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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, amylodiosis, antiarrhythmic drugs, arrhythmia, aortic dissection, aortic valve, asystole, arrhythmia, atrial fibrillation, atrioventricular block, atrine, 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, clobetasol, 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, Lyne 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, T-ray computed, transcatheter aortic valve replacement, transcatheter pacemaker, transesophageal echocardiogram, transient, treatment, vagal, vagally mediated, vagally mediated AV block, ventricular arrhythmia risk, ventricular remodeling

Abbreviations: 1st indicates primary; 2nd, 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; ax, 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,
<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published; PMID</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
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</table>
| 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 | **1ª 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 |
| Thiruganasambamdamothry 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 | **1ª endpoint:** Composite of death, MI, arrhythmias, and “cardiac procedures” over 30 d  
**Results:** 49 serious outcomes including 27 cardiac 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) | **1st 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 EGYS 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 | **1st 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 |
<table>
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<tr>
<th>19 centers participating in main trial</th>
<th>data, presenting ECG and 1-γ follow-up was available</th>
<th>(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.</th>
<th>intraventricular conduction disturbance</th>
</tr>
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<tr>
<td>Exclusion criteria: N/A</td>
<td>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.</td>
<td>• 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.</td>
<td></td>
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Data Supplement 2. Nonrandomized Trials, Observational Studies, and/or Registries of Exercise Stress Testing in Bradycardia and Conduction Disturbances (Section 4.2.2)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published; PMID</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| 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 β-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 VO2 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 |
<table>
<thead>
<tr>
<th>Study type:</th>
<th>Inclusion criteria:</th>
<th>1st endpoint:</th>
<th>Results:</th>
</tr>
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<tr>
<td>Prospective cohort study</td>
<td>Unexplained syncope or presyncope (18 exercise-related, 26 exercise-unrelated)</td>
<td>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&lt;80 mm Hg and/or heart rate&lt;40 bpm)</td>
<td>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&lt;0.05); Specificity =95 and 95% (p=NS); Accuracy =86% and 52% (p&lt;0.05) in exercise-related and exercise-unrelated syncpe respectively.</td>
</tr>
<tr>
<td>Size: 44 pts and 20 normal controls</td>
<td>Structural heart disease, PAF, thyroid disease</td>
<td></td>
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</table>

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

1st 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 syncpe 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.
<table>
<thead>
<tr>
<th>Woelfel AK, et al. 1983 (8)</th>
<th>Study type: Case series</th>
<th><strong>Inclusion criteria:</strong> Pts with exercise-related palpitations or dizziness, or ask 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</th>
<th><strong>1° endpoint:</strong> N/A</th>
<th>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.</th>
</tr>
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</table>
| Boran KJ, et al. 1983 (9) | Study type: Retrospective case series | **Inclusion criteria:** 1) Symptom-limited ECG showing ischemic ST segment changes and intraventricular conduction disturbance. 2) Subsequent coronary angiography | **Exclusion criteria:** N/A | **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 3 V disease. | • 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.  
• 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  
**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:** 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.

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.

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,

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

### 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 - age - HR_{rest}) ÷ (MET_{stage} - MET_{rest}) / (MET_{peak} - MET_{rest})

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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)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published’ PMID</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| 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 | **1st 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  
**1st 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) | • 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. |
| **Study type:** Retrospective observational | **Inclusion criteria:** Review articles and case reports | **1º endpoint:** Relative diagnostic yield of the different monitoring devices | **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 |
| **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 | **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 | **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 |
| Reiffel JA, et al. 2005 (16) 15842970 | **Exclusion criteria:** N/A | | |
Sivakumaran S, et al. 2003 (17) 12867227

<table>
<thead>
<tr>
<th>Study type:</th>
<th>Prospective randomized observational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size:</td>
<td>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)</td>
</tr>
</tbody>
</table>

**Inclusion criteria:** Pts with syncope or pre-syncope referred from all sources for Holter monitor or external loop recorder

**Exclusion criteria:** N/A

**1º 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
| Study type: Retrospective observational | 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 | 1st endpoint: Diagnostic yield of external loop recorder | • 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 | Inclusion criteria: Unexplained syncope or presyncope, referred for pt-activated external loop recorder | 1st endpoint: Diagnostic yield of external loop recorder | • 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 |

Brown AP, et al. 1987 (18) 3663425

| Study type: Retrospective observational | Inclusion criteria: Unselected pts who had undergone pt-activated electrocardiography for up to 3 wk. 42 had undergone prior 24 h Holter of which 17 (40%) were abnormal | 1st endpoint: Diagnostic yield of external loop recorder | • “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 |

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

Exclusion criteria: Incomplete case notes (N=6)

Study type: Retrospective observational

Size: N=39 Derived from first 48 pts referred for pt-activated external cardiac loop recorder

Exclusion criteria: No documented Hx of syncope or presyncope

Study type: Retrospective observational

Size: 100 unselected pts who had Holter. None had an arrhythmia identified as the cause of presenting symptoms, 12 (22%) had arrhythmia excluded as a cause.

Study type: Retrospective observational

Size: 100 unselected pts who had Holter. None had an arrhythmia identified as the cause of presenting symptoms, 12 (22%) had arrhythmia excluded as a cause.

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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. 

| SYNAAR-Flash | Study type: Prospective observational multicenter | 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 | 1st 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 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 |

| Study type: Prospective observational multicenter | 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 | 1st 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 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 |

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| SYNAAR-Flash | Study type: Prospective observational multicenter | 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 | 1st 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 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 |
w/o significant arrhythmia and 6 had symptomatic arrhythmia (all 6 were either bradycardia or conduction disorder)
• Of the 16 ax 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).

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 adhesive patch monitor |
| 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 adhesive patch monitor |

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.
<table>
<thead>
<tr>
<th>Study type: Prospective observational</th>
<th>Inclusion criteria: PAF, referred for Holter monitor as part of clinical management</th>
<th>1(^\circ) endpoint: Comparative diagnostic utility of the 2 devices</th>
</tr>
</thead>
<tbody>
<tr>
<td>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)</td>
<td>Exclusion criteria: 1 potential participant was excluded because the adhesive patch monitor was inadvertently not activated during placement</td>
<td>Results:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 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)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 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±14.2% on adhesive patch monitor (r=0.96; p&lt;0.0001)</td>
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<tr>
<td></td>
<td></td>
<td>• 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</td>
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<td></td>
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<td>Conclusions:</td>
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<td>• 14 d adhesive patch monitoring is a useful tool to refine assessment of PAF, due to the benefits of prolonged monitoring</td>
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<tr>
<td></td>
<td></td>
<td>• 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.</td>
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<td></td>
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<td>• 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).</td>
</tr>
<tr>
<td>Study type:</td>
<td>Cross-sectional retrospective observational</td>
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<tr>
<td>Size:</td>
<td>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)</td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td>Consecutive pts referred for first-time, clinically indicated Zio Patch monitor</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>Excluded data from repeated or subsequent studies</td>
<td></td>
</tr>
</tbody>
</table>

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

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<table>
<thead>
<tr>
<th>Study type:</th>
<th>Retrospective observational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>Referred for clinically</td>
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</tbody>
</table>

1° endpoint: Diagnostic yield

Results:
- Early evaluation of new technology at the time
<table>
<thead>
<tr>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>1st endpoint</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective, multicenter</td>
<td>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.</td>
<td>Confirmation or exclusion of a probable arrhythmic cause of their symptoms</td>
<td>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.</td>
</tr>
<tr>
<td>Prospective observational</td>
<td>≥1 episode of unexplained syncope</td>
<td>Utility of external loop recorder after indeterminate Holter</td>
<td>Early study of external loop recorder in syncope that suggests utility, but</td>
</tr>
<tr>
<td>Prospective observational</td>
<td>York 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%; &lt;18 y; inability to complete or comply with protocol</td>
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</table>

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

Linzer M, et al. 1990 (26) 2371954

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.
| **Framingham**  
Schneider JF, et al.  
1979 (27)  
[154870]  |
<table>
<thead>
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<tbody>
<tr>
<td><strong>Study type:</strong> Prospective observational community-based study</td>
</tr>
<tr>
<td><strong>Size:</strong> 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</td>
</tr>
</tbody>
</table>
| **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 |

<table>
<thead>
<tr>
<th><strong>Size:</strong> N=57 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exclusion criteria:</strong> Prior EPS</td>
</tr>
</tbody>
</table>
| **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 |

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- 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)

<table>
<thead>
<tr>
<th>Framingham Schneider JF, et al. 1980 (28) 7350871</th>
<th>Study type: Prospective observational community-based study</th>
<th>Inclusion criteria: New RBBB</th>
<th>1st 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)</th>
<th>Strengths: Large population-based study with lengthy follow-up and rigorous data collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>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</td>
<td>Exclusion criteria: Extant RBBB (N=16) at first visit</td>
<td>Results: Mean age at Dx of RBBB=60 y (38–77) Prevalence increased with age At all ages &lt;70 y, RBBB more common in men than women 70% of cases of RBBB associated with antecedent CVD, most commonly HTN (60%)</td>
<td>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</td>
</tr>
<tr>
<td>Conclusion:</td>
<td></td>
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</table>

© 2018 American College of Cardiology Foundation, American Heart Association, Inc., and the Heart Rhythm Society.
• 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 QRS >130 ms and LAD (frontal plane axis: -45°—90°) identified those with RBBB Most likely to have underlying CV abnormalities
<table>
<thead>
<tr>
<th>Framingham</th>
<th>Study type: Prospective observational community-based study</th>
<th>Inclusion criteria: New LBBB or RBBB</th>
<th>1º 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)</th>
<th>Strengths: Large population-based study with lengthy follow-up and rigorous data collection</th>
</tr>
</thead>
</table>
| Schneider JF, et al. 1981 (29) | 6452050 | Exclusion criteria: Extant L (N=17) or R (N=16) BBB at first visit | 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) | 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 |

- 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=N5 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)
• 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

**Conclusion:**

• 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.

<table>
<thead>
<tr>
<th>Study type:</th>
<th>Longitudinal prospective community-based study</th>
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<tbody>
<tr>
<td>Size:</td>
<td>N=855</td>
</tr>
<tr>
<td>Study design:</td>
<td>Longitudinal prospective community-based study</td>
</tr>
</tbody>
</table>
| 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 |
| 1st 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 LBB near 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 who develop RBBB. |
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)
- Those who develop BBB (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.

<p>| 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 |
| 1st 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&lt;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&lt;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 (&lt;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. |</p>
<table>
<thead>
<tr>
<th>Study type: Case-control</th>
<th>Inclusion criteria:</th>
<th>1st endpoint: Incidence and mortality of LBBB</th>
<th>Strengths:</th>
<th>Limitations:</th>
<th>Conclusion:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size:</strong></td>
<td>Atomic bomb survivors in Hiroshima and Nagasaki, Japan, participants in biennial health exams (including CXR and ECG) from 1958–2002</td>
<td></td>
<td>Large population-based study with lengthy follow-up and rigorous data collection</td>
<td>Although larger than Framingham study, still a limited number of cases of incident LBBB to analyze</td>
<td>Incident LBBB is independently predictive of CHF-related mortality (RR &gt;3) but not all-cause mortality</td>
</tr>
<tr>
<td>N=17,361 (6,663 men) screened</td>
<td>LBBB at initial exam (N=9) Controls with PPM or AF (no cases of LBBB had AF)</td>
<td></td>
<td>40-y follow-up</td>
<td>Lack of echo or cath data may underestimate the prevalence of underlying CMP or valvar heart disease</td>
<td>Incident LBBB is associated with antecedent or coincident markers of</td>
</tr>
</tbody>
</table>
| Framingham Dhingra R, et al. 2006 (33) 16585411 | **Study type:** Prospective, longitudinal, community-based study | **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.

**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

**1º 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

<table>
<thead>
<tr>
<th>Study type:</th>
<th>Retrospective cross – sectional study</th>
</tr>
</thead>
</table>
| 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. |
| 1º 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 |
<p>| Conclusion: | ECG abnormalities are “poorer predictors of heart disease in asx apparently healthy men than in hospital or clinic populations.” |</p>
<table>
<thead>
<tr>
<th>Study type: Prospective, observational cohort study</th>
<th>Study type: Prospective observational cohort study</th>
<th>Study type: Prospective observational cohort study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size: N=29</td>
<td>Size: N=66,450 (1,739 with BBB, of which 708 had clinical evidence of CV disease)</td>
<td>Size: N=66,450 (1,739 with BBB, of which 708 had clinical evidence of CV disease)</td>
</tr>
<tr>
<td>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</td>
<td>Derived from 68,133 participants in the Women’s Health Initiative study with interpretable ECG</td>
<td>Derived from 68,133 participants in the Women’s Health Initiative study with interpretable ECG</td>
</tr>
<tr>
<td><strong>Inclusion criteria:</strong> 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</td>
<td><strong>Inclusion criteria:</strong> Participants in the Women’s Health Initiative with interpretable ECG</td>
<td><strong>Inclusion criteria:</strong> Participants in the Women’s Health Initiative with interpretable ECG</td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong> 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</td>
<td><strong>Exclusion criteria:</strong> No available electronic ECG (N=960)</td>
<td><strong>Exclusion criteria:</strong> No available electronic ECG (N=960)</td>
</tr>
<tr>
<td><strong>1st endpoint:</strong> Death, including sudden death during follow-up, association of ECG findings antecedent to the Dx of LBBB with the development of subsequent LBBB</td>
<td><strong>1st endpoint:</strong> CHD-related and all-cause mortality associated with L and R BBB</td>
<td><strong>1st endpoint:</strong> CHD-related and all-cause mortality associated with L and R BBB</td>
</tr>
<tr>
<td><strong>Results:</strong></td>
<td><strong>Results:</strong></td>
<td><strong>Results:</strong></td>
</tr>
<tr>
<td>• Mean age at entry=30.8 y.</td>
<td>• Mean follow-up=14.2 y</td>
<td>• Mean follow-up=14.2 y</td>
</tr>
<tr>
<td>• Average follow-up=29 y</td>
<td>• Avg. age=63 y; 10% African American</td>
<td>• Avg. age=63 y; 10% African American</td>
</tr>
<tr>
<td>• Only 1 case of LBBB present at entry</td>
<td>• 19% had h/o CVD or ECG evidence of prior MI</td>
<td>• 19% had h/o CVD or ECG evidence of prior MI</td>
</tr>
<tr>
<td>• 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)</td>
<td>• 2.6% BBB (714 LBBB, 832 RBBB, 122 NSIVCD, 71 RBBB with LAFB)</td>
<td>• 2.6% BBB (714 LBBB, 832 RBBB, 122 NSIVCD, 71 RBBB with LAFB)</td>
</tr>
<tr>
<td>• Only the prevalence of LVH was significantly different from the population free of incident LBBB (14% vs. 3.5%; p&lt;0.05)</td>
<td>• 18% with BBB died</td>
<td>• 18% with BBB died</td>
</tr>
<tr>
<td>• Risk of SCD: 6/29 (20.7%) was &gt;10 fold higher than in those w/o LBBB (1.6%); p&lt;0.01</td>
<td>• 8% with LBBB had fatal CHD events</td>
<td>• 8% with LBBB had fatal CHD events</td>
</tr>
</tbody>
</table>

**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.

**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.
| 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 | 1º 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 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  
**1º 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) | • 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. |
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.

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**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.

**1st 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  
**Exclusion criteria:**  
N/A

- Definitive acute MI with either STE or new/ presumed to be new LBBB  
- 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)

**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

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**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:**  
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

**1st 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) | Median age: STE=60 [interquartile range 51.0, 71.0], nLBBB=74.0 [63.0, 82.0]; p<0.0001 | Insufficient angiographic data to distinguish AMI with LBBB vs. other causes of biomarker elevation in the setting of LBBB |
| • Subsequent admissions in those with multiple admissions (only the index admission was used; N=79) | • Missing ECG data or isolated posterior MI (N=160) | • 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) |
| • 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) | No data on pre-existing LBBB prior to incident AMI |
| • Unadjusted all-cause in-hospital mortality: nLBBB compared to STEMI (13.3% vs. 5.6%; p<0.0001) | 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 |
### Framingham

**Dhingra R, et al. 2005 (42)**

| **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)

**1st 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)

| **Study type:** Prospective case-control study |
| **Size:** N= 300 |

**Inclusion criteria:** Consecutive inpatients referred for echocardiographic assessment of LV systolic function

**1st 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

<table>
<thead>
<tr>
<th>Mendu ML, et al. 2009 (44) 19636031</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study type:</strong> Retrospective observational</td>
</tr>
<tr>
<td><strong>Size:</strong> N=2106 consecutive admissions for 1920 individuals ≥65 y admitted following syncope from 7/2002 to 12/2006</td>
</tr>
<tr>
<td><strong>Inclusion criteria:</strong> ≥65 y admitted following syncope</td>
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<tr>
<td><strong>Exclusion criteria:</strong> Documented pre-syncope, 103 cases omitted for complete lack of data</td>
</tr>
<tr>
<td><strong>1st endpoint:</strong> Diagnostic yield of a broad spectrum of clinical assessments</td>
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</tbody>
</table>
| **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 institution
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 | **Inclusion criteria:** All pts admitted to a university teaching hospital due to syncope over a 7 mo period | **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 |

| Sarasin FP, et al. 2002 (46) 12231593 | **Study type:** Prospective observational with 18 mo-follow-up | **Inclusion criteria:** Syncope with clinical suspicion of cardiac valve disease or unexplained syncope after Hx, physical and ECG | **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-up |

**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.

| 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 |

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)

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

those w/o evidence of cardiac disease on initial evaluation

Dagres N, et al. 2013 (47)

24280765

Study type: Descriptive survey of member institutions of the EHRA EP research network

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%)
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- 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
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<tr>
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<th>Inclusion criteria:</th>
<th>1st endpoint:</th>
<th>Strengths:</th>
<th>Limitations:</th>
<th>Conclusions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Badheka AO, et al. 2013 (48) 23726176</td>
<td>Retrospective cohort study on prospectively collected data from NHANES III</td>
<td>NHANES III enrollee with available ECG data</td>
<td>Describe the relationship between QRSd on routine ECG and CV mortality</td>
<td>• Large representative cross section of US population (part of a cohort of 72,062,796 in NHANES III). • Prospectively acquired data</td>
<td>Increased QRSd in general and LBBB and RBBB specifically are all associated with increased risk of risk-adjusted CV death.</td>
</tr>
<tr>
<td>Study type:</td>
<td>Inclusion criteria:</td>
<td>1st endpoint:</td>
<td>Strengths:</td>
<td>Limitations:</td>
<td>Conclusions:</td>
</tr>
<tr>
<td>Secondary analysis of a prospective, observational, cohort study</td>
<td>Presented to a single, large urban teaching hospital emergency department with syncope</td>
<td>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</td>
<td>• Busy ED with 55,000 annual visits • Prospectively acquired data • 99% follow-up • Assessed current clinical practice (tests ordered according to clinical suspicion)</td>
<td>• Observational • Testing not ordered systematically (not all pts had all tests)</td>
<td>• Mean age was 57.2 ± 24.5 y • Female: 64% • Admitted to hospital: 60.2%</td>
</tr>
</tbody>
</table>
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)

**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:** 1° 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)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published’</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mendu ML, et al. 2009 (44)</td>
<td>Study type: Retrospective observational</td>
<td>Inclusion criteria: ≥65 y. admitted following syncope</td>
<td>1° endpoint: Diagnostic yield of a broad spectrum of clinical assessments</td>
<td></td>
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<tr>
<td></td>
<td>Size: N=2106 consecutive admissions for 1920 individuals ≥65 y admitted following syncope</td>
<td>Exclusion criteria: Documented pre-syncope, 103 cases omitted for complete lack of data</td>
<td>Results: • 163 (8.5%) had &gt;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</td>
<td>• 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.</td>
</tr>
<tr>
<td>Recchia D, et al.1995 (45)</td>
<td>Study type: Retrospective observational</td>
<td>Inclusion criteria: All pts admitted to a university teaching hospital due to</td>
<td>1° endpoint: Dx yield of echo beyond that provided by Hx, physical, and ECG</td>
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<td>• Limitations: Small sample size, test ordering at the discretion of the clinicians, did not address the...</td>
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<tr>
<td>Study type: Prospective observational with 18-mo follow-up</td>
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<tr>
<td><strong>Size:</strong> N=128</td>
<td><strong>Size:</strong> N=128</td>
<td><strong>Size:</strong> 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.</td>
<td><strong>Size:</strong> 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.</td>
<td></td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong> Syncope of known cause, presyncope, obvious seizure, referred for EPS</td>
<td><strong>Exclusion criteria:</strong> Syncope of known cause, presyncope, obvious seizure, referred for EPS</td>
<td><strong>Exclusion criteria:</strong> Those presenting with syncope who did not complete the standardized evaluation (105) or refused to participate (33)</td>
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<tr>
<td><strong>Inclusion criteria:</strong> Syncope with clinical suspicion of cardiac valve disease or unexplained syncope after Hx, physical and ECG</td>
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<tr>
<td>• 48/128 (37.5%) had a cause of syncope identified. Of these 37/48 (77%) were diagnosed by Hx, physical and ECG.</td>
<td>• 48/128 (37.5%) had a cause of syncope identified. Of these 37/48 (77%) were diagnosed by Hx, physical and ECG.</td>
<td>• 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</td>
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</tr>
<tr>
<td>• 82/128 (64%) underwent echo</td>
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<td>• 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)</td>
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</tr>
<tr>
<td>• 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)</td>
<td>• 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)</td>
<td>• 71/155 (46%) had “abnormal but not-relevant” echo findings that include clinically relevant findings such as severe MR, moderate PH, moderate MS, LVH</td>
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</tr>
<tr>
<td>• Echo confirmatory in 48% of those with suspected heart diseases and refuted it in 52%</td>
<td>• Echo confirmatory in 48% of those with suspected heart diseases and refuted it in 52%</td>
<td>• Echo provided no etiology of syncope that was unsuspected on clinical grounds</td>
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<tr>
<td><strong>1st endpoint:</strong> Diagnostic yield of echo, either confirming a suspected Dx or revealing an unexpected one</td>
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<tr>
<td><strong>Conclusions</strong></td>
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</tr>
<tr>
<td>• 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.</td>
<td>• 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.</td>
<td>• Echo is unlikely to yield a clinically unexpected etiology of syncope in those w/o evidence of cardiac disease on initial evaluation</td>
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<tr>
<td>• 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</td>
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</tbody>
</table>

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)

1st 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)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMALS</td>
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<tr>
<td>Brodsky M, et al. 1977 (51) 65912</td>
<td>Study type: Prospective observational – 24h Holter</td>
<td>Inclusion criteria: Healthy, Caucasian, male medical students, age 23–27 y with sinus bradycardia &lt;40 bpm is common in healthy young men (none trained athletes),</td>
<td>1° endpoint: Define rates of arrhythmia on 24 h Holter in normal young Caucasian men</td>
<td></td>
</tr>
<tr>
<td>Study type:</td>
<td>Prospective observational – 24 h Holter</td>
<td>Inclusion criteria: Healthy middle age and older volunteers (40–79 y). 65% male. Mean age: male =53 y; female =56 y</td>
<td>1° endpoint: Establish norms for mean 24 h heart rate, minimal HR, and pauses</td>
<td>Results:</td>
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<tr>
<td>Size: 260</td>
<td>normal exam, ECG, cardiac silhouette on CXR, and echo</td>
<td>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○</td>
<td>• 50% marked sinus arrhythmia • 24% SB &lt;40 bpm at least once/night • 28% &gt;1.75 s pause • 4% pause &gt;2 s • 8% 1° AVB (1/2 exclusively nocturnal. 1/2 both d and night) • 6% type 1 2nd degree AVB-virtually all nocturnal</td>
<td>Pauses &gt;2 s and type 1 second-degree AVB are uncommon (4%–6%)</td>
</tr>
<tr>
<td>Bjerregaard P, 1983 (52) 7160388</td>
<td>Study type: Prospective observational – 24 h Holter</td>
<td>Inclusion criteria: Healthy middle age and older volunteers (40–79 y). 65% male. Mean age: male =53 y; female =56 y</td>
<td>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)</td>
<td>• 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 • &lt;1% had pause &gt;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 &lt;40 bpm) • Males, non-smokers, and physically active had lower mean and minimal HR by ANOVA (no p value reported). Age differences NS.</td>
</tr>
<tr>
<td>Clarke JM, et al. 1976 (53) 74472</td>
<td>Study type: Prospective observational, 2 separate 24 h Holter</td>
<td>Inclusion criteria: Healthy volunteers (16–65 y) with normal clinical exam, ECG, and biochemical/hematologic screening</td>
<td>1° endpoint: Describe the distribution and frequency of arrhythmias in 2 separate 24 h Holter monitors in healthy subjects (41 male, 45 female)</td>
<td>Results:</td>
</tr>
</tbody>
</table>
### Table 1: Bradyarrhythmias in Healthy Elderly Adults

<table>
<thead>
<tr>
<th>Study</th>
<th>Size</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>1° endpoint</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fleg JL, et al. 1982 (54) 7056104</td>
<td>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.</td>
<td>Participates in the Baltimore Longitudinal Study on Aging  &gt;60 y  No CV Hx or sx  No systemic illness  NL exam  BP &lt;160/95  NL CXR  No MI, atrial abnormality, LVH, RVH or BBB on ECG  NL PFT  NL ETT  No meds affecting heart rate/rhythm</td>
<td>8/38 had abnormal thallium  1/38 had abnormal echo  3 technically unsatisfactory Holter</td>
<td>Describe frequency and distribution of arrhythmias in healthy elderly adults</td>
<td>Marked SB (heart rate &lt;40 bpm): 2/98 (2%)  Sinus pause &gt;1.5 s: 2/98 (2%). No pause &gt;2 s  2nd degree AVB: 1/98 (1%)  All bradyarrhythmias occurred during sleep</td>
<td>Healthy, active elderly individuals screened for significant cardiac and pulmonary disease manifest rare nocturnal bradyarrhythmias (1–2%)</td>
</tr>
<tr>
<td>Meytes I, et al. 1975 (55) 1163436</td>
<td>126</td>
<td>Athletes from Israeli national teams</td>
<td>N/A</td>
<td>Frequency of conduction disturbances on awake 12-lead ECG after 15 min. of resting recumbency</td>
<td>11/126 (8.7%) 1st degree AVB (P-R ≥0.21 s)</td>
<td>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.”</td>
</tr>
</tbody>
</table>
• 3/126 (2.4%) type I 2\textsuperscript{nd} 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 2\textsuperscript{nd} degree AVB on awake routine ECG

| Study type: Prospective observational – Nocturnal Holter | \begin{itemize} \item \text{Inclusion criteria:} \begin{itemize} \item \text{≥5 y of intensive physical training} \item Normal clinical exam \item No “changes” in resting 12-lead ECG \item \text{H/O CV disease or other disease known to affect the CV system} \item \text{CXR findings other than those associated with athletic heart} \item “Permanently” under medication \item Taking meds at the time of the study \item Smoker \item URI within 1 mo of the study \end{itemize} \item \text{Exclusion criteria:} \begin{itemize} \item \text{H/O CV disease or other disease known to affect the CV system} \item \text{CXR findings other than those associated with athletic heart} \item “Permanently” under medication \item Taking meds at the time of the study \item Smoker \item URI within 1 mo of the study \end{itemize} \item \text{1\textsuperscript{st} 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 \item \text{Results:} \begin{itemize} \item 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) \item 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 \item 1\textsuperscript{st} 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 1\textsuperscript{st} degree AVB exclusively during sleep \item Type 1 2\textsuperscript{nd} 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 2\textsuperscript{nd} degree AVB exclusively during sleep \item AVN Wenckebach and SB with junctional or idioventricular escape rhythm are both fairly common in young male athletes (≥20%) and occur primarily while asleep. \item AVN Wenckebach is infrequent in untrained young men (<6%) and occurs exclusively while asleep. \item SB with junctional or idioventricular escape rhythm and type 2 second-degree AVB are exceedingly rare in untrained healthy young men. \end{itemize} \end{itemize} | |}
<table>
<thead>
<tr>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>1st endpoint</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northcote RJ, et al. 1989 (57)</td>
<td>Prospective observational – 48 h Holter</td>
<td>• Age &gt;45 y (mean =56±7) • &gt;25 y regular running • &gt;25 miles/wk</td>
<td>In this older cohort of distance runners, bradycardia and AVB was more common than in previously studied younger cohorts of athletes</td>
</tr>
<tr>
<td>Size: 20 male Scottish veteran runners and 20 age-matched sedentary male controls</td>
<td>Exclusion criteria: • Smoking • Medications • Hx CV disease.</td>
<td>Result:</td>
<td>• Bradydcardia and AVB are more frequent in distance runners than in healthy, active age-matched controls and predominantly nocturnal in both groups</td>
</tr>
<tr>
<td>1st Degree AVB (PR &gt;220 ms) Athletes: 6/20 (30%) Controls: 0/20 (0%)</td>
<td>Type 2 2nd Degree AVB Athletes: 4/20 (20%) Controls: 0/20 (0%)</td>
<td>CHB Athletes: 3/20 (15%) Controls: 0/20 (0%)</td>
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<tr>
<td>Heart rate &lt;35 bpm Athletes: 8/20 (40%) Controls: 1/20 (5%)</td>
<td>Mean nocturnal heart rate Athletes: 51±8.5 bpm Controls: 66±13.2 bpm</td>
<td>Sinus pauses (1.8–15 s) Athletes: 8/20 (40%) – &gt;80% nocturnal Controls: 2/20 (10%)</td>
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</tr>
<tr>
<td>Tilkian AG, et al. 1977 (58)</td>
<td>Prospective observational</td>
<td>1st endpoint: Describe distribution of ECG abnormalities and arrhythmias in middle-aged male athletes detected with resting, exercise, and 48 H ambulatory ECG</td>
<td>In pts with fairly profound OSA, bradycardia and conduction</td>
</tr>
<tr>
<td>Study type</td>
<td>Inclusion criteria</td>
<td>1st endpoint: Describe the distribution and frequency of arrhythmias while awake and asleep in pts with OSA and evaluate the</td>
<td></td>
</tr>
<tr>
<td>Sleep Apnea</td>
<td>OSA identified on PSG. All male. Mean age =44 y (30–60). Mean time in apnea</td>
<td>Would think about generating a table with more specific information about the study design, inclusion and exclusion criteria, and the study results.</td>
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</table>
### 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

### 1st 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 O2 sat threshold of 72% for nocturnal bradycardia which 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

### Confounders
- No AHI reported
- Highly selected population
- Particularly unnatural sleeping environment
- No normal comparator group

### 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

### Exclusion Criteria
N/A

### 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

### Conclusions
- In aggregate, nocturnal arrhythmias 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

### Disturbances
- 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
<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Endpoint 1</th>
<th>Endpoint 2</th>
<th>Results</th>
<th>Conclusions</th>
<th>Confounders</th>
</tr>
</thead>
</table>
| Shepard JW Jr, et al. 1985 (60) 2411477 | age =48 y (19–71 y). 16 women, median age 59 (25–68 y) | Clinically referred males with OSA (apnea index 44±26/h and hypopnea index 1±24/h). Age 55±11 y (range 30–76) | N/A | Determine the relationship between ventricular ectopy and the severity of oxyhemoglobin desaturation during sleep | • Arrhythmias (except for PVCs) seen only with O₂ sat <72% (93% occurred with O₂ 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 | • 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 | • Highly selected population  
• No normal comparator group |
| Hoffstein V, et al. 1994 (61) 7774322 | 48±13 y. BMI 31±7 kg/m² | Consecutive, unselected pts referred for PSG (primarily for snoring). Age 48±13 y. BMI 31±7 kg/m² | N/A | 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. | • Profound SB (heart rate <30 bpm): 10%  
• Sinus pauses (2–13 s): 10%  
• 2nd degree AVB: 6% | • 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 | • Primary data not reported in original study or in subsequent review article. |
<table>
<thead>
<tr>
<th>Study type: Prospective observational - Holter</th>
<th><strong>Inclusion criteria:</strong> 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</th>
<th><strong>1° endpoint:</strong> Describe the incidence of primary cardiac abnormalities in pts with SDB</th>
<th><strong>Confounders</strong></th>
</tr>
</thead>
</table>
| 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 | **Exclusion criteria:** N/A | **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 | • Too few bradycardic events to correlate with AHI or hypoxemia.  
• No data regarding profound bradycardia, sinus pauses, etc |

| Study type: Prospective, cross-sectional, observational | **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 | **Conclusions** |
|---|---|---|---|
| Size: 228 SAS (RDI ≥30) | | **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 |

**70% (X² =9.2; p=0.002); mean O₂ sat <90%: 82%; mean O₂ sat >90%: 40% (X² =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

**SHHS Mehra R, et al. 2006 (63) 16424443**

**Boudoulas H, et al. 1983 (62) 6580372**

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| 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%)
- 1° degree AVB: 1/23 (4.3%)
- Type I 2° 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 2° degree AVN occur infrequently in pts with SAS (<5% each)
- Such bradyarrhythmias are far more common while asleep than awake in this cohort.

