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SYSTEMATIC REVIEW

Pacing as a Treatment for Reflex-Mediated (Vasovagal, Situational, or Carotid Sinus Hypersensitivity) Syncope: A Systematic Review for the 2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society

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ABSTRACT

OBJECTIVES To determine, using systematic review of the biomedical literature, whether pacing reduces risk of recurrent syncope and relevant clinical outcomes among adult patients with reflex-mediated syncope.

METHODS MEDLINE (through PubMed), EMBASE, and the Cochrane Central Register of Controlled Trials (through October 7, 2015) were searched for randomized trials and observational studies examining pacing and syncope, and the bibliographies of known systematic reviews were also examined. Studies were rejected for poor-quality study methods and for the lack of the population, intervention, comparator, or outcome(s) of interest.

RESULTS Of 3,188 citations reviewed, 10 studies met the inclusion criteria for systematic review, including a total of 676 patients. These included 9 randomized trials and 1 observational study. Of the 10 studies, 4 addressed patients with carotid sinus hypersensitivity, and the remaining 6 addressed vasovagal syncope. Among the 6 open-label (unblinded) studies, we found that pacing was associated with a 70% reduction in recurrent syncope (relative risk [RR]: 0.30; 95% confidence interval [CI]: 0.15–0.60). When the 2 analyzable studies with double-blinded methodology were considered separately, there was no clear benefit (RR: 0.73; 95% CI: 0.25–2.1), but confidence intervals were wide. The strongest evidence was from the randomized, double-blinded ISSUE-3 (Third International Study on Syncope of Uncertain Etiology) trial, which demonstrated a benefit of pacing among patients with recurrent syncope and asystole documented by implantable loop recorder.

CONCLUSIONS There are limited data with substantive evidence of outcome ascertainment bias, and only 2 studies with a double-blinded study design have been conducted. The evidence does not support the use of pacing for reflex-mediated syncope beyond patients with recurrent vasovagal syncope and asystole documented by implantable loop recorder.

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INTRODUCTION

Reflex-mediated (vasovagal, situational, or carotid sinus hypersensitivity) syncope is common, occurring at least once in more than 40% of women and nearly one-third of men by age 60 years (1-3), and can be associated with cardioinhibitory bradycardia. Studies have presented mixed results in terms of the benefits of pacemakers in patients with reflex-mediated syncope, with some suggesting benefit (4-9) and others suggesting either no benefit or unclear benefit (10-15). A 2007 systematic review found significant heterogeneity and concern about an "expectation effect," a form of outcome ascertainment bias based on the awareness of the presence of a pacemaker in unblinded trials, when no benefit was seen in double-blinded trials (16). A 2010 systematic review by the United Kingdom's National Institute for Health and Care Excellence (NICE) (17) concluded that there was low-quality evidence with significant heterogeneity that potentially demonstrated a benefit of pacing. A separate 2013 review published by the Cochrane Library (18) concluded that current evidence does not support pacemaker implantation in this population. None of these reviews, however, included more recently published studies.

In support of the "2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope" (19), and in alignment with the "ACC/AHA Clinical Practice Guideline Methodology Summit Report" (20), the present Evidence Review Committee (ERC) sought to determine whether the evidence from randomized trials and observational studies suggests that pacemaker therapy reduces risk of recurrent syncope and other relevant outcomes over a minimum of 1 year of follow-up among adults with reflex-mediated syncope.

METHODS

The ERC partnered with Doctor Evidence, LLC (DRE) to conduct a systematic review addressing the question: *What is the effectiveness of pacemaker therapy in patients with vasovagal, carotid sinus, or situational syncope in adults?* This systematic review complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (21) and with recommendations of the "ACC/AHA Clinical Practice Guideline Methodology Summit Report" (20).

Search Strategy

Searches were conducted on October 7, 2015, in PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials and included all studies published from inception of the databases to the date of the search. Synonyms of "syncope" and "pacemaker" (**Table 1** footnotes) were used in the searches. References of published systematic reviews were also searched to identify any additional studies.

Eligibility Criteria

Randomized controlled trials (RCTs) and observational studies were selected for inclusion if they compared the use of all types of pacemakers programmed "ON" with pacemakers programmed "OFF" or no pacemaker (including medical therapy or usual care alone) for adult patients at least 18 years of age with vasovagal, carotid sinus, or situational syncope. Studies were included if they had a minimum follow-up of at least 1 year and were conducted in the ambulatory, outpatient, or community-based settings. Studies had to be published and in English to be included in the review. The outcomes of interest included syncope recurrence (primary outcome), falls, all-cause mortality, hospitalization due to cardiovascular causes, other symptoms attributable to the underlying condition (such as presyncope, injury, and quality of life), and adverse events resulting in an intervention.

Methods of Review

A medical librarian screened the titles and abstracts of studies against predefined selection criteria by using a software environment that allows for color coding of relevant key words and ranking of titles on the basis of key words. A second medical librarian performed quality control using the aforementioned tools. The chief medical officer and a methodologist reviewed all included and excluded abstracts, managed any discrepancies between librarians, and dealt with studies of uncertain eligibility. Members of the ERC (L.Y.C., P.A.N., A.L.M., D.J.S., and V.T.) were divided into pairs and performed dual independent review of full-text articles in the DOC Library software platform. Disagreements were resolved through discussion between the 2 reviewers and then by the ERC Chair (P.D.V.). Two DRE methodologists performed independent quality assessment of the included studies using the Cochrane Collaboration Risk of Bias Tool for RCTs (22) and the Newcastle-Ottawa Scale for cohort studies (23). Disagreements were resolved by a third methodologist. Data extraction took place in the DOC Data 2.0 software platform, with a standard template used for predefined data points. The first author was contacted in the case of a single study (10) for which more information was needed, but the data were no longer

available for analysis. Included studies were single-extracted by a member of the DRE team of evidence analysts, with each study verified against the source article by a quality control analyst (single extraction with sequential quality control). Discrepancies were resolved by the DRE project methodologist and/or chief medical officer. Subsequent dataset-level quality control (to identify outliers and ensure consistency of data across studies) was performed by a DRE audit specialist. A DRE ontology specialist managed the naming of outcomes on the basis of author-named outcomes and relevant definitions.

