criteria:** Pacemaker dependent with CRT upgrade **Exclusion criteria:** None	**1° endpoint:** Complications/mortality **Results:** Pts w/o CAD had fewer comorbidities, longer survival, and low risk of appropriate shocks	• Better outcomes in the absence of CAD
Kirkfeldt RE, et al. 2014 (468) 24347317	**Aim:** Evaluate risks and benefits with different device types **Study type:** Retrospective subanalysis **Size:** 5,918 pts	**Inclusion criteria:** CIED implant in Denmark **Exclusion criteria:** None	**1° endpoint:** Complications/mortality **Results:** • Overall complication rate was 9.5% • More complex procedures with worse outcomes ○ Dual chamber: 2.0; 95% CI: 1.4–2.7 ○ CRT-D: 2.6; 95% CI: 1.9–3.4	• Complications are relatively common, particularly with complex devices
Acosta J, et al. 2017 (469) 28780194	**Aim:** Evaluate use of defibrillator capabilities in pts who were eligible for CRT **Study type:** Prospective, nonrandomized **Size:** 217 pts	**Inclusion criteria:** Class I indication for CRT and cardiac MRI **Exclusion criteria:** None	**1° endpoint:** Appropriate ICD therapy or SCD **Results:** • 1° endpoint in 11.5% of cases • No 1° endpoint in pts w/o myocardial scar	• MRI may be helpful for identifying those pts at risk for sustained ventricular arrhythmias

			• Scar mass, "channel mass," were predictors of 1° endpoint	
Martens P, et al. 2017 (470) 28716973	**Aim:** Evaluate use of defibrillator capabilities in pts who were eligible for CRT **Study type:** Retrospective **Size:** 687 pts	**Inclusion criteria:** CRT implant **Exclusion criteria:** None	**1° endpoint:** Mortality **Results:** • All-cause mortality was higher in pts with CRT-P vs. CRT-D (21% vs. 12%; p=0.003), even after adjusting for baseline characteristics (HR: 2.5; 95% CI: 1.36–4.60; p=0.003). • Multivariate analysis revealed that age >80 y, New York Heart Association class IV, intolerance to BBs and underlying nonischemic CMP were independently associated with little incremental value of a primary prevention ICD on top of CRT.	• Weighing the risk of arrhythmia and nonarrhythmia risk helpful
Yokoshiki H, et al. 2017 (471) 28626201	**Aim:** Evaluate use of defibrillator capabilities in pts who were eligible for CRT **Study type:** Retrospective **Size:** 717 pts	**Inclusion criteria:** CRT implant **Exclusion criteria:** None	**1° endpoint:** Mortality **Results:** • Combined events for all-cause death or HFH (whichever came first) diverged between the CRT-D (N=620) and CRT-P(N=97) groups with a rate of 22% vs. 42%, respectively, at 24 mo (p=0.0011). • Did not remain statistically significant after controlling for baseline variables	• Weighing the risk of arrhythmia and nonarrhythmia risk helpful

Ip JE, et al. 2017 (472) 28185354	**Aim:** Evaluate ECG suitability of a subcutaneous ICD in pts with PMs **Study type:** Prospective **Size:** 100 pts	**Inclusion criteria:** Transvenous CIED **Exclusion criteria:** None	**1° endpoint:** ECG analysis **Results:** • 58% of pts would still be possible candidates for subcutaneous ICD based on ECG morphology. • RV septal pacing or CRT more likely to qualify vs. RV apical pacing (67% and 80% vs. 37%)	• Transvenous pacing and subcutaneous ICD may be compatible
Maisel WH, et al. 2006 (473) 16639048	**Aim:** Evaluate ICD and PPM malfunction from annual manufacturer FDA reports **Study type:** Retrospective **Size:** 2.25 million PM implants and 416,000 ICDs from 1990–2002; 17,323 explanted due to malfunction	**Inclusion criteria:** Manufacturer report for explant **Exclusion criteria:** None	**1° endpoint:** Device failures, deaths **Results:** • Battery/capacitor abnormalities (4,085 malfunctions [23.6%]) and electrical issues (4,708 malfunctions [27.1%]) accounted for half of the total device failures. • Overall, the annual ICD malfunction replacement rate was significantly higher than the PM malfunction replacement rate (mean [SD]: 20.7 [11.6] vs. 4.6 [2.2] replacements per 1,000 implants; p<0.001; rate ratio, 5.9; 95% CI: 2.7–9.1]).	• Device malfunction has affected pt healthcare outcomes
Maisel WH, 2006. (474) 16639052	**Aim:** Evaluate ICD and PPM malfunction from published meta-analyses **Study type:** Meta-analyses **Size:** 100 pts	**Inclusion criteria:** ICD or PPM implant **Exclusion criteria:** None	**1° endpoint:** Device failure **Results:** • There were 2,981 PM and 384 ICD generator malfunctions. • Morphology Overall, the mean annual ICD malfunction rate was about 20-fold higher than the PM malfunction rate (26.5 [3.8] vs1.3 [0.1] malfunctions per 1000 person-y; p<0.001).	• CD failures more common than PM failures