**Comments**

|  | • RDI ≥30  
|  | • Comparison group RDI <5  
|  | • Matched for age, sex, race/ethnicity, and BMI (N=338)  

**Exclusion criteria:** BMI <18 or >40 kg/m²  

|  | • 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. non SDB)  
|  | • Sinus pause ≥3 s: 11 vs. 8.6%; p=0.34  
|  | • 1° degree AVB: 25 vs. 22.5%; p=0.49  
|  | • Type I 2° degree AVB: 1.8 vs. 0.3%; p=0.07  
|  | • Type II 2° 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 2° degree AVB was ~15% in the SDB group, however.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>1^st endpoint</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flemons WW, et al. 1993 (65) 8368632</td>
<td>Prospective observational – nocturnal Holter</td>
<td>Completed PSG and Holter overnight. Compared 76 with SAS (AHI &gt;10) vs. no SAS</td>
<td>Describe the frequency and distribution of arrhythmias during sleep in pts with SAS</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Size: 173 /263 consecutive pts referred for PSG and underwent complete PSG and simultaneous Holter</td>
<td>Previous assessment of or treatment for SAS (N=7)</td>
<td>• Median AHI in SAS group =33</td>
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<td>Referred for a specific condition other than SAS (N=9)</td>
<td>• Age of SAS group 48.5±11.3</td>
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<tr>
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<td></td>
<td>Rx for severe psychiatric condition (N=8)</td>
<td>• SAS: 87% male; mean BMI 32.9±6.1</td>
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<tr>
<td></td>
<td></td>
<td>Major medical condition (N=21)</td>
<td>• 26% of SAS had O&lt;sub&gt;2&lt;/sub&gt; sat &lt;80 more than 3% of the study time, 11% has O&lt;sub&gt;2&lt;/sub&gt; sat &lt;70 more than 1 % of the study time, and 4.1% had O&lt;sub&gt;2&lt;/sub&gt; sat &lt;60 more than 1% of the study time (Guilleminault and Shepard)</td>
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<tr>
<td></td>
<td></td>
<td>9 technically inadequate (7 Holter and 2 PSG)</td>
<td>• 2^nd degree AVB: SAS =1.3% (95% CI: 0.4–6.9) vs. No SAS =4.1% (95% CI: 1.6–10.1). p=NS</td>
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<tr>
<td></td>
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<td>14 no show</td>
<td>• Sinus arrest: SAS =5.2% (95% CI: 2.2–12.6) vs. No SAS =1.0% (95% CI: 0.2–5.6) p=NS</td>
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<tr>
<td></td>
<td></td>
<td>3 Intercurrent illness</td>
<td>• 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</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>1 declined to participate</td>
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<td></td>
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</tbody>
</table>

**EFFECT OF CPAP ON ARRHYTHMIAS - OBSERVATIONAL**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>1^st endpoint</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Becker H, et al. 1995 (66) 7812557</td>
<td>Prospective observational</td>
<td>Sleep apnea and Mobitz type 2^nd degree</td>
<td>Describe the frequency and distribution of arrhythmias during sleep in pts with SAS and assess the effect of nCPAP</td>
<td>CPAP effectively suppresses sleep and sleep apnea</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Koehler U, et al. 1998 (67)</th>
<th><strong>Study type:</strong> Prospective observational</th>
<th><strong>Inclusion criteria:</strong> Sleep apnea (AHI &gt;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</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size:</strong> 16</td>
<td><strong>Exclusion criteria:</strong> AVN blocking or AADs</td>
<td><strong>1st endpoint:</strong> 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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Results:</strong></td>
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<tr>
<td></td>
<td></td>
<td>• Mean age=49.6 (±10.4) y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• BMI 36.8 (±7.9) kg/m²</td>
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<tr>
<td></td>
<td></td>
<td>• 13/16 (81.3%) HTN; 0 MI; 2/16 (12.5%) DM; 11/16 (68.8%) LVH by echo; 7/16 (43.8%) COPD</td>
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<tr>
<td></td>
<td></td>
<td>• 651 episodes of HB; 87.9% during REM and 12.1% during stages 1 and 2 non-REM</td>
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<td>• (p&lt;0.001)</td>
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<tr>
<td></td>
<td></td>
<td><strong>Conclusions</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CPAP effectively suppresses sleep apnea associated “heart block” in pts with fairly advanced SA.</td>
</tr>
<tr>
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<td><strong>Comments</strong></td>
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<tr>
<td></td>
<td></td>
<td>• Potential referral bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Non-randomized, observational</td>
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<tr>
<td></td>
<td></td>
<td>• 14/16 subjects were male</td>
</tr>
</tbody>
</table>

**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

**Exclusion criteria:** N/A

**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

**Conclusions**

- CPAP effectively suppresses sleep apnea associated “heart block” in pts with fairly advanced SA.

**Comments**

- Potential referral bias
- Non-randomized, observational
- 16/17 subjects were male

**Study type:** Prospective observational

**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

**1st 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 =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
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- 12/17 (70.6%) manifested no arrhythmia on CPAP
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**Conclusions**

- CPAP effectively suppresses sleep apnea associated “heart block” in pts with fairly advanced SA.

**Comments**

- Potential referral bias
- Non-randomized, observational
- 16/17 subjects were male

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609/651 (93.5%) occurred during apnea/hypopnea with desaturation ≥4% (but no correlation to nadir O₂ 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.

**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)

**1ª 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/m²
- 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
| Harbison J, et al. 2000 (69) 10988177 | **Study type:** Prospective observational | **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. | **1ª 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. |
| | **Size:** 45 consecutive eligible pts from a university hospital’s dedicated sleep disorders unit referred to initiate nCPAP | **Exclusion criteria:** N/A | **Results:**
- 91% male
- Mean age: 50 (SD: 13.1) y
- BMI: 32.7 (SD: 6.0) kg/m²
- 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 |

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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

**ASYX BRADYCARDIA AS A MARKER OF OSA - OBSERVATIONAL**

| 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 axillary bradycardias |
| Inclusion criteria: Referred for PPM for axillary 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:**
- Mediations include beta blocker, digoxin or verapamil.
- None were trained athletes

**1º endpoint:** Prevalence of SAS as indicated by PSG in those with axillary bradycardia and sx suggestive of SAS.

**Results:**
- All had normal resting awake heart rates during all EP clinic visits before and after enrollment
- Bradycardias 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 bradycardia 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**
- Axillary bradycardias 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 axillary 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 bradycardia 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
| European Multicenter Polysomnography Study | **Study type:** Prospective observational cohort study | **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 | **1º 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 | **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 |  
| Garrigue S, et al. 2007 (71) 17353437 | **Size:** 98 consecutive pts with PPM from 11 European centers | **Exclusion criteria:**  
- Recent (<6 mo) MI, USA, or coronary revascularization  
- Permanent atrially paced rhythm | **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/m²  
- 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) | **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. | • 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 |
| • 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) | |
Data Supplement 6. RCTs of Implantable Loop Recorder in Patients With Documented or Suspected Bradycardia or Conduction Disorders (Section 4.3.1)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published; PMID</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2º Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAST</td>
<td>Aim: To find out whether prolonged monitoring strategy is better than conventional strategy in the evaluation of recurrent syncope</td>
<td>Inclusion criteria: Recurrent unexplained syncope or syncope X 1 associated with injury Exclusion criteria: LVEF &lt;35%, &lt;1 y expected survival, unable to provide follow-up or consent, clear NMS</td>
<td>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.</td>
<td>• Dx obtained in 14 of 27 pts (ILR group) vs. 6 of 30 pts (conventional group) (52% vs. 20%; p=0.012)</td>
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<td></td>
<td>Study type: Prospective randomized trial Size: 60 pts</td>
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<tr>
<td>EaSyAS</td>
<td>Aim: Investigate the impact of ILRs on unselected population of syncopal pts presenting to one institution</td>
<td>Inclusion criteria: recurrent syncope but no definitive Dx following initial clinical w/u (including CSM and TTT) Exclusion criteria: Structural heart disease</td>
<td>Interventions: CSM+TTT+implantation of loop recorder (N=103) Comparator: CSM+TTT+conventional investigation (N=98) Mean follow-up 276 d</td>
<td>EKG Dx made: 34 (33%) in ILR group vs. 4 (4%) in conventional group (HR: 8.93; 95% CI: 3.17–25; p&lt;0.0001) • Total medical costs: £406 in ILR group vs. £1210 in conventional group (mean difference £809; 95% CI: 123–2730)</td>
<td></td>
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<tr>
<td></td>
<td>Study type: Randomized trial Size: 201 pts</td>
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<tr>
<td>FRESH</td>
<td>Aim: To compare conventional evaluation vs. early use of ILR in low-risk pts with syncope in France</td>
<td>Inclusion criteria: Any recent unexplained syncope (after basic clinical exam)</td>
<td>Intervention: ILR group (N=39) Comparator: Conventional evaluation strategy group (N=39) F/u 14 mo</td>
<td>• Identification of cause: 18 (46.2%) pts in ILR group vs. 2 (5%) pts in conventional group (p&lt;0.001)</td>
<td>• Quality of life was no different between the 2 groups</td>
</tr>
<tr>
<td><strong>Study type:</strong></td>
<td><strong>Exclusion criteria:</strong></td>
<td><strong>Days of hospitalization:</strong></td>
<td></td>
<td></td>
<td></td>
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<td>----------------</td>
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<td>-----------------------------</td>
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<td></td>
</tr>
<tr>
<td>Prospective open-label randomized multicenter study</td>
<td>Significant heart disease, EF &lt;40%, Hx of MI or unstable CAD, Hx of arrhythmia, family Hx of SCD, conduction disturbance on EKG, HOCM, AS, potentially arrhythmogenic drug use</td>
<td>• Days of hospitalization: 5.7 d in ILR group vs. 8.0 d in conventional group (p=0.55)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Size:</strong> 78 pts</td>
<td></td>
<td>• Number of advanced cardiac tests needed: 0.03/pt in ILR group vs. 0.2/pt in conventional group (p=0.05)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 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)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published; PMID</th>
<th>Study Type/Design; Study Size (N)</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results</th>
<th>Summary/Conclusion; Comments</th>
</tr>
</thead>
</table>
| 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)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| 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:O/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 |
| **Study type**: Observational, retrospective, single center |
| **Inclusion criteria**: Pts presenting to ED with symptomatic bradycardia of <60 bpm |
| **Exclusion criteria**: Asymptomatic bradycardia |
| **1º endpoint**: 30 d mortality |
| **Results**: 107 of 277 pts did well with flat positioning. Of 170 with persisting symptoms, 141 received atropine, 92 catecholamines (oriprenaline 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 |
| **1º 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)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| 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 | **1º 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. |
<p>| Swart, G, et al. 1999 (80) 10597081   | <strong>Study type:</strong> Retrospective observational study of | <strong>Inclusion criteria:</strong> Prehospital pts with hemodynamically | <strong>1º endpoint:</strong> Heart rate response that occurred within | • There were no differences in response to atropine in AMI vs. non-AMI pts with |</p>
<table>
<thead>
<tr>
<th>Study type:</th>
<th>Retrospective observational study of pts with AMI and bradycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size:</td>
<td>N=70</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inclusion criteria:</th>
<th>Pts in early phase of AMI with heart rate &lt;60 bpm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion criteria:</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endpoint:</th>
<th>Mortality</th>
</tr>
</thead>
</table>

| 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.

<table>
<thead>
<tr>
<th>Prehospital, emergency department, and hospital records</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size: 172 pts met criteria, data available for 131; 45 presented with AMI</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unstable bradycardia or AVB who received atropine by EMS.</th>
</tr>
</thead>
</table>

| 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 |

<table>
<thead>
<tr>
<th>1 min following each dose of atropine</th>
</tr>
</thead>
</table>

| 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. |

<table>
<thead>
<tr>
<th>Hemodynamically unstable bradycardia or AVB.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamically unstable AVB was associated with AMI in 55.6% of pts.</td>
</tr>
<tr>
<td>Study type</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Observational, single center</td>
</tr>
<tr>
<td>Size: N=56</td>
</tr>
</tbody>
</table>
## Data Supplement 10. Nonrandomized Trials, Observational Studies, and/or Registries of Isoproterenol Effect in Electrophysiology Laboratory (Section 5.3.2.1)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| 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)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘PrePACE’ Morrison LJ, et al. 2006 (86) 17933452</td>
<td><strong>Aim:</strong> To evaluate the feasibility of a RCT of transcutaneous pacing vs. dopamine for atropine and fluid refractory bradycardia in the prehospital setting.  <strong>Study type:</strong> RCT  <strong>Size:</strong> 151 met criteria, 82 enrolled</td>
<td><strong>Inclusion criteria:</strong> Unstable bradycardia unresponsive to fluid and atropine: heart rate &lt;60/min and systolic BP (SBP) &lt;80 mm Hg; or heart rate &lt;60/min and SBP &lt;100 mm Hg and at least one additional sign/symptom  <strong>Exclusion criteria:</strong> Advance directives, trauma, hyperthermia, hypothermia or cardiac arrest, pts in whom it was not possible to start an intravenous line.</td>
<td><strong>Intervention:</strong> 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  <strong>Comparator:</strong> 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</td>
<td><strong>1° endpoint:</strong> Survival to hospital discharge  <strong>Safety endpoint (if relevant):</strong> Ventricular arrhythmia, cutaneous burns, chest wall discomfort, cardiac arrest, TCP failure.</td>
<td></td>
</tr>
</tbody>
</table>

### 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)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howarth DM, et al. 1994 (87) 7909677</td>
<td><strong>Study type:</strong> Multi-center observational study of CCB</td>
<td><strong>Inclusion criteria:</strong> Admission for CCB overdose  <strong>Exclusion criteria:</strong> N/A</td>
<td><strong>1° endpoint:</strong> Clinical outcome</td>
<td>• Atropine was only effective after IV calcium was administered  • Calcium often reversed hypotension and bradycardia, but...</td>
</tr>
<tr>
<td>Study type:</td>
<td>Study type:</td>
<td>Inclusion criteria:</td>
<td>Exclusion criteria:</td>
<td>1° endpoint:</td>
</tr>
<tr>
<td>------------</td>
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</tr>
</tbody>
</table>
| Retrospective, observational, 3 poison control centers | Hospitalized pts with CCB ingestion | N/A | Clinical outcomes | 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 without 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.

| Systematic review | Studies examining effects of various treatments for CCB poisoning for efficacy. | N/A | Efficacy of treatments for CCB poisoning with primary outcomes of mortality and hemodynamic parameters | 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. |

| Retrospective, observational, single center | Pts presenting with symptomatic bradycardia who received glucagon therapy. | Clinical response to atropine | Clinical improvement in heart rate and perfusion. | 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. |

**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.

**Study type:** Retrospective, observational, 3 poison control centers

- **Results:**
  - Atropine and inotropic support were frequently required.
  - 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.

**Inclusion criteria:** Hospitalized pts with CCB ingestion

**Exclusion criteria:** N/A

**1° endpoint:** Clinical outcomes

- 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 without effect on heart rate.

**Study type:** Systematic review

- **Results:**
  - 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.

**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

- 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.

**Study type:** Retrospective, observational, single center

- **Results:**
  - 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.

- **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.

- 9 pts were receiving BB, CCB, or digoxin therapy. Heart rate and BP increased significantly in all but one pt who received glucagon.
<table>
<thead>
<tr>
<th>Study type: Systematic review</th>
<th>Study type: Systematic review</th>
<th>Study type: Systematic review</th>
<th>Study type: Systematic review</th>
<th>Study type: Systematic review</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size:</strong> N=30 (all animal)</td>
<td><strong>Size:</strong> 216 studies</td>
<td><strong>Size:</strong> 72 studies</td>
<td><strong>Size:</strong> 216 studies</td>
<td><strong>Size:</strong> Prospective, single center, observational</td>
</tr>
<tr>
<td><strong>Inclusion criteria:</strong> Studies evaluating glucagon use in BB and CCB overdose.</td>
<td><strong>Inclusion criteria:</strong> Studies examining effects of various treatments for CCB poisoning for efficacy.</td>
<td><strong>Inclusion criteria:</strong> N/A</td>
<td><strong>Inclusion criteria:</strong> N/A</td>
<td><strong>Inclusion criteria:</strong> Pts with CCB toxicity and hypotension treated with HDIT</td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong> Case report or case series.</td>
<td><strong>Exclusion criteria:</strong> N/A</td>
<td><strong>Exclusion criteria:</strong> N/A</td>
<td><strong>Exclusion criteria:</strong> N/A</td>
<td><strong>1° endpoint:</strong> Pts with CCB toxicity and hypotension treated with HDIT</td>
</tr>
<tr>
<td><strong>1° endpoint:</strong> Effect of glucagon on heart rate, arterial pressure, contractility, cardiac output and survival in BB or CCB overdose.</td>
<td><strong>1° endpoint:</strong> Efficacy of treatments for CCB poisoning with primary outcomes of mortality and hemodynamic parameters</td>
<td><strong>1° endpoint:</strong> Efficacy</td>
<td><strong>1° endpoint:</strong> Efficacy</td>
<td><strong>1° endpoint:</strong> Safety of HDIT in CCB overdose.</td>
</tr>
<tr>
<td><strong>Results:</strong> 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.</td>
<td><strong>Results:</strong> One observational study in humans of HDIT showed improved hemodynamic parameters and decreased mortality with risk of hypoglycemia and hypokalemia.</td>
<td><strong>Results:</strong> 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.</td>
<td><strong>Results:</strong> Observational data demonstrate improved hemodynamics and survival.</td>
<td><strong>Results:</strong> 6/7 pts survived.</td>
</tr>
<tr>
<td>• 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.</td>
<td>• Evidence to support HDIT is of low quality, but validates safety and efficacy in the treatment of BB and CCB toxicity.</td>
<td>• Evidence to support HDIT is of low quality, but validates safety and efficacy in the treatment of BB and CCB toxicity.</td>
<td>• Evidence to support HDIT in CCB overdose is of low quality, but observational data demonstrate improved hemodynamics and survival.</td>
<td>• HDIT in the setting of hemodynamically significant CCB overdose was safe in a critical care setting. Systolic BP was</td>
</tr>
</tbody>
</table>
**Data Supplement 13. RCTs Comparing Anti-Digoxin Fab to placebo (Section 5.3.2.3)**

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2º Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| 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 | **1º 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)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| 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<sup>°</sup> **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<sup>°</sup> **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<sup>°</super> **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<sup>°</sup> **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)  
**Size:** N=26 | **Inclusion criteria:** Pts with life-threatening digitalis toxicity. | 1<sup>°</sup> **endpoint:** Clinical outcome | • Life-threatening digoxin toxicity can be safely and effectively treated with digoxin Fab. |
<table>
<thead>
<tr>
<th>Study type</th>
<th>Exclusion criteria</th>
<th>Results:</th>
<th>Size: N=63</th>
<th>Exclusion criteria: N/A</th>
<th>Results: Reversal of clinical toxicity within 30 min of administration. Digoxin concentration decreased to undetectable. No adverse reactions.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antman EM, et al. 1990 (100) 2188752</td>
<td>Study type: Observational multicenter (21)</td>
<td>Inclusion criteria: Pts with digitalis toxicity and life-threatening cardiac rhythm disturbances or hyperkalemia refractory or likely to be refractory to conventional therapy.</td>
<td>Inclusion criteria: Pts with digitalis toxicity and life-threatening cardiac rhythm disturbances or hyperkalemia refractory or likely to be refractory to conventional therapy.</td>
<td>1° endpoint: Response to therapy.</td>
<td>119/148 resolved all clinical evidence of toxicity, 14 improved, 15 showed no response. 5 pts were on hemodialysis and improved.</td>
</tr>
<tr>
<td>Hickey AR, et al. 1991 (101) 1993775</td>
<td>Study type: Observational, retrospective.</td>
<td>Inclusion criteria: Adults who received digoxin Fab for digitalis intoxication.</td>
<td>Inclusion criteria: Adults who received digoxin Fab for digitalis intoxication.</td>
<td>1° endpoint: Clinical response</td>
<td>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.</td>
</tr>
<tr>
<td>Wenger TL, 1991 (102) 1997017</td>
<td>Study type: observational, retrospective</td>
<td>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.</td>
<td>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.</td>
<td>1° endpoint: Clinical response</td>
<td>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.</td>
</tr>
</tbody>
</table>
Data Supplement 15. Nonrandomized Trials, Observational Studies, and/or Registries of Dialysis for Digoxin Toxicity (Section 5.3.2.3 – Patton)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXTRIP Mowry JB, et al. 2016 (103)</td>
<td>Study type: Systematic review</td>
<td>Inclusion criteria: Use of dialysis in digitalis toxicity</td>
<td>1º 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.</td>
<td>• The workgroup suggested against the use of dialysis in cases of digoxin toxicity, whether or not digoxin Fab was available.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2º Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abu-Laban RB, et al. 2006 (104)</td>
<td>Aim: To determine if administration of aminophylline increases ROSC in bradycardic cardiac arrest</td>
<td>Inclusion criteria: Asystole, or PEA &lt;60 bpm, unresponsive to epinephrine and atropine</td>
<td>Intervention: 250 mg aminophylline IV x2. Comparator: Placebo</td>
<td>1º endpoint: ROSC Safety endpoint (if relevant): N/A</td>
<td>• 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</td>
</tr>
<tr>
<td>Hurley KF, et al. 2015 (105)</td>
<td>Study type: Systematic Review of effects of aminophylline in the treatment of</td>
<td>Inclusion criteria: All randomized trials of aminophylline vs. placebo in adults with</td>
<td></td>
<td>1º endpoint: Survival to hospital discharge.</td>
<td>• Prehospital administration of aminophylline in</td>
</tr>
</tbody>
</table>
### 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)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population Description</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Post-heart Transplant</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
| 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 | **1º 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 | **1º 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 | **1º 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. |                               |
<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heinz G, et al. 1993 (109) 8427182</td>
<td>Pts with and w/o SND after heart transplant</td>
<td>Changes in sinus node recovery time from baseline after aminophylline infusion</td>
<td>Sinus node testing was performed in electrophysiology lab before and after infusion of 6 mg/kg of aminophylline. Aminophylline can improve sinus node function in heart transplant recipients with SND</td>
</tr>
<tr>
<td>Spinal Cord Injury</td>
<td>Pts with severe bradycardia and spinal cord injury</td>
<td>Effects of aminophylline</td>
<td>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</td>
</tr>
<tr>
<td>Pasnoori VR, et al. 2004 (110) 14766019</td>
<td>Pts with severe bradycardia due to spinal cord injury</td>
<td>Heart rate response to theophylline</td>
<td>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.</td>
</tr>
<tr>
<td>Sadaka F, et al. 2010 (111) 20878263</td>
<td>Pts with severe bradycardia due to spinal cord injury</td>
<td>Heart rate response to theophylline</td>
<td>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</td>
</tr>
<tr>
<td>Schulz-Stübner S, 2005 (112) 16301263</td>
<td>Pts with severe bradycardia due to spinal cord injury</td>
<td>Heart rate response to theophylline</td>
<td>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.</td>
</tr>
<tr>
<td>Study Acronym; Author; Year Published</td>
<td>Aim of Study; Study Type; Study Size (N)</td>
<td>Patient Population</td>
<td>Study Intervention (# patients) / Study Comparator (# patients)</td>
</tr>
<tr>
<td>---------------------------------------</td>
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</tr>
<tr>
<td>Smith I, et al. 1994 (76) 7906108</td>
<td><strong>Aim:</strong> To compare the effectiveness in the treatment of intraoperative bradycardia of transesophageal atrial pacing, atropine, and glycopyrrolate <strong>Study type:</strong> RCT <strong>Size:</strong> N=64, of which 45 had treatment for bradycardia</td>
<td><strong>Inclusion criteria:</strong> Men undergoing elective radical prostatectomy with sufentanil/N₂O/vecuronium anesthetic resulting in bradycardia (&lt;50 bpm or &lt;60 bpm and hypotension) <strong>Exclusion criteria:</strong> Pts not ASA status I-II.</td>
<td><strong>Intervention:</strong> 15 pts were randomized to each group. <strong>Comparator:</strong> TAP vs. atropine vs. glycopyrrolate</td>
</tr>
<tr>
<td>Ferguson JD, et.al. 1997 (113) 9217762</td>
<td><strong>Aim:</strong> To compare effectiveness of conventional TTVP with balloon floatation pacing catheters. <strong>Study type:</strong> Randomized, parallel-group trial <strong>Size:</strong> N= 40</td>
<td><strong>Inclusion criteria:</strong> Pts needing TTVP. <strong>Exclusion criteria:</strong> N/A</td>
<td><strong>Intervention:</strong> Balloon flotation pacing catheter. <strong>Comparator:</strong> Conventional TTVP.</td>
</tr>
</tbody>
</table>

Data Supplement 19. Nonrandomized Trials, Observational Studies, and/or Registries of Temporary Transvenous Pacing (TTVP) (Section 5.3.3)
<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Year</th>
<th>Study type</th>
<th>Inclusion Criteria</th>
<th>1st Endpoint</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopez Ayerbe J, et al.</td>
<td>2004 (114)</td>
<td>Retrospective, observational, single-center</td>
<td>Pts who underwent TTVP for symptomatic bradycardia.</td>
<td>Clinical outcomes</td>
<td>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%.</td>
<td>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.</td>
</tr>
<tr>
<td>Hynes JK, et al.</td>
<td>1983 (115)</td>
<td>Retrospective, observational, single-center</td>
<td>Pts in the coronary care unit with TTVP.</td>
<td>Clinical outcomes</td>
<td>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.</td>
<td>TTVP was associated with an overall risk of complications in approximately 14% of pts.</td>
</tr>
<tr>
<td>Murphy JJ, 1996 (116)</td>
<td>8620131</td>
<td>Retrospective, observational, multicenter</td>
<td>Pts undergoing TTVP.</td>
<td>Clinical outcomes</td>
<td>129/194 TTVP were implanted for CHB. Immediate or delayed complications occurred in 68 pts.</td>
<td>TTVP was associated with complications in 35% of pts, including vascular access difficulties, dislodgement, infection, and sepsis.</td>
</tr>
<tr>
<td>Austin JL, et al.</td>
<td>1982 (117)</td>
<td>Retrospective, observational. Single center</td>
<td>Pts who received TTVP.</td>
<td>Complications and malfunction</td>
<td>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.</td>
<td>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</td>
</tr>
<tr>
<td>Munoz Bono JM, et al.</td>
<td>2011 (118)</td>
<td>Prospective, observational</td>
<td>Pts in cardiac intensive care</td>
<td>Clinical indications, morbidity, mortality.</td>
<td>TTVP was associated with a risk of complications in 40%.</td>
<td></td>
</tr>
<tr>
<td><strong>Study type</strong></td>
<td><strong>Inclusion criteria</strong></td>
<td><strong>Exclusion criteria</strong></td>
<td><strong>1^ endpoint</strong></td>
<td><strong>Results</strong></td>
<td><strong>Comments</strong></td>
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<tr>
<td>Prospective, observational, multi-center (S).</td>
<td>Pts requiring TTVP</td>
<td>N/A</td>
<td>Procedural and pt characteristics, outcomes.</td>
<td>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.</td>
<td>TTVP was indicated for SND in 9.3%, and bradycardia from drug intoxication in 12.1%</td>
<td></td>
</tr>
<tr>
<td>Retrospective, observational, single center</td>
<td>Pts admitted to coronary care unit who underwent TTVP.</td>
<td>N/A</td>
<td>Clinical outcomes.</td>
<td>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.</td>
<td>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%)</td>
<td></td>
</tr>
<tr>
<td>Prospective, observational, single center</td>
<td>Pts with bradycardia and conduction disease in the acute setting</td>
<td>N/A</td>
<td>Clinical response and stability.</td>
<td>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.</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Study type</td>
<td>Inclusion criteria</td>
<td>1st endpoint</td>
<td>Results</td>
<td>Notes</td>
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<tr>
<td>Garcia Guerrero JJ, et al. 2010 (122) 20667893</td>
<td>Pts requiring TTVP who underwent novel active fixation femoral TTVP.</td>
<td>Rate of deep venous thrombosis</td>
<td>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.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nolewajka AJ, et al. 1980 (123) 7398027</td>
<td>Pts requiring TTVP.</td>
<td>Femoral vein thrombosis and pulmonary emboli</td>
<td>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.</td>
<td></td>
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</tr>
<tr>
<td>Sodeck GH, et al. 2006 (77) 17212976</td>
<td>Pts presenting to ED with compromising bradycardia</td>
<td>30 d mortality</td>
<td>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</td>
<td></td>
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<tr>
<td>Jou YL, et al. 2010 (124) 20946290</td>
<td>Pts presenting with bradycardia requiring temporary pacing</td>
<td>Clinical characteristics and underlying etiologies</td>
<td>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.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>McCann P, 2006 (125) 17235372</td>
<td>Studies of temporary pacing wires</td>
<td>Complication by access site, outcomes</td>
<td>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</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study type: Observational, prospective, 5 center study</td>
<td>Inclusion criteria: All pts with temporary cardiac pacing wires</td>
<td>1° endpoint: Complications, outcomes</td>
<td>Antibiotics and ultrasound access reduced the risk of complications.</td>
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<tr>
<td>Size: N = 50</td>
<td>Exclusion criteria: N/A</td>
<td>Results: 30% with SND. Permanent pacing required in 60%, repeat procedures in 12%, mortality 18%, bacteremia 6%.</td>
<td>Methodologic limitations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bjornstad CC, et al. 2012 (126) 22390277</td>
<td></td>
<td></td>
<td>High rates of subsequent PPM implantation</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>High rates of complications.</td>
<td></td>
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</tr>
</tbody>
</table>
### Data Supplement 20. RCTs of Transcutaneous Pacing (Section 5.3.3)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2nd Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrePACE Morrison LJ et al. 2006 (86) 17933452</td>
<td><strong>Aim:</strong> To evaluate the feasibility of a RCT of transcutaneous pacing vs. dopamine for atropine and fluid refractory bradycardia in the prehospital setting. <strong>Study type:</strong> RCT <strong>Size:</strong> 151 met criteria, 82 enrolled</td>
<td><strong>Inclusion criteria:</strong> Unstable bradycardia unresponsive to fluid and atropine: heart rate &lt;60 per minute and systolic BP (SBP) &lt;80 mm Hg; or heart rate &lt;60/min and SBP &lt;100 mm Hg and at least one additional sign/symptom <strong>Exclusion criteria:</strong> Advance directives, trauma, hyperthermia, hypothermia or cardiac arrest, pts in whom it was not possible to start an intravenous line.</td>
<td><strong>Intervention:</strong> 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. <strong>Comparator:</strong> 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</td>
<td><strong>1st endpoint:</strong> Survival to hospital discharge <strong>Safety endpoint (if relevant):</strong> Ventricular arrhythmia, cutaneous burns, chest wall discomfort, cardiac arrest, TCP failure.</td>
<td>• Survival to hospital discharge was similar in both groups (70% vs. 69%; p=0.93), as were 2nd outcomes. • Paramedics chose not to enroll 20 pts due to pain concerns. 71% of TCP pts experienced chest discomfort during pacing.</td>
</tr>
<tr>
<td>Barthell E, et al. 1988 (127) 3056132</td>
<td><strong>Aim:</strong> To determine if prehospital cardiac pacing affects mortality <strong>Study type:</strong> RCT <strong>Size:</strong> N=239; 226 pulseless (asystole and EMD); 13 with hemodynamically significant bradycardia</td>
<td><strong>Inclusion criteria:</strong> Pts with hemodynamically significant bradycardia <strong>Exclusion criteria:</strong> N/A</td>
<td><strong>Intervention:</strong> Transcutaneous pacing <strong>Comparator:</strong> ACLS</td>
<td><strong>1st endpoint:</strong> Survival to hospital admission (21.4% in pacing group vs. 20.6%) and survival to discharge (6.8% vs. 4.4%) <strong>Safety endpoint:</strong> None</td>
<td>• 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)</td>
</tr>
</tbody>
</table>