Statistical Analysis

When at least 4 studies included analyzable outcomes, meta-analyses were performed in DOC Data 2.0 with the integrated R statistical package Metafor and random-effects models (24). RCTs were analyzed separately from observational studies because of differences in study design. A statistical test for heterogeneity was also performed for each outcome, and funnel plots were examined for the presence of publication bias, but there was not convincing evidence that publication bias was present. Out of concern for the possibility that outcome ascertainment bias (on the presence/absence of blinding to intervention [pacing] status) could be present, analyses were stratified by blinding status. To test for statistical evidence that study blinding status modified the apparent association of pacing with reduction in recurrent syncope, random-effects meta-regression was performed.

RESULTS

Study Selection

After removing duplicates, a total of 3,188 titles were screened (2,563 from EMBASE, 1,638 from Medline, and 138 from Cochrane), and 40 of these were found to be relevant for full-text review (**Figure 1**). Each of these was reviewed by 2 ERC members, with a third member providing adjudication in cases of discordance. After full-text review, 10 studies (4,6,7,9-14,25), including a total of 676 adult patients with vasovagal, situational, and/or carotid sinus hypersensitivity syncope, that compared pacing to pacing off (or no pacemaker) and had at least 1 year of follow-up were included in the systematic review.

Study Results

Among the 10 studies meeting the inclusion criteria, there were 9 randomized trials (n=642) (4,6-11,13,14) and 1 observational study (n=34) (12). Among the 9 randomized trials, only 3 (7,10,11) included a double-blinded methodology. However, only 2 of these (7,11) included analyzable data involving implantation of a pacemaker in all patients but with programming pacing functions off according to random assignment with blinded ascertainment of outcomes. These 10 studies (4 vasovagal, 6 carotid sinus hypersensitivity, and 0 situational) are summarized in **Table 1**.

Studies Addressing Carotid Sinus Hypersensitivity Syncope

A 1992 open-label study found that at 3 years, syncope had recurred in 57% of patients randomly assigned to no pacemaker but in only 9% assigned to receive a pacemaker (p=0.0002) (8). There were no differences in mortality rate between groups.

In the 2001 SAFE PACE (Syncope and Falls in the Elderly—Pacing and Carotid Sinus Evaluation) open-label randomized trial (13), syncope had recurred by 12 months among 11% of the 87 patients with a pacemaker and among 22% of the 88 patients without a pacemaker (p=0.063). Falls were substantially reduced among patients with a pacemaker (669 versus 216 falls; odds ratio: 0.42; 95% confidence interval [CI]: 0.23 to 0.75).

A 2007 unblinded randomized trial had similar results when 10% of patients randomized to receive a pacemaker had recurrence of syncope at 12 months, whereas 40% without a pacemaker had recurrent syncope (p=0.008) (6).

In the subsequent 2010 SAFE PACE 2 trial (10), which was a double-blinded RCT, randomly assigned patients underwent either pacemaker implantation or loop recorder implantation. There was no benefit of pacing in terms of recurrent syncope, quality of life, or cognitive function, but the act of intervention (implantation of a device) was associated with substantially lower than expected event rates in both groups after device implantation. Unfortunately, data from this study could not be included in the meta-analysis because the raw numerator/denominator data for the key outcome of recurrent syncope are no longer accessible to the investigators.

Studies Addressing Vasovagal Syncope

An open-label randomized trial in 1999 found that over a mean of 52 months of follow-up, syncope had recurred among 6 of 10 patients who were assigned to receive a pacemaker but in none of the 10 patients who did not receive a pacemaker (p<0.02) (14).

The 2004 SYNPACE (Vasovagal Syncope and Pacing) RCT with double-blinding included 29 patients with severe recurrent tilt-induced vasovagal syncope who underwent pacemaker implantation (11). Among these, 16 patients were assigned to DDD mode pacing with rate drop response, and 13 were assigned to pacemaker OFF

(OOO mode). At a median of 23.8 months of follow-up, 8 of 15 (50%) assigned to pacing and 5 of 13 (38%) assigned to OOO mode had experienced recurrent syncope (p=0.38).

In an observational cohort study published in 2007 of 34 patients with tilt-induced asystole, researchers found that by a mean of 18.6 months of follow-up, syncope had recurred among 5 of 22 (23%) patients who received a pacemaker and among 3 of 12 (25%) who did not (p>0.05) (12). Interestingly, and similar to the findings of the SAFE PACE 2 trial (10), rates of syncope were substantially lower after enrollment in both groups.

The ISSUE-3 (Third International Study on Syncope of Uncertain Etiology) trial was an RCT with double-blinding conducted in 2012 (7). All of the 77 subjects with at least 3 prior syncopal episodes who were subsequently documented by implantable loop recorder to have asystole (at least 3 seconds associated with syncope or at least 6 seconds associated with presyncope) received a pacemaker. Of these, 38 were randomly assigned to DDD mode pacing with a rate drop response, and 39 were assigned to have pacing functions off. Over 2 years of follow-up, syncope recurred in 19 patients assigned to pacing "off" and in 8 of the patients assigned to DDD pacing with rate drop response (p=0.039).

In a single-blinded randomized crossover trial published in 2013, researchers implanted pacemakers in 50 patients with recurrent tilt-induced vasovagal syncope, and all received DDD pacing (9). Patients were randomly assigned to closed-loop stimulation (CLS) programmed "on" or "off," and then after 18 months and a subsequent 1-month washout period, patients were crossed over to the other group. The authors found that there were only 2 syncopal episodes during assignment to CLS ON, but there were 15 while CLS was programmed OFF (p=0.007). Because there was no comparison group that received no pacing, this study was not included in the meta-analysis.