Maron BJ, et al. 2007 (412) • 17652294	**Aim:** Evaluate appropriate ICD use in HCM **Study type:** Retrospective **Size:** 506 pts with ICD	**Inclusion criteria:** Multicenter Registry of pts with HCM receiving an ICD **Exclusion criteria:** NR	**1° endpoint:** ICD treated VT/VF **Results:** • Appropriate ICD therapy: • Primary prevention: 3.6%/y • Secondary prevention: 10.6%/y Similar event rates for 1,2, or 3 risk factors for SCD	• Presence of any risk factor sufficient to confer risk
Sochala M, et al. 2017 (458) 28598855	**Aim:** Evaluate arrhythmias in pts with myotonic dystrophy **Study type:** Retrospective **Size:** 914 pts with 23 pts with an ICD matched with 46 pts with a PPM	**Inclusion criteria:** Myotonic dystrophy **Exclusion criteria:** Matched	**1° endpoint:** Arrhythmias (bradycardia, tachycardia), complications **Results:** • Over a 6-y follow-up period, we observed device-related complications in 9 ICD recipients (inappropriate shocks in 5, lead dysfunction in 5, infection in 2) and in 3 PM recipients (lead dysfunction in 3). Pts with an ICD had, compared to those with a PM, higher rates of complications (39.1% vs. 6.5%; p=0.0006) and more frequent complications requiring hospitalization and/or re-intervention (respectively 30.4% and 21.7% vs. 0%).	• ICD associated with higher complication rates
Benhayon D, et al. 2015 (475) 25546341	**Aim:** Evaluate arrhythmias in pts with myotonic dystrophy **Study type:** Retrospective **Size:** 37 pts	**Inclusion criteria:** Myotonic dystrophy **Exclusion criteria:** None	**1° endpoint:** Arrhythmias (bradycardia, tachycardia) **Results:** • Pts with MD1 were more likely to have evidence of conduction disease abnormalities (40% vs. 8.3%; p=NS) and had a higher all-cause mortality (16% vs. 0%) than those with MD2	• Presence of AV conduction abnormalities in the setting of myotonic dystrophy associated with ventricular arrhythmias

Takaya Y, et al. 2015 (223) 25529542	**Aim:** Evaluate arrhythmias in pts with cardiac sarcoidosis **Study type:** Retrospective **Size:** 53 pts	**Inclusion criteria:** Cardiac sarcoidosis **Exclusion criteria:** None	**1° endpoint:** Arrhythmias (bradycardia, tachycardia) **Results:** • Similar rates of SCD regardless of whether presenting with HF/ventricular arrhythmias or high-grade AVB	• ICD should be considered in all pts with cardiac sarcoidosis
Anselme F, et al. 2013 (275) 23811080	**Aim:** Evaluate arrhythmias in pts with lamin A/C mutation **Study type:** Retrospective **Size:** 47 pts	**Inclusion criteria:** Lamin A/C mutation **Exclusion criteria:** None	**1° endpoint:** Arrhythmias (bradycardia, tachycardia) **Results:** • 21 pts received an ICD for severe conduction disorders • Among ICD recipients, no pt died suddenly and 11 (52%) pts required appropriate ICD therapy during a median follow-up of 62 mo.	• ICD should be considered in all pts with lamin A/C mutations
Ha AH, et al. 2012 (206) 22385162	**Aim:** Evaluate arrhythmias in pts with myotonic dystrophy **Study type:** Retrospective **Size:** 226 pts	**Inclusion criteria:** Myotonic dystrophy **Exclusion criteria:** None	**1° endpoint:** Arrhythmias (bradycardia, tachycardia) **Results:** • Pacemakers or defibrillators were implanted in 14% of all pts, including 65% of pts with severe ECG abnormalities. • During 57±46 mo, 13 pts died (1.16%/y), including 3 pts who died suddenly, 2 of whom had normally functioning PMs.	• Pts with PM may have sudden cardiac death
Bhakta D, et al. 2012 (209) 22035077	**Aim:** Evaluate arrhythmias in pts with myotonic dystrophy **Study type:** Retrospective **Size:** 406 pts	**Inclusion criteria:** Myotonic dystrophy **Exclusion criteria:** None	**1° endpoint:** Arrhythmias (bradycardia, tachycardia) **Results:**	• Pts with PM may have sudden cardiac death

			• 46 (11.3%) had or received a PM and 21 (5.2%) received an ICD. • 5 (10.9%) PM pts underwent upgrade to an ICD, 3 for LV systolic dysfunction, 1 for VT/VF, and 1 for progressive conduction disease. • 24 (52.2%) PM pts died including 13 of respiratory failure and 7 of sudden death. 7 (33.3%) ICD pts died including 2 of respiratory failure and 3 of sudden death. The pts with ICDs and sudden death all had LV systolic dysfunction and 1 death was documented due to inappropriate therapies.	
Faber TS, et al. 2007 (476) 17636308	**Aim:** Evaluate presence of ventricular arrhythmias in pts with a PPM for bradycardia **Study type:** Retrospective **Size:** 231 pts	**Inclusion criteria:** PPM **Exclusion criteria:** None	**1° endpoint:** Ventricular arrhythmias **Results:** In 54 (25.7%) of 210 pts with at least 1 follow-up, episodes of nonsustained VT were documented by stored ECGs. 1 pt received an ICD	• Pts with PM will have NSVT
Lazarus A, et al. 2002 (207) 12427418	**Aim:** Evaluate arrhythmias in pts with myotonic dystrophy **Study type:** Retrospective **Size:** 49 pts	**Inclusion criteria:** PPM implant **Exclusion criteria:** None	**1° endpoint:** Mortality **Results:** Paroxysmal arrhythmias in 84% of pts	• Arrhythmias particularly in the setting of infraHisian disease associated with arrhythmias

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