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

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

© 2018 American College of Cardiology Foundation, American Heart Association, Inc., and the Heart Rhythm Society.
<table>
<thead>
<tr>
<th>Study type: Systematic review of the efficacy of transcutaneous pacing in the management of symptomatic bradycardia and bradyasystolic arrest in the prehospital setting</th>
<th>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.</th>
<th>1° endpoint: Survival to hospital discharge</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sherbino J, et al. 2006 (128) 16814446</td>
<td>Aims: To determine the importance of hemodynamic status and effect of prehospital transcutaneous pacing in pts with symptomatic bradycardia</td>
<td>Inclusion criteria: Witnessed CV decompensation and initial bradycardia</td>
<td>1° endpoint: Survival to hospital discharge. Safety endpoint: N/A</td>
</tr>
<tr>
<td>Hedges JR, et al. 1991 (129) 1721129</td>
<td>Aim: To determine the importance of hemodynamic status and effect of prehospital transcutaneous pacing in pts with symptomatic bradycardia</td>
<td>Exclusion criteria: N/A</td>
<td>• 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 &lt;80 mm Hg, change in mental status, angina, or pulmonary edema; the relevance to acute SND is therefore unclear. • Survival to hospital discharge showed a trend towards improvement in the pacing group (15% vs. 0%; p=0.07)</td>
</tr>
</tbody>
</table>
### Zoll PM, et al., 1985 (130) 3886190

**Aim:** To evaluate the effectiveness of external noninvasive TCP  
**Study type:** Prospective, observational, multicenter (3)  
**Size:** N=51  
**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

**Aim:** Emergency room pts with hypotension and bradycardia  
**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.

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

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published; PMID</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| ADEPT Lamas GA, et al. 2007 (132) 17765608 | To determine whether DDDR pacing improves QOL when | **Inclusion criteria:** Age ≥21 y, Class I or 2A indication for pacing, demonstrated chronotropic incompetence, | 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

THEOPACE

**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)

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**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)**

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| Sasaki Y, et al. 1988 (134) 2462243 | Long-term follow-up of pts with SSS | **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
<table>
<thead>
<tr>
<th>Study</th>
<th>Significance of asx bradycardia for subsequent PM implantation and mortality in pts age &gt;60 y</th>
<th>Inclusion criteria: Age &gt;60 y, resting heart rate &lt;55 bpm (bradycardia group, N=470) or heart rate between 60–70 bpm (control group, N=2,090)</th>
<th>Results:</th>
<th>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&lt;0.01)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldberger JJ, et al. 2011 (135) 21757182</td>
<td>Significance of asx bradycardia for subsequent PM implantation and mortality in pts age &gt;60 y</td>
<td>Exclusion criteria: PPM implantation within 2 wk of initial EKG, heart rate outside the above range Mean follow-up 7.2 ± 2.9 y</td>
<td>Incidence of PPM placement: 9% in bradycardia cohort vs. 5% in control group; p&lt;0.001</td>
<td>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 (&lt;1%/y) of subsequent PPM implantation. Asymptomatic bradycardia has no adverse impact on all-cause mortality and may even be protective.</td>
</tr>
<tr>
<td>Denniss AR, et al. 1992 (75) 1572741</td>
<td>Electrophysiologic studies in pts with unexplained syncope</td>
<td>Inclusion criteria: Unexplained syncope, prior general medical evaluation (H&amp;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</td>
<td>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&lt;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&lt;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&lt;0.05) No recurrent syncope in 27 pts treated with PPM vs. recurrent syncope in 20 of 84 pts (24%) not given PPM (p&lt;0.05)</td>
<td>Diagnostic yield of EPS is increased in pts with heart disease. Pts with no heart disease had no mortality.</td>
</tr>
<tr>
<td>Teichman SL, et al. 1985 (136) 4025122</td>
<td>The value of EPS in syncope of undetermined origin: Report of 150 cases</td>
<td>Inclusion criteria: Pts with syncopal and near-syncopal events (SUO) unexplained after general physical examination.</td>
<td>EP abnormality that could explain SUO was demonstrated in 36% of pts</td>
<td>Presence of organic heart disease increased the incidence of positive EPS finding.</td>
</tr>
</tbody>
</table>
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)**

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published; PMID</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2º Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| 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  
**Comparator:** DDDR pacing programmed to | **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) | • 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)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published: PMID</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| **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) |
<table>
<thead>
<tr>
<th>MOST</th>
<th>Lamas GA, et al. 2002 (141) 12063369</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aim:</strong></td>
<td>To compare DC vs. ventricular only pacing to treat pt with clinically significant bradycardia due to SND</td>
</tr>
<tr>
<td><strong>Inclusion criteria:</strong></td>
<td>≥21 y old, in SR, undergoing DC PPM implant for symptomatic SND</td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong></td>
<td>Serious concurrent illnesses</td>
</tr>
<tr>
<td><strong>Intervention:</strong></td>
<td>Dual chamber PPM programmed DDDR and programmed to LR limit of ≥60 bpm (N=1,014)</td>
</tr>
<tr>
<td><strong>Comparator:</strong></td>
<td>Dual chamber PPM programmed VVIR and programmed to LR limit of ≥60 bpm (N=996)</td>
</tr>
<tr>
<td><strong>Results:</strong></td>
<td>• Death or nonfatal stroke occurred in 21.5% of DDDR pts vs. 23.0% of VVIR pts (p=0.48)</td>
</tr>
<tr>
<td></td>
<td>• 31.4% (313) of pts in the VVIR group was crossed over to DDDR group</td>
</tr>
<tr>
<td></td>
<td>• 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)</td>
</tr>
<tr>
<td></td>
<td>• 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)</td>
</tr>
<tr>
<td></td>
<td>• Combined clinical endpoint (death, stroke or HF) 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)</td>
</tr>
<tr>
<td></td>
<td>• DDDR pacing resulted in better improvement in QOL as compared with VVIR pacing.</td>
</tr>
<tr>
<td></td>
<td><strong>Adverse events:</strong> Total 30 d rate of complication 4.8% (1.8% A-lead issue, 1.5% pneumothorax, 1.1% V-lead issue)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CTOPP</th>
<th>Connolly SJ, et al. 2000 (142) 10805823</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aim:</strong></td>
<td>To assess whether physiologic pacing or ventricular pacing is better for pts with symptomatic bradycardia</td>
</tr>
<tr>
<td><strong>Inclusion criteria:</strong></td>
<td>≥18 y old</td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong></td>
<td>Chronic AF, s/p AV nodal ablation, life expectancy &lt;2 y</td>
</tr>
<tr>
<td><strong>Intervention:</strong></td>
<td>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)</td>
</tr>
<tr>
<td><strong>Comparator:</strong></td>
<td>VVI pacing (N=1,474)</td>
</tr>
<tr>
<td><strong>Results:</strong></td>
<td>• PPM indications: 60% AVB, 42% SND</td>
</tr>
<tr>
<td></td>
<td>• 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)</td>
</tr>
<tr>
<td></td>
<td>• Subgroup analysis showed that pt with SND received no particular benefit from physiologic pacing compared to VVI pacing</td>
</tr>
<tr>
<td></td>
<td>• 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)</td>
</tr>
<tr>
<td></td>
<td>• 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)</td>
</tr>
<tr>
<td></td>
<td>• Annual rate of stroke was 1.1% for VVI pacing vs. 1.0% for physiologic pacing</td>
</tr>
</tbody>
</table>
## SAVE PACe

**Sweeney MO, et al. 2007 (143)**

**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 with in 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:** More common in physiologic pacing group primarily due to atrial lead complications

## DANPACE

**Nielsen JC, et al. 2011 (138)**

**Aim:** To compare the efficacy of AAIR vs. DDR 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:** DDR 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)
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>SND subgroup</th>
<th>ADS subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Healey JS, et al. 2006 (144) 16801463</strong>&lt;br&gt;<strong>DANISH Andersen HR, et al. 1994 (145) 7983951</strong>&lt;br&gt;<strong>MOST sub-study Sweeney MO, et al. 2003 (146) 12782566</strong></td>
<td><strong>To determine whether atrial-based pacing (AAI or DDD) prevents MACE as compared to VVI pacing in pts with bradycardia</strong>&lt;br&gt;<strong>To determine whether single chamber atrial or ventricular pacing is better in pts with SSS</strong>&lt;br&gt;<strong>To examine the effect of pacing-induced ventricular desynchronization in pts with SND and normal QRSd</strong></td>
<td><strong>Publications since 1980, randomized controlled parallel design, have pt level data on outcomes</strong>&lt;br&gt;<strong>Post cardiac surgery or AV node ablation pts, multi-site A or V pacing, follow-up &lt;6 mo</strong>&lt;br&gt;<strong>Symptomatic bradycardia &lt;50 bpm or pause &gt;2 s</strong>&lt;br&gt;<strong>SND, SR at the time of assignment, baseline QRSd &lt;120 ms</strong></td>
<td><strong>Studies including pts who were AAI or DDD paced (atrial-based) pacing</strong>&lt;br&gt;<strong>Studies including pts who were VVI paced (ventricular-based) pacing</strong>&lt;br&gt;<strong>Single chamber atrial pacing (only if 1:1 AV conduction at atrial pacing rate of 100bpm) (N=110)</strong>&lt;br&gt;<strong>Single chamber ventricular pacing (N=115)</strong>&lt;br&gt;<strong>DDD pacing (N=707)</strong>&lt;br&gt;<strong>VVI pacing (N=632)</strong></td>
<td><strong>Overall mortality: ABP vs. VVI pacing (HR 0.92; 95% CI 0.81–1.05; p=NS)</strong>&lt;br&gt;<strong>Entire group:</strong>&lt;br&gt;• AF: ABP vs. VVI pacing (HR: 0.80; 95% CI: 0.72–0.89; p=0.00003)&lt;br&gt;• Stroke: ABP vs. VVI pacing (HR: 0.81; 95% CI: 0.67–0.99; p=0.035)&lt;br&gt;• Implant complication rate: ABP 6.2% vs. VVI pacing 3.2%</td>
<td><strong>LA diameter increased by more in the ventricular (p=0.0001) group vs. the atrial group (p=0.037) compared with preop values</strong>&lt;br&gt;• 2 pts in the atrial group developed AVB<strong>Adverse events:</strong>&lt;br&gt;• More common in atrial group (most common, lead dislodgement) than ventricular group (most common, PPM syndrome)</td>
</tr>
<tr>
<td>Study type: Post-hoc analysis of RCT</td>
<td>Exclusion criteria: Baseline QRSd &gt;120 ms</td>
<td>Median follow-up 33.1 mo compared to &lt;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 &gt;80% of time as compared to &lt;80% of time was associated HR: 2.50 (p=0.0012)</td>
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<tr>
<td>Nielsen JC, et al. 2003 (147) 12932590</td>
<td>Inclusion criteria: SSS, normal AV conduction, symptomatic bradycardia &lt;40 b symptomatic QRS pause of &gt;2 s, age&gt;18 y</td>
<td>Intervention 1: AAIR (N=54)</td>
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<tr>
<td>Aim: To present a long-term outcome of initial DANPACE trial</td>
<td>Exclusion criteria: BBB, AVB, chronic AF, cerebral disease, planned cardiac or major surgery, cancer</td>
<td>Intervention 2: DDDR with short AV delay (&lt;150 ms) (DDDR-s) (N=60)</td>
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<tr>
<td>DANPACE Brandt NH, et al. 2016 (148) 28039212</td>
<td>Intervention 3: DDDR with fixed long AV delay (300 ms) (DDDR-I) (N=63)</td>
<td>Intervention 4: 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)</td>
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<tr>
<td>Study type: Long-term follow-up of RCT</td>
<td>Mean follow-up 2.9 y</td>
<td>Comparator: DDDR pacing programmed to LR of 60 ppm AND to minimize V pacing (N=688)</td>
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<tr>
<td>Size: 177 pts</td>
<td>LA diameter increased significantly in both DDDR groups (p&lt;0.05)</td>
<td>Mean follow-up 8.9 y</td>
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<tr>
<td>Size: 1,384 pts</td>
<td>LVES diameter increased significantly in both DDDR groups (p&lt;0.05)</td>
<td>All-cause mortality: 59.3% AAIR vs. 53.3% DDDR (HR: 1.03; 95% CI: 0.90–1.19; p=0.65)</td>
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<tr>
<td>Size: 1,339 pts</td>
<td>LVED diameter increased significantly in DDDR-I group (p&lt;0.01)</td>
<td>• AF incidence at follow-up: AAIR 7.4%, DDDR-s 23.3%, DDDR-I 17.5% (p=0.03)</td>
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<tr>
<td>Size: 177 pts</td>
<td>LVFS decreased significantly in DDDR group (p&lt;0.01)</td>
<td>Stroke: AAIR 5.6%, DDDR-s 11.7%, DDDR-I 6.3% (p=0.32)</td>
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<tr>
<td>Size: 1,384 pts</td>
<td>Percent Vp: 90% in DDDR-s vs. 17% in DDDR-I</td>
<td>Death: AAIR 16.7%, DDDR-s 23.3%, DDDR-I 22.2% (p=0.51)</td>
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<tr>
<td>Size: 1,339 pts</td>
<td>• LA diameter increased significantly in both DDDR groups (p&lt;0.05)</td>
<td>CV death: AAIR 7.4%, DDDR-s 11.7%, DDDR-I 14.3% (p=0.43)</td>
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<tr>
<td>Size: 177 pts</td>
<td>• LVES diameter increased significantly in both DDDR groups (p&lt;0.05)</td>
<td>• Stroke: AAIR 5.6%, DDDR-s 11.7%, DDDR-I 6.3% (p=0.32)</td>
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<tr>
<td>Size: 1,384 pts</td>
<td>• LVED diameter increased significantly in DDDR-I group (p&lt;0.01)</td>
<td>• Death: AAIR 16.7%, DDDR-s 23.3%, DDDR-I 22.2% (p=0.51)</td>
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<td>Size: 1,339 pts</td>
<td>• LVFS decreased significantly in DDDR group (p&lt;0.01)</td>
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<tr>
<td>Size: 177 pts</td>
<td>• Percent Vp: 90% in DDDR-s vs. 17% in DDDR-I</td>
<td>• Stroke: AAIR 5.6%, DDDR-s 11.7%, DDDR-I 6.3% (p=0.32)</td>
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<tr>
<td>Size: 1,384 pts</td>
<td>• Death: AAIR 16.7%, DDDR-s 23.3%, DDDR-I 22.2% (p=0.51)</td>
<td>• CV death: AAIR 7.4%, DDDR-s 11.7%, DDDR-I 14.3% (p=0.43)</td>
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</tbody>
</table>
### 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 MHR (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
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Intervention 1</th>
<th>Comparator</th>
<th>Intervention 2</th>
<th>Comparator</th>
<th>Follow-up</th>
<th>Findings</th>
</tr>
</thead>
</table>
| 15246645      | To compare conventional evaluation vs. early use of ILR in low-risk pts with syncope in France | Any recent unexplained syncope (after basic clinical exam)                         | ILR group (N=39) | Conventional evaluation strategy group (N=39) | DDR PPM programmed to lower rate of 60–70 ppm and prolonged AV delay (N=36) | No treatment (N=35) | Mean follow-up 276 d | Identification of cause: 18 (46.2%) pts in ILR group vs. 2 (5%) pts in conventional group (p<0.001) |}
| THEOPACE      | To prospectively assess the effects of PPMs and theophylline in pts with SSS | Age ≥45 y, mean resting sinus rate <50 bpm and/or intermittent SA block, symptoms attributable to SND | Oral theophylline 550 mg/d (N=36) | No treatment (N=35) | PPM programmed to lower rate of 60–70 ppm and prolonged AV delay (N=36) | 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) | Quality of life was no different between the 2 groups | Thromboembolism: 3 (9%) theophylline, 3 (9%) PPM, 1 (3%) 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)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenneback G, et al. 2007 (149) 17255148</td>
<td>Study type: Single-center, prospective cohort (Sweden) <strong>Size:</strong> N=17 (53% men), mean age 77 y</td>
<td><strong>Inclusion criteria:</strong> 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. <strong>Exclusion criteria:</strong> Valve surgery in past year, permanent AF</td>
<td><strong>1° endpoint:</strong> Recurrence of AVB detected by PM algorithm over 2 y <strong>Results:</strong> 9/12 pts (75%) with QRS &gt;120 ms and 1/5 pts (20%) developed recurrent AVB. 6/17 pts (35%) developed atrial tachyarrhythmias requiring AAD tx</td>
<td>• Appropriate to place PPM in pts with AVB and QRS &gt;120 ms w/o further delay or evaluation.</td>
</tr>
<tr>
<td>Knudsen MB, et al. 2013 (150) 23869746</td>
<td>Study type: Single-center, retrospective cohort (Denmark) <strong>Size:</strong> N=55 (55% male, mean age 77 y)</td>
<td><strong>Inclusion criteria:</strong> Pts admitted with 2/3 AVB, had temporary wire, were on class II-IV AADs or digoxin. <strong>Exclusion criteria:</strong> No ECG documentation, AVB due to other identified cause, prior PPM explant, died within several days</td>
<td><strong>1° endpoint:</strong> Need for PPM; complications of TPM <strong>Results:</strong> 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</td>
<td>• 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”</td>
</tr>
<tr>
<td>Osmonov D, et al. 2012 (151) 22530749</td>
<td>Study type: Single-center retrospective cohort (Turkey) <strong>Size:</strong> N=108 (16% of all 668 pts admit with 2/3 AVB). 30/108 (28%) had AF with SVR</td>
<td><strong>Inclusion criteria:</strong> All pts admitted with 2/3 AVB who were on AV nodal blocking drugs 2008–9 <strong>Exclusion criteria:</strong> MI, electrolyte disturbances, digoxin toxicity, vasovagal syncope</td>
<td><strong>1° endpoint:</strong> Resolution/ recurrence AVB, need for PPM <strong>Results:</strong> 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.</td>
<td>• 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</td>
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<tr>
<td>Study type</td>
<td>Inclusion criteria</td>
<td>1° endpoint</td>
<td>Notes</td>
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<tr>
<td>Single-center retrospective cohort (Israel)</td>
<td>All pts admitted with 2/3 AVB 1999–2003.</td>
<td>Resolution/recurrence AVB, need for PPM</td>
<td>Overall, only 15% of pts with AVB on nodal blocking drugs had AVB “caused by drugs”</td>
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<tr>
<td>Retrospective single-center/region cohort study (Denmark)</td>
<td>All pts referred for urgent PPM in 2009</td>
<td>d to implant, complications during wait</td>
<td>Pt harm results from delay to PPM for capacity issues.</td>
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<tr>
<td>Retrospective single-center cohort (Spain)</td>
<td>Consecutive pts with “reversible” 3rd degree AVB not undergoing initial PPM implant</td>
<td>Persistence/recurrence of AVB, PPM implant</td>
<td>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</td>
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<tr>
<td>Multi-center US national prospective cohort</td>
<td>All pts in US receiving anti-digoxin Fab fragments</td>
<td>Resolution of symptoms of digoxin toxicity</td>
<td>No separate analysis of AVB pts</td>
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<tr>
<td>Study</td>
<td>Study type</td>
<td>Size</td>
<td>Inclusion criteria</td>
<td>1° endpoint</td>
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<tr>
<td>Sadek MM, et al. 2013 (155) 23623644</td>
<td>Systematic review</td>
<td>N=717; 40% men, mean age 74 y</td>
<td>English language, original outcome data on pts with cardiac sarcoidosis tx with steroids.</td>
<td>Reversal or improvement in AVB</td>
</tr>
<tr>
<td>Kandolin R, et al. 2011 (156) 21427276</td>
<td>Single-center retrospective cohort (Finland)</td>
<td>N=133; 72 pts with unexplained AVB</td>
<td>Pts. 18–55 y who had PPM implant for unexplained 2nd/3rd-degree AVB</td>
<td>Dx of cardiac sarcoidosis; reversal of AVB with treatment.</td>
</tr>
<tr>
<td>Ozcan KS, et al. 2012 (157) 22738687</td>
<td>Single-center retrospective cohort (Turkey)</td>
<td>N=50 (29 hypothyroid, 21 hyperthyroid)</td>
<td>All pts. with 2nd/3rd degree AVB who had hyper- or hypothyroidism</td>
<td>Persistent AVB despite treatment of thyroid abnormalities</td>
</tr>
<tr>
<td>Forrester JD, et al. 2014 (158) 24879781</td>
<td>Systematic review of case reports and case series</td>
<td>34 manuscripts reporting 45 cases</td>
<td>English language case reports or series in peer-reviewed journal of pts with Lyme disease and ECG-documented 3rd degree AVB</td>
<td>Outcomes, need for PPM, persistence of AVB</td>
</tr>
<tr>
<td>Van der Linde, MR, 1991 (159) 1947815</td>
<td>Review of published case reports in Europe and North</td>
<td>Published case reports 1977–90,</td>
<td></td>
<td>Outcome, resolution of AVB, need for PPM</td>
</tr>
<tr>
<td>Study Acronym; Author; Year Published</td>
<td>Aim of Study; Study Type; Study Size (N)</td>
<td>Patient Population</td>
<td>Study Intervention (# patients) / Study Comparator (# patients)</td>
<td>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</td>
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| 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) | • 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 | **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 |
<table>
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<tr>
<th>Study Acronym; Author; Year Published</th>
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<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| 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 | |
### Study Types, Inclusion Criteria, and Endpoints

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<tr>
<th>Study</th>
<th>Type</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>1st Endpoint</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
</table>
| 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 | 1st 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 | 1st 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 |
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 | 1st 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 | 1st 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 |
<table>
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<th>Study type</th>
<th>Inclusion criteria</th>
<th>1st endpoint</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-center case series in United Kingdom</td>
<td>Pts with atropine-resistant AVB with acute inferior MI treated with streptokinase. All had hypotension</td>
<td>Restoration of 1-1 AV conduction</td>
<td>1-1 AV conduction restored promptly with resolution of hypotension in all</td>
<td>No controls, Very small case series</td>
</tr>
<tr>
<td>Single center case series in US</td>
<td>Pts presenting with symptomatic bradycardia resistant to atropine 1 mg who received IV glucagon 1–7 mg then 3–5 mg/h</td>
<td>Improvement in bradycardia and hemodynamics</td>
<td>All pts improved at least transiently</td>
<td>Most pts had BBs and/or CCBs as significant co-factors, Unknown how many had AVB</td>
</tr>
<tr>
<td>Single center cohort undergoing invasive EP study in US</td>
<td>42 pts with heart disease undergoing invasive EPS w/o and with isoproterenol</td>
<td>Improvement in AV conduction and change in ventricular rate</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Single center prospective cohort from Norway</td>
<td>Pts with acute MI treated 1966–1970 with 2nd or 3rd degree AVB treated with isoproterenol, generally 1–3 mcg/min</td>
<td>Improvement in heart rate</td>
<td>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</td>
<td>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</td>
</tr>
</tbody>
</table>

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

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<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| 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 |
<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| 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 | **1º 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 | **1º 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 | **1º 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 |
<table>
<thead>
<tr>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>1° endpoint</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahapatra S, et al. 2005 (171)</td>
<td>Pts undergoing PPM 1995–2003 with perforation and new effusion.</td>
<td>Risk factors for perforation after PPM. 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)</td>
<td>Suggests benefit to avoiding TVP prior to permanent pacing unless essential</td>
</tr>
<tr>
<td>Winner S and Boon N, 1989 (173)</td>
<td>Consecutive pts referred to regional center for PPM</td>
<td>Complications, defined as “major problems”: dislodgement, infection, pericarditis/perforation, thrombosis, wire in left ventricle</td>
<td>Advise avoiding TVP before PPM unless absolutely necessary</td>
</tr>
<tr>
<td>Size: 266 pts/ 158 (59%) had temporary TVP</td>
<td>Results: 36% rate of major problems, much higher rate at smaller referral hospitals. 6% infection; 30% failure to pace, 4% pericarditis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>López Ayerbe J, et al. 2004 (114) 15544753</td>
<td></td>
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<tr>
<td><strong>Study type:</strong> Retrospective single center cohort in Barcelona, Spain</td>
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<tr>
<td><strong>Inclusion criteria:</strong> Pts receiving TVP 1997–2003. All via femoral route (99%) with fluoroscopic guidance</td>
<td></td>
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</tr>
<tr>
<td><strong>Exclusion criteria:</strong> Pts transferred out with no available f-u (N=38)</td>
<td></td>
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</tr>
<tr>
<td>1° endpoint: Complications, outcomes</td>
<td></td>
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</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Complication rates improved compared with series from 1980s and 1990s (18–43%)</td>
<td></td>
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<tr>
<td>Lower use in pts with acute MI seen</td>
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</tr>
</tbody>
</table>

| Size: N=530; mean age 74 y, 54% male; 51% AVB. |

| Size: N=50; 45% AVB; mean age 79 y, 62% male |

| Study type: Prospective regional 5 hospital study in Norway 2010–11. |
| **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 |

| Study type: Systematic review 1973–2004 |
| **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 |

| Size: 15 studies; N=3737; mean age 71 y |

| Study type: Single center retrospective cohort in Taiwan 2002–8 |
| **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 |

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<table>
<thead>
<tr>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective single-center cohort at academic medical center in Denmark 2000–11.</td>
<td>Pts getting TVP wire 2000–11 who had AVB and potential culprit drug discontinued</td>
<td>Indication for PPM despite drug discontinuation; complications and outcomes</td>
<td>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</td>
</tr>
<tr>
<td>Prospective cohort in 18 hospitals in Northern England over 6 mo</td>
<td>All TVP implants in 18 hospitals.</td>
<td>Complications</td>
<td>Immediate complications in 12/194 (6%) – VT/VF in 6, arterial puncture (3), pneumothorax (2), brachial plexus injury (1). Late comp in 22/194 (11%) – VT/VF 10, definite/possible sepsis in 10 (5.2%) – almost all had TVP&gt;48 h. 38/194 (20%) needed repositioning. Total comp 35%. 11/194 (5.5%) died within 1 h of procedure. 56/194 (29%) had PPM</td>
</tr>
<tr>
<td>Single-center nonrandomized controlled study.</td>
<td>Consecutive pts requiring TVP 2003–2010. Pts underwent TVP guided by echo (N=53) or fluoroscopy (N=53) based on operator preference.</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Study type: Non-randomized prospective controlled study comparing externalized active-fixation lead vs. standard temporary TVP wire</td>
<td>Inclusion criteria: Pts with systemic infection requiring VVI pacing &gt;48 h</td>
<td>Exclusion criteria: None stated</td>
<td>1° endpoint: Implant success, pacing thresholds, acute complications, dislodgement rate</td>
</tr>
<tr>
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<tr>
<td>Braun MU, et al. 2006 (175) 16923004</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>de Cock CC, et al. 2003 (176) 12765453</td>
<td>Study type: Non-randomized single-center comparison of TVP by femoral route with active vs. passive fixation wire in Netherlands 1998–2001</td>
<td>Inclusion criteria: Consecutive pts requiring TVP at single center requiring prolonged temporary pacing (&gt;48 h) – mean 6 d</td>
<td>Exclusion criteria: None stated</td>
</tr>
<tr>
<td>Kawata H, et al. 2013 (177) 23482613</td>
<td>Study type: Single center retrospective cohort study of temp active fix lead (TPPM) after lead extraction at UCSD</td>
<td>Inclusion criteria: 23/47 pts undergoing extraction for CIED infection who were PM-dependent 2010–12</td>
<td>Exclusion criteria: None stated</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>1st endpoint</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chihrin SM, et al. 2006 (178) 17145220</td>
<td>Pts implanted with TPPM via left subclavian vein or right internal jugular vein over 5 y period</td>
<td>Pacing duration, complications, costs</td>
<td>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</td>
<td>• Despite higher lead cost, TPPM cost-effective after 24 h due to lower complications and less intensive bed use</td>
</tr>
<tr>
<td>Lever N, et al. 2003 (179) 12527682</td>
<td>Consecutive pts requiring prolonged temp pacing due to infection or drug washout who had tunneled TPPM</td>
<td>Pacing duration, outcome, complications</td>
<td>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</td>
<td>• TPPM safe and effective, allows early mobility for pts requiring prolonged temporary pacing</td>
</tr>
<tr>
<td>Kornberger A, et al. 2013 (180) 23718817</td>
<td>Consecutive pts implanted with TPPM for CIED infection (70%) or other reasons (30%) 2000–2009</td>
<td>Duration of pacing, outcomes, complications at 30 d</td>
<td>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.</td>
<td>• TPPM safe and effective option for prolonged temporary pacing</td>
</tr>
<tr>
<td>Zei P, et al. 2006 (181) 16580542</td>
<td>All pts getting TPPM for prolonged temp pacing at BWH 2000–2004</td>
<td>Duration of pacing, outcomes, complications</td>
<td>Median duration 7.5 d. 66% went on to have PPM. No deaths from arrhythmia, no complications from TPPM, no dislodgements</td>
<td>• TPPM safe and effective option for prolonged temporary pacing. • Allows management in lower cost less intensive setting</td>
</tr>
<tr>
<td>Study Acronym; Author; Year Published PMID</td>
<td>Study type: Single EMS-system cohort in US</td>
<td>Aim of Study; Study Type; Study Size (N)</td>
<td>Patient Population</td>
<td>Study Intervention (# patients) / Study Comparator (# patients)</td>
</tr>
<tr>
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</tbody>
</table>
| 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 | 1º 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 bradycardia | Size: 7 studies, N=1487 | Inclusion criteria: Euthermic, nontraumatized adults who experience prehospital hemodynamically symptomatic bradycardia or bradysystolic cardiac arrest | 1º endpoint: Survival to hospital discharge | Results: No benefits to TCP for bradysystolic 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 | 1º 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)
**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

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

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published PMID</th>
<th>Study Intervention (pts) / Study Comparator (pts)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guerrero-Marquez FJ, et al. 2016 (183) 28496928</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Aim:</strong> To write a featured review of paroxysmal AVB</td>
<td><strong>Intervention:</strong> N/A</td>
<td>• 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</td>
</tr>
<tr>
<td><strong>Study type:</strong> Review</td>
<td><strong>Comparator:</strong> N/A</td>
<td>• Etiology unknown</td>
</tr>
<tr>
<td><strong>Size:</strong> N/A</td>
<td></td>
<td>• 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)</td>
</tr>
<tr>
<td>Brignole M, et al. 2011; (184) 21570228</td>
<td></td>
<td>• Other causes of AVB; extrinsic vagal effect, Lev-Lenegre disease, SLE, bacterial endocarditis with abscess, sarcoid, Lyme disease, sickle cell</td>
</tr>
<tr>
<td><strong>Aim:</strong> Follow 18 pts with unexplained syncope</td>
<td><strong>Inclusion criteria:</strong> N/A</td>
<td>PPM relieved symptoms in all pts</td>
</tr>
<tr>
<td><strong>Inclusion criteria:</strong> Normal EKG, no SHD , parox CHB per monitoring</td>
<td><strong>Exclusion criteria:</strong> N/A</td>
<td>None progressed to perm AVB</td>
</tr>
<tr>
<td><strong>Intervention:</strong> EPS, Adenosine plasma level, ATP test, TTT, CSM</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published PMID</th>
<th>Study Intervention (pts) / Study Comparator (pts)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brignole M, et al. 2001 (185) 11673344</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Aim:</strong> Determine mechanism of syncope in pts with BBB and neg EPS</td>
<td><strong>Inclusion criteria:</strong> 52 pts with syncope, BBB, QRS &gt;100, neg EPS</td>
<td><strong>Results:</strong> Most frequent cause of recurrent finding was sudden onset AVB with pauses (63%); CHB typically lasts 2–10 d</td>
</tr>
<tr>
<td><strong>Study type:</strong> Single arm prospective</td>
<td><strong>Intervention:</strong> ILR</td>
<td></td>
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</tbody>
</table>

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

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
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

Aim: Editorial
Study type: N/A
Size: N=N/A
Opinion: PMs can be used especially in pts with normal LVEF