In 2000, the VASIS (Vasovagal Syncope International Study) open-label randomized trial (4) published results comparing DDI pacemaker with rate hysteresis to no pacemaker among patients with severe cardioinibitory tilt-positive vasovagal syncope (defined as asystole >3 seconds during tilt-table test). The authors found that over a mean of 3.7 years of follow-up, 1 of 19 patients (5%) with a pacemaker and 14 of 23 patients (61%) with no pacemaker (p=0.0006) had recurrence of syncope. Interestingly, repeat tilt-table testing within 15 days of enrollment (including after pacemaker implantation) demonstrated similar rates of tilt-induced syncope in both groups (59% versus 61%; p=not significant).

Notable Studies Excluded From Systematic Review

It is worth mentioning, however, that the VPS (Vasovagal Pacemaker Study) (5) and the subsequent VPS II (Vasovagal Pacemaker Study II) (15) were not included in the systematic review because they did not have follow-up of at least 1 year. In VPS (5), which was an open-label (unblinded) randomized trial, 54 patients were assigned to receive a pacemaker or no pacemaker. An 85% relative risk (RR) reduction was found to be associated with pacing. Because the authors were suspicious that the lack of blinding (because of the open-label study design) could result in substantive outcome ascertainment bias, they conducted the subsequent VPS II (15) as a randomized trial with double-blinding; all patients were assigned to receive a pacemaker, but 48 were assigned to DDD mode, and 52 were assigned to pacing off (ODO mode). At 6 months of follow-up, no significant benefit of pacing was evident; 22 of 52 patients (42%) assigned to ODO mode and 16 of 48 (33%) assigned to DDD mode had experienced recurrent syncope (1-sided p=0.14).

Risk of Bias

The findings of VPS (Vasovagal Pacemaker Study) (5) and VPS II (Vasovagal Pacemaker Study II) (15), as well as the fact that after enrollment, lower than expected rates of syncope were reported in patients both with and without pacemakers (10,12), suggest the possibility that outcome ascertainment bias may be present. As such, we decided to proceed with meta-analysis for the primary outcome of recurrent syncope stratified by blinding status of the relevant studies.

Synthesis of Results

Although we considered multiple outcomes, including recurrent syncope (primary outcome), death, falls, traumatic injury, hospitalization, adverse events, and symptoms attributable to the underlying condition (e.g., presyncope, quality of life), only for recurrent syncope and death were there a minimum of 4 studies with analyzable data suitable for meta-analysis.

Among the 8 studies with analyzable data for the primary outcome of recurrent syncope over at least 1 year of follow-up, only 2 were conducted with a double-blinded study design (7,11), and the remaining 6 studies (n=424) were conducted with an open-label (unblinded) design (4,6,8,12-14). Among the open-label studies, after meta-analysis using random-effects models (**Figure 2A**), we found an apparent 70% reduction in recurrent syncope associated with pacing (RR: 0.30; 95% CI: 0.15 to 0.60). When the open-label studies were excluded from analysis, the double-blinded studies (n=89) revealed no

apparent benefit from pacing (RR: 0.73; 95% CI: 0.25 to 2.1) (**Figure 2B**).

Random-effects meta-regression failed to demonstrate statistically significant evidence that blinding status modified the association of pacing with outcome (beta coefficient, 0.35; 95% CI: −0.54 to 1.2; p=0.38). In the setting of only 2 studies with double-blinded study design included in the analysis, confidence intervals were quite wide.

Four studies (n=315) included data on mortality rate suitable for meta-analysis (6,8,13,14). Among these, we found no evidence that open-label pacemaker implantation was associated with reduced mortality rate (RR: 1.1; 95% CI: 0.5 to 2.4; p=0.81), but CIs were wide (**Figure 3**).

DISCUSSION

Summary of Evidence

In this systematic review, among unblinded studies, we found evidence that pacing reduced the risk of recurrent reflex-mediated syncope; among the 2 double-blinded randomized trials, there was no apparent benefit. These findings suggest that an expectation effect exists among open-label (unblinded) studies (16). This expectation effect is a form of outcome ascertainment bias in which the knowledge of the presence of a pacemaker may lead to expectation of benefit on the part of both patients and clinicians.

When these 10 studies, comprising a total of 676 subjects, are considered, there is very limited evidence beyond small, unblinded studies to suggest a benefit of pacing in patients with reflex-mediated syncope, with 1 notable, but limited exception. The ISSUE-3 trial (7), which used a randomized, double-blinded study design, demonstrated a reduction in recurrent syncope among patients with recurrent vasovagal syncope in whom clinically relevant asystole had been documented by implantable loop recorder.

LIMITATIONS

This systematic review has important limitations. Although all the studies included involved reflex-mediated syncope, the primary analysis included studies with both vasovagal syncope and carotid sinus hypersensitivity syncope, and as a result, there are challenges in interpreting the results. In addition, the limited number of studies and relatively small number of subjects constitute a limitation, but the methodological concern about outcome ascertainment bias among the majority of these studies (those without blinding) is an even greater problem. The small number of double-blinded studies (2 trials) means that the meta-regression analysis using statistical tools to determine whether the blinding status of studies modifies the apparent association of pacing with a reduction in recurrent syncope results in a coefficient with CIs so wide that meaningful interaction cannot be excluded.

CONCLUSIONS

There are very limited data on the benefits of pacing among patients with reflex-mediated (vasovagal, situational, and carotid sinus hypersensitivity) syncope. The apparent lower incidence of syncope observed with pacing among open-label studies, compared with the lack of benefit of pacing among the blinded studies, suggests that an expectation effect (a form of outcome ascertainment bias) may be present. Unfortunately, only 2 studies with a double-blinded study design met criteria for inclusion. The evidence does not support the routine use of pacing for reflex-mediated syncope beyond patients with recurrent syncope and asystole documented by implantable loop recorder, such as those meeting the entry criteria for the ISSUE-3 trial (7). These findings suggest that additional rigorously designed randomized trials with double-blinded study design are needed, and these studies should include sufficient sample sizes and duration of follow-up to provide enough statistical power to answer definitively the important scientific and clinical questions about the potential benefits of pacing among patients with vasovagal, situational, and/or carotid sinus hypersensitivity syncope.