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

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
<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| 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=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 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 |
<table>
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<tr>
<th>Study type</th>
<th>Exclusion criteria</th>
<th>Size</th>
<th>1° endpoint</th>
<th>Results</th>
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<tr>
<td>Risgaard B, et al. 2012 (153) 22333242</td>
<td>MI, digoxin toxicity, vasovagal syncope</td>
<td>N=169 (60% male, mean age 78 y). 92/169 (54%) receiving AV nodal blockers</td>
<td>resolution of AVB. 18/32 had relapse of AVB within 3 wk</td>
<td></td>
</tr>
<tr>
<td>Farre N, et al. 2014 (154) 24491864</td>
<td>Discharged from hospital before implant, referred from outpatient department</td>
<td>N=259 (mean age 78 y, 46% male). 49.7% had 2/3 AVB. 15% had AF-slow ventricular response</td>
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<tr>
<td>Antman EM, et al. 1990 (100) 2188752</td>
<td>Consecutive pts with “reversible” 3rd degree AVB not undergoing initial PPM implant</td>
<td>N=150 pts (79=53% with high-degree AVB). 46% male, mean age 65 y</td>
<td></td>
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<tr>
<td>Hickey AR, et al. 1991 (101) 1993775</td>
<td>Anti-digoxin Fab fragments in trial 1974–86</td>
<td>N=717; 40% men, mean age 74 y</td>
<td></td>
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<tr>
<td>Sadek MM, et al. 2013 (155) 23623644</td>
<td>English language, original outcome data</td>
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<tr>
<th>Study</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Results</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Kandolin R, et al. 2011 (156) 21427276</td>
<td>10 publications; 299 pts</td>
<td>on pts with cardiac sarcoidosis tx with steroids.</td>
<td>Reports less than 5 subjects or less than 3-mo follow-up</td>
<td>27/57 (47%) cases treated with steroids had improved or recovered AV conduction vs. 0/16 pts. w/o steroid treatment.</td>
<td>“Improvement” in AV conduction not defined. Outcome not defined in terms of need for PM.</td>
</tr>
<tr>
<td>Ozcan KS, et al. 2012 (157) 22738687</td>
<td>N=133; 72 pts with unexplained AVB</td>
<td>Pts. 18–55 y who had PPM implant for unexplained 2nd/3rd-degree AVB</td>
<td>None described</td>
<td>18/72 (25%) had probable (4) or definite (14) cardiac sarcoidosis AVB reversed in only 2/16 pts (13%) treated with steroids.</td>
<td>Selected population, tertiary referral center. Little data about AVB described. Overall suggests low chance of reversing AVB with steroid treatment.</td>
</tr>
<tr>
<td>Forrester JD, et al. 2014 (158) 24879781</td>
<td>Study type: Single-center retrospective cohort (Finland)</td>
<td>All pts. with 2nd/3rd degree AVB who had hyper- or hypothyroidism</td>
<td>MI, electrolytes abnormalities, digoxin toxicity, vasovagal syncope, on AADs</td>
<td>Persistent AVB despite treatment of thyroid abnormalities.</td>
<td>Thyroid abnormalities are rarely a cause of reversible AVB.</td>
</tr>
<tr>
<td>Van der Linde, MR, 1991 (159) 1947815</td>
<td>Study type: Systematic review of case reports and case series</td>
<td>English language case reports or series in peer-reviewed journal of pts with Lyme disease and ECG-documented 3rd degree AVB</td>
<td>Not in English, pt not US, no pt variables reported</td>
<td>Outcomes, need for PPM, persistence of AVB.</td>
<td>AVB with Lyme carditis almost always resolves with treatment.</td>
</tr>
</tbody>
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<table>
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<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| 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) | • 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 | **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 |
<table>
<thead>
<tr>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1st endpoint</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brady WJ, et al. 1999 (79) 10459592</td>
<td>Study type: Single-EMS system retrospective cohort in US</td>
<td><strong>Inclusion criteria:</strong> All nontraumatized pts from 1990–1993 who experienced bradycardia with associated hemodynamic instability who received atropine in field.</td>
<td><strong>Exclusion criteria:</strong> Not stated, but presumably cardiac arrest. Also excluded pre-hospital deaths (N=16)</td>
<td><strong>1st endpoint:</strong> “Response” in 4 categories – adverse, none, partial, complete</td>
<td><strong>Results:</strong> 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</td>
</tr>
<tr>
<td>Feigl D, et al. 1984 (160) 6736451</td>
<td>Study type: Single center retrospective cohort study in Israel 1978–1982</td>
<td><strong>Inclusion criteria:</strong> 2nd or 3rd degree AVB developing in course of IMI who survived &gt;72 h</td>
<td><strong>Exclusion criteria:</strong> None</td>
<td><strong>1st endpoint:</strong> Outcomes, response to atropine</td>
<td><strong>Results:</strong> Of 15 pts with early AVB (&lt;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</td>
</tr>
<tr>
<td>Sclarovsky S, 1984 (161) 6731277</td>
<td>Study type: Single center retrospective cohort study in Israel 1972–1982</td>
<td><strong>Inclusion criteria:</strong> All pts with acute inferior MI who developed 2nd or 3rd degree AVB in hospital</td>
<td><strong>Exclusion criteria:</strong> Combined AMI and IMI</td>
<td><strong>1st endpoint:</strong> Description of outcomes, response to atropine and isoproterenol</td>
<td><strong>Results:</strong> 6/14 (36%) of pts with early AVB improved vs. 13/17 (77%) pts with late AVB (p&lt;0.05). 2/8 (25%) of pts with early block and 2/6 (33%). 50% of pts had TPM</td>
</tr>
<tr>
<td>Chihrin SM, et al. 2008 (162) 18308011</td>
<td>Study type: Single center prospective cohort in Canada</td>
<td><strong>Inclusion criteria:</strong> Consecutive pts from 2003–2006 undergoing PPM generator change who were PM dependent</td>
<td><strong>Exclusion criteria:</strong> None</td>
<td><strong>1st endpoint:</strong> Elicitation of escape rhythm with PM stepdown to 30 bpm or isoproterenol 1–2 mcg/min</td>
<td><strong>Results:</strong> 59% demonstrated intrinsic rhythm with stepdown alone. Of remaining 41 pts, 28 (68%) demonstrated intrinsic rhythm with isoproterenol. No adverse events.</td>
</tr>
<tr>
<td>Study type</td>
<td>Inclusion criteria</td>
<td>1st endpoint</td>
<td>Results</td>
<td>Notes</td>
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<tr>
<td>Systematic review of 5 RCTs</td>
<td>RCTs of aminophylline used for pre-hospital resuscitate of bradyasystolic cardiac arrest</td>
<td>Survival to discharge/admission, ROSC</td>
<td>No improvement in outcome by any measure with aminophylline. Overall survival extremely low.</td>
<td>Aminophylline not useful in out of hospital bradyasystolic arrest</td>
<td></td>
</tr>
<tr>
<td>Retrospective analysis of single ED registry from tertiary center in Austria</td>
<td>Consecutive pts admitted to ED 1994–2004 with symptomatic, hemodynamically significant bradycardia</td>
<td>Use of drugs for bradycardia, use of pacing</td>
<td>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</td>
<td>Descriptive study with no control group. Pt s with AVB not separately reported or analyzed. Minimal information on clinical effects of intervention given</td>
<td></td>
</tr>
<tr>
<td>Single-center observational cohort in US</td>
<td>Pts with significant AVB developing within 4 h of admission for acute inferior MI, resistant to atropine, given IV theophylline up to 250 mg</td>
<td>Restoration of 1-1 AV conduction</td>
<td>All 8 pts had restoration of 1-1 AV conduction within 3 min lasting at least 24 h</td>
<td>No controls. Very small, single-center experience</td>
<td></td>
</tr>
<tr>
<td>Single-center observational cohort in Turkey</td>
<td>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</td>
<td>Restoration of AV conduction</td>
<td>Aminophylline restored 1-1 AV conduction in 7 pts and Mobitz I AVB in 1. No adverse effects. AVB relapsed in 1 pt only</td>
<td>No controls. Very small, single-center experience</td>
<td></td>
</tr>
<tr>
<td>Single-center case series in United Kingdom</td>
<td>Pts with atropine-resistant AVB with acute inferior MI treated with</td>
<td>Restoration of 1-1 AV conduction</td>
<td></td>
<td>No controls. Very small case series</td>
<td></td>
</tr>
<tr>
<td>Study Acronym; Author; Year Published</td>
<td>Study Type; Study Size (N)</td>
<td>Patient Population</td>
<td>Study Intervention (# patients) / Study Comparator (# patients)</td>
<td>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</td>
<td>Relevant 2º Endpoint (if any); Study Limitations; Adverse Events</td>
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</table>
| 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 | 1º endpoint: Improvement in AV conduction and change in ventricular rate | 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 | 1º 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 | 1º 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 |
| **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 |
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<tr>
<td><strong>Inclusion criteria:</strong> Undergoing temporary VVI pacing (85% with AVB) guided by fluoroscopy</td>
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</table>
| **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 |

| **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 |
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<tr>
<td><strong>Inclusion criteria:</strong> All adult, nontraumatic bradyasystolic episodes or arrests treated by Milwaukee County Paramedic System Oct 1986–May 1987</td>
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</table>
| **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) |
| • 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 |

| **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 |
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<tr>
<td><strong>Inclusion criteria:</strong> All cardiac arrests in Seattle area over 3 y period; Primary group was those with asystole as first rhythm</td>
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</tbody>
</table>
| **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) |
| • 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  

**1º 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  

**1º 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

### 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  

**1º 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
<table>
<thead>
<tr>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>1st endpoint</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brikhahn RH, et al. 2004 (170) 15039689</td>
<td>All pts with temporary TVP placed in ED, intensive care unit, or ward 1999–2002. Only 3% placed under fluoroscopy</td>
<td>Successful temporary TVP placement. Complication rate.</td>
<td>88% success on first attempt. 17% serious complication rate. 96% placed by cephalic approach. 67% had PPM. 23% in-hospital mortality</td>
<td>Similar success rates between ED physicians and cardiologists. High overall success rate of implantation of TVP. Cephalic route rarely used in general practice today.</td>
</tr>
<tr>
<td>Betts TR, 2003 (119) 12954959</td>
<td>All TVPs placed over 9 mo period in 1999</td>
<td>General overview of procedure technique, outcomes, complications</td>
<td>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 &gt;48 h (17/86) than &lt;48 h (2/55). 23% of comps resulted in delayed PPM</td>
<td>Suggests benefit to TVP implant by cardiologists/ experienced operators. Greater infection risk for TVP wires left in &gt;48 h. High rate of overall complications seen. 23% of comps delayed PPM implantation.</td>
</tr>
<tr>
<td>Mahapatra S, et al. 2005 (171) 16171740</td>
<td>Pts undergoing PPM 1995–2003 with perforation and new effusion.</td>
<td>Risk factors for perforation after PPM</td>
<td>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)</td>
<td>Suggests benefit to avoiding TVP prior to permanent pacing unless essential.</td>
</tr>
<tr>
<td>Lang R, et al. 1981 (172) 6169032</td>
<td>Consecutive pts requiring emergency or semi-urgent temporary TVP at a single Israeli center</td>
<td>Successful implant, procedure time, threshold, multiple safety endpoints</td>
<td>Superiority of balloon-tipped, flow guided electrode catheter for temporary TVP demonstrated.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Description</td>
<td>Size</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
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<tr>
<td>Hynes JK, et al. 1983 (115)</td>
<td>Study type: Retrospective single-center cohort at Mayo Clinic</td>
<td>1022 pts, mean age 68 y, (65% male)</td>
<td>Consecutive pts undergoing temporary TVP wire in Mayo Clinic coronary care unit 1976–81.</td>
<td>None stated</td>
</tr>
<tr>
<td>Winner S and Boon N, 1989 (173)</td>
<td>Study type: Retrospective single region cohort study</td>
<td>266 pts/ 158 (59%) had temporary TVP</td>
<td>Consecutive pts referred to regional center for PPM</td>
<td>Missing records</td>
</tr>
<tr>
<td>López Ayerbe J, et al. 2004 (114)</td>
<td>Study type: Retrospective single center cohort in Barcelona, Spain</td>
<td>N=530; mean age 74 y, 54% male; 51% AVB.</td>
<td>Pts receiving TVP 1997–2003. All via femoral route (99%) with fluoroscopic guidance</td>
<td>Pts transferred out with no available f-u (N=38)</td>
</tr>
</tbody>
</table>

**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.
<table>
<thead>
<tr>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>1st endpoint</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type: Prospective regional 5 hospital study in Norway 2010–11.</td>
<td>All pts with TVP in 5 hospitals March 2010–March 2011. All with fluoroscopy</td>
<td>Complications, outcomes</td>
<td>96% TVP; 4% TCP. 60% received PPM; 14% died. 30% rate of “serious complications” including 6% death from sepsis</td>
<td>Fewer TVPs being performed by more physicians with less experience</td>
</tr>
<tr>
<td>Size: N=50; 45% AVB; mean age 79 y, 62% male</td>
<td>None stated</td>
<td></td>
<td></td>
<td>Lower complication rate with more experienced implanter</td>
</tr>
<tr>
<td>Study type: Systematic review 1973–2004</td>
<td>Cohort studies of TVP published 1973–2004</td>
<td>Complications, outcomes</td>
<td>Overall complication rate 26.5%: 15% failed access, 10% failed placement, 9% sepsis, 4% arterial puncture, 2% lung/myocardium puncture</td>
<td>Methodologically limited systematic review</td>
</tr>
<tr>
<td>Size: 15 studies; N=3737; mean age 71 y</td>
<td>None stated</td>
<td></td>
<td></td>
<td>Higher complication rate in older pts</td>
</tr>
<tr>
<td>Study type: Single center retrospective cohort in Taiwan 2002–8</td>
<td>All pts with TVP 2002–8 at single center</td>
<td>Trends in use</td>
<td>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.</td>
<td>High rate of PPM for degenerative AVB</td>
</tr>
<tr>
<td>Size: N=509; mean age 77 y, 74% male; 64% AVB</td>
<td>None stated</td>
<td></td>
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<tr>
<td>Study type: Retrospective single-center cohort at academic medical center in Denmark 2000–11.</td>
<td>Pts getting TVP wire 2000–11 who had AVB and potential culprit drug discontinued</td>
<td>Indication for PPM despite drug discontinuation; complications and outcomes</td>
<td>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</td>
<td>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.”</td>
</tr>
<tr>
<td>Size: N=575 with TVP. N=55 with AVB and potential culprit drug. Mean age 77 y, 56% male</td>
<td>No ECG documentation; other etiology of bradycardia documented; PPM infection; in hospital death</td>
<td></td>
<td></td>
<td>“In the elderly, the drug is virtually never the sole culprit; rather, it just exposes the underlying weakness of the aging conduction system</td>
</tr>
<tr>
<td>Reference</td>
<td>Study type:</td>
<td>Inclusion criteria:</td>
<td>1° endpoint:</td>
<td>Results:</td>
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<tr>
<td>Murphy JJ, 1996 (116) 8620131</td>
<td>Prospective cohort in 18 hospitals in Northern England over 6 mo</td>
<td>All TVP implants in 18 hospitals.</td>
<td>Complications</td>
<td>Immediate complications in 12/194 (6%) – VT/VF in 6, arterial puncture (3), pneumothorax (2), brachial plexus injury (1). Late comp in 22/194 (11%) – VT/VF 10, definite/possible sepsis in 10 (5.2%) – almost all had TVP&gt;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.</td>
</tr>
<tr>
<td>Pinneri F, et al. 2013 (174) 22240748</td>
<td>Single-center nonrandomized controlled study.</td>
<td>Consecutive pts requiring TVP 2003–2010. Pts underwent TVP guided by echo (N=53) or fluoroscopy (N=53) based on operator preference.</td>
<td>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.</td>
<td>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&lt;0.001). Comp rate lower in echo (11%) than fluoroscopy (41%) group; p&lt;0.001.</td>
</tr>
<tr>
<td>Braun MU, et al. 2006 (175) 16923004</td>
<td>Nonrandomized prospective controlled study comparing externalized active-fixation lead vs. standard temporary TVP wire</td>
<td>Pts with systemic infection requiring VVI pacing &gt;48 h</td>
<td>Implant success, pacing thresholds, acute complications, dislodgement rate</td>
<td>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.</td>
</tr>
<tr>
<td>Study Type</td>
<td>Size: 49 pts, mean age 72 y, 63% male</td>
<td>Study Type: Non-randomized single-center comparison of TVP by femoral route with active vs. passive fixation wire in Netherlands 1998–2001</td>
<td>1° endpoint: Implant parameters, dislodgments, other adverse events</td>
<td>Results: Threshold higher in active (1.38V) than passive (0.7V). Dislodgement lower in active (2/36) than passive (12/36) groups (p&lt;0.001). Other comps similar</td>
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<tr>
<td>de Cock CC, et al. 2003 (176)</td>
<td><strong>Study type:</strong> Single center retrospective cohort study of temp active fix lead (TPPM) after lead extraction at UCSD</td>
<td><strong>Inclusion criteria:</strong> Consecutive pts requiring TVP at single center requiring prolonged temporary pacing (&gt;48 h) – mean 6 d</td>
<td><strong>Exclusion criteria:</strong> None stated</td>
<td></td>
</tr>
<tr>
<td>Size: N=72 pts; mean age 70 y, 51% male</td>
<td><strong>Inclusion criteria:</strong> 23/47 pts undergoing extraction for CIED infection who were PM-dependent 2010–12</td>
<td><strong>Exclusion criteria:</strong> None stated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kawata H, et al. 2013 (177)</td>
<td><strong>Study type:</strong> Single center retrospective cohort in Canada 2001–5</td>
<td><strong>1° endpoint:</strong> Duration of TPPM, complications</td>
<td>• Fewer dislodgments using an active fixation lead using femoral approach</td>
<td></td>
</tr>
<tr>
<td>Size: N=20 pts; median 2 d; mean age 62 y; 75% male</td>
<td><strong>Inclusion criteria:</strong> Pts implanted with TPPM via left subclavian vein or right internal jugular vein over 5 y period</td>
<td><strong>Results:</strong> 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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chihrin SM, et al. 2006 (178)</td>
<td><strong>Study type:</strong> Single center retrospective cohort in Canada 2001–5</td>
<td><strong>Exclusion criteria:</strong> None stated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size: N=20 pts; median 2 d; mean age 62 y; 75% male</td>
<td><strong>Inclusion criteria:</strong> Consecutive pts requiring TVP at single center requiring prolonged temporary pacing (&gt;48 h) – mean 6 d</td>
<td>• TPPM is a safe and effective option for PM-dependent pts awaiting reimplant after CIED infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1° endpoint:</strong> Duration of TPPM, complications</td>
<td>• Allows earlier mobilization and potential discharge to home/nursing facility to await CIED reimplant</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Results:</strong> 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.</td>
<td></td>
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</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lever N, et al. 2003 (179) 12527682</td>
<td>Single center cohort in United Kingdom</td>
<td>Consecutive pts requiring prolonged temp pacing due to infection or drug washout who had tunneled TPPM</td>
<td>Pacing duration, outcome, complications</td>
<td>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</td>
<td>TPPM safe and effective, allows early mobility for pts requiring prolonged temporary pacing</td>
</tr>
<tr>
<td>Kornberger A, et al. 2013 (180) 23718817</td>
<td>Single center cohort in Germany</td>
<td>Consecutive pts implanted with TPPM for CIED infection (70%) or other reasons (30%) 2000–2009</td>
<td>Duration of pacing, outcomes, complications at 30 d</td>
<td>Successful in 98% - VVI in 56, DDD in 3) Duration mean 15 d. Intraoperative comp in 2 pts (3.3% - one venous thromboembolism and tamponade, one dislodgement during lead extraction). 4 late comp (6.7%) – 3 possible lead infections, 1 dislodgement.</td>
<td>TPPM safe and effective option for prolonged temporary pacing</td>
</tr>
<tr>
<td>Zei P, et al. 2006 (181) 16580542</td>
<td>Single-center cohort in Boston MA</td>
<td>All pts getting TPPM for prolonged temp pacing at BWH 2000–2004</td>
<td>Duration of pacing, outcomes, complications</td>
<td>Median duration 7.5 d. 66% went on to have PPM. No deaths from arrhythmia, no complications from TPPM, no dislodgements</td>
<td>TPPM safe and effective option for prolonged temporary pacing. Allows management in lower cost less intensive setting</td>
</tr>
<tr>
<td>Zoll PM, et al. 1985 (130) 3886190</td>
<td>Prospective 5-center cohort study in US</td>
<td>All ED and hospital pts in whom TCP applied</td>
<td>Stimulation effectiveness, clinical usefulness, survival in-hospital</td>
<td>QRS response to TCP in 78%, deemed clinically useful in 61%, survival in 62%</td>
<td>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.”</td>
</tr>
</tbody>
</table>
### 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)

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

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<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| Dhingra RC, et al. 1974 (196) 4817704 | **Aim:** Describe natural Hx of 2nd AVB+ BBB  
  **Study type:** Prospective observational  
  **Size:** 15 | **Inclusion criteria:** BB+ 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:** Survival 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 | |
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edhag O, et al. 1976 (200) 1015354</td>
<td><strong>Aim:</strong> Report natural Hx of pts with CHB or arrhythmic syncope</td>
<td>Retrospective</td>
<td>101</td>
<td>PM not implanted</td>
<td>None</td>
<td><strong>Results:</strong> CHB with Adams-Stokes had worse survival than asx CHB</td>
<td>Survival at 1 y=68%, at 5 y=37%</td>
</tr>
<tr>
<td>Shaw DB, et al. 1985 (201) 4005079</td>
<td><strong>Aim:</strong> Compare outcomes in pts with type I and type II 2nd degree AVB</td>
<td>Observational</td>
<td>214 (77 Mobitz I, 86 Mobitz II, 51 2:1)</td>
<td>2nd degree AVB</td>
<td>PM</td>
<td><strong>Results:</strong> 5-y survival for pts with PM=78%; survival for those w/o a PM=41%</td>
<td>Pts with Mobitz I and Mobitz II had similar prognosis</td>
</tr>
<tr>
<td>Wahbi K, et al. 2012 (202) 22453570</td>
<td><strong>Aim:</strong> Determine whether EPS+ prophylactic PM improves survival in MD</td>
<td>Retrospective study using DM1 Heart Registry</td>
<td>486</td>
<td>PR &gt;200, QRS &gt;100, or both</td>
<td>EPS and implant PM if HV &gt;70 ms</td>
<td><strong>Results:</strong> 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)</td>
<td>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%)</td>
</tr>
<tr>
<td>Buckley AE, et al. 1999 (203) 10377322</td>
<td><strong>Aim:</strong> Describe cardiac involvement in Emery Dreifuss</td>
<td>Small case series</td>
<td>N/A</td>
<td>Pts with Emery Dreifuss and cardiac involvement</td>
<td>PM</td>
<td><strong>Results:</strong> The pts exhibited atrial tachycardia, AF, and atrial standstill with junctional bradycardia.</td>
<td>N/A</td>
</tr>
<tr>
<td>Study</td>
<td>Size</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Intervention</td>
<td>Results</td>
<td>Notes</td>
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<tr>
<td>Kitaguchi T, et al. 2001 (204) 11525883</td>
<td>3</td>
<td>Describe a proband and his family</td>
<td>Family members with limb girdle MD</td>
<td>PM</td>
<td>All family members had AVB and arrhythmias requiring PM</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Finsterer J, et al. 2016 (205) 27014341</td>
<td>14</td>
<td>Thorough review of all neuromuscular disease and cardiac involvement</td>
<td>Comprehensive list of search terms and manual searches</td>
<td>N/A</td>
<td>Several aspects of cardiac involvement were including hypertrophic CM, DCM, CHF, SCD, arrhythmias</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Ha AH, et al. 2012 (206) 22385162</td>
<td>224 papers</td>
<td>Determine predictors of AVB in MD pts</td>
<td>MD type I and II</td>
<td>PM and ICD</td>
<td>23.8% of DM I and 16.7% of DM II pts had a severe ECG abnormality (defined as PR &gt;240 ms or QRS &gt;120 ms). PMs and ICDs were implanted in 14% overall but in 65% of those with severe ECG abnormality</td>
<td>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%)</td>
<td></td>
</tr>
<tr>
<td>Lazarus A, et al. 2002 (207) 12427418</td>
<td>236</td>
<td>Document incidence of AVB in MD pts with HV&gt;70 but no symptoms</td>
<td>MD pts with HV &gt;70 regardless of symptoms</td>
<td>PM</td>
<td>43% developed CHB, 51% had atrial tachyarrhythmias and 26.5% had VA.</td>
<td>No deaths due to AVB. 4 sudden deaths; 2 of which did not have arrhythmia cause per PM interrogation</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Size</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Intervention</td>
<td>Results</td>
<td>Comments</td>
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<tr>
<td>Facenda-Lorenzo M, et al. 2013 (208) 24775453</td>
<td>49</td>
<td>Document frequency of arrhythmias in MD type I pts</td>
<td>Pts with genetic tested Dx of type I MD pts referred to cardiology</td>
<td>EPS, PM, ICD per physician discretion</td>
<td>At baseline visit, 71.6% had a normal ECG. At follow-up, 48.8% had sinus bradycardia and 31.3% had PR &gt;220 ms</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Bhakta D, et al. 2011 (209) 22035077</td>
<td>81</td>
<td>Assess implantation of PM and ICD rates in type I MD pts</td>
<td>Pts seen at 23 different neuromuscular clinics in US</td>
<td>PM or ICD per physician discretion</td>
<td>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 &gt;240 or QRSd &gt;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</td>
<td></td>
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</tr>
<tr>
<td>Groh WJ, et al. 2008 (210) 18565861</td>
<td>406</td>
<td>Assess if ECG can predict SCD in MD type I pts</td>
<td>Pts seen at 23 different neuromuscular clinics in US; including those with either non-SR, PR &gt;240 ms, QRS ≥120 ms, 2nd/3rd degree AVB (termed “severe ECG abnormality”)</td>
<td>PM or ICD per physician discretion</td>
<td>20% died; 33% were sudden death. 41 received PM; 27 were prophylactic. Atrial tachyarrhythmias were common (30%). Risk factors for sudden death were severe ECG abnormalities and atrial tachyarrhythmias</td>
<td></td>
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</tr>
<tr>
<td>Groh WJ, 2012 (211) 22760083</td>
<td>N/A</td>
<td>Contemporary review and expert opinion</td>
<td>N/A</td>
<td>N/A</td>
<td>Reviews role of PM and ICD. Conduction abnormalities are frequent</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Study type:</td>
<td>N/A</td>
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<td>Size:</td>
<td>N/A</td>
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<tr>
<td><strong>Study type:</strong></td>
<td>Systematic review of arrhythmias in Kearns-Sayre pts</td>
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<tr>
<td><strong>Inclusion criteria:</strong></td>
<td>Specific search terms</td>
<td></td>
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<tr>
<td><strong>Intervention:</strong></td>
<td>PM or ICD</td>
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</tbody>
</table>
| **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 |

Kabunga P, et al. 2015 (212) 25540845

| Study type: | Literature review |
|---|---|---|
| Size: | 54 studies |
| **Aim:** | Look at Holter and correlate to cerebral symptoms |
| **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 |

Saxon LA, et al. 1990 (213) 1695352

| Study type: | Retrospective |
|---|---|---|
| Size: | 411 |
| **Aim:** | Look at 3 s pauses on Holter and correlate clinical outcomes |
| **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 |