FIGURE 1 PRISMA Diagram

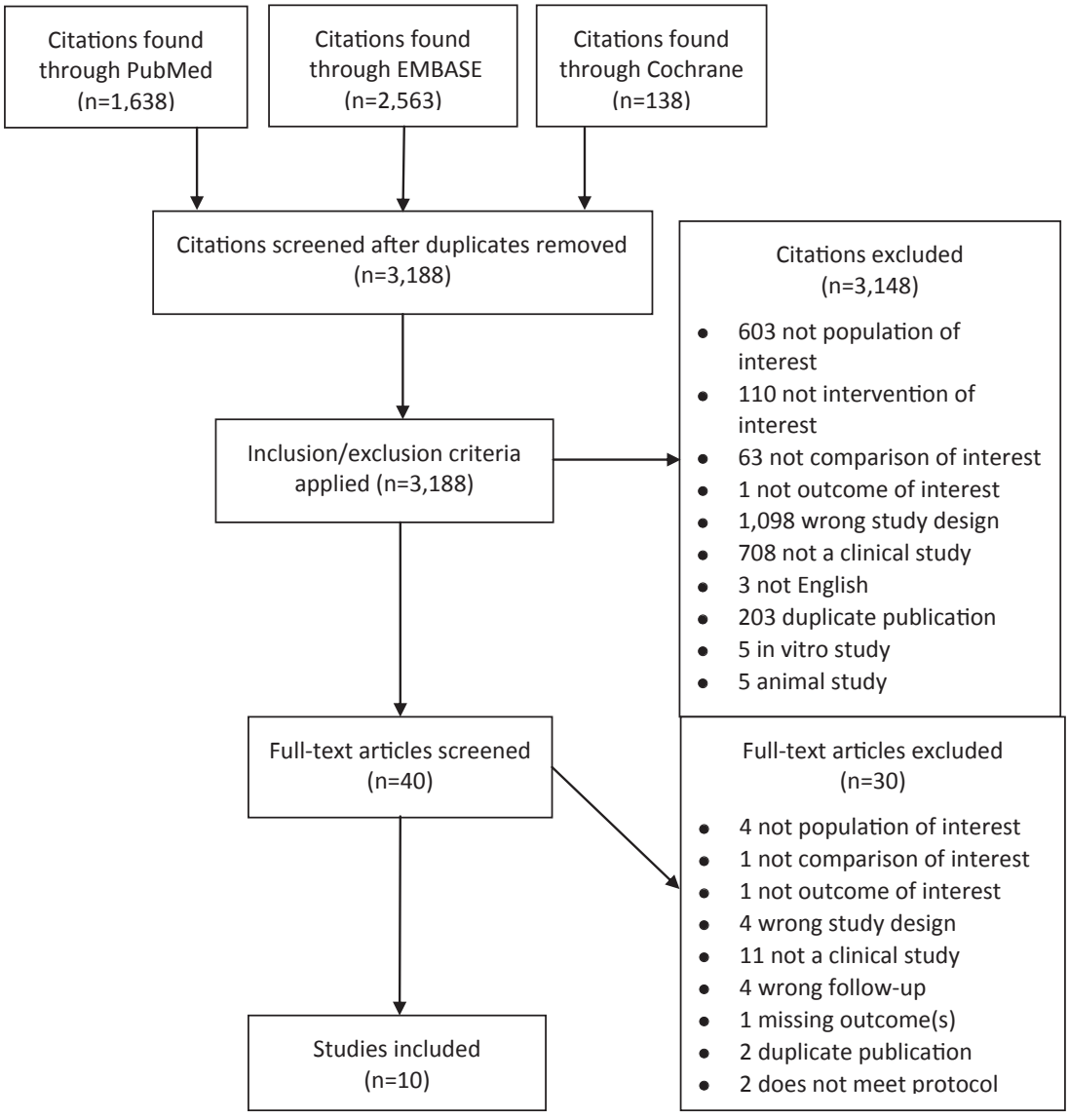

TABLE 1 Summary of Included Studies

Study Acronym; Author; Year Published (Ref. No.)	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (No. of patients)/ Study Comparator (No. of patients)	Endpoint Results (Absolute Event Rates, p Values; OR or RR; and 95% CI)	Study Limitations; Adverse Events
Studies Addressing Carotid Sinus Syncope					
Brignole M, 1992 (8)	**Syncope type:** CSS **Aim:** A randomized treatment/ nontreatment prospective study was performed in pts with CSS resulting in major trauma or interfering with daily activity. **Study type:** RCT **Size:** Randomized (n=60)	**Inclusion criteria:** History of recurrent episodes of reproduction of spontaneous symptoms by means of CSM that caused a ventricular asystole lasting ≥3 s with CSM; no other identifiable cause of symptoms; pts with mild signs of sinus dysfunction or atrioventricular conduction abnormalities. **Exclusion criteria:** Pts with: persistent diurnal sinus bradycardia <50 bpm; intermittent or mild sinus bradycardia <60 bpm with abnormal electrophysiological evaluation of sinus node function; second- or third-degree AV block; baseline His-Ventricular interval ≥70 ms; or infrahisian second- or third-degree AV block during incremental atrial pacing or intravenous ajmaline administration (1 mg/kg).	**Intervention:** DDDR or VVI pacemaker programmed ON (n=32) **Comparator:** No pacemaker (n=28) **Blinding:** Open label (not blinded)	**1° endpoints:** ■ Recurrent syncope after at a mean of 36 mo: Pacemaker 3 (9%); No pacemaker 16 (57%); p=0.0002 ■ Recurrent syncope at a mean of 36 mo: Pacemaker 29 (91%); No pacemaker 12 (43%) ■ Syncope recurrent events after average of 36 mo: Pacemaker ON 4 events; Pacemaker OFF 22 events **2° endpoints:** ■ All-cause mortality after average of 36 mo: Pacemaker 4 (12.5%); No pacemaker 5 (17.9%) ■ Pts with syncope-related injury after average of 36 mo: Pacemaker ON 0 (0%); Pacemaker OFF 0 (0%) ■ Syncope-related injury events after average of 36 mo: Pacemaker ON 0 events; Pacemaker OFF 0 events	**Study limitations:** Not reported **Adverse events:** ■ Cardiovascular adverse events: Pacemaker 10 (31.3%); No pacemaker 16 (57.1%) ■ After 8.2 ± 10.0 mo, 19 pts withdrew from follow-up, because it was decided that they needed a pacemaker implantation (VVI in 12 cases, DDD in 7). The reasons for implantation were recurrence of syncope, alone or in association with minor symptoms (n=15), or frequent recurrence of distressing severe or mild dizziness (n=4).
Claesson JE, 2007 (6)	**Syncope type:** CSS **Aim:** To examine the effect on symptoms in pts with induced cardioinhibitory CSS when treated with pacemaker or without this treatment. **Study type:** RCT **Size:** Randomized (n=60)	**Inclusion criteria:** Pts were included if they had a positive carotid sinus stimulation test at enrollment and at least 1 episode of syncope or presyncope. **Exclusion criteria:** Pts were excluded because of geographic location and diminished cognitive function.	**Intervention:** DDDR, VVIR, or AAIR pacemaker programmed ON (n=30) **Comparator:** No pacemaker (n=30) **Blinding:** Open label (not blinded)	**1° endpoints:** ■ Pts with syncope recurrence at 12 mo: Pacemaker 3 (10%); No pacemaker 12 (40%); p=0.008 ■ Pts with no syncope recurrence at 12 mo: Pacemaker 27 (90%); No pacemaker 18 (60%) **2° endpoints:** ■ Presyncope at 12 mo: Pacemaker 8 (27%); No pacemaker 2 (7%) ■ All-cause mortality at 12 mo: Pacemaker 1 (3.3%); No pacemaker 2 (6.7%)	**Study limitations:** Limitations of this study are the absence of double-blinded design and not using a placebo control arm. **Adverse events:** Not reported

Continued on the next page

TABLE 1 Continued

Study Acronym; Author; Year Published (Ref. No.)	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (No. of patients)/ Study Comparator (No. of patients)	Endpoint Results (Absolute Event Rates, p Values; OR or RR; and 95% CI)	Study Limitations; Adverse Events
SAFE PACE Kenny RA, 2001 (13)	**Syncope type:** CSS **Aim:** To determine whether cardiac pacing reduces falls in older adults with CICSH. **Study type:** RCT **Size:** Randomized (n=175)	**Inclusion criteria:** Cognitively normal pts (Mini-Mental State Examination) in excess of 23 out of a total of 30 points) who were adults (≥50 y of age) and attended the accident and emergency department because of a nonaccidental fall. **Exclusion criteria:** Pts were excluded if they had cognitive impairment, were <50 y of age, or attended the accident and emergency department for a fall due to an accidental event, such as a slip or trip, or not attributable to a medical cause, such as epilepsy, stroke, alcohol excess, orthostatic hypotension, other bradyarrhythmias, or tachyarrhythmias.	**Intervention:** Dual-chamber DDD RDR pacemaker programmed ON (n=87) **Comparator:** No pacemaker (n=88) **Blinding:** Open label (not blinded)	**1° endpoints:** ■ Pts with syncope recurrence at 12 mo: Pacemaker 10 (11%); No pacemaker 19 (22%); p=0.063 ■ Pts with no syncope recurrence at 12 mo: Pacemaker 77 (89%); No pacemaker 69 (78%) ■ Syncope recurrent events at 12 mo: Pacemaker 22 events; No pacemaker 47 events; OR: 0.53; 95% CI: 0.23–1.2 **2° endpoints:** ■ Fall events at 12 mo: Pacemaker 216 events; No pacemaker 699 events ■ Pts with fracture due to fall at 12 mo: Pacemaker 3 (3.4%); No pacemaker 4 (4.5%) ■ Pts with soft-tissue injury due to fall at 12 mo: Pacemaker 26 (29.9%); No pacemaker 32 (36.4%) ■ All-cause mortality at 12 mo: Pacemaker 5 (5.7%); No pacemaker 3 (3.4%)	**Study limitations:** A much larger sample size would be required to determine whether pacing reduces fracture rates, hospitalizations, and mortality in older adults with CSH and nonaccidental falls. **Adverse events:** Not reported
SAFE PACE 2 Ryan DJ, 2010 (10)	**Syncope type:** CSS **Aim:** To determine whether, in a multicenter study, cardiac pacing for recurrent falls in pts with CICSH would reduce subsequent falls. **Study type:** RCT **Size:** Randomized (n=141) ITT (n=129)	**Inclusion criteria:** Participants >65 y of age who had CICSH as a possible attributable cause of symptoms with a minimum of 2 unexplained falls and/or 1 syncope in the past year. All participants had in excess of 3 s of asystole in response to CSM; a Mini-Mental State Examination score >19. **Exclusion criteria:** Pts with evidence of neoplasm, renal or hepatic failure; and at time of randomization, evidence of significant heart failure.	**Intervention:** Dual-chamber RDR pacemaker programmed ON (ITT: n=68) **Comparator:** No pacemaker (implantable loop recorder) (ITT: n=61) **Blinding:** Double-blinded	**1° endpoints:** ■ Pts with syncope recurrence not reported for this study ■ Pts reporting syncope after pacemaker implantation RR: 0.47 (95% CI: 0.26–0.86) ■ Syncope recurrent events at 24 mo: Pacemaker 0.42 mean events; No pacemaker 0.66 mean events; RR: 0.87; 95% CI: 0.3–2.48 **2° endpoints:** ■ Pts with falls at 24 mo: Pacemaker 44 (67%); No pacemaker 33 (53%); RR: 1.25; 95% CI: 0.93–1.67 ■ Syncope-related falls at 24 mo: Pacemaker 4.33 events; No pacemaker 6.52 events; RR: 0.79; 95% CI: 0.41–1.5	**Study limitations:** The technique of CSM is operator dependent, and it was not possible to standardize it in this multicenter trial. This possibly influenced recruitment. Recruitment itself was also more challenging when the study was rolled out to a multicenter design and used centers without systems in place for managing older pts with falls and syncope. Thus, the study may have been underpowered to show a significant difference between groups. **Adverse events:** Not reported