Hilgard J, et al. 1985 (214) 3984858

| Study type: | Retrospective |
|---|---|---|
| Size: | 52 |
| **Aim:** | Assess etiology of pauses and indications for PM |
| **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 |
<table>
<thead>
<tr>
<th>Size: 2350 Holters; 53 had pauses</th>
<th>Inclusion criteria: Isolated CCHB diagnosed in pts 15 y or younger; mean age at follow-up was 38 y</th>
<th>Intervention: 54 implanted with a PM</th>
<th>Results: • Stokes Adams attacks occurred in 27, 8 of whom died • 24 women w/o PM gave birth, 6 had syncope during pregnancy</th>
<th>• 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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michaelsson M, et al. 1995 (216) 7634461</td>
<td>Aim: Assess long-term outcome of adults with CCHB</td>
<td>Study type: Prospective observational</td>
<td></td>
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</tr>
<tr>
<td>Size: 102</td>
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<tr>
<td></td>
<td>Inclusion criteria: Children with isolated CCHB 1955–1985 at Boston Children’s Hospital</td>
<td>Intervention: PM for symptoms only, not EKG or Holter findings</td>
<td>Results: • 29 remained free of symptoms • 14 had symptoms (near syncope, exercise intolerance), 1 had CHF at birth, 1 had cardiac arrest</td>
<td>• Heart rate on ECG or Holter did not predict need for PM</td>
</tr>
<tr>
<td>Sholler GF, et al. 1989 (217) 2480059</td>
<td>Aim: Identify factors that predict need for PM in congenital CHB pts</td>
<td>Study type: Retrospective chart review</td>
<td></td>
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<tr>
<td>Size: 43</td>
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<tr>
<td></td>
<td>Inclusion criteria: Case report</td>
<td>Intervention: PM</td>
<td>Results: During a hemodynamic assessment, atrial contraction was seen to occur while AV valves are closed, similar to PM syndrome</td>
<td>• AV delay decreased from 290 to 150 with PM improved symptoms</td>
</tr>
<tr>
<td>Size: 1</td>
<td>Inclusion criteria: Case report</td>
<td>Intervention: PM</td>
<td>Results: At baseline, pt had PR=480 ms, intermittent cannon A waves. Symptoms of dizziness and dyspnea improved with PM</td>
<td>• N/A</td>
</tr>
<tr>
<td>Carroz P, et al. 2010 (191) 19946114</td>
<td>Aim: Report pseudo PM syndrome</td>
<td>Study type: Case report</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size: 1</td>
<td>Inclusion criteria: Case report of pt with marked 1st degree AV block</td>
<td>Intervention: Rapid atrial pacing and atropine injection</td>
<td>Results:</td>
<td>• N/A</td>
</tr>
<tr>
<td>Reference</td>
<td>Aim</td>
<td>Study type</td>
<td>Size</td>
<td>Inclusion criteria</td>
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<tr>
<td>Kim YH, et al. 1993 (218) 8269289</td>
<td><strong>Aim:</strong> Describe symptoms of pseudo-PM syndrome</td>
<td><strong>Study type:</strong> Case report</td>
<td><strong>Size:</strong> 1</td>
<td><strong>Inclusion criteria:</strong> Case report of pseudo-PM syndrome after fast PW ablation and resultant long PR</td>
</tr>
<tr>
<td>Barold SS, 1996 (193) 8734740</td>
<td><strong>Aim:</strong> Editorial to discuss role of PM in 1st degree AVB</td>
<td><strong>Study type:</strong> N/A</td>
<td><strong>Size:</strong> N/A</td>
<td><strong>Inclusion criteria:</strong> N/A</td>
</tr>
<tr>
<td>Alboni P, et al. 2013 (219) 23286970</td>
<td><strong>Aim:</strong> Describe vagally mediated AVB</td>
<td><strong>Study type:</strong> N/A</td>
<td><strong>Size:</strong> N/A</td>
<td><strong>Inclusion criteria:</strong> N/A</td>
</tr>
<tr>
<td>Massie B, et al. 1978 (220) 668079</td>
<td><strong>Aim:</strong> Describe EPS findings in pts with Mobitz II AVB</td>
<td><strong>Study type:</strong> Case series</td>
<td><strong>Size:</strong> 13</td>
<td><strong>Inclusion criteria:</strong> Mobitz type II with concomitant sinus slowing</td>
</tr>
<tr>
<td>Mosqueda-Garcia, R et al. 2000 (221) 11104751</td>
<td><strong>Aim:</strong> Attempt to explain the pathophysiology of neurally mediated syncope</td>
<td><strong>Study type:</strong> N/A</td>
<td><strong>Size:</strong> N/A</td>
<td><strong>Inclusion criteria:</strong> N/A</td>
</tr>
<tr>
<td>Study type:</td>
<td>Comprehensive review</td>
<td>Size: N/A</td>
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<td><strong>Guerrero-Marquez FJ, et al. 2016 (183) 28496928</strong></td>
<td><strong>Aim:</strong> To write a featured review of paroxysmal AVB</td>
<td><strong>Inclusion criteria:</strong> N/A</td>
<td><strong>Conclusions:</strong> Idiopathic AVB is paroxysmal 3rd degree heart block with no other rhythm abnormalities pre or post in pts with normal heart and EKG</td>
<td>Other causes of AVB include; extrinsic vagal effect, Lev-Lenegre disease, SLE, bacterial endocarditis with abscess, sarcoid, Lyme disease, sickle cell</td>
</tr>
<tr>
<td><strong>Study type:</strong> Review</td>
<td><strong>Size:</strong> N/A</td>
<td><strong>Intervention:</strong> N/A</td>
<td></td>
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<tr>
<td><strong>Kato Y, et al. 2003 (222) 12870723</strong></td>
<td><strong>Aim:</strong> Assess efficacy of steroids for resolution of AVB in sarcoidosis</td>
<td><strong>Inclusion criteria:</strong> Pts with cardiac sarcoid, AVB and normal EF</td>
<td><strong>Results:</strong> Of the 7 treated with steroids 4 had resolution of AVB, 6 had steroid side effects</td>
<td>• None of the 13 untreated pts resolved the AVB</td>
</tr>
<tr>
<td><strong>Study type:</strong> retrospective</td>
<td><strong>Size:</strong> 20</td>
<td><strong>Intervention:</strong> Steroids per physician discretion</td>
<td></td>
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<tr>
<td><strong>Takaya Y, et al. 2015 (223) 25529542</strong></td>
<td><strong>Aim:</strong> Assess outcomes of sarcoid pts with AVB as initial manifestation</td>
<td><strong>Inclusion criteria:</strong> Consecutive cardiac sarcoid pts with either AVB or VT or CHF</td>
<td><strong>Results:</strong> 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</td>
<td>• Of the 17 pts with AVB, 7 died of fatal SCD including 3 who responded to steroids for AVB</td>
</tr>
<tr>
<td><strong>Study type:</strong> Retrospective observational study</td>
<td><strong>Size:</strong> 53</td>
<td><strong>Intervention:</strong> PM or ICD per physician</td>
<td></td>
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<tr>
<td><strong>Padala SK, et al. 2017 (224) 27836297</strong></td>
<td><strong>Aim:</strong> Assess impact of steroids given early on AVB, VA, and LVEF</td>
<td><strong>Inclusion criteria:</strong> Cardiac sarcoid pts given steroids early after Dx</td>
<td><strong>Results:</strong> Only those where steroids started within 30 d had improvement in LVEF</td>
<td>• Pts who did not receive early steroid treatment did not have any improvement</td>
</tr>
<tr>
<td><strong>Study type:</strong> retrospective</td>
<td><strong>Size:</strong> 53</td>
<td><strong>Intervention:</strong> Steroids</td>
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<tr>
<td><strong>Aim:</strong></td>
<td>Review literature on cardiac sarcoid</td>
<td><strong>Inclusion criteria:</strong></td>
<td><strong>Intervention:</strong></td>
<td><strong>Results:</strong></td>
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<tr>
<td><strong>Study type:</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>RBBB is more common than LBBB. Epsilon waves are rare.</td>
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<tr>
<td><strong>Size:</strong></td>
<td>30</td>
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<thead>
<tr>
<th><strong>Aim:</strong></th>
<th>Systematic review and meta-analysis of cardiac sarcoidosis and steroids</th>
<th><strong>Inclusion criteria:</strong></th>
<th><strong>Intervention:</strong></th>
<th><strong>Results:</strong></th>
<th><strong>There are no RCT looking at steroid use in cardiac sarcoid</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study type:</strong></td>
<td>N/A</td>
<td>Published studies on steroids for cardiac sarcoidosis</td>
<td>Steroids</td>
<td>Overall steroids beneficial for recovery of AVB with 47.4% of pts improved</td>
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<tr>
<td><strong>Size:</strong></td>
<td>N/A</td>
<td>10 studies</td>
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<table>
<thead>
<tr>
<th><strong>Aim:</strong></th>
<th>Determine outcome of cardiac sarcoidosis in a single institution</th>
<th><strong>Inclusion criteria:</strong></th>
<th><strong>Intervention:</strong></th>
<th><strong>Results:</strong></th>
<th><strong>Lack of ICD or PM predicted increased mortality</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study type:</strong></td>
<td>Retrospective</td>
<td>All pts who met criteria for sarcoid</td>
<td>Per physician discretion</td>
<td>Heart block was present in 19.2% of pts. 5-y survival overall was 95.5%.</td>
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<tr>
<td><strong>Size:</strong></td>
<td>73</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Aim:</strong></th>
<th>Characterize the bradyarrhythmias in cardiac AL amyloid pts</th>
<th><strong>Inclusion criteria:</strong></th>
<th><strong>Intervention:</strong></th>
<th><strong>Results:</strong></th>
<th>Baseline ECG showed 1st degree AVB in 45% and 1 pt had Mobitz type I at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study type:</strong></td>
<td>Single arm prospective</td>
<td>AL amyloidosis + (pre) syncope symptoms</td>
<td>All pts received ILR</td>
<td>13 of the 20 died with median survival 60 d 8 of the 13 had bradycardia (heart rate &lt;35 bpm) preceding PEA</td>
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<tr>
<td><strong>Size:</strong></td>
<td>20</td>
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</tbody>
</table>
| Reisinger J, et al. | **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 (2 had PM and 1 had ICD) |
|---|---|---|---|---|
| Panic G, et al. | **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. | **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. | **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. | **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 |
<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size (N)</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results</th>
<th>Summary/Conclusion; Comments</th>
</tr>
</thead>
</table>
| **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 |
| **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 |
<table>
<thead>
<tr>
<th>Source</th>
<th>Aim:</th>
<th>Inclusion criteria:</th>
<th>1° endpoint:</th>
<th>Results:</th>
<th>Notes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginks WR, et al. 1977 (233) 836733</td>
<td>Determine the need for permanent PM in pts with Anterior MI and temp. pacing for CHB</td>
<td>Anterior MI, CHB 2 had CHB, narrow QRS 50 had QRS &gt;120</td>
<td>Of the 25 survivors, 4 required permanent pacing</td>
<td>27 of the 52 died</td>
<td>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</td>
</tr>
<tr>
<td>Singh SM, et al. 2015 (234) 25205530</td>
<td>Determine incidence of high-grade AVB in ACS</td>
<td>GRACE Registry subject with high-grade AVB</td>
<td>2.9% of subjects had high-grade AVB</td>
<td>Rate of high-grade AVB decreased over time.</td>
<td>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&lt;0.001) • Of the 1701, 100 (5.9%) required permanent PM</td>
</tr>
<tr>
<td>Osmonov D, et al. 2012 (151) 22530749</td>
<td>Single-center retrospective cohort of pts with drug induced AVB</td>
<td>All pts admitted with Mobitz type II or 3rd degree AVB or 2:1 AVB who were on AV nodal blocking drugs</td>
<td>Resolution/ recurrence AVB, need for PPM</td>
<td>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.</td>
<td>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</td>
</tr>
<tr>
<td>Zeltser D, et al. 2004 (152) 15234417</td>
<td>Single-center retrospective cohort</td>
<td>All pts admitted with 2nd or 3rd degree AVB 1999–2003.</td>
<td>Resolution/ recurrence AVB, need for permanent PM</td>
<td>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</td>
<td>Overall, only 15% of pts with AVB on nodal blocking drugs had AVB &quot;caused by drugs&quot; • AVB may recur despite remaining off the drug</td>
</tr>
<tr>
<td>Knudsen MB, et al. 2013 (150) 23869746</td>
<td>Single-center, retrospective cohort</td>
<td>Pts admitted with 2nd or 3rd degree AVB, had</td>
<td>Need for permanent PM after drug discontinuation; complications of TPM</td>
<td>Pts with AVB on AADs or digoxin do not benefit from temp. PM and</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Size</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>Results</td>
<td>Notes</td>
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<tr>
<td>Ozcan KS, et al. 2012 (157) 22738687</td>
<td>N=55</td>
<td>temporary pacing wire, were on class II-IV AADs or digoxin.</td>
<td>AVB due to other identified cause, prior PM explant, died within several days</td>
<td>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)</td>
<td>drug washout. Should proceed to PPM w/o delay.</td>
</tr>
<tr>
<td>Farre N, et al. 2014 (154) 24491864</td>
<td>N=50 (29 hypothyroid, 21 hyperthyroid)</td>
<td>All pts. with 2nd/3rd degree AVB who had hyper- or hypothyroidism</td>
<td>MI, electrolytes abnormalities, digoxin toxicity, on AADs</td>
<td>46/50 (92%) pts required permanent PM; 2 additional pts had persistent AVB. 76% of hypothyroid and 86% of hyperthyroid had irreversible AVB.</td>
<td>Thyroid abnormalities are rarely a cause of reversible AVB.</td>
</tr>
<tr>
<td>Panic G, et al. 2011 (190) 20226549</td>
<td>79 pts with reversible AVB; grp A=ACS, N=52 Grp B=non-ACS, N=27</td>
<td>reversible CHB, no indwelling PM</td>
<td>Felt not to be reversible</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Kostic T, et al. 2017 (235) 28082088</td>
<td>1</td>
<td>Pt with Lyme disease and high-grade 2nd degree AVB</td>
<td>AVB is the most common conduction disorder with Lyme carditis</td>
<td>Pt presented with high-grade AVB which resolved after 12 d of antibiotics</td>
<td>Manifestations of AVB may progress rapidly in hours or days</td>
</tr>
<tr>
<td>Study type: Review</td>
<td>Inclusion criteria: N/A</td>
<td>Results: 1.1% of Lyme disease reported to CDC between 2000–2010 included cardiac manifestations</td>
<td>• N/A</td>
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<tr>
<td>Carano N, et al. 2012 (186) 23110777</td>
<td>Aim: Case report and review of rheumatic HD and CHB Study type: Literature review and case report Size: 1</td>
<td>Inclusion criteria: N/A</td>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koehler U, et al. 1998 (67) 9551750</td>
<td>Aim: Assess effect of OSA Rx on brady Study type: Prospective single arm Size: 16</td>
<td>Inclusion criteria: Pts with OSA, and negative EPS, echo, EKG, stress test 1ª 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&lt;0.01) • 4 pts received PM for continued pauses despite effective OSA therapy</td>
<td></td>
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</tr>
<tr>
<td>Maeno K, et al. 2009 (188) 19466526</td>
<td>Aim: Report the interaction of hypoxia and AVB Study type: Case report, literature review Size: 1</td>
<td>Inclusion criteria: N/A 1ª 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</td>
<td></td>
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</tr>
<tr>
<td>Becker H, et al. 1995 (66) 7812557</td>
<td>Aim: Assess effect of CPAP on AVB and bradycardia Study type: Prospective single arm observational Size: 17</td>
<td>Inclusion criteria: All referrals for sleep apnea and if 2nd or 3rd degree AVB or asystole &gt;2 s. noted during sleep study 1ª 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</td>
<td></td>
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</tr>
<tr>
<td>Grimm W, et al. 2000 (68) 10980227</td>
<td>Aim: Assess outcomes of pts with OSA-related bradycardia Study type: Prospective single arm</td>
<td>Inclusion criteria: Negative EPS and Holter for AVB Exclusion criteria: Taking digoxin/BB/CCB 1ª endpoint: Effect of CPAP Results: CPAP resolved &gt;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</td>
<td></td>
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</tbody>
</table>
### Data Supplement 37. RCT data of additional testing for Bradycardia due to AV block (Section 6.4.3)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sivakumaran S, et al. 2003 (17)</td>
<td>Aim: Compare utility of loop recorder vs. Holter</td>
<td>Inclusion criteria: Syncope or presyncope</td>
<td>Intervention: 48 h Holter (n=51) vs. 30 d event (n=49)</td>
<td>Diagnostic yield was 63% for loop vs. 24 % for Holter (p&lt;0.0001)</td>
<td>• 23% of loop recorder pts failed to activate during symptoms</td>
</tr>
<tr>
<td>Study Acronym; Author; Year Published</td>
<td>Study Type; Study Size (N)</td>
<td>Patient Population</td>
<td>Study Intervention (Comparator) / Study Comparator (Comparator)</td>
<td>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</td>
<td></td>
</tr>
<tr>
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</tr>
<tr>
<td><strong>Kinlay S, et al. 1996 (239) 7503472</strong></td>
<td>Study type: RCT Size: 100</td>
<td><strong>Aim:</strong> Compare 3-month event monitor to 48-h Holters</td>
<td><strong>Inclusion criteria:</strong> Pts with palpitations and no prior testing</td>
<td><strong>Intervention:</strong> Received a 90-d Event monitor</td>
<td><strong>Results:</strong> Event monitors were more likely to provide a Dx (67% vs. 35%; p&lt;0.001). Holter not a good test for intermittent symptoms or events</td>
</tr>
<tr>
<td><strong>Giada F, et al. 2007 (240) 17498580</strong></td>
<td>Study type: RCT Size: 43</td>
<td><strong>Aim:</strong> Compare Holter+event+ EPS to ILR for diagnostic yield</td>
<td><strong>Inclusion criteria:</strong> Infrequent palpitations that last &gt;1 min</td>
<td><strong>Intervention:</strong> ILR</td>
<td><strong>Results:</strong> ILR more effective in establishing etiology of palpitations (73% vs. 21%; p&lt;0.001)</td>
</tr>
<tr>
<td><strong>FRESH Podoleanu C, et al. 2014 (74) 25241220</strong></td>
<td>Study type: RCT Size: 78</td>
<td><strong>Aim:</strong> Role of ILR for syncope evaluation</td>
<td><strong>Inclusion criteria:</strong> Syncope</td>
<td><strong>Intervention:</strong> ILR</td>
<td><strong>Results:</strong> ILR yield is superior (cause of syncope identified in 46.2% vs. 5%; p&lt;0.001)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Inclusion criteria:</th>
<th>Intervention:</th>
<th>Comparator:</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
</tr>
</thead>
</table>
| **Katritsis DG, et al. 2017 (241) 28507743** | **Aim:** Review the role of EPS in bradycardia | N/A | N/A | 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 |
<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| 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 testing | • 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  
**Size**: 1 | **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)**

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<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>1º endpoint</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPace</td>
<td>Assess mortality benefit from dual vs. ventricular pacing in pts with AVB</td>
<td>Age &gt;70 y, 2nd or 3rd degree AVB (73.3% had CHB)</td>
<td>Randomized to dual PM, or ventricular PM-fixed rate, or to ventricular PM-adaptive rate</td>
<td>No all-cause mortality benefit for DC pacing at 3 y (7.2% vs. 7.4%; p=NS; CI: 0.83–1.11)</td>
<td>More procedural complications in the DC group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Comparator: Compare DC pacing to ventricular pacing</td>
<td></td>
<td>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</td>
</tr>
<tr>
<td>PASE</td>
<td>Determine difference in health related QOL in ventricular vs. DC pacing in pts &gt;65 y</td>
<td>&gt;65 y, SR (49% had AVB at baseline)</td>
<td>Implanted with DC PM; randomized to ventricular or DC pacing</td>
<td>QOL improved for both groups compared to baseline (p&lt;0.001) but no difference between pacing modes.</td>
<td>No difference in death, stroke, AF rates</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Comparator: Ventricular pacing</td>
<td></td>
<td>AVB subgroup did not experience better QOL or functional status</td>
</tr>
<tr>
<td>MOST</td>
<td>Assess mortality and stroke benefit with DC pacing</td>
<td>SND (21% with concomitant AVB)</td>
<td>Implanted with DC PM, randomized to pacing mode</td>
<td>All-cause mortality+ nonfatal stroke in DC pacing (21.5%) vs. ventricular pacing (23%) was not significant (p=0.48)</td>
<td>No subgroup analysis of AVB group done</td>
</tr>
<tr>
<td></td>
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<td>Comparator: Ventricular pacing</td>
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<tr>
<td>MOST Vp40%</td>
<td>Use MOST database to assess whether RV pacing increases HFH and AF</td>
<td>MOST trial subjects with % ventricular pacing data</td>
<td>Implanted DC PM, randomized to pacing mode</td>
<td>Ventricular pacing &gt;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</td>
<td>The increasing risk of HFH with increasing ventricular pacing levels off after 40%</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Intervention</td>
<td>1° endpoint</td>
<td>Notes</td>
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<tr>
<td>CTOPP Connolly SJ, et al. 2000 (142) 10805823</td>
<td><strong>Aim:</strong> Assess for reduction in stroke and CV mortality with DC pacing vs. ventricular pacing</td>
<td>Indicated for PM (60% had AVB)</td>
<td>Randomized to ventricular or DC PM</td>
<td>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)</td>
<td>All-cause mortality was 6.6% vs 6.3% (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</td>
</tr>
<tr>
<td>CTOPP Extended Kerr CR, et al. 2004 (258) 14707022</td>
<td><strong>Aim:</strong> Reassess primary endpoint of stroke and CV mortality at 6 y of follow-up</td>
<td>Undergoing PM for bradycardia (60% had AVB)</td>
<td>Randomized to ventricular or DC PM</td>
<td>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)</td>
<td></td>
</tr>
<tr>
<td>BLOCK-HF Curtis AB, et al. 2013 (259) 23614585</td>
<td><strong>Aim:</strong> Whether BiV pacing reduces mortality+ morbidity or LV remodeling in AVB pts</td>
<td>Pts with AVB indicated for PM, LVEF ≤50%</td>
<td>BiV PM or ICD, randomized to RV or BiV pacing</td>
<td>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)</td>
<td></td>
</tr>
<tr>
<td>Gierula J, et al. 2013 (260) 23736807</td>
<td><strong>Aim:</strong> Assess benefit of CRT upgrade in CHB PM pts</td>
<td>PM dep pts (pacing &gt;80%), LVEF &lt;50%</td>
<td>Upgrade to BiV PM</td>
<td>Change in LVEF at 6 months was significantly improved in the CRT group (9% vs. -1.5%; p&lt;0.0001)  • 2° endpoints: pVO₂, QOL, and NT-proBNP improved with CRT (p≤0.03 for all 3 outcomes)  • Reduction in LVEDD did not reach statistical significance</td>
<td></td>
</tr>
<tr>
<td>HOBIPACE Kindermann M, et al. 2006 (261)</td>
<td><strong>Aim:</strong> Assess benefit of CRT in pts with depressed LVEF who</td>
<td>LVEF ≤40%, LVEDD</td>
<td>CRT devices implanted</td>
<td>1° endpoints: (1) With CRT, LVESV decreased 17% (p&lt;0.001), (2) LVEF  • NT-proBNP reduced 31% with CRT (p&lt;0.002)</td>
<td></td>
</tr>
<tr>
<td>Study Reference</td>
<td>Study Type</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>Intervention</td>
<td>Comparator</td>
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<tr>
<td>16697307</td>
<td>Prospective randomized crossover</td>
<td>≥60 mm, PM indication with AVB</td>
<td>Not meeting inclusion criteria</td>
<td>Comparator: After 3-month run in period, 3 months of RV pacing compared to 3 months of CRT</td>
<td>Increased 22% (p&lt;0.0002), (3) pVO2 increased 12% (p&lt;0.0003)</td>
</tr>
<tr>
<td>DAVID Wilkoff BL, et al. 2002 (262) 12495391</td>
<td>Aim: Compare DC pacing to VVI backup pacing in ICD indicated pts with no pacing indication</td>
<td>Inclusion criteria: ICD indicated, LVEF ≤40%</td>
<td>Exclusion criteria: Any PM indication</td>
<td>Intervention: All pts were implanted with a DC ICD</td>
<td>Comparator: Ventricular back up pacing vs. DC pacing</td>
</tr>
<tr>
<td>PAVE Doshi RN, et al. 2005 (263) 16302897</td>
<td>Aim: Compare RV to BiV pacing in pts with AVN ablation for AF</td>
<td>Inclusion criteria: Any LVEF, AF, AVN ablation, NYHA class IV</td>
<td>Exclusion criteria: NYHA class IV</td>
<td>Intervention: AVN ablation + dual or BiV PM</td>
<td>Comparator: RV pacing</td>
</tr>
<tr>
<td>APAF Brignole M, et al. 2011 (264) 21606084</td>
<td>Aim: Compare RV pacing to CRT in pts undergoing AV node ablation</td>
<td>Inclusion criteria: Permanent AF undergoing AV node ablation with or w/o refractory HF and reduced EF</td>
<td>Exclusion criteria: NYHA class IV with systolic BP ≤80 mm Hg, prior PM</td>
<td>Intervention: All subjects implanted with CRT</td>
<td>Comparator: RV pacing to CRT pacing 1:1 randomization</td>
</tr>
</tbody>
</table>
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

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

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

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
</tr>
</thead>
</table>
| Brignole M, et al. 2012 (266) 22095616 | Aim: Identify predictors of improvement after AV node ablation | Inclusion criteria: Subjects enrolled in APAF with Z-y follow-up | Intervention: CRT vs. RV pacing after AV node ablation | 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 | Inclusion criteria: RCT and crossover studies comparing DDD and VVI PMs | Intervention: 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 |
<table>
<thead>
<tr>
<th>Study authors</th>
<th>Year (Ref)</th>
<th>Aim</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dhingra RC, et al.</td>
<td>1974 (196)</td>
<td>Natural Hx of 2nd AVB + BBB</td>
<td>Prospective observational</td>
<td>N=15</td>
<td>BBB+2nd degree AVB</td>
<td>EPS; follow-up</td>
<td>N/A</td>
<td>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</td>
</tr>
<tr>
<td>Shaw DB, et al.</td>
<td>1970 (197)</td>
<td>Determine prevalence of pts with 2nd and 3rd degree AVB pts and record their symptoms</td>
<td>Observational</td>
<td>N=100</td>
<td>2nd 3rd degree AVB</td>
<td>None</td>
<td>N/A</td>
<td>48% had syncopal events • 9% had CHF • No reported deaths</td>
</tr>
<tr>
<td>Simon AB, et al.</td>
<td>1978 (198)</td>
<td>Follow natural Hx and survival of AVB pts who underwent PM implant</td>
<td>Retrospective</td>
<td>N=246</td>
<td>2nd or 3rd degree AVB</td>
<td>Ventricular PM</td>
<td>Historical reports of pts w/o a PM</td>
<td>Natural Hx of CHB is 50% mortality in the first year based on prior historical literature • Survival improved to 61% at 5 y w/ a PM • Post PM, new CV events were common including MI, CHF, and stroke and SCD was the most common mode of death</td>
</tr>
<tr>
<td>Strasberg B, et al.</td>
<td>1981 (199)</td>
<td>Assess natural Hx of 2nd AVB</td>
<td>Retrospective, observational</td>
<td>N=56</td>
<td>Consecutive pts with chronic 2nd AVB and EPS positive for 2nd AVB</td>
<td>None</td>
<td>N/A</td>
<td>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</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Findings</td>
<td></td>
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<tr>
<td>Vatankulu MA, et al. 2009 (268) 19406272</td>
<td><strong>Aim:</strong> Assess LV remodeling in CHB PM pts after PM upgrade to CRT</td>
<td>CHB, upgraded PM to CRT, on optimal GDMT</td>
<td>BiV upgrade +/- defibrillator</td>
<td>None</td>
<td>NYHA improved by one class in most subjects, Mean EF increased from 39% to 46%, 25% decrease in mean LVEF, 18% decrease in mean LVEDV, No clinical hard endpoints such as HF or mortality</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Kiehl EL, et al. 2016 (269) 27855853</td>
<td><strong>Aim:</strong> Determine incidence of PM-induced CM, and identify predictors of RV-pacing induced CM</td>
<td>Consecutive pts receiving PM between 2000–2014 for CHB; LVEF &gt;50%; many pts had procedural/surgical AVB</td>
<td>CRT upgrade in some PM pts</td>
<td>Compared those with RV-induced CM and those w/o</td>
<td>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%, LVEV decreased by 45%, RV pacing burden of 20% seemed to delineate increased risk of developing HF</td>
<td></td>
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</tr>
<tr>
<td>MOST Ellenbogen KA, et al. 2003 (270) 12972124</td>
<td><strong>Aim:</strong> Characterize complications from DC PM implants using the MOST database</td>
<td>DDDR PM implanted for SND; SR</td>
<td>Dual chamber PM</td>
<td>Ventricular single chamber PM</td>
<td>Most common complication in the DC PM group was atrial lead dislodgement (1.7%), Female sex seemed to predict risk of complication</td>
<td></td>
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</tr>
<tr>
<td>FOLLOWPACE Udo EO, et al. 2012 (271) 22182495</td>
<td><strong>Aim:</strong> Determine incidence and predictors of PM complications</td>
<td>All pts undergoing initial PM implant</td>
<td>PM implant</td>
<td>None</td>
<td>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</td>
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<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Notes</td>
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<tr>
<td>Ellenbogen KA, et al. 2000 (272)</td>
<td>Determine predictors of PM syndrome in the PASE study</td>
<td>Indication for PM implant; in SR</td>
<td>Randomized to single or DC PM</td>
<td>Compare the 2 arms</td>
<td>Predictors of PM syndrome in a Cox multivariate regression model include: reduced systolic BP with VVI pacing, use of BB, DCM</td>
<td>26% crossed over from ventricular to DC pacing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOST Link MS, et al. 2004 (273)</td>
<td>Determine incidence and predictors of PM syndrome in SND pts treated with ventricular pacing using the MOST database</td>
<td>Randomized to ventricular pacing and meet criteria for PM syndrome</td>
<td>PM syndrome pts crossed over to DC pacing</td>
<td>Pts compared to themselves pre-crossover</td>
<td>18.3% met criteria for PM syndrome</td>
<td>Predictors of PM syndrome include lower sinus rate, higher paced rate, higher % paced beats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arbustini E, et al. 2002 (274)</td>
<td>Assess prevalence of LMNA mutations in a DCM cohort</td>
<td>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</td>
<td>Genetic testing (73)</td>
<td>Genetic testing (107)</td>
<td>LMNA gene mutations accounted for 33% of the pts with DCM with AVB</td>
<td>AVB associated with DCM is a reason for LMNA gene molecular screening</td>
<td>None of the DCM pts with intact AV conduction had any LMNA defects</td>
<td></td>
</tr>
</tbody>
</table>
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)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion</th>
<th>Comment(s)</th>
</tr>
</thead>
</table>
| 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 | 1st 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 |
<table>
<thead>
<tr>
<th>Author/Year Reference</th>
<th>Aim</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fahy GJ, et al. 1996 (31) 8651093</td>
<td><strong>Aim:</strong> Determine the long-term outcome of pts with BBB and no clinical evidence of CV disease</td>
<td><strong>Study type:</strong> Nested case-control</td>
<td><strong>Size:</strong> 310 pts with BBB, 310 matched controls out of 110,000 participant screening program in Ireland</td>
<td><strong>Inclusion criteria:</strong> BBB/age- and sex-matched controls</td>
<td><strong>Exclusion criteria:</strong> Suspected heart disease</td>
<td><strong>1° endpoint:</strong> Long-term “outcome” of BBB pts</td>
<td><strong>Results:</strong> 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).</td>
<td>• Isolated left BBB is associated with an increased risk of developing overt CV disease and increased cardiac mortality.</td>
</tr>
<tr>
<td>Talreja D, et al. 2000 (43) 10689252</td>
<td><strong>Aim:</strong> Assess ability to predict LV dysfunction on echo, by historic, clinical, radiographic, and ECG parameters</td>
<td><strong>Study type:</strong> Cross-sectional</td>
<td><strong>Size:</strong> 300</td>
<td><strong>Inclusion criteria:</strong> Consecutive inpatients referred for the echocardiographic assessment of LV function</td>
<td></td>
<td><strong>1° endpoint:</strong> LVER &lt;45%</td>
<td><strong>Results:</strong> 124 (41%) had LVEF &lt;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</td>
<td>• 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.</td>
</tr>
<tr>
<td>Eriksson P, et al. 1998 (30) 9832497</td>
<td><strong>Aim:</strong> Assess prevalence of BBB, its impact on mortality and coexisting CV conditions</td>
<td><strong>Study type:</strong> Prospective cohort</td>
<td><strong>Size:</strong> 855 men who were 50 y old in 1963 followed for 30 y 82 developed BBB 22 of those were LBBB</td>
<td><strong>Inclusion criteria:</strong> Random sampling of Swedish men</td>
<td><strong>Exclusion criteria:</strong> N/A</td>
<td><strong>1° endpoint:</strong> Mortality and CV disease</td>
<td><strong>Results:</strong> 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</td>
<td>• 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*</td>
</tr>
</tbody>
</table>
| **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 sarcoidosis | • 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 AVB 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 | **Results:** A higher percentage of pts with syncope were shown to develop CHB (17%) vs. those w/o syncope (2%) |  
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**Kwok CS, et al. 2016 (279) 26879241**

<table>
<thead>
<tr>
<th><strong>Size:</strong> 554 pts 351 had EPS and 203 refused it</th>
<th><strong>Exclusion criteria:</strong> Terminal non-cardiac disease; symptoms already documented as due to bradycardia prior to study</th>
<th><strong>Safety endpoint:</strong> N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aim:</strong> Determine if prolonged PR interval is associated with adverse CV outcomes and mortality. <strong>Study type:</strong> Systemic review + meta-analysis</td>
<td><strong>Inclusion criteria:</strong> Studies that evaluated clinical outcomes associated with prolonged and normal PR intervals <strong>Exclusion criteria:</strong> 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)</td>
<td><strong>1° endpoint:</strong> Mortality <strong>Results:</strong> 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.</td>
</tr>
<tr>
<td><strong>Boriani G, et al. 2003 (280) 12649505</strong></td>
<td><strong>Size:</strong> 18 pts (age 42.8±19.6 y) with genetically confirmed X-linked (N=10) or autosomal dominant (N=8) EDMD</td>
<td><strong>Inclusion criteria:</strong> N/A <strong>Exclusion criteria:</strong> N/A</td>
</tr>
<tr>
<td><strong>Results:</strong> Pacemakers were required by 10 of 18 (56%) pts for bradyarrhythmia</td>
<td><strong>Possible association between prolonged PR interval and significant increases in AF, HF and mortality.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Mymim D, et al. 1986 (281) 3762641</strong></td>
<td><strong>Study type:</strong> Longitudinal, Observational</td>
<td><strong>Inclusion criteria:</strong> Healthy males <strong>Exclusion criteria:</strong> Females</td>
</tr>
<tr>
<td><strong>Size:</strong> 3983 healthy men</td>
<td><strong>1° endpoint:</strong> 1°AVB <strong>Results:</strong> 52 initial cases plus 124 new cases over 30 y. No difference in all-cause mortality</td>
<td>**Primary first-degree heart block with moderate PR prolongation is a benign condition <strong>may not apply to more marked prolongation of the PR interval</strong></td>
</tr>
<tr>
<td><strong>Huhta JC, et al. 1983 (282) 6851033</strong></td>
<td><strong>Study type:</strong> Retrospective review</td>
<td><strong>107 pts with ccTGA</strong> 23 of 107 (21%) developed naturally occurring AVB at a rate of 2% per yr. 12 of 49 (24%) developed AVB at VSD closure.</td>
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</table>

• 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 ax pts
<table>
<thead>
<tr>
<th>Study type</th>
<th>Study Type</th>
<th>Subjects</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective review</td>
<td>52 pts with ccTGA</td>
<td>9 or 52 (17.3%) developed spontaneous AVB; 9 of 52 (17.3%) developed postoperative AVB</td>
<td></td>
</tr>
<tr>
<td>Retrospective review</td>
<td>54 pts with postoperative heart block following congenital heart surgery</td>
<td>31 of 32 pts who recovered AV conduction did so by the 9th postoperative day.</td>
<td></td>
</tr>
<tr>
<td>Prospective observational</td>
<td>19 pts with lamin A mutations referred for pacing and receiving an ICD</td>
<td>9 pts (46%) received an appropriate shock for ventricular tachyarrhythmias</td>
<td></td>
</tr>
<tr>
<td>Retrospective multicentered cohort</td>
<td>269 pts with LMNA mutations</td>
<td>Malignant ventricular arrhythmias occurred (5%/y) in pts with ≥2 of: NSVT, LVEF &lt;45% at the first clinical contact, male sex, and non-missense mutations</td>
<td></td>
</tr>
<tr>
<td>Retrospective review</td>
<td>325 pts</td>
<td>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)</td>
<td></td>
</tr>
<tr>
<td>Case series</td>
<td>2 pts</td>
<td>Pts with fascicular block progressed to PM-dependent complete block</td>
<td></td>
</tr>
<tr>
<td>Retrospective review</td>
<td>35 pts</td>
<td>PM/ICD required in 31% (11 pts) 4 pts (11%) in the series died, but all deaths were from sudden cardiac events.</td>
<td></td>
</tr>
<tr>
<td>Systematic Review</td>
<td>Case reports on CHB following blunt cardiac injury were available for 50 pts</td>
<td>PPM implantation was indicated in ~50% of early survivors because of recurrent or permanent CHB. BBB was present in &gt;70% of pts A fatal outcome occurred in 20% of pts; structural damage of AV</td>
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</table>

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

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
</table>
| Chierichini A, et al. 2015 (292)       | **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)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrocco-Trischitta MM, et al. 2016 (293) 27177706</td>
<td><strong>Aim:</strong> Evaluate use of temporary transvenous pacing (TTVP) for pts with CEA and TTVP</td>
<td>Inclusion criteria: Database searched for pts with CEA and TTVP</td>
<td>1° endpoint: 4/34 CEA surgeries with TTVP had PM activation</td>
<td>• Temporary transvenous pacing may be useful in pts undergoing CEA</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>Results</td>
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<tr>
<td>Cheung CC, et al. 2015 (294) 25541033</td>
<td><strong>Aim:</strong> Evaluate prevalence of hypotension and bradycardia during elective noncardiac surgery</td>
<td><strong>Inclusion criteria:</strong> Post-hoc analysis of prospectively acquired data from a study evaluating withdrawal/management of a loop diuretic prior to surgery</td>
<td>None</td>
<td><strong>Results:</strong> 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)</td>
</tr>
<tr>
<td>Bauer AM, et al. 2014 (295) 24651937</td>
<td><strong>Aim:</strong> Case report</td>
<td><strong>Inclusion criteria:</strong> N/A</td>
<td>None</td>
<td><strong>Results:</strong> Single pt with a carotid body tumor who became asystolic during surgery</td>
</tr>
<tr>
<td>Fritsch G, et al. 2012 (296) 22188223</td>
<td><strong>Aim:</strong> Identify factors associated with surgical complications</td>
<td><strong>Inclusion criteria:</strong> 1,363 consecutive pts in a 3 mo period scheduled for elective surgery</td>
<td>None</td>
<td><strong>Results:</strong> Did not specifically analyze pts with bradycardia</td>
</tr>
</tbody>
</table>