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TABLE 1 Continued

Study Acronym; Author; Year Published (Ref. No.)	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (No. of patients)/ Study Comparator (No. of patients)	Endpoint Results (Absolute Event Rates, p Values; OR or RR; and 95% CI)	Study Limitations; Adverse Events
Studies Addressing VVS					
ISSUE-3 Brignole M, 2012 (7)	**Syncope type:** VVS **Aim:** To determine whether pacing therapy reduces syncopal recurrences in pts with severe asystolic NMS. **Study type:** RCT **Size:** Randomized (n=77)	**Inclusion criteria:** Pts included in this study were ≥40 y of age and had experienced, in the previous 2 y, ≥3 syncopal episodes of likely NMS etiology. Pts with positive and negative tilt-table testing were included. **Exclusion criteria:** Pts were excluded if they had ≥1 of the following features: cardiac abnormalities that suggested cardiac syncope; symptomatic orthostatic hypotension diagnosed by standing blood pressure measurement; nonsyncopal loss of consciousness. Pts with CSS and documented symptomatic bradycardia during CSM were also excluded.	**Intervention:** Dual-chamber DDD RDR pacemaker programmed ON (n=38) **Comparator:** Dual-chamber sensing only on (n=39) **Blinding:** Double-blinded	**1° endpoints:** ■ Pts with syncope recurrence at 24 mo: Pacemaker ON 8 (21.1%); Pacemaker OFF 19 (48.7%); RRR: -57%; 95% CI: -81% to -4%; p=0.039 ■ Pts with no syncope recurrence at 24 mo: Pacemaker ON 30 (78.9%); Pacemaker OFF 20 (51.3%) **2° endpoints:** ■ All-cause mortality at 24 mo: 1 (1.3%)	**Study limitations:** The authors were unable to evaluate whether the rate drop response algorithm used in this trial provided an additional benefit to that of a DDD pacemaker without this feature. Although first-event occurrence is optimal for single or rare serious outcomes (e.g., death or hospitalization), it is not optimal for repetitive, relatively benign events such as NMS recurrence. All randomized trials considered first syncope as the primary outcome of the study. In the case of syncope trials, syncope burden would likely give a better picture of the clinical benefit of pacemaker therapy. Because of its sequential design, the study is underpowered to make any subgroup analysis. **Adverse events:** Pacemaker-related adverse events: 5 (6.5%)
Flammang D, 1999 (14)	**Syncope type:** VVS **Aim:** To determine whether pacing reduced the risk of symptom recurrence in pts with VVS and abnormal response to ATP testing. **Study type:** RCT **Size:** Randomized (n=20)	**Inclusion criteria:** To be included, pts needed to meet both of the following conditions: syncope of vasovagal origin and abnormal cardioinhibitory (i.e., electrocardiographic) response during ATP test. **Exclusion criteria:** Syncope of neurological, metabolic, and arrhythmological origins.	**Intervention:** Dual-chamber pacemaker programmed ON (n=10) **Comparator:** No pacemaker (n=10) **Blinding:** Open label (not blinded)	**1° endpoints:** ■ Pts with syncope recurrence at average of 52 mo: Pacemaker 0 (0%); No pacemaker 6 (60%) ■ Pts with no syncope recurrence at average of 52 mo: Pacemaker 10 (100%); No pacemaker 4 (40%) **2° endpoints:** ■ All-cause mortality at average of 52 mo: Pacemaker 3 (30%); No Pacemaker 1 (10%)	**Study limitations:** The number of pts included in this study was very small. It is possible that the ATP test is demonstrating a treatable cause of syncope previously unrecognized in this patient group and that these elderly pts are atypical for those now considered to have VVS. Less severe symptoms such as dizziness and syncope were not recorded in this study. **Adverse events:** Not reported