**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
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perreira ID, et al. 2011 (297)</td>
<td><strong>Aim:</strong> Identify factors associated with intraoperative bradycardia</td>
<td>&gt;18 y old</td>
<td>None</td>
<td>Sinus bradycardia</td>
<td>• Sinus bradycardia more common with age &lt;18–40 y: 2.5% 41–60 y: 4.1% &gt;61 y: 5.2%</td>
<td>• Pacemaker activated in PM group or AVB in no PM group in pts with RCA or Cx PCI</td>
</tr>
<tr>
<td></td>
<td><strong>Study type:</strong> Retrospective</td>
<td></td>
<td></td>
<td>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%</td>
<td>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)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Size:</strong> 80,660 pts with neuraxial anesthesia from a single center</td>
<td></td>
<td></td>
<td><strong>Exclusion criteria:</strong> None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitar MD, et al. 2015 (298)</td>
<td><strong>Aim:</strong> Evaluate pacing requirement for rotational atherectomy</td>
<td>Consecutive pts undergoing rotational atherectomy</td>
<td>None</td>
<td>(2nd degree AVB or asystole &gt;2 s in the no PM group</td>
<td>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%)</td>
<td>Pacemaker activated in PM group or AVB in no PM group in pts with RCA or Cx PCI</td>
</tr>
<tr>
<td></td>
<td><strong>Study type:</strong> Retrospective</td>
<td></td>
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</tr>
<tr>
<td></td>
<td><strong>Size:</strong> 138 pts</td>
<td>Temporary pacing in 67 No temporary pacing in 67</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Im SH, et al. 2008 (299)</td>
<td><strong>Aim:</strong> Evaluate utility of transcutaneous pacing with carotid angioplasty and stenting</td>
<td>Consecutive pts who underwent elective carotid angioplasty and stenting and placement of a transcutaneous pacing system.</td>
<td>None</td>
<td>Transcutaneous pacing use</td>
<td>24/31 required transcutaneous pacing (77%) Continuous pacing for 10–30 min required in 5/31 pts (16%)</td>
<td>Pacing support often required with elective carotid angioplasty and stenting</td>
</tr>
<tr>
<td></td>
<td><strong>Study type:</strong> Retrospective cohort</td>
<td></td>
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<tr>
<td></td>
<td><strong>Size:</strong> 30 pts and 31 procedures</td>
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<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>1° endpoint</td>
<td>Results</td>
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</tr>
<tr>
<td>Bush RL, et al. 2004 (300) 15181504</td>
<td><strong>Aim:</strong> Evaluate incidence of bradycardia with carotid stenting procedures</td>
<td>Carotid artery stenting procedures in consecutive pts who were thought to be of unacceptable risk for carotid artery endarterectomy.</td>
<td>Clinically significant bradycardia or hypotension</td>
<td>Access site hematomas in 2 pts (4%)&lt;br&gt;Significant bradycardia or asystole in 11/49 (22%) of procedures&lt;br&gt;Mean time of pacing was 6.6±1.2 min (range: 2.2–20.1 min)&lt;br&gt;No correlation between preprocedural cardiac status (History of MI or CABG) and development of bradycardia and hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harrop JS, et al. 2001 (301) 11564241</td>
<td><strong>Aim:</strong> Evaluate hypotension and bradycardia associated with carotid artery interventional procedures</td>
<td>All pts undergoing carotid artery procedures</td>
<td>Use of pacing for bradycardia and hypotension</td>
<td>Pacemaker activation common with CEA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gauss A, et al. 1999 (302) 10456813</td>
<td><strong>Aim:</strong> Evaluation of transcutaneous pacing in pts thought to be at risk for bradycardia (trifascicular block)</td>
<td>Consecutive pts with asx chronic 1st degree AVB and LBBB or bifascicular block.</td>
<td>Progression of AVB, asystole &gt;5 s or bradycardia &lt;40 bpm &gt;10 s)</td>
<td>No pts absolutely required pacing for rate support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Killeavey ES, et al. 1990 (303) 15227187</td>
<td><strong>Aim:</strong> Evaluate the use of transvenous pacing during PCI</td>
<td>Consecutive pts undergoing PCI</td>
<td>Requirement for pacing</td>
<td>Requirement for pacing low</td>
<td></td>
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</tr>
<tr>
<td>Study type</td>
<td>Exclusion criteria</td>
<td>Inclusion criteria</td>
<td>1° endpoint</td>
<td>Results</td>
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<tr>
<td>Study type</td>
<td>Exclusion criteria</td>
<td>Inclusion criteria</td>
<td>1° endpoint</td>
<td>Results</td>
<td></td>
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</tr>
</tbody>
</table>

- **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. |  |
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
<th>Exclusion criteria</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seo KC, et al. 2010 (311) <a href="#">20498810</a></td>
<td>Identify possible factors contributing to bradycardia and hypotension during shoulder surgery</td>
<td>ASA I/II pts who received interscalene block for arthroscopic shoulder surgery in the sitting position</td>
<td>Bradycardia (&lt;50 bpm) and/or hypotension (&lt;100 mm Hg or use of ephedrine)</td>
<td>13/63 with bradycardia and hypotension</td>
<td>N/A</td>
<td>Bradycardia and hypotension more common with tight sided procedures.</td>
</tr>
<tr>
<td>Jeyabalan G, et al. 2010 (312) <a href="#">20557186</a></td>
<td>Identify factors associated with bradycardia during pharmacomechanical thrombectomy for deep vein thrombosis</td>
<td>Consecutive pts who underwent pharmacomechanical (AngioJet) therapy for deep vein thrombosis</td>
<td>Bradycardia</td>
<td>7/57 (12.3%) had bradyarrhythmias</td>
<td>N/A</td>
<td>Bradycardia observed with AngioJet procedures.</td>
</tr>
<tr>
<td>Usami K, et al. 2010 (313) <a href="#">20448432</a></td>
<td>Describe 3 pts who developed bradycardia with surgery for cerebellopontine angle meningiomas</td>
<td>Case series of pts with bradycardia during meningioma surgery</td>
<td>Bradycardia</td>
<td>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</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Lubbers HT, et al. 2010 (314) <a href="#">20347202</a></td>
<td>Describe 3 pts who developed bradycardia with craniomaxillofacial surgery</td>
<td>Case series, N/A</td>
<td>Bradycardia</td>
<td>Describe 3 pts identified from a single center surgical database with bradycardia during craniomaxillofacial surgery</td>
<td>N/A</td>
<td>Purely descriptive with no specific recommendations or findings.</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>1&lt;sup&gt;o&lt;/sup&gt; endpoint</td>
<td>Results</td>
<td>Notes</td>
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<tr>
<td>Christensen RE, et al.</td>
<td>Describe outcomes in pts with surgically corrected D transposition of the great arteries (D-TGA) undergoing noncardiac surgery</td>
<td>Consecutive pts with surgically corrected D-TGA undergoing noncardiac surgery (43 pediatric and 7 adults)</td>
<td>Adverse events including bradycardia</td>
<td>4 adverse events. 1 pt with severe bradycardia during abdominal insufflation</td>
<td>• 4 adverse events observed in pts with congenital heart disease and noncardiac surgeries.</td>
<td></td>
</tr>
<tr>
<td>Jacques F, et al. 2009</td>
<td>Compare regional anesthesia and general anesthesia for CEA surgery</td>
<td>Consecutive pts undergoing CEA from a single center</td>
<td>Hypotension and bradycardia (&lt;60 bpm)</td>
<td>Regional anesthesia associated with less intraoperative bradycardia</td>
<td>• Regional anesthesia associated with less intraoperative bradycardia</td>
<td></td>
</tr>
<tr>
<td>Hanss R, et al. 2008</td>
<td>Evaluate heart rate variability as a tool to identify pts who will have hypotension or bradycardia during surgery</td>
<td>High perioperative risk (ASA III/IV) undergoing major vascular or abdominal surgery</td>
<td>Bradycardia and hypotension</td>
<td>Regional anesthesia associated with less intraoperative bradycardia (4%) when compared to general anesthesia (63%)</td>
<td>• Small numbers of bradycardia (mostly hypotension)</td>
<td></td>
</tr>
<tr>
<td>Reddy MK, et al. 2008</td>
<td>Describe a pt who developed bradycardia during surgical positioning of an unstable cervical spine</td>
<td>N/A</td>
<td>Bradycardia</td>
<td>Case report of bradycardia with skull positioning</td>
<td>• Case report of bradycardia with skull positioning</td>
<td></td>
</tr>
</tbody>
</table>
### Study type: Case report  
**Size:** 1

#### 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.

- Atropine and beta agonists not successful but surgical repositioning of the spine led to resolution and development of a heart rate 100 bpm

- Transient bradycardia can be observed with vagal stimulation.

### Study type: Case report  
**Size:** 1

#### 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

### Study type: Meta-analysis  
**Size:** N/A

#### 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

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

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

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<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P value; OR or RR; &amp; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Supplement 46. Nonrandomized data for Permanent Pacing for TAVI/valve surgery</td>
<td></td>
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</tr>
<tr>
<td>Morris D, et al. 1987 (322) 3675104</td>
<td><strong>Aim:</strong> Evaluate the incidence of CHB in pts with LBBB undergoing PA catheter placement</td>
<td><strong>Inclusion criteria:</strong> All pts with LBBB who underwent PA catheter placement</td>
<td><strong>1° endpoint:</strong> CHB</td>
<td>• Authors do not recommend prophylactic temporary transvenous pacing</td>
</tr>
<tr>
<td></td>
<td><strong>Study type:</strong> Retrospective</td>
<td><strong>Exclusion criteria:</strong> None</td>
<td><strong>Results:</strong></td>
<td>• 5 episodes of CHB in the setting of old LBBB but none temporally related to PA catheter placement</td>
</tr>
<tr>
<td></td>
<td><strong>Size:</strong> 47 pts who underwent 82 PA catheter placements</td>
<td></td>
<td></td>
<td>• 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</td>
</tr>
<tr>
<td>Elliott CG, et al. 1979 (323) 510002</td>
<td><strong>Aim:</strong> Evaluate complications associated with PA catheter placement</td>
<td><strong>Inclusion criteria:</strong> Consecutive pts undergoing PA catheter placement</td>
<td><strong>1° endpoint:</strong> Arrhythmias, ECG changes, or complications</td>
<td>• Transient RBBB fairly rare</td>
</tr>
<tr>
<td></td>
<td><strong>Study type:</strong> Prospective</td>
<td><strong>Exclusion criteria:</strong> None</td>
<td><strong>Results:</strong></td>
<td>• Transient RBBB in 3% of pts</td>
</tr>
<tr>
<td></td>
<td><strong>Size:</strong> 116 PA catheters</td>
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<tr>
<td>Unnikrishnan D, et al. 2003 (324) 14570803</td>
<td><strong>Aim:</strong> Describe complications associated with PA catheter placement</td>
<td><strong>Inclusion criteria:</strong> N/A</td>
<td><strong>1° endpoint:</strong> N/A</td>
<td>• Transient CHB may occur with placement of central venous catheter</td>
</tr>
<tr>
<td></td>
<td><strong>Study type:</strong> Case report</td>
<td><strong>Exclusion criteria:</strong> N/A</td>
<td><strong>Results:</strong></td>
<td>• Complete heart block with central venous line placement in a pt with LBBB</td>
</tr>
<tr>
<td></td>
<td><strong>Size:</strong> 1</td>
<td></td>
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<tr>
<td>Study type</td>
<td>Size: N=90</td>
<td>Inclusion criteria: Consecutive TAVI pts</td>
<td>Intervention: TAVI</td>
<td>Results: Post TAVI QRSd &lt;128 ms predicted no PM needed</td>
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<tr>
<td>Rabinovitz, E et al. 2016 (326) 26936468</td>
<td></td>
<td></td>
<td></td>
<td>20% required PPM</td>
</tr>
<tr>
<td>PARTNER Leon MB, et al. 2010 (327) 20961243</td>
<td></td>
<td></td>
<td></td>
<td>3.4% underwent PPM after TAVI</td>
</tr>
<tr>
<td>Kogan A, et al. 2015 (328) 25583151</td>
<td></td>
<td></td>
<td></td>
<td>PARTNER trial: SAVR had 3.6% PPM</td>
</tr>
<tr>
<td>Rivard L, et al. 2015 (329) 25446155</td>
<td></td>
<td></td>
<td></td>
<td>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%.</td>
</tr>
<tr>
<td>Rene AG, et al. 2013 (330) 24028584</td>
<td></td>
<td></td>
<td></td>
<td>Of the 98 with CHB, 77% became PM dependent</td>
</tr>
<tr>
<td>Steyers CM, et al. 2015 (331) 26470027</td>
<td></td>
<td></td>
<td></td>
<td>PM dependency was highly variable</td>
</tr>
</tbody>
</table>

**Aim:** Assess need for PM

**Study type:** Observational

**Size:** N=302

**Inclusion criteria:** Consecutive TAVI pts

**Intervention:** TAVI

**Results:** 20% required PPM

**PARTNER trial:** SAVR had 3.6% PPM

**Aim:** Assess TAVI in severe AS pts

**Study type:** Observational

**Size:** N=302

**Inclusion criteria:** Consecutive TAVI pts

**Intervention:** TAVI vs. medical Rx

**Results:** 3.4% underwent PPM after TAVI

**PARTNER trial:** SAVR had 3.6% PPM

**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

**Intervention:** 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

**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

**Intervention:** EPS, assess HV interval

**Results:** 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

**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

**Results:** 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

**Aim:** Comprehensive review of AVB post cardiac surgery

**Study type:** Review

**Inclusion criteria:** AVR, MVR, CABG, CABG/valve

**Intervention:** N/A

**Results:** PM dependency was highly variable Recovery of AV conduction highly variable

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<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Aim of Study; Study Type; Study Size (N)</th>
<th>Patient Population</th>
<th>Study Intervention (# patients) / Study Comparator (# patients)</th>
<th>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Birmingham Trial Watson RD, et al. 1984 (231) 6475712</td>
<td>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</td>
<td>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)</td>
<td>Intervention: Permanent pacing Comparator: No permanent pacing Resting intracardiac conduction times were measured in both groups prior to pacing</td>
<td>1° endpoint: No difference in mortality Safety endpoint (if relevant): N/A</td>
<td>• 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</td>
</tr>
<tr>
<td>Dawkins S, et al. 2008 (332) 18154792</td>
<td>Aim: Identify incidence and predictors of AVB after AVR Study type: Retrospective observational Size: N=10 studies, 780 pts</td>
<td>Inclusion criteria: Surgical AVR</td>
<td>Intervention: PM</td>
<td>• Optimal timing for PM (how long to wait for recovery) not established • 7% needed PM in AS pts • 16% needed PM in AI pts</td>
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<tr>
<td>Viles-Gonzalez JF, et al. 2014 (333) 24526511</td>
<td>Aim: Observe natural Hx of AVB after MVR Inclusion criteria: 290 MVR pts Retrospective observational study</td>
<td></td>
<td></td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Merin O, et al. 2009 (334) 19140907</td>
<td>Aim: Study type: Size: N=4,999</td>
<td>Inclusion criteria: CABG, AVR, MVR</td>
<td>Intervention: PM</td>
<td>• 81% had a CABG • Predictor for PM=LBBB • 1.5% got a PM • 1/3 recovered AV conduction at late follow-up</td>
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</tr>
<tr>
<td>Study Acronym; Author; Year Published</td>
<td>Study Type/Design; Study Size</td>
<td>Patient Population</td>
<td>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</td>
<td>Summary/Conclusion Comment(s)</td>
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<tr>
<td>The Framingham Study</td>
<td>Aim: Assess the clinical implications of LBBB</td>
<td>Inclusion criteria: LBBB and age- and sex-matched control pts who did not</td>
<td>1&lt;sup&gt;o&lt;/sup&gt; endpoint: Development of CV disease</td>
<td>• Comparison with age- and sex-matched control subjects free from LBBB suggests that newly acquired</td>
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<td>Study Type/Design; Study Size</td>
<td>Pat</td>
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<tr>
<td></td>
<td>Size: 50 pts</td>
<td>ents with left bundle branch block were not included due to the difficulty in identifying the ECG features of AMI.</td>
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<tr>
<td></td>
<td>Study type:</td>
<td>Exclusion criteria:</td>
<td>Comparator: Nonfunctional infraHisian 2° AVB</td>
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<tr>
<td></td>
<td>Size: 192 pts.</td>
<td></td>
<td>1&lt;sup&gt;o&lt;/sup&gt; 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.</td>
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<tr>
<td>The PRESS Study Santini M, et al. 2013 (182) 23390123</td>
<td>Aim: To demonstrate a reduction in symptomatic events in pts with bifascicular block and syncope of undetermined origin implanted with PPM.</td>
<td>Inclusion criteria:</td>
<td>Intervention: Permanent DDD pacing with a low rate of 60 bpm</td>
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<tr>
<td></td>
<td>Study type:</td>
<td>Exclusion criteria:</td>
<td>Comparator: Permanent DDI pacing with a low rate of 30 bpm</td>
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<tr>
<td></td>
<td>Size: 100 pts</td>
<td></td>
<td>1&lt;sup&gt;o&lt;/sup&gt; 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).</td>
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<td></td>
<td></td>
<td></td>
<td>• Incremental atrial pacing identified pts at high risk of development of spontaneous infraHisian AVB</td>
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<td></td>
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<td></td>
<td>• DDD60 led to a significant reduction of syncope or symptomatic events associated with a cardioinhibitory origin, compared with DDI30 programming</td>
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<tr>
<td>Year</td>
<td>Study Type</td>
<td>Aim</td>
<td>Inclusion Criteria</td>
<td>1st Endpoint</td>
<td>Results</td>
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<tr>
<td>1979 (27)</td>
<td>Nested case-control in Framingham cohort</td>
<td>Develop LBBB from Framingham cohort</td>
<td>Exclusion criteria: N/A</td>
<td>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</td>
<td>LBBB is most often a hallmark of advanced hypertensive or ischemic heart disease, or both</td>
</tr>
<tr>
<td>Fahy GJ, et al. 1996 (31) 8651093</td>
<td>Determine the long-term outcome of pts with BBB and no clinical evidence of CV disease</td>
<td>BBB/age- and sex-matched controls</td>
<td>Exclusion criteria: Suspected heart disease</td>
<td>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).</td>
<td>• Isolated left BBB is associated with an increased risk of developing overt CV disease and increased cardiac mortality.</td>
</tr>
<tr>
<td>Talreja D, et al. 2000 (43) 10689252</td>
<td>Assess ability to predict LV dysfunction on echo, by historic, clinical, radiographic, and ECG parameters</td>
<td>Consecutive inpatients referred for the echocardiographic assessment of LV function</td>
<td>Results: 124 (41%) had LVEF &lt;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</td>
<td>• 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.</td>
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</tr>
<tr>
<td>Authors</td>
<td>Aim:</td>
<td>Inclusion criteria:</td>
<td>1° endpoint:</td>
<td>Results:</td>
<td>Additional Notes:</td>
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<tr>
<td>Eriksson P, et al. 1998 (30) 9832497</td>
<td>Assess prevalence of BBB, its impact on mortality and coexisting CV conditions</td>
<td>Random sampling of Swedish men</td>
<td>Mortality and CV disease</td>
<td>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.</td>
<td>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*</td>
</tr>
<tr>
<td>Mahmod M, et al. 2012 (277) 21805313</td>
<td>Evaluate the diagnostic value of CMR in axs pts with LBBB</td>
<td>Asymptomatic adults with complete LBBB referred for cardiac MR</td>
<td>Pathologic findings on MR</td>
<td>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.</td>
<td>CMR detects subclinical CMP in 1/3 of axs 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 axs LBBB.</td>
</tr>
<tr>
<td>Brignole M, et al. 2001 (185) 11673344</td>
<td>To analyze the clinical outcomes of pts with syncope and BBB following a systematic diagnostic approach: 3-phase: clinical evaluation, EPS, ILR</td>
<td>BBB and negative conventional workup</td>
<td>Rhythm at syncope recurrence as assessed by ILR</td>
<td>In pts with BBB and negative EPS, most syncopal recurrences result from prolonged asystolic pauses, mainly attributable to paroxysmal AVB.</td>
<td></td>
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<tr>
<td>Moya A, et al. 2011 (189) 21444367</td>
<td></td>
<td></td>
<td></td>
<td>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</td>
<td></td>
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</tbody>
</table>
<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

### 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

### McAnulty JH, et al. 1982 (278)

**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

### Kwok CS, et al. 2016 (279)

**Aim:** Determine if prolonged PR interval is associated with adverse CV outcomes and mortality.  
**Study type:** Systemic review + meta-analysis  
**Size:** 14 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.
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Study Type</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Size</th>
<th>Results</th>
<th>Exclusion Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boriani G, et al.</td>
<td>2003 (280)</td>
<td>Longitudinal, Observational</td>
<td>N/A</td>
<td>N/A</td>
<td>18 pts (age 42.8±19.6 y) with genetically confirmed X-linked (N=10) or autosomal dominant (N=8) EDMD</td>
<td>Pacemakers were required by 10 of 18 (56%) pts for bradyarrhythmia</td>
<td>• &gt;50% of pts with muscular dystrophy (EDMD) require PM implant. • Survival after PM implant is very reasonable</td>
</tr>
<tr>
<td>Mymin D, et al.</td>
<td>1986 (281)</td>
<td>Retrospective review</td>
<td>Healthy males</td>
<td>Females</td>
<td>107 pts with ccTGA</td>
<td>23 of 107 (21%) developed naturally occurring AVB at a rate of 2% per yr. 12 of 49 (24%) developed AVB at VSD closure.</td>
<td>• Primary first-degree heart block with moderate PR prolongation is a benign condition • may not apply to more marked prolongation of the PR interval</td>
</tr>
<tr>
<td>Huhta JC, et al.</td>
<td>1983 (282)</td>
<td>Retrospective review</td>
<td>52 pts with ccTGA</td>
<td>N/A</td>
<td>9 or 52 (17.3%) developed spontaneous AVB; 9 of 52 (17.3%) developed postoperative AVB</td>
<td>• 17% of pts developed progressive AVB unrelated to surgery</td>
<td></td>
</tr>
<tr>
<td>Connelly MS, et al.</td>
<td>1996 (283)</td>
<td>Retrospective review</td>
<td>52 pts with ccTGA</td>
<td>N/A</td>
<td>19 pts with lamin A mutations referred for pacing and receiving an ICD</td>
<td>9 pts (46%) received an appropriate shock for ventricular tachyarrhythmias</td>
<td>• The implantation of an ICD, rather than a PM, should be considered for these pts</td>
</tr>
<tr>
<td>Weidling SN, et al.</td>
<td>1998 (284)</td>
<td>Retrospective review</td>
<td>54 pts with postoperative heart block following congenital heart surgery</td>
<td>N/A</td>
<td>9 pts (46%) received an appropriate shock for ventricular tachyarrhythmias</td>
<td>31 of 32 pts who recovered AV conduction did so by the 9th postoperative day.</td>
<td>• 43% did not recover conduction • 97% of those who recovered conduction – did so by d 9</td>
</tr>
<tr>
<td>Meune C, et al.</td>
<td>2006. (285)</td>
<td>Retrospective observational</td>
<td>52 pts with ≥2 of: NSVT, LVEF &lt;45% at the first clinical contact, male sex, and non-missense mutations</td>
<td>N/A</td>
<td>269 pts with LMNA mutations</td>
<td>Malignant ventricular arrhythmias occurred (5%/y) in pts with ≥2 of: NSVT, LVEF &lt;45% at the first clinical contact, male sex, and non-missense mutations</td>
<td>• Specific risk factors portend a higher risk of ventricular arrhythmia in carriers of LMNA mutations</td>
</tr>
<tr>
<td>Maury P, et al.</td>
<td>2013. (287)</td>
<td>Retrospective review</td>
<td>325 pts</td>
<td>N/A</td>
<td>1204 pts; 12 had device implant during follow-up for bradyarrhythmias</td>
<td>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)</td>
<td>• First degree AVB is independently linked to outcome and may be proposed to be used for individual risk stratification</td>
</tr>
<tr>
<td>O’Mahony C, et al.</td>
<td>2011. (288)</td>
<td>Observational, longitudinal, retrospective cohort study</td>
<td>N/A</td>
<td>N/A</td>
<td>20 pts; 12 had device implant during follow-up for bradyarrhythmias</td>
<td>Independent predictors of future antibradycardia pacing were (in a multivariable Cox model): QRSd and PR interval duration</td>
<td>• Pacing for AV and sinus node disease is common (±8%) • Pts with QRS ≥110 ms should be closely monitored for bradyarrhythmias</td>
</tr>
<tr>
<td>Study Acronym; Author; Year Published</td>
<td>Aim of Study; Study Type; Study Size (N)</td>
<td>Patient Population</td>
<td>Study Intervention (# patients) / Study Comparator (# patients)</td>
<td>Endpoint Results (Absolute Event Rates, P values; OR or RR; &amp; 95% CI)</td>
<td>Relevant 2° Endpoint (if any); Study Limitations; Adverse Events</td>
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<tr>
<td>Polak PE, et al. 1989 (289) 2707275</td>
<td><strong>Study type:</strong> Case series</td>
<td>2 pts</td>
<td>Pts with fascicular block progressed to PM-dependent complete block</td>
<td>• N/A</td>
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<tr>
<td>Khambatta S, et al. 2014 (290) 25061332</td>
<td><strong>Study type:</strong> Retrospective review</td>
<td>35 pts</td>
<td>PM/ICD required in 31 % (11 pts) 4 pts (11%) in the series died, but all deaths were from sudden cardiac events.</td>
<td>• High incidence of device implantation implant and sudden death</td>
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<tr>
<td>Ali H, et al. 2017 (291) 28583850</td>
<td><strong>Study type:</strong> Systematic Review</td>
<td>Case reports on CHB following blunt cardiac injury were available for 50 pts</td>
<td>PPM implantation was indicated in ~50% of early survivors because of recurrent or permanent CHB. BBB was present in &gt;70% of pts A fatal outcome occurred in 20% of pts; structural damage of AV conduction system in 50% of necropsies</td>
<td>• 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</td>
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<tr>
<td>Study Acronym; Author; Year Published</td>
<td>Study Type/Design; Study Size</td>
<td>Patient Population</td>
<td>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</td>
<td>Summary/Conclusion Comment(s)</td>
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| 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 |
<table>
<thead>
<tr>
<th>Author et al.</th>
<th>Year/Ref</th>
<th>Aim</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Bauer AM, et al.</td>
<td>2014 (295)</td>
<td><strong>Aim:</strong> Study type: Case report</td>
<td></td>
<td></td>
<td>N/A</td>
<td>None</td>
<td>N/A</td>
<td>Single pt with a carotid body tumor who became asystolic during surgery</td>
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<tr>
<td>Fritsch G, et al.</td>
<td>2012 (296)</td>
<td><strong>Aim:</strong> Identify factors associated with surgical complications</td>
<td>Study type: Retrospective analysis</td>
<td>1,363 consecutive pts</td>
<td>1,363 consecutive pts in a 3 mo period scheduled for elective surgery</td>
<td>None</td>
<td>86 pts (6.3%) developed some complication. Hypotension most common but 20 pts (1.5%) developed hemodynamically relevant bradycardia</td>
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<tr>
<td>Perreira ID, et al.</td>
<td>2011 (297)</td>
<td><strong>Aim:</strong> Identify factors associated with intraoperative bradycardia</td>
<td>Study type: Retrospective</td>
<td>80,660 pts with neuraxial anesthesia from a single center</td>
<td>&gt;18 y old</td>
<td>None</td>
<td>Sinus bradycardia</td>
<td></td>
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<tr>
<td>Mitar MD, et al.</td>
<td>2015 (298)</td>
<td><strong>Aim:</strong> Evaluate pacing requirement for rotational atherectomy</td>
<td>Study type: Retrospective</td>
<td>Consecutive pts undergoing rotational atherectomy</td>
<td>None</td>
<td>(2nd degree AVB or asystole &gt;2 s in the no PM group</td>
<td>Pacemaker activated in PM group or AVB in no PM group in pts with RCA or Cx PCI</td>
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© 2018 American College of Cardiology Foundation, American Heart Association, Inc., and the Heart Rhythm Society.
| Im SH, et al. 2008 (299)  
18254669 | **Size:** 138 pts  
Temporary pacing in 67  
No temporary pacing in 67 | • LAD: 2/38 (5%)  
• Cx: 10/25 (40%)  
• RCA: 28/51 (55%) | • Pacing support often required with elective carotid angioplasty and stenting |
|---|---|---|---|
| **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%) | |
| Bush RL, et al. 2004 (300)  
15181504 | **Size:** 48 pts who underwent 51 procedures | **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 | **Size:** 43 pts underwent 47 carotid artery angioplasty and stenting procedures | **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 |
<table>
<thead>
<tr>
<th>Reference</th>
<th>Aim</th>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
<th>1° endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gauss A, et al. 1999 (302) 10456813</td>
<td>Evaluation of transcutaneous pacing in pts thought to be at risk for bradycardia (trifascicular block)</td>
<td>Consecutive, prospective</td>
<td>Consecutive pts with asx chronic 1st degree AVB and LBBB or bifascicular block.</td>
<td>Progression of AVB, asystole &gt;5 s or bradycardia &lt;40 bpm &gt;10 s</td>
<td>• 37 of 39 pts could be paced transcutaneously</td>
<td>Requirement for pacing rate support</td>
<td>• No pts absolutely required pacing for rate support</td>
</tr>
<tr>
<td>Killeavey ES, et al. 1990 (303) 15227187</td>
<td>Evaluate the use of transvenous pacing during PCI</td>
<td>Retrospective</td>
<td>Consecutive pts undergoing PCI</td>
<td>Requirement for pacing</td>
<td>• 2 pts developed ventricular arrhythmias associated with prophylactic pacing (0.5%)</td>
<td>Requirement for pacing low</td>
<td></td>
</tr>
<tr>
<td>Chowdhury T, et al. 2015 (304) 26656339</td>
<td>Propofol boluses aborted the trigeminal cardiac reflex (TCR) induced severe bradycardia during dural manipulation.</td>
<td>Case report</td>
<td>N/A</td>
<td>N/A</td>
<td>During dural stimulation, propofol 50 mg IV terminated sinus bradycardia</td>
<td>Case report discussing that during dural stimulation, propofol 50 mg IV terminated sinus bradycardia</td>
<td></td>
</tr>
<tr>
<td>Yong J, et al. 2015 (305) 26424701</td>
<td>Evaluate development of cardiac arrest during laparoscopic surgery</td>
<td>N/A</td>
<td>Cardiac arrest pts</td>
<td>Cardiac arrest (bradycardia)</td>
<td>• 9/14 bradycardia</td>
<td>Bradycardia common during laparoscopy</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study type</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective analysis of the Australian Incident Monitoring Study (AIMS) database</td>
<td>Case report of asystole during dural manipulation</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Bradycardia and asystole during dural manipulation and excision of a temporal lobe meningioma (near the left insula)</td>
</tr>
<tr>
<td>Size: 14 cases from &gt;11,000 pt database</td>
<td></td>
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<tr>
<td>Insufflation or establishment of pneumoperitoneum (12/14; 86%) Anesthesia induction (2/14; 14%)</td>
<td></td>
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<tr>
<td>Vimala S, et al. 2016 (306) 26114985</td>
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</tr>
<tr>
<td>Aim: Evaluate the use of transvenous pacing during PCI</td>
<td>Case report of asystole during dural manipulation</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Bradycardia and asystole during dural manipulation and excision of a temporal lobe meningioma (near the left insula)</td>
</tr>
<tr>
<td>Study type: Case report</td>
<td>Inclusion criteria: 60 y undergoing maxillectomy for squamous cell cancer</td>
<td>Exclusion criteria: N/A</td>
<td>1° endpoint: N/A</td>
<td>Results: Asystole during posterior osteotomy Bradycardia again during manipulation of the posterior maxillary tuberosity Treatment by atropine and minimizing surgical manipulation</td>
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<tr>
<td>Size: 1</td>
<td></td>
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<tr>
<td>Mohan S, et al. 1990 (307) 24788865</td>
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</tr>
<tr>
<td>Aim: Evaluate the use of cilostazol for preventing bradycardia during carotid artery stenting</td>
<td>Case report of asystole during dural manipulation</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Bradycardia and asystole during dural manipulation and excision of a temporal lobe meningioma (near the left insula)</td>
</tr>
<tr>
<td>Study type: Case report</td>
<td>Inclusion criteria: Pts who underwent carotid artery stenting at a single institution</td>
<td>Exclusion criteria: None</td>
<td>1° endpoint: Bradycardia (&lt;50 bpm or hypotension (&lt;90 mm Hg)</td>
<td>Results: Intraprocedural bradycardia: Cilostazol: 4/26 (15%) No cilostazol: 15/28 (54%) Postprocedure bradycardia Cilostazol: 0/26 No cilostazol: 3/28 (11%)</td>
<td></td>
</tr>
<tr>
<td>Size: 53 pts who underwent 54 carotid artery stenting procedures divided into procedures where pts received cilostazol (26) and those who did not (28)</td>
<td></td>
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<tr>
<td>Ishii D, et al. 1990 (308) 23834853</td>
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</tr>
<tr>
<td>Aim: Evaluate the use of cilostazol for preventing bradycardia during carotid artery stenting</td>
<td>Case report of asystole during dural manipulation</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Bradycardia and asystole during dural manipulation and excision of a temporal lobe meningioma (near the left insula)</td>
</tr>
<tr>
<td>Study type: Retrospective</td>
<td>Inclusion criteria: Pts who underwent carotid artery stenting at a single institution</td>
<td>Exclusion criteria: None</td>
<td>1° endpoint: Bradycardia (&lt;50 bpm or hypotension (&lt;90 mm Hg)</td>
<td>Results: Intraprocedural bradycardia: Cilostazol: 4/26 (15%) No cilostazol: 15/28 (54%) Postprocedure bradycardia Cilostazol: 0/26 No cilostazol: 3/28 (11%)</td>
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<td>Study</td>
<td>Aim</td>
<td>Study type</td>
<td>Size</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
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<tr>
<td>Schipke JD, et al. 2013 (309) 23332411</td>
<td>1 pt who developed asystole during paranasal sinus surgery</td>
<td>Case report</td>
<td>1</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Haldar R, et al. 2013 (310) 23242253</td>
<td>1 pt who developed bradycardia during skull pin fixation</td>
<td>Case report</td>
<td>1</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Seo KC, et al. 2010 (311) 20498810</td>
<td>Identify possible factors contributing to bradycardia and hypotension during shoulder surgery</td>
<td>Retrospective</td>
<td>63</td>
<td>ASA I/II pts who received interscalene block for arthroscopic shoulder surgery in the sitting position</td>
<td>N/A</td>
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<tr>
<td>Jeyabalan G, et al. 2010 (312) 20557186</td>
<td>Identify factors associated with bradycardia during pharmacomechanical thrombectomy for deep vein thrombosis</td>
<td>Retrospective</td>
<td>57 pts</td>
<td>Consecutive pts who underwent pharmacomechanical (AngioJet) therapy for deep vein thrombosis</td>
<td>N/A</td>
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<tr>
<td>Usami K, et al. 2010 (313) 20448432</td>
<td>Describe 3 pts who developed bradycardia with surgery for cerebellopontine angle meningiomas</td>
<td>Case series of pts with bradycardia during meningioma surgery</td>
<td>3</td>
<td>N/A</td>
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</tr>
<tr>
<td>Study type: Case series</td>
<td>Exclusion criteria: N/A</td>
<td>Inclusion criteria: Case series, N/A</td>
<td>Lubbers HT, et al. 2010 (314) 20347202</td>
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<tr>
<td><strong>Aim:</strong> Describe 3 pts who developed bradycardia with craniomaxillofacial surgery.</td>
<td><strong>Exclusion criteria:</strong> N/A</td>
<td><strong>1° endpoint:</strong> Bradycardia</td>
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<tr>
<td><strong>Study type:</strong> Case series</td>
<td><strong>Exclusion criteria:</strong> N/A</td>
<td><strong>Results:</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Size:</strong> 3</td>
<td><strong>Inclusion criteria:</strong> Case series, N/A</td>
<td>• Describe 3 pts identified from a single center surgical database with bradycardia during craniomaxillofacial surgery</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Inclusion criteria:</strong> Case series, N/A</td>
<td><strong>1° endpoint:</strong> Adverse events including bradycardia</td>
<td></td>
<td>Christensen RE, et al. 2010 (315) 19933174</td>
<td></td>
<td></td>
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<tr>
<td><strong>Aim:</strong> Describe outcomes in pts with surgically corrected D transposition of the great arteries (D-TGA) undergoing noncardiac surgery</td>
<td><strong>Exclusion criteria:</strong> N/A</td>
<td><strong>Results:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study type:</strong> Retrospective</td>
<td><strong>1° endpoint:</strong> Adverse events including bradycardia</td>
<td>• 4 adverse events observed in pts with congenital heart disease and noncardiac surgeries.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Size:</strong> 50 procedures (34 pts)</td>
<td><strong>Inclusion criteria:</strong> Consecutive pts with surgically corrected D-TGA undergoing noncardiac surgery (43 pediatric and 7 adults)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong> N/A</td>
<td></td>
<td></td>
<td>Jacques F, et al. 2009 (316) 18657390</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Aim:</strong> Compare regional anesthesia and general anesthesia for CEA surgery</td>
<td><strong>Inclusion criteria:</strong> Consecutive pts undergoing CEA from a single center</td>
<td><strong>1° endpoint:</strong> Hypotension and bradycardia (&lt;60 bpm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study type:</strong> Retrospective</td>
<td><strong>Exclusion criteria:</strong> None</td>
<td><strong>Results:</strong> Regional anesthesia associated with less intraoperative bradycardia (4%) when compared to general anesthesia (63%)</td>
<td></td>
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</tr>
<tr>
<td><strong>Size:</strong> 72 Regional anesthesia: 25 General anesthesia: 47</td>
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</tbody>
</table>