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TABLE 1 Continued

Study Acronym; Author; Year Published (Ref. No.)	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (No. of patients)/ Study Comparator (No. of patients)	Endpoint Results (Absolute Event Rates, p Values; OR or RR; and 95% CI)	Study Limitations; Adverse Events
Lelonek M, 2007 (12)	**Syncope type:** VVS **Aim:** To determine the association of pacing with risk of recurrent events among pts with VVS. **Study type:** Prospective observational study **Size:** n=34	**Inclusion criteria:** Fainting pts with tilt-induced cardiodepressive syncope with asystole >3 s were included. Diagnosis was based on a positive tilt test after exclusion of other possible causes of syncope by complete cardiac and neurological evaluation. **Exclusion criteria:** Exclusion criteria included: congestive heart failure, previous MI and concomitant severe chronic diseases or life expectance <1 y.	**Intervention:** Dual-chamber DDI pacemaker programmed ON (n=22) **Comparator:** No pacemaker (n=12) **Blinding:** None (observational)	**1° endpoints:** ■ Pts with syncope recurrence at 18 mo: Pacemaker 5 (23%); No pacemaker 3 (25%); p>0.05 ■ Pts with no syncope recurrence at 18 mo: Pacemaker 17 (77%); No pacemaker 9 (75%) ■ Syncope recurrent events at 18 mo: Pacemaker 2.05 mean events (SD±4.1); No pacemaker 0.83 mean events (SD±1.57); p>0.05 **2° endpoints:** ■ Pts with syncope-related injury at 18 mo: Pacemaker 0 (0%); No pacemaker 0 (0%)	**Study limitations:** Limitations include low enrolled population and lack of randomization and control group. **Adverse events:** Not reported
Vasovagal Syncope and Pacing (SYNPACE) trial Raviele A, 2004 (11)	**Syncope type:** VVS **Aim:** To ascertain whether, in pts with recurrent tilt-induced VVS, the implantation of a dual-chamber, pacemaker programmed to ON, reduced the number of pts suffering syncopal relapses and/or prolonged the time to the first recurrence in comparison with the implantation of a pacemaker programmed to OFF. **Study type:** RCT **Size:** Randomized (n=29)	**Inclusion criteria:** To be enrolled, all pts had to meet the following criteria: frequently recurrent syncope and positive head-up tilt testing with asystolic or mixed response; at least 6 syncopal events in the patient's lifetime; the last occurring no more than 6 mo before enrollment; at least 1 recurrence within 12 mo following positive head-up tilt testing; >18 y of age. **Exclusion criteria:** Exclusion of any other cause of syncope after a complete work-up.	**Intervention:** Dual-chamber DDD RDR pacemaker programmed ON (n=16) **Comparator:** Dual-chamber OOO pacemaker programmed OFF (n=13) **Blinding:** Double-blinded	**1° endpoints:** ■ Pts with syncope recurrence at median of 23.8 mo: Pacemaker ON 8 (50%); Pacemaker OFF 5 (38%) ■ Pts with no syncope recurrence at median of 23.8 mo: Pacemaker ON 8 (50%); Pacemaker OFF 8 (62%) ■ Syncope recurrent events at median of 23.8 mo: Pacemaker ON 0.04 mean events/30 d (SD±0.06); Pacemaker OFF 0.08 mean events/30 d (SD±0.15) **2° endpoints:** ■ Pts with presyncope at median of 23.8 mo: Pacemaker ON 12 (75%); Pacemaker OFF 5 (38%) ■ Pts with severe syncope-related injury at median of 23.8 mo: Pacemaker ON 0 (0%); Pacemaker OFF 0 (0%) ■ Pts with minor syncope-related injury at median of 23.8 mo: Pacemaker ON (not reported); Pacemaker OFF 1 (7.7%) ■ All-cause mortality at median of 23.8 mo: Pacemaker ON 0 (0%); Pacemaker OFF 0 (0%)	**Study limitations:** The enrolled pts were highly selected and were estimated to be only 1.8% of the source population; they had a much higher number of syncopal spells in their lifetime than the average of pts affected by VVS. This study was done on a relatively small sample of pts. A trend toward a prolonged time to first syncopal relapse was observed in the active pacing arm; with a higher number of pts the difference could have become significant. **Adverse events:** Mild palpitations in Pacemaker ON group 6 (37.5%); the only complications of pacemaker implantation were 2 cases of generator-related pain, 1 requiring repositioning of the device.

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TABLE 1 Continued

Study Acronym; Author; Year Published (Ref. No.)	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (No. of patients)/ Study Comparator (No. of patients)	Endpoint Results (Absolute Event Rates, p Values; OR or RR; and 95% CI)	Study Limitations; Adverse Events
Russo V, 2013 (9)	**Syncope type:** VVS **Aim:** To evaluate the effect of dual-chamber CLS in the prevention of syncope recurrence in pts with refractory VVS and a cardioinhibitory response to head-up tilt-test during a 36-mo follow-up. **Study type:** Randomized crossover study **Size:** Randomized (n=50)	**Inclusion criteria:** The study involved only pts who: were aged >40 y; were in sinus rhythm; had recurrent unpredictable syncope of unknown origin after the first evaluation; took no medication that could affect circulatory control; developed cardioinhibitory VVS associated with asystole >3 s during tilt test (Vasovagal Syncope International study [VASIS] 2B type); were refractory to conventional drug therapy and/or tilt training. **Exclusion criteria:** Pts with other possible causes of syncope were excluded.	**Intervention:** Dual-chamber DDD pacemaker programmed ON with CLS ON (n=50 with CLS ON) **Comparator:** Dual-chamber DDD pacemaker programmed ON with CLS OFF (same 50 pts went through CLS OFF phase) **Blinding:** Double-blinded	**1° endpoints:** ■ Pts with syncope recurrence at 18 mo: Pacemaker CLS ON 1 (2%); Pacemaker CLS OFF 8 (16%) ■ Pts with no syncope recurrence at 18 mo: Pacemaker CLS ON 49 (98%); Pacemaker CLS OFF 42 (84%) ■ Syncope recurrent events at 18 mo: Pacemaker CLS ON 2 events; Pacemaker CLS OFF 15 events; p=0.007 **2° endpoints:** ■ Pts with presyncope at 18 mo: Pacemaker CLS ON 4 (8%); Pacemaker CLS OFF 18 (27.8%) ■ Pts with syncope-related injury at 18 mo: Pacemaker CLS ON 0 (0%); Pacemaker CLS OFF 0 (0%)	**Study limitations:** A more extensive study, including a greater number of pts, is needed to confirm the findings. The patient population was highly selected. The interpretation of crossover studies may be complicated by carryover effects. **Adverse events:** Not reported
VASIS Sutton R, 2000 (4)	**Syncope type:** VVS **Aim:** To evaluate the ability of pacing to reduce the interval to first recurrence of syncope. **Study type:** RCT **Size:** Randomized (n=42)	**Inclusion criteria:** To be included in the study, the pts affected by NMS had to fulfill the following 3 conditions: ≥3 syncopal episodes in the past 2 y, with the last episode occurring within 6 mo of enrollment and with an interval between the first and the last episode of >6 mo; positive VASIS type 2A or 2B cardioinhibitory response to head-up tilt testing (definitions in the Tilt Test Protocol Section); and >40 y of age or, if <40 y of age, proven refractoriness to conventional drug therapy. **Exclusion criteria:** Pts were excluded if a cause of syncope other than VVS was known or suspected. Other exclusion criteria included recent (<6 mo) MI, severe heart failure (NYHA class III or IV), concomitant severe chronic diseases (e.g., diabetes mellitus, neurological diseases, terminal diseases, and neoplasia), and pts refusal to participate in the study.	**Intervention:** DDI pacemaker with rate hysteresis programmed ON (n=19) **Comparator:** No pacemaker (n=23) **Blinding:** Open label (not blinded)	**1° endpoints:** ■ Pts with syncope recurrence at 80 mo: Pacemaker 1 (5%); No pacemaker 14 (61%); RR: 0.04; 95% CI: 0.005–0.3; p=0.0006 ■ Pts with no syncope recurrence at 80 mo: Pacemaker 18 (95%); No pacemaker 9 (39%) ■ Syncope events at 80 mo: Pacemaker 2 events; No pacemaker 26 events **2° endpoints:** ■ Pts with syncope-related injury at 80 mo: Pacemaker 0 (0%); No pacemaker 0 (0%)	**Study limitations:** Despite randomization, pacemaker pts were older than no-pacemaker pts. The study was not blinded, with no device implantation in the control arm. Recurrences of presyncope and dizziness were not collected. It is possible that pacemaker therapy aborted syncope in many pts, but they were still symptomatic with dizziness or presyncope. A longer follow-up is necessary to assess any potential deleterious effect of long-term pacing in the same cohort of pts. **Adverse events:** 3 pts developed stable or paroxysmal second-degree AV block during follow-up. There were 2 deaths in the pacemaker arm, 1 caused by stroke, and 1 by cancer.

Search Terms and Date: syncope, faint, carotid sinus hypersensitivity, carotid sinus syndrome, loss of consciousness - LOC, tLOC, vasovagal attack, vasovagal response, vasovagal reaction, vasovagal episode, vasovagal syndrome, vasovagal collapse, pacemaker, pacing, cardiac resynchronization therapy, CRT device, implantable cardiac device, cardiovascular implantable electronic device, cardiac implantable device; October 7, 2015.

ATP indicates adenosine triphosphate; AV, atrioventricular; CI, confidence interval; CICSH, cardioinhibitory carotid sinus hypersensitivity; CLS, closed-loop stimulation; CSH, carotid sinus hypersensitivity; CSM, carotid sinus massage; CSS, carotid sinus syndrome; HR, hazard ratio; ITT, intention-to-treat; MI, myocardial infarction; N/A, not available; NMS, neurally mediated syncope; NYHA, New York Heart Association classification; OR, odds ratio; pts, patients; RCT, randomized controlled trial; RR, relative risk; RRR, relative risk reduction; and VVS, vasovagal syncope.

FIGURE 2A Forest Plot of Meta-Analysis of Recurrent Syncope (Unblinded Studies)

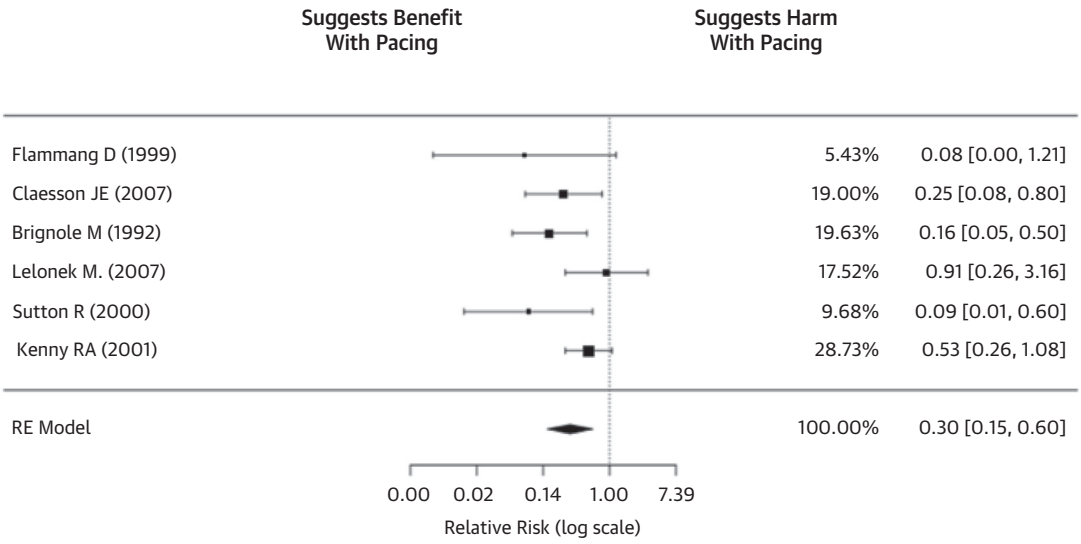


FIGURE 2B Forest Plot of Meta-Analysis of Recurrent Syncope (Double-Blinded Studies)

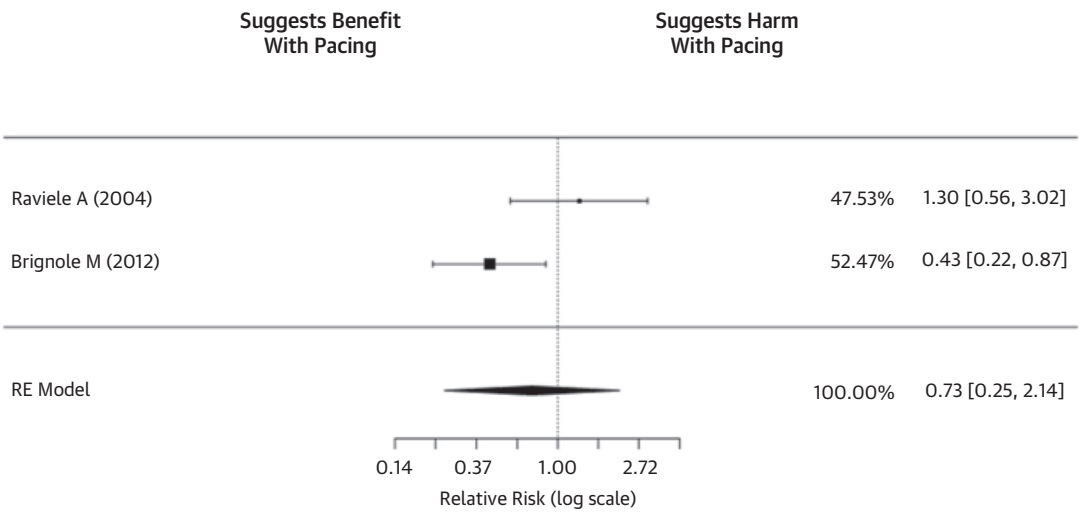