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<table>
<thead>
<tr>
<th>Reference</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1º endpoint</th>
<th>Results</th>
</tr>
</thead>
</table>
| 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 | | **1º endpoint:** Bradycardia and hypotension  
**Results:**  
- No specific data on bradycardia but those pts with lower heart rate variability (stratified by a total power $<500 \text{Ms}^2\text{Hz}^{-1}$) were more likely to develop hypotension and bradycardia  
- 4/50 pts in the retrospective model development group had bradycardia ($<50 \text{bpm}$) | • 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 | | **1º 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 | | **1º 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 | | **1º endpoint:** Bradycardia  
**Results:**  
- Bradycardia (35 bpm) with induction of anesthesia | • Bradycardia (35 bpm) with induction of anesthesia |
**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).  

---

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| 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 |
### Data Supplement 47. Nonrandomized Trials, Observational Studies, and/or Registries of CABG (Section 8.1.2.1)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| 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  
**1º 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  
**1º 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  
**1º 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 |
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>Intervention</th>
<th>Comparator</th>
<th>1° endpoint</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspi Y, et al. 1987 (339)</td>
<td>Identify incidence of conduction block after CABB</td>
<td>Pts undergoing CABG</td>
<td>CABG</td>
<td>Pts who did not have conduction block</td>
<td>17% had new bundle branch block associated with preop MI, low cardiac output and death</td>
<td>Small. retrospective. Potentially dated due to changes in surgical technique</td>
</tr>
<tr>
<td>Zeldis SM, et al. 1978 (340)</td>
<td>Identify frequency of new fascicular conduction disturbances after CABG</td>
<td>Isolated CABG</td>
<td>CABG</td>
<td>Pts who did not have conduction block</td>
<td>20% new disturbances, 6% RBBB, 6% LAH. Pts with transient or persistent LBB or L anterior hemiblock had increased late mortality and MI</td>
<td>Small, retrospective. Potentially dated due to changes in surgical technique</td>
</tr>
<tr>
<td>Cook DJ, et al. 2005 (341)</td>
<td>Assess incidence of new conduction defects over time after isolated CABG</td>
<td>Isolated CABG pts</td>
<td>CABG</td>
<td>Pts whose operations were performed in 1991 vs. 2001</td>
<td>Decline in conduction defects from 19% to 6%. Associated with year of operation, age, IABP use, number of vessels bypassed and crystalloid cardioplegia</td>
<td>Small, retrospective</td>
</tr>
<tr>
<td>Tuzcu EM, et al. 1990 (342)</td>
<td>Identify incidence and significance of new conduction defects after CABG</td>
<td>Isolated elective CABG</td>
<td>CABG</td>
<td>Matched pts w/o conduction defects</td>
<td>5.5% new conduction block, 85% RBBB, 4% LBBB. No difference in late mortality or need for PM with matched group</td>
<td>Small, retrospective</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Year</td>
<td>PMID</td>
<td>Study Type</td>
<td>Size</td>
<td>Aim</td>
<td>Inclusion Criteria</td>
</tr>
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<tr>
<td>Ngaage DL, et al.</td>
<td>2007 (343)</td>
<td>17198809</td>
<td>Observational, matched</td>
<td>526</td>
<td>Influence of preop AF on outcomes after CABG</td>
<td>Pts undergoing CABG with preop AF</td>
</tr>
<tr>
<td>Yesil M, et al.</td>
<td>2008 (344)</td>
<td>18855876</td>
<td>Observational</td>
<td>53</td>
<td>Determine effect of revascularization on present conduction disturbances</td>
<td>Pts with CAD and 3rd degree block</td>
</tr>
<tr>
<td>Satinsky JD, et al.</td>
<td>1974 (345)</td>
<td>4843620</td>
<td>Retrospective case series</td>
<td>280 pts</td>
<td>Evaluate effects of cardiac surgery on new conduction defects</td>
<td>Pts undergoing cardiac surgery</td>
</tr>
<tr>
<td>Study Acronym; Author; Year Published’ PMID</td>
<td>Study Type/Design; Study Size</td>
<td>Patient Population</td>
<td>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</td>
<td>Summary/Conclusion Comment(s)</td>
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<tr>
<td>Dawkins S, et al. 2008 (332) 18154792</td>
<td><strong>Aim</strong>: Determine incidence and predictors of PPM after AVR&lt;br&gt;<strong>Study type</strong>: Observational&lt;br&gt;<strong>Size</strong>: 354</td>
<td><strong>Inclusion criteria</strong>: Pts undergoing AVR&lt;br&gt;<strong>Exclusion criteria</strong>: Pts with preop pacer</td>
<td><strong>Intervention</strong>: PM placement&lt;br&gt;<strong>Comparator</strong>: No pacer required&lt;br&gt;<strong>1º endpoint</strong>: 8.5% required permanent pacer. Only predictor: preop conduction system disease (RR: 2.88).</td>
<td>• Small, retrospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limongelli G, et al. 2003 (346) 12860869</td>
<td><strong>Aim</strong>: Identify incidence and predictors of PPM after AVR&lt;br&gt;<strong>Study type</strong>: Observational cohort&lt;br&gt;<strong>Size</strong>: 276</td>
<td><strong>Inclusion criteria</strong>: Pts undergoing AVR</td>
<td><strong>Intervention</strong>: PPM&lt;br&gt;<strong>Comparator</strong>: No PPM&lt;br&gt;<strong>1º endpoint</strong>: 3.2% required PPM. Risk factors: preop AI, MI, PHTN, and postop electrolyte abnormalities.</td>
<td>• Small, retrospective&lt;br&gt;• Did not control for preop conduction abnormalities</td>
<td></td>
<td></td>
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<tr>
<td>Bagur R, et al. 2011 (347) 21828221</td>
<td><strong>Aim</strong>: Identify incidence and predictors of PPM after AVR in elderly&lt;br&gt;<strong>Study type</strong>: Observational cohort&lt;br&gt;<strong>Size</strong>: 780</td>
<td><strong>Inclusion criteria</strong>: Pts ≥70 y undergoing isolated AVR&lt;br&gt;<strong>Exclusion criteria</strong>: Age &lt;70 y, preop PPM/AICD, ascending aortic replacement</td>
<td><strong>Intervention</strong>: PPM&lt;br&gt;<strong>Comparator</strong>: NO PPM&lt;br&gt;<strong>1º endpoint</strong>: 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.</td>
<td>• Small, retrospective</td>
<td></td>
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</tr>
<tr>
<td>Baraki H, et al. 2013 (348) 23300203</td>
<td><strong>Aim</strong>: Determine if AVN function recovers after PPM post AVR&lt;br&gt;<strong>Study type</strong>: Observational cohort&lt;br&gt;<strong>Size</strong>: 138/2,106</td>
<td><strong>Inclusion criteria</strong>: PPM post AVR&lt;br&gt;<strong>Exclusion criteria</strong>: Death</td>
<td><strong>Intervention</strong>: PM interrogation&lt;br&gt;<strong>1º endpoint</strong>: only 10% of survivors were no longer pacer-dependent</td>
<td>• Small, retrospective</td>
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<tr>
<td>Reference</td>
<td><strong>Aim:</strong> Determine if PPM after AVR effects survival</td>
<td><strong>Inclusion criteria:</strong> Pts undergoing AVR</td>
<td><strong>Intervention:</strong> PPM within 30 d of surgery (N=146)</td>
<td><strong>Comparator:</strong> No PPM</td>
<td><strong>1° endpoint:</strong> PPM associated with increased mortality (HR: 1.49).</td>
<td><strong>Study type:</strong> Observational cohort</td>
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<td>Greason KL, et al. 2017 (349)</td>
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<td>28433222</td>
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<tr>
<td>Berdajs D, et al. 2008 (350)</td>
<td><strong>Aim:</strong> Identify cause of conduction block after MV surgery</td>
<td><strong>Inclusion criteria:</strong> 2 populations: (1) those undergoing MV operations and (2) cadaver dissection</td>
<td><strong>Intervention:</strong> (1) MVR +/- PPM: (2) dissection</td>
<td><strong>1° endpoint:</strong> (1) 23% AVB, 4% needed PPM. (2) 23% of cadavers had AV nodal artery running near MV annulus</td>
<td><strong>Study type:</strong> Observational cohort, autopsy</td>
<td><strong>Size:</strong> 391/92/55</td>
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<td>18482844</td>
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<tr>
<td>Goldstein D, et al. 2016 (351)</td>
<td><strong>Aim:</strong> Compare outcomes between chordal-sparing mitral replacement and mitral repair</td>
<td>N/A</td>
<td><strong>Intervention:</strong> Mitral valve repair or replacement</td>
<td><strong>1° endpoint:</strong> Readmission higher in MV repair group largely due to higher rate of PPM/AICD placement (59 vs. 38)</td>
<td><strong>Study type:</strong> RCT sub-analysis</td>
<td><strong>Size:</strong> 256</td>
</tr>
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<td>26550689</td>
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<tr>
<td>Saint LL, et al. 2013 (352)</td>
<td><strong>Aim:</strong> Identify incremental risk of adding a maze operation in MV surgery</td>
<td>N/A</td>
<td><strong>Intervention:</strong> MV surgery plus Maze</td>
<td><strong>Comparator:</strong> MV surgery w/o Maze</td>
<td><strong>Study type:</strong> Observational cohort</td>
<td><strong>Size:</strong> 213</td>
</tr>
<tr>
<td></td>
<td>23998785</td>
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<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>Intervention</td>
<td>Comparator</td>
<td>1° endpoint</td>
<td>Safety endpoint</td>
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<tr>
<td>Gammie JS, et al. 2008 (353) 18291169</td>
<td><strong>Aim:</strong> Identify if AF surgery increased risk in pts undergoing mitral surgery</td>
<td>All pts in database</td>
<td>MV surgery + preop AF + AF correction</td>
<td>MV surgery + preop AF - AF correction</td>
<td>Mortality same: PPM higher in Maze group (AOR: 1.26)</td>
<td></td>
</tr>
<tr>
<td>Gillinov AM, et al. 2015 (354) 25853744</td>
<td><strong>Aim:</strong> Determine if the addition of AF surgery to MV surgery is effective</td>
<td>Pre-op AF + MV surgery</td>
<td>MV+ AF surgery</td>
<td>MV – AF surgery</td>
<td>Lower rate of AF post maze (63% vs. 24%), Higher need for PPM (21 vs. 8 per 100 pt y)</td>
<td></td>
</tr>
<tr>
<td>Phan K, et al. 2014 (355) 24650881</td>
<td><strong>Aim:</strong> Determine efficacy of AF surgery</td>
<td>RCT</td>
<td>AF surgery</td>
<td>No AF surgery</td>
<td>No difference in mortality</td>
<td></td>
</tr>
<tr>
<td>Chikwe J, et al. 2015 (356) 25936265</td>
<td><strong>Aim:</strong> To assess long-term effect of TV repair</td>
<td>Mitral surgery</td>
<td>Tricuspid repair</td>
<td>No TV repair</td>
<td>No difference in morbidity, mortality or PPM (2.4% vs. 1.3%)</td>
<td></td>
</tr>
<tr>
<td>Scully HE, et al. 1995 (357) 7776666</td>
<td><strong>Aim:</strong> Describe early and late results after tricuspid valve replacement</td>
<td>Pts undergoing tricuspid valve surgery</td>
<td>Tricuspid replacement</td>
<td></td>
<td></td>
<td>Small, retrospective, Potentially outdated surgical technique</td>
</tr>
</tbody>
</table>
### Data Supplement 49. Nonrandomized Trials, Observational Studies, and/or Registries of Conduction Abnormalities After TAVR (Section 8.1.2.4)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published; PMID</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence of Conduction Abnormality and PPM</strong></td>
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<tr>
<td>Piazza N, et al. 2008 (360) 19463319</td>
<td><strong>Study type</strong>: Retrospective</td>
<td><strong>Inclusion criteria</strong>: CoreValve TAVR 11/2005 3/2008</td>
<td><strong>1° endpoint</strong>: Conduction abnormalities and the need for pacing</td>
<td>• Significant increase in LBBB • Pts with RBBB may be at risk for CHB</td>
</tr>
<tr>
<td></td>
<td><strong>Size</strong>: 40</td>
<td><strong>Results</strong>:</td>
<td></td>
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<tr>
<td>Roten L, et al. 2010 (361) 21059439</td>
<td><strong>Study type</strong>: Observational</td>
<td><strong>Inclusion criteria</strong>: MDT or Edwards TAVI Follow-up: &gt;30 d</td>
<td><strong>1° endpoint</strong>: AV conduction abnormality and/or need for PPM</td>
<td>• TAVI associated with AV conduction impairment • 3°HB resolves in over half pts • Preexisting RBBB at risk for 3°HB</td>
</tr>
<tr>
<td></td>
<td><strong>Size</strong>: 67</td>
<td><strong>Exclusion criteria</strong>: Pre-existing PPM</td>
<td><strong>Results</strong>: PPP 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)</td>
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<tr>
<td>Study type</td>
<td>Size</td>
<td>Inclusion criteria</td>
<td>1° endpoint</td>
<td>Results</td>
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<tr>
<td>van der Boon, RM, et al. 2013 (362)</td>
<td>167 pts from 11/2005–2/2011</td>
<td>who received new PPM after TAVR</td>
<td>Number pacer dependent at median follow-up 11.5 mo (IQR 5–18)</td>
<td>16 of 30 (53.3%) with HDAVB Overall 20 of 36 (55.6%)</td>
</tr>
<tr>
<td>Siontis, GC, et al. 2014 (363)</td>
<td>41 studies encompassing 11,210 pts</td>
<td>Studies reporting incidence of PPM after TAVR</td>
<td>PPM post TAVR</td>
<td>Increased risk of PPM Men- RR: 1.23; p&lt;0.01 1°block- RR: 1.52; p&lt;0.01 L ant hemiblock-RR: 2.89; p&lt;0.01 RBBB- RR: 2.89; p&lt;0.01 AVB- RR: 3.49; p&lt;0.01</td>
</tr>
<tr>
<td>Boerlage-Van Dijk K, 2014 (364)</td>
<td>121</td>
<td>Single center TAVR 10/2007–6/2011 Follow-up 1, 3 and 12 mo</td>
<td>Conduction abnormalities and new PPM</td>
<td>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</td>
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<tr>
<td>Nazif TM, et al. 2015 (365)</td>
<td>1973</td>
<td>In PARTNER Registry</td>
<td>New PPM</td>
<td>8% new PPM Predictors: RBBB (OR: 7.03, 4.92–10.06; p&lt;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</td>
</tr>
<tr>
<td>FRANCE 2</td>
<td>833</td>
<td>centers in FRANCE 2 registry</td>
<td>Incidence of new PPM or Mortality at 242±179 d</td>
<td>All-cause mortality same in PPM vs. no PPM at mean follow-up of 8 mo</td>
</tr>
<tr>
<td>Study type</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>Results</td>
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<tr>
<td>Abramowitz Y, et al. 2017 (367) 28039339</td>
<td>Inclusion criteria: 3 y series of TAVR at Cedars-Sinai</td>
<td>Exclusion criteria: N/A</td>
<td>1° endpoint: 30 d mortality ± MAC</td>
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<td></td>
<td>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)</td>
<td>• 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</td>
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<td>Results: New LBBB in 26.5% (ESV 13.5%, MCVS 50%) Persistent LBBB at discharge= 17.2% New PPM=12.7% (2° CHB, bradycardia)</td>
<td>• LBBB was NOT a predictor of: PPM, overall mort, cardiac mort, at 1 y</td>
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<tr>
<td>Urena M, et al. 2012 (369) 23040577</td>
<td>Study type: Observational</td>
<td>Size: 202, median follow-up 12 mo</td>
<td>Inclusion criteria: TAVR 1° endpoint: New onset LBBB</td>
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<td>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&lt;0.001) no increase in global or cardiac mortality</td>
<td>• 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</td>
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<td>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)</td>
<td>• 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</td>
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<tr>
<td>Egger F, et al. 2014 (371)</td>
<td>Study type: Single center prospective</td>
<td>Inclusion criteria: TAVR 1° endpoint: Development of high degree AVB</td>
<td>• In pts with LBBB after TAVR, intensified</td>
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<tr>
<td>Study</td>
<td>Size</td>
<td>Inclusion criteria</td>
<td>Exclusion criteria</td>
<td>Results</td>
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<tr>
<td>25034184</td>
<td>50</td>
<td>10 with pre-existing LBBB and 7 with new LBBB received new DDD PMI</td>
<td></td>
<td>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)</td>
</tr>
<tr>
<td>Schymik G, et al. 2015 (372) 25388650</td>
<td>197</td>
<td>New onset LBBB after TAVR</td>
<td>N/A</td>
<td>Mortality</td>
</tr>
<tr>
<td>Regueiro A, et al. 2016 (373) 27169577</td>
<td>17 studies 4,756 pts w/new LBBB 7,032 pts w/new LBBB&amp;PPI</td>
<td>New LBBB post TAVR</td>
<td>N/A</td>
<td>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 -&gt; NO protective effect on cardiac death (RR: 0.78, 0.6–1.03)</td>
</tr>
<tr>
<td>Mauri V, et al. 2016 (374) 27832845</td>
<td>229 8/2013–1/2016</td>
<td>TAVR with Edwards SAPIEN 3</td>
<td>N/A</td>
<td>PPI</td>
</tr>
<tr>
<td>OCEAN–TAVI Wantanabe, Y, et al. 2016 (375) 27832846</td>
<td>749, 102 with RBBB 10/2013–8/2015</td>
<td>TAVR at 8 Japanese centers</td>
<td>N/A</td>
<td>Incidence of PPI and death with pre-existent RBBB</td>
</tr>
<tr>
<td>Reference</td>
<td>Study type</td>
<td>Inclusion criteria</td>
<td>1° endpoint</td>
<td>Results</td>
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<tr>
<td>Nazif TM, et al. 2015 (365) 25616819</td>
<td>Analysis of PARTNER Trial and Registry post hoc</td>
<td>TAVR</td>
<td>Requiring ppm</td>
<td>New PPM RBBB vs. no RBBB: 47.6% vs. 12.8%; p&lt;0.001</td>
</tr>
<tr>
<td>Auffret V, et al 2017 (376) 28734885</td>
<td>Multicenter</td>
<td>TAVR</td>
<td>Complications and death</td>
<td>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&lt;0.001)</td>
</tr>
<tr>
<td>Rampat R, et al. 2017 (377) 28641846</td>
<td>Retrospective multicenter</td>
<td>LOTUS TAVR</td>
<td>PPM</td>
<td>PPM in 64 pts for AVB or LBBB and first degree AVB. Preprocedural conduction abnormality associated with higher likelihood for PPM</td>
</tr>
<tr>
<td>Nombela-Franco L, et al. 2015 (378) 26476610</td>
<td>Observational</td>
<td>TAVR</td>
<td>Early readmission &lt;30 d Late readmission 30–365 d</td>
<td>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)</td>
</tr>
<tr>
<td>Urena, M, et al. 2015 (379) 25660921</td>
<td>Observational</td>
<td>TAVR at 18 centers</td>
<td>Death from HF and SCD post TAVR mean follow-up 22 mo</td>
<td>• New onset persistent LBBB is a predictor of SCD post TAVR • PPI in LBBB is not protective against SCD</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>1st endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series of pts in PARTNER Trial and Registry - post hoc analysis</td>
<td>Trial and registry, 1-y follow-up</td>
<td>1 y mortality and re-hospitalization</td>
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<thead>
<tr>
<th>Size</th>
<th>Exclusion criteria</th>
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</thead>
</table>
| Prior ppm: 586
New ppm: 173
No ppm: 1612
LBBB& no ppm: 160 | N/A |

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)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| 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 biaatrial 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 biaatrial 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 study  
**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 | |
<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1st endpoint</th>
<th>Results</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knight CS, et al. 2010 (385) 19144548</td>
<td>Case series</td>
<td>Pts identified from a transplant database with syncope due to bradycardia</td>
<td>None</td>
<td>Pathologic evaluation</td>
<td>Autopsy revealed preferential severe rejection in the cardiac conduction system</td>
<td>Rejection can preferentially affect the conduction system</td>
</tr>
<tr>
<td>Braith RW, et al. 2000 (386) 11144044</td>
<td>Prospective treadmill testing</td>
<td>Transplant with PPM</td>
<td>None</td>
<td>Treadmill performance</td>
<td>Chronotropic support improves treadmill times (14.6 min vs. 12.4 min) and peak VO₂ (18.9 vs. 15.4 mL/kg/min)</td>
<td>Rate adaption helpful</td>
</tr>
<tr>
<td>Bacal F, et al. 2000 (387) 10904516</td>
<td>Single center retrospective</td>
<td>Transplant</td>
<td>None</td>
<td>Temporary or permanent pacing</td>
<td>14/114 (12%) required temporary pacing mainly for SND (78.5%), 4 pts required PPM, 3 for SND Rejection with AF</td>
<td>SND main reason for PPM or temporary pacing after transplant</td>
</tr>
<tr>
<td>Nagele H, et al. 1998 1998 (388) 9773864</td>
<td>Single center retrospective</td>
<td>Transplant and placement of epicardial biatrial pacing</td>
<td>None</td>
<td>NYHA class, hemodynamic parameters</td>
<td>Modest improvement with biatrial pacing</td>
<td>Biatrial pacing may be beneficial</td>
</tr>
<tr>
<td>Jones DG, et al. 2011 (389) 21783383</td>
<td>Single center retrospective</td>
<td>PPM after transplant</td>
<td>None</td>
<td>Prognosis</td>
<td>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.</td>
<td>Late pacing not associated with rejection</td>
</tr>
</tbody>
</table>
Late pacing not associated with rejection

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| Cantillon DJ, et al. 2010 (390) 20601151 | **Study type:** UNOS **Size:** 35,998 pts | **Inclusion criteria:** Transplant and PPM **Exclusion criteria:** None | **1º endpoint:** Outcomes  
• 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 |
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
<th>2° endpoint</th>
<th>Results</th>
</tr>
</thead>
</table>
| Liebregts M, et al. 2017 (391) | Evaluate use of ASA particularly in younger pts | Retrospective analysis of 3 registries | 1,197 pts who underwent ASA | International multicenter study of pts who underwent ASA (National registries of Germany, Netherlands, Denmark) | None | All-cause mortality Adverse arrhythmic event (VT, VF, appropriate ICD shocks) | • 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%) | Periprocedural AVB (<30 d) PPM | 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) | Evaluate outcomes between ASA and myectomy | Systematic search | 15 articles-14 observational and 1 meta-analysis | Systematic search-keywords: Cardiomyopathy and myectomy and ablation 218 studies | 15 studies chosen as best nonoverlapping studies | Multiple depending on study | • PPM implant:  
  - ASA: 1.7–22%  
  - Myectomy: 2.4%–12.5% | | |
| Axelsson A, et al. 2014 (393) | Evaluate AV conduction over time after ASA | | Pts who underwent ASA | Baseline CIED | Pacing and AV conduction over time | Late PPM in 3 pts at variable times after ASA  
About 40% of pts who need PPM will have recurrent 1:1 AV | | |
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Inclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veselka J, et al. 2014 (394) 24360153</td>
<td>Evaluate outcomes in pts with PPM for AVB after ASA</td>
<td>167 consecutive pts with HCM who underwent ASA for LVOT gradients</td>
<td>17 pts (10%) required PPM placed 3–15 d after ASA</td>
<td>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.</td>
<td>Recovery of AV conduction was high at 6 mo. Pacemakers placed if conduction block &gt;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.</td>
</tr>
<tr>
<td>El-Jack SS, et al. 2007 (395) 17300408</td>
<td>Evaluate ECG changes after ASA</td>
<td>50 pts who underwent ASA</td>
<td>ECG changes</td>
<td>ECG changes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• New RBBB (57%)</td>
<td>• PPM placed if CHB &gt;24 h.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>• Transient CHB with recovery &lt;24 h: 10 pts (20%)</td>
<td>• PPM more likely with baseline LBBB.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>• Persistent CHB (&gt;24 h) requiring PPM: 9 pts (18%)</td>
<td>• 7/9 were still PPM dependent at 14 d.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• PPM more likely with baseline LBBB.</td>
<td>• New RBBB common (57%).</td>
</tr>
<tr>
<td>McCann, GP et al. 2007 (396) 17293204</td>
<td>Evaluate scarring after ASA</td>
<td>Consecutive pts undergoing ASA</td>
<td>ECG changes</td>
<td>ECG after ASA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 2 with persistent RBBB</td>
<td>• New RBBB suggestive of more extensive septal infarct.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>At 6-mo follow-up no new PPM.</td>
</tr>
</tbody>
</table>

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)

Veselka J, et al. 2014 (394)

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.

El-Jack SS, et al. 2007 (395)

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

McCann, GP et al. 2007 (396)

Aim: Evaluate scarring after ASA
Study type: Retrospective
Exclusion criteria: None

Inclusion criteria: Consecutive pts undergoing ASA

1° endpoint: ECG changes
Results:
- ECG after ASA
  - 2 with persistent RBBB

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| Study | Size: 27 pts evaluated with MRI at baseline and at 1 mo. 25 pts with baseline, 1 mo, 6 mo | 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 |
|---|---|---|---|---|---|---|
| Faber L, et al. 2007 (397) | 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) | 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 |
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. |
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
<th>Safety endpoint</th>
<th>Notes</th>
</tr>
</thead>
</table>
| 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 | | 30 d all-cause mortality | | 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 | | Late CHB (First identified >48 h after ASA) | | 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 provable LVOT (OR for each 10 mm Hg: 1.14; 95% CI:1.00–1.20)  
- High provable 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 |
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Aim</th>
<th>Study type</th>
<th>Size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veselka J, et al. 2013 (402) 23927866</td>
<td>Evaluate predictors of complications after ASA</td>
<td>Retrospective multicenter</td>
<td>421 pts from 8 European Centers</td>
<td>421 pts who underwent ASA</td>
<td>If outside 2003–5 (to include only “low dose” era)</td>
<td>CHB &gt;10 s Early &lt;24 h, late &gt;24 h</td>
<td>• 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</td>
<td>Authors suggest close post procedural monitoring and 5 d hospitalizations after ASA</td>
</tr>
<tr>
<td>Kim LK, et al. 2016 (403) 27438114</td>
<td>Evaluate effect of hospital volume on complications after ASA or myectomy</td>
<td>Retrospective evaluation of the Nationwide Inpatient Sample from 2003 to 2011</td>
<td>11,248 patients underwent septal reduction procedures</td>
<td>All pts who underwent septal reduction procedures</td>
<td>N/A</td>
<td>Mortality, PPM, bleeding</td>
<td>• 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 %</td>
<td>PPM common in both myectomy and ASA at discharge • No data on post discharge outcomes after myectomy and ASA.</td>
</tr>
<tr>
<td>Liebregts M, et al. 2015 (404) 26454847</td>
<td>Evaluate ASA or myectomy</td>
<td>Systematic review</td>
<td>16 myectomy cohorts and 15 ASA cohorts</td>
<td>Studies of myectomy of ASA</td>
<td>N/A</td>
<td>Mortality, PPM, SCD</td>
<td>• PPM: • ASA: 10 % • Myectomy: 4.4%</td>
<td>ASA with similar mortality compared to septal myectomy but with higher PPM rate and higher likelihood of repeat procedures</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>1° endpoint</td>
<td>Results</td>
<td>Exclusion criteria</td>
<td></td>
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</tr>
<tr>
<td>Balt JC, et al. 2015 (405) 25073885</td>
<td>Evaluate use of continuous ECG monitoring after ASA</td>
<td>Pts undergoing ASA with PPM or ILR</td>
<td>VT/VF or other events recorded on the ILR</td>
<td>Pts with VT/VF often had associated CHB (during hospitalization) No late AVB identified</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qin JX, et al. 2004 (406) 14715342</td>
<td>Evaluate conduction tissue after ASA or myectomy</td>
<td>Pts undergoing ASA or myectomy</td>
<td>ECG</td>
<td>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%</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chang SM, et al. 2003 (407) 12875767</td>
<td>Evaluate conduction tissue after ASA</td>
<td>Pts undergoing ASA</td>
<td>ECG/PPM</td>
<td>Independent predictors for CHB: Women (OR: 4.33) Bolus injection (OR: 51) &gt;1septal (OR: 4.6) Baseline LBBD (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</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen AA, et al. 2006 (408) 16442376</td>
<td>Evaluate conduction tissue after ASA</td>
<td>Pts undergoing ASA</td>
<td>ECG/PPM</td>
<td>Acute CHB in 62% of pts; all normalized within 24 h</td>
<td>N/A</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

• ILR did not identify any arrhythmias with 3 y monitoring after ASA
• 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
• Similar hemodynamic benefit regardless of whether a PPM required or not
• 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
### 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 QR5d before or after ASA  
- PPM in 20 pts

- Recurrent CHB in 13 pts (25%), 36±22 h

- Intact VA conduction a helpful sign for determining whether a PPM will be required

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

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| 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  
**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

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

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year</th>
<th>Aim of Study</th>
<th>Study Type</th>
<th>Study Size (N)</th>
<th>Patient population</th>
<th>Primary endpoint results (p values OR or RR; &amp; 95% CI)</th>
<th>Relevant 2° Endpoint (if any)</th>
<th>Study limitations Adverse events</th>
</tr>
</thead>
</table>
| 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 |
<table>
<thead>
<tr>
<th>Study type</th>
<th>Study type</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective observational; 727 consecutive pts with CHD; longitudinal follow-up</td>
<td>Retrospective observational; 359 pts with transposition and atrial switch; longitudinal follow-up</td>
<td>Retrospective observational; 334 pts with prior Fontan surgery; longitudinal follow-up</td>
</tr>
<tr>
<td>antiarrhythmic therapy, functional class, and peak VO₂</td>
<td>Development of atrial arrhythmias</td>
<td>The presence of SND was associated with a higher incidence of atrial flutter (p&lt;0.001).</td>
</tr>
</tbody>
</table>

**Janousek J, et al. 1994 (417) 7846933**

**Aim:** Determine the natural history for pts with an atrial switch

**Study type:** Retrospective observational; 727 consecutive pts with CHD; 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; 359 pts with transposition and atrial switch; 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
<table>
<thead>
<tr>
<th>Reference</th>
<th>Aim</th>
<th>Study type</th>
<th>Study population</th>
<th>Outcome</th>
<th>PM implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graham TP, et al. 2000 (421)</td>
<td>Long-term outcome in ccTGA</td>
<td>Multicenter retrospective</td>
<td>182 pts from 19 institutions</td>
<td>41% required PPM</td>
<td>PM implantation common. Also associated with systemic ventricular dysfunction</td>
</tr>
<tr>
<td>Khairy P, et al. 2006 (422)</td>
<td>Assess risk of thromboemboli in pts with transvenous pacing leads and intracardiac shunts</td>
<td>Multicenter, retrospective cohort study of 202 pts with intracardiac shunts</td>
<td>N/A</td>
<td>Transvenous leads an independent predictor of systemic thromboemboli (HR: 2.6; p=0.0265)</td>
<td>Transvenous leads incur a &gt;2-fold increased risk of systemic thromboemboli in pts with intracardiac shunts</td>
</tr>
<tr>
<td>DeSimone CV, et al. 2013 (423)</td>
<td>Stroke or TIA in pts with endocardial leads and a PFO</td>
<td>Retrospective observational; 6,075 pts (364 with PFO)</td>
<td>N/A</td>
<td>1st 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&lt;0.0001)</td>
<td>Presence of a PFO is associated with a substantially increased risk of embolic stroke/TIA</td>
</tr>
<tr>
<td>Kim MH, et al. 2001 (424)</td>
<td>Assess prevalence and natural history of complete AVB after valvular heart surgery. Assess the optimal timing of PM implantation</td>
<td>Retrospective observational; 155 pts with valvular surgery; 17 (11%) pts had complete AVB in the postop period</td>
<td>N/A</td>
<td>• 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</td>
<td>If complete AVB is present after aortic and mitral valve surgery within the first 24 h postop and persists for &gt;48 h, it is unlikely to resolve within the next 1–2 wk</td>
</tr>
<tr>
<td>Glikson M, et al. 1997 (425)</td>
<td>Define long-term dependency in permanent pacing after cardiac surgery</td>
<td>Retrospective observational; 120 adults post-cardiac surgery who received PPM</td>
<td>N/A</td>
<td>Postop complete AVB is the most important predictor of PM dependency</td>
<td>In pts with complete AVB, an early decision to implant a permanent PM is probably justified</td>
</tr>
<tr>
<td>Edwards W, et al. 1978 (426)</td>
<td>Examination of postmortem findings of the sinus nodal tissue in pts with an atrial switch procedure</td>
<td>N/A</td>
<td>Sinus nodal artery damage</td>
<td>• The sinus node showed acute necrosis or compression in 77% of cases</td>
<td></td>
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<tr>
<td>Study type</td>
<td>Aim</td>
<td>Study type</td>
<td>Study type</td>
<td>Study type</td>
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<tr>
<td>32 pts; atrial switch pts; postmortem pathological analyses</td>
<td>Atrial mapping in pts with SND</td>
<td>32 pts, 16 pts with SND, 16 controls; case control comparative analysis</td>
<td>Normal hearts with no evidence of SND</td>
<td>Para-nodal areas were damaged in 100% of pts</td>
<td></td>
</tr>
<tr>
<td>Sanders P, et al. 2004 (427) 15007004</td>
<td>• 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</td>
<td>Bolens M and Friedli B 1984 (428) 6720586</td>
<td>EP mapping of sinus and AV nodal function in pts with secundum ASD</td>
<td>Prior to surgery</td>
<td>Following ASD repair</td>
</tr>
<tr>
<td>Gillette PC, et al. 1974 (429) 4818151</td>
<td>Electrophysiological examination of atrial, sinus and AV nodal function</td>
<td>Case control comparative analysis; 18 pts studied before and after surgical closure</td>
<td>N/A</td>
<td>SND was the primary abnormality detected</td>
<td></td>
</tr>
<tr>
<td>Garson A, et al. 1985 (430) 4031302</td>
<td>Identify predictors of death in younger pts (predominantly CHD) and atrial flutter</td>
<td>Prospective observational</td>
<td>16 pts studied following atrial switch surgery (Mustard)</td>
<td>N/A</td>
<td>Effective control of atrial flutter was associated with improved outcomes</td>
</tr>
<tr>
<td>Albin G, et al. 1985 (431) 4033231</td>
<td>SND in young adult pts: treatment by implantation of a PPM</td>
<td>Retrospective observational; 39 pts, mean age 23 y; most commonly TGA; mean follow-up of 50.5 mo</td>
<td>No PM-related deaths</td>
<td>N/A</td>
<td>Permanent pacing is an effective therapeutic modality</td>
</tr>
<tr>
<td>Reference</td>
<td>Aim:</td>
<td>Study type:</td>
<td>Re-intervention was driven primarily by lead failure (49%)</td>
<td>N/A</td>
<td>Epicardial systems were most likely to develop lead failure, predominantly in the ventricular lead</td>
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<tr>
<td>McLeod CJ, et al. 2010 (432) 20563634</td>
<td>Epicardial versus endocardial permanent pacing in adults with congenital heart disease</td>
<td>Retrospective observational; 106 pts and 259 PM procedures: SND in 20%, heart block (25%); followed for 11.6±14 y</td>
<td>N/A</td>
<td>Lead complications were not significantly different for epicardial vs. endocardial improved lead survival in pts with endocardial leads</td>
<td></td>
</tr>
<tr>
<td>Walker F, et al. 2004 (433) 15145118</td>
<td>Long-term outcomes of cardiac pacing in adults with congenital heart disease</td>
<td>Retrospective observational; 168 adults with CHD, and with PMs; mean age at implant was 28 y; mean pacing duration 11 y at follow-up</td>
<td>N/A</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Bink-Boelkens M, et al. 1983 (434) 6869177</td>
<td>Identification of surgical factors which affect the development of bradycardia and arrhythmias</td>
<td>Retrospective observational; 204 pts with secundum ASD repair, 50 pts with atrial switch (Mustard)</td>
<td>N/A</td>
<td>Atrial tachycardias in congenital heart disease are amenable to ATP algorithms</td>
<td></td>
</tr>
<tr>
<td>Stephenson E, et al. 2003 (435) 14516898</td>
<td>Efficacy of atrial ATP in treating atrial flutter in ACHD pts</td>
<td>Retrospective observational; 204 pts with secundum ASD repair, 50 pts with atrial switch (Mustard)</td>
<td>N/A</td>
<td>Atrial tachycardias in congenital heart disease are amenable to ATP algorithms</td>
<td></td>
</tr>
<tr>
<td>Rhodes LA, et al. 1995 (436) 7659551</td>
<td>Atrial ATP in ACHD after repair of congenital heart disease</td>
<td>Prospective cohort 18 pts (2–32 y with a variety of antitachycardia congenital heart lesions underwent atrial PM</td>
<td>Over 4–30 mo, 6 pts had 189 episodes of tachycardia successfully converted with atrial ATP</td>
<td>N/A</td>
<td>In selected cases, atrial ATP is a useful tool in the management of pts with congenital heart disease and atrial arrhythmias</td>
</tr>
<tr>
<td>Study</td>
<td>Study type</td>
<td>Aim</td>
<td>Study type</td>
<td>Recovery of AV conduction occurred by postoperative day 9 in 97% of pts with transient heart block</td>
<td>The greatest risk for CHB occurred in surgery for:</td>
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<tr>
<td>Weindling SN, et al. 1998 (284) 9723647</td>
<td><strong>Study type</strong>: Out of 2,698 cardiac surgeries 54 (2%) were complicated by CHB</td>
<td></td>
<td><strong>Study type</strong>: Out of 2,698 cardiac surgeries 54 (2%) were complicated by CHB</td>
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<td><strong>Study type</strong>: Out of 2,698 cardiac surgeries 54 (2%) were complicated by CHB</td>
</tr>
<tr>
<td>Ayyildiz P, et al. 2015 (437) 26517970</td>
<td><strong>Aim</strong>: Evaluation for AVB following pediatric cardiac surgery for CHD</td>
<td><strong>Study type</strong>: Retrospective observational; 1,550 pts with CHD surgery between 2010–2015; median age 0.5–1 y</td>
<td><strong>Study type</strong>: Retrospective observational; 1,550 pts with CHD surgery between 2010–2015; median age 0.5–1 y</td>
<td><strong>Study type</strong>: Retrospective observational; 1,550 pts with CHD surgery between 2010–2015; median age 0.5–1 y</td>
<td><strong>Study type</strong>: Retrospective observational; 1,550 pts with CHD surgery between 2010–2015; median age 0.5–1 y</td>
</tr>
<tr>
<td>Aziz PF, et al. 2013 (438) 23179430</td>
<td><strong>Aim</strong>: Evaluation for AVB following pediatric cardiac surgery for CHD</td>
<td><strong>Study type</strong>: Retrospective, observational, single center, cohort; pediatric not adult group; 44 pts in this study who experienced TCHB - 37 recovered completely</td>
<td><strong>Study type</strong>: Retrospective, observational, single center, cohort; pediatric not adult group; 44 pts in this study who experienced TCHB - 37 recovered completely</td>
<td><strong>Study type</strong>: Retrospective, observational, single center, cohort; pediatric not adult group; 44 pts in this study who experienced TCHB - 37 recovered completely</td>
<td><strong>Study type</strong>: Retrospective, observational, single center, cohort; pediatric not adult group; 44 pts in this study who experienced TCHB - 37 recovered completely</td>
</tr>
<tr>
<td>Lin A, et al. 2010 (439) 20381087</td>
<td><strong>Aim</strong>: Evaluation for AVB following pediatric cardiac surgery for CHD</td>
<td><strong>Study type</strong>: Retrospective, observational, single center; 922 pts, median age 6 mo</td>
<td><strong>Study type</strong>: Retrospective, observational, single center; 922 pts, median age 6 mo</td>
<td><strong>Study type</strong>: Retrospective, observational, single center; 922 pts, median age 6 mo</td>
<td><strong>Study type</strong>: Retrospective, observational, single center; 922 pts, median age 6 mo</td>
</tr>
</tbody>
</table>

**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)**
<table>
<thead>
<tr>
<th>Study Acronym; Author; Year</th>
<th>Aim of Study; Study Type</th>
<th>Patient Population</th>
<th>Study Intervention / Study Comparator</th>
<th>Primary endpoint results (p values OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domenghetti G, et al. 1980 (440) 7363920</td>
<td><strong>Aim</strong>: Examine impact of acute intraventricular conduction abnormalities on survival following acute MI</td>
<td></td>
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</tbody>
</table>
|                             | **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 |
<table>
<thead>
<tr>
<th>Reference</th>
<th>Aim</th>
<th>Study type</th>
<th>Study size demographics</th>
<th>Intervention/Comparator</th>
<th>Endpoint</th>
<th>Safety endpoint</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hindman MC, et al. 1978 (445, 446)</td>
<td>Aim: To identify determinants of SCD or recurrent high degree AVB in pts following MI with BBB</td>
<td>Retrospective observational</td>
<td>432 pts with AMI and BBB</td>
<td>N/A</td>
<td>• Mortality</td>
<td>• Pts with progression to 2nd or 3rd degree AV have increased mortality</td>
<td>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</td>
</tr>
<tr>
<td>Ginks WR, et al. 1977 (233)</td>
<td>Aim: Assess long-term prognosis of AMI with AVB</td>
<td>Retrospective observational</td>
<td>52 pts with CHB and AMI</td>
<td>21 hospital survivors w/o PPM followed for 49 months</td>
<td>10 /14 survived w/o PPM • PPM failed to prevent sudden death in 2/4</td>
<td>Recommendation: PPM implant is not justified in pts with partial bilateral bundle-branch block following AMI</td>
<td></td>
</tr>
<tr>
<td>The Birmingham Trial</td>
<td>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.</td>
<td>RCT</td>
<td>50 pts</td>
<td>Permanent pacing Comparator: No permanent pacing</td>
<td>1º endpoint: No difference in mortality</td>
<td>• 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</td>
<td></td>
</tr>
<tr>
<td>Meine TJ, et al. 2005 (447)</td>
<td>Aim: Incidence, predictors, and outcomes of high-degree AVB</td>
<td>N/A</td>
<td>70,742 pts with STEMI compared</td>
<td>N/A</td>
<td>• Incidence of AVB was 6.9%</td>
<td>In the thrombolytic era:</td>
<td></td>
</tr>
<tr>
<td>Study ID</td>
<td>Title</td>
<td>Type</td>
<td>Details</td>
<td>Results</td>
<td></td>
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</table>
| 15990751 | AVB in AMI treated with thrombolytics | 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) |
| Gang UJ, et al. 2012 (448) 22645234 | High-grade AVB in STEMI pts treated with PCI | Retrospective observational | 2073 STEMI pts with primary PCI from Danish National Registry | High-grade AVB: 3.2%  
Early mortality higher  
Yet equal mortality at 30 d compared with pts w/o AVB |
| Auffret V, et al. 2016 (449) 26660871 | High-grade AVB complicating STEMI (2006–2013) | Large prospective registry | 6,662 pts with STEMI | AVB in 3.5%  
AVB at admission or in first 24 h had higher mortality rates (18.1% and 28.6%) |
| Kim HL, et al. 2014 (450) 25304975 | High-grade AVB on 30-d outcome following AMI in the drug-eluting stent era | Retrospective observational | 13,862 pts with AMI, registered in the nation-wide AMI database from 2005–2013 | 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 |
| Singh SM, et al. 2015 (234) 25205530 | High-grade AVB in acute coronary syndromes | GRACE registry | 59,229 pts with ACS between 1999 and 2007 | 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 |
| Ranganathan N, et al. 1972 (451) 5009474 | Determine the validity of His bundle recordings in managing BBB | | 20 pts with BBB and 13 pts w/o BBB | Abnormal His-Purkinje conduction  
BBB may be associated with infra-nodal conduction abnormalities as evidenced by an abnormal His recording |

Aim: Determine the validity of His bundle recordings in managing BBB  
Study type: GRACE registry  
Details: 20 pts with BBB and 13 pts w/o BBB  
Results: Abnormal His-Purkinje conduction  
BBB may be associated with infra-nodal conduction abnormalities as evidenced by an abnormal His recording  

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<table>
<thead>
<tr>
<th>Study type:</th>
<th>Prospective observational</th>
<th>Aim: Use of atropine in pts with acute MI and sinus bradycardia</th>
<th>56pts with AMI and sinus brady</th>
<th>N/A</th>
<th>Atropine improved AV conduction in 11 of 13 pts (85%) acute inferior MIs (with 2nd or 3rd degree AVB)</th>
<th>Atropine recommended as drug of choice for sinus brady and AMI; 7 pts developed 10 side effects: VT/VF, ventricular ectopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type:</td>
<td>Retrospective observational</td>
<td>56pts with AMI and sinus brady</td>
<td>1157275</td>
<td></td>
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</tr>
<tr>
<td>Swart G, et al. 1999 (80) 10597081</td>
<td>Aim: Use of atropine in acute MI in prehospital setting</td>
<td>131 pts with acute MI and associated bradycardia</td>
<td>Atropine</td>
<td>N/A</td>
<td>No difference in response to atropine between AMI vs. non-AMI pts; MI pts are more likely to recover conduction in hospital</td>
<td></td>
</tr>
<tr>
<td>Study type:</td>
<td>Retrospective Observational</td>
<td>10597081</td>
<td></td>
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</tr>
<tr>
<td>Feigl D, et al. 1984 (160) 6736451</td>
<td>Aim: Early and late AVB in acute inferior MI</td>
<td>34 pts with 2nd or 3rd degree AVB developing in course of AMI who survived &gt;72 h</td>
<td>Atropine</td>
<td></td>
<td>Of 15 pts with early AVB (&lt;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</td>
<td></td>
</tr>
<tr>
<td>Study type:</td>
<td>Single center retrospective cohort</td>
<td>6736451</td>
<td></td>
<td></td>
<td>No adverse events to drug therapy reported</td>
<td></td>
</tr>
<tr>
<td>Bertolet BD, et al. 1995 (163) 7661495</td>
<td>Aim: Theophylline for the treatment of AVB after MI</td>
<td>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</td>
<td>Aminophylline</td>
<td></td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Study type:</td>
<td>Single center retrospective cohort</td>
<td>7661495</td>
<td></td>
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</tr>
<tr>
<td>Altun A, et al. 1998 (164) 9789698</td>
<td>Aim: Effect of aminophylline in pts with atropine-resistant later advanced AVB during acute inferior MI</td>
<td>8 pts with 2nd or 3rd degree AVB after IMI for at least 1 h, resistant to atropine.</td>
<td>Given 2 doses of aminophylline 240 mg 1 h apart</td>
<td></td>
<td>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</td>
<td></td>
</tr>
<tr>
<td><strong>Study type:</strong> Retrospective observational</td>
<td><strong>Aim:</strong> Conservative treatment of AVB in AMI</td>
<td><strong>Study type:</strong> Results in 105 consecutive pts</td>
<td><strong>Hynes JK, et al. 1983 (115) 6823157</strong></td>
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<tr>
<td><strong>Hatle L, et al. 1971 (167) 5557475</strong></td>
<td>Pts with acute MI treated with 2nd or 3rd degree AVB</td>
<td>Treated with isoproterenol, generally 1–3 mcg/min</td>
<td>Pts with acute MI treated with 2nd or 3rd degree AVB</td>
<td><strong>1st endpoint:</strong> Clinical outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study type:</strong> Retrospective, observational, single-center</td>
<td><strong>Study type:</strong> Retrospective, observational, single-center</td>
<td><strong>Size:</strong> N = 1,022</td>
<td><strong>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.</strong></td>
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<tr>
<td><strong>14 pts treated with TVP, 3 of whom died from ventricular fibrillation</strong></td>
<td><strong>TTVP was associated with an overall risk of complications in approximately 14% of pts.</strong></td>
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</table>

<table>
<thead>
<tr>
<th><strong>Study type:</strong> Retrospective, observational, single-center</th>
<th><strong>Aim:</strong> Temporary transvenous cardiac pacing: 6 y experience in 1 coronary care unit</th>
<th><strong>Study type:</strong> Retrospective, observational, single-center</th>
<th><strong>Jowett NI, et al. 1989 (120) 2594596</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rotman M, et al. 1972 (452) 4551931</strong></td>
<td>162 pts admitted to coronary care unit who underwent TTVP.</td>
<td><strong>Temporary transvenous pacing</strong></td>
<td><strong>142 pts in the coronary care unit with TTVP.</strong></td>
</tr>
<tr>
<td><strong>162 pts admitted to coronary care unit who underwent TTVP.</strong></td>
<td><strong>Temporary transvenous pacing</strong></td>
<td><strong>1st endpoint:</strong> Clinical outcomes</td>
<td></td>
</tr>
<tr>
<td><strong>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.</strong></td>
<td><strong>TTVP was associated with a 19.8% complication rate. Some TTVP was prophylactic and may not have been indicated.</strong></td>
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<td><strong>A minority of TTVP was performed for SND (15%)</strong></td>
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Data Supplement 55. Nonrandomized Data for Predicting Bradycardia Associated with Seizures (Section 8.4.1)

<table>
<thead>
<tr>
<th>Study Acronym; Author; Year Published</th>
<th>Study Type/Design; Study Size</th>
<th>Patient Population</th>
<th>Primary Endpoint and Results (P values; OR or RR; &amp; 95% CI)</th>
<th>Summary/Conclusion Comment(s)</th>
</tr>
</thead>
</table>
| 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 |
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:
  o Temporal: 80–82%
  o Frontal: 6–10%
  o Insular: 3–5%
  o Other 3–11%
• Duration
  o <30 s: 90%
  o >30 s: 10%
• Rx:
  o Pacemaker: 35/68
  o Adjusted AED: 25/33 pts who did not receive a PPM
  o Surgery: 8/33
    o Rx response:
      o Pacemaker: no asystole falls, 14/33 with recurrent seizures, 19/33 w/o recurrent seizures
      o Adjusted AED: 5/23 with recurring asystolic falls, 6/23 with recurrent seizures (w/o asystole), 12/23 w/o recurrent seizures
      o Surgery:
        o 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)

<table>
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<th>Size</th>
<th>Inclusion criteria</th>
<th>1° endpoint</th>
<th>Results</th>
<th>Exclusion criteria</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ogunbayo GO, et al. 2017 (457) 28735733</td>
<td>Evaluate incidence of pneumothorax associated with CIED implant</td>
<td>Retrospective evaluation of National Inpatient Sample</td>
<td>3.7 million people underwent CIED implant</td>
<td>Database searched for pts with primary implantation of a CIED with at least 1 vascular access</td>
<td>Pneumothorax</td>
<td>Pneumothorax occurred in 1.6% of cases, associated with increased length of stay and increased mortality (1.2% vs. 0.7%), associated with older age, female sex, chronic obstructive lung disease, DC device</td>
<td>None</td>
<td>Pneumothorax remains an important complication</td>
</tr>
<tr>
<td>Sochala M, et al. 2017 (458) 28598855</td>
<td>Evaluate risk of complication after CIED implant for myotonic dystrophy</td>
<td>Retrospective</td>
<td>914 pts with myotonic dystrophy Type 1–23 with an ICD and 46 with a PPM</td>
<td>Myotonic dystrophy type 1 and CIED placement</td>
<td>Complications</td>
<td>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)</td>
<td>None</td>
<td>Increased risk of complications with ICD though small numbers</td>
</tr>
<tr>
<td>Bai Y, et al. 2017 (459) 28587353</td>
<td>Evaluate incidence of hematoma after CIED</td>
<td>Retrospective</td>
<td>339 pts from a single center undergoing CIED placement</td>
<td>Pts undergoing CIED placement</td>
<td>Hematoma</td>
<td>History of allergy associated with hematoma, Hematoma more common with larger devices (ICD and CRT): 30% vs. 8%</td>
<td>None</td>
<td>Larger devices type though do not address vascular access, Only 27 pts with larger device</td>
</tr>
<tr>
<td>Hosseini SM, et al. 2017 (460) 28329322</td>
<td>Evaluate complications associated with CRT</td>
<td>Retrospective</td>
<td>439,010 pts from National Inpatient Sample undergoing CRT</td>
<td>CRT device</td>
<td>In-hospital complications</td>
<td>6.1% of pts with at least one complication, Complications more likely in older pts, women, elective admission,</td>
<td>None</td>
<td>Increased complication rate over time, No difference between CRT-P and CRT-D</td>
</tr>
<tr>
<td>Study ID</td>
<td>Authors</td>
<td>Year</td>
<td>Study Title</td>
<td>Study Type</td>
<td>Size</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>1st Endpoint</td>
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<tr>
<td>(461)</td>
<td>Gupta N, et al. 2016</td>
<td>26961369</td>
<td>Evaluate complications associated different CIED</td>
<td>Retrospective-Kaiser database</td>
<td>11,924 ICDs, 33,519 PPMs, 4,472 CRT</td>
<td>CIED implant</td>
<td>None</td>
<td>In-hospital complications, 30 d failure rates, outcomes</td>
</tr>
<tr>
<td>(462)</td>
<td>Friedman DJ, et al. 2015</td>
<td>26670062</td>
<td>Evaluate complications associated CRT in pts with moderate renal dysfunction</td>
<td>Retrospective-NCDR and matched to Medicare</td>
<td>9.525 CRT-D vs. propensity matched ICD only (1,421)</td>
<td>CRT eligible pts with stage 3–5 CKD</td>
<td>None</td>
<td>Mortality, HFH</td>
</tr>
<tr>
<td>(463)</td>
<td>Witt CT, et al. 2016</td>
<td>26378089</td>
<td>Evaluate complications associated ICD Rx with CRT</td>
<td>Retrospective-single center</td>
<td>917 HF pts-427 with NICM and 490 with ICM</td>
<td>CRT and HF</td>
<td>None</td>
<td>Mortality</td>
</tr>
<tr>
<td>(464)</td>
<td>Gadler F, et al. 2015</td>
<td>25336667</td>
<td>Evaluate complications associated with CIED implant</td>
<td>Retrospective-multicenter registry (Sweden)</td>
<td>6,617 PPM, 1,298 ICD</td>
<td>First CIED implant</td>
<td>None</td>
<td>Complications</td>
</tr>
<tr>
<td>authors</td>
<td>year</td>
<td>citation</td>
<td>aim</td>
<td>study type</td>
<td>size</td>
<td>inclusion criteria</td>
<td>1st endpoint</td>
<td>results</td>
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<tr>
<td>Essebag V, et al.</td>
<td>2015</td>
<td>(465)</td>
<td>Evaluate complications associated with CRT upgrade vs. de novo implant</td>
<td>Subgroup analysis of the Canadian cohort</td>
<td>Pts with CRT: 644 de Novo and 80 upgrade</td>
<td>Randomized to CRT-D</td>
<td>Complications</td>
<td>Similar results for CRT-D whether de Novo or as an upgrade</td>
</tr>
<tr>
<td>Chung MK, et al.</td>
<td>2014</td>
<td>(466)</td>
<td>Evaluate mortality associated with different cardiac procedures</td>
<td>Retrospective subanalysis</td>
<td>1,744 pts with CIED replacement</td>
<td>CIED replacement</td>
<td>Complications/mortality</td>
<td>Complications, mortality due to comorbidities</td>
</tr>
<tr>
<td>Adelstein E, et al.</td>
<td>2014</td>
<td>(467)</td>
<td>Evaluate risks and benefits with device upgrades</td>
<td>Retrospective subanalysis</td>
<td>157 pts</td>
<td>Pacemaker dependent with CRT upgrade</td>
<td>Complications/mortality</td>
<td>Better outcomes in the absence of CAD</td>
</tr>
<tr>
<td>Kirkfeldt RE, et al.</td>
<td>2014</td>
<td>(468)</td>
<td>Evaluate risks and benefits with different device types</td>
<td>Retrospective subanalysis</td>
<td>5,918 pts</td>
<td>CIED implant in Denmark</td>
<td>Complications/mortality</td>
<td>Complications are relatively common, particularly with complex devices</td>
</tr>
<tr>
<td>Acosta J, et al.</td>
<td>2017</td>
<td>(469)</td>
<td>Evaluate use of defibrillator capabilities in pts who were eligible for CRT</td>
<td>Prospective, nonrandomized</td>
<td>217 pts</td>
<td>Class I indication for CRT and cardiac MRI</td>
<td>Appropriate ICD therapy or SCD</td>
<td>MRI may be helpful for identifying those pts at risk for sustained ventricular arrhythmias</td>
</tr>
<tr>
<td>Study</td>
<td>Aim</td>
<td>Inclusion criteria</td>
<td>1° endpoint</td>
<td>Results</td>
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<tr>
<td>Martens P, et al. 2017 (470) 28716973</td>
<td>Evaluate use of defibrillator capabilities in pts who were eligible for CRT implant</td>
<td>CRT implant</td>
<td>Mortality</td>
<td>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 &gt;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.</td>
<td>Weighing the risk of arrhythmia and nonarrhythmia risk helpful</td>
<td></td>
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</tr>
<tr>
<td>Yokoshiki H, et al. 2017 (471) 28626201</td>
<td>Evaluate use of defibrillator capabilities in pts who were eligible for CRT implant</td>
<td>CRT implant</td>
<td>Mortality</td>
<td>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</td>
<td>Weighing the risk of arrhythmia and nonarrhythmia risk helpful</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Scar mass, “channel mass,” were predictors of 1° endpoint
| 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) | **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) | **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) | **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**  

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<th>1st endpoint</th>
<th>Results</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Takaya Y, et al. 2015 (223) 25529542</td>
<td>Evaluate arrhythmias in pts with cardiac sarcoidosis</td>
<td>Cardiac sarcoidosis</td>
<td>None</td>
<td>Arrhythmias (bradycardia, tachycardia)</td>
<td>Similar rates of SCD regardless of whether presenting with HF/ventricular arrhythmias or high-grade AVB</td>
<td>ICD should be considered in all pts with cardiac sarcoidosis</td>
</tr>
<tr>
<td>Anselme F, et al. 2013 (275) 23811080</td>
<td>Evaluate arrhythmias in pts with lamin A/C mutation</td>
<td>Lamin A/C mutation</td>
<td>None</td>
<td>Arrhythmias (bradycardia, tachycardia)</td>
<td>21 pts received an ICD for severe conduction disorders</td>
<td>ICD should be considered in all pts with lamin A/C mutations</td>
</tr>
<tr>
<td>Ha AH, et al. 2012 (206) 22385162</td>
<td>Evaluate arrhythmias in pts with myotonic dystrophy</td>
<td>Myotonic dystrophy</td>
<td>None</td>
<td>Arrhythmias (bradycardia, tachycardia)</td>
<td>Pacemakers or defibrillators were implanted in 14% of all pts, including 65% of pts with severe ECG abnormalities.</td>
<td>Pts with PM may have sudden cardiac death</td>
</tr>
<tr>
<td>Bhakta D, et al. 2012 (209) 22035077</td>
<td>Evaluate arrhythmias in pts with myotonic dystrophy</td>
<td>Myotonic dystrophy</td>
<td>None</td>
<td>Arrhythmias (bradycardia, tachycardia)</td>
<td>Pacemakers or defibrillators were implanted in 14% of all pts, including 65% of pts with severe ECG abnormalities.</td>
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• 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

References


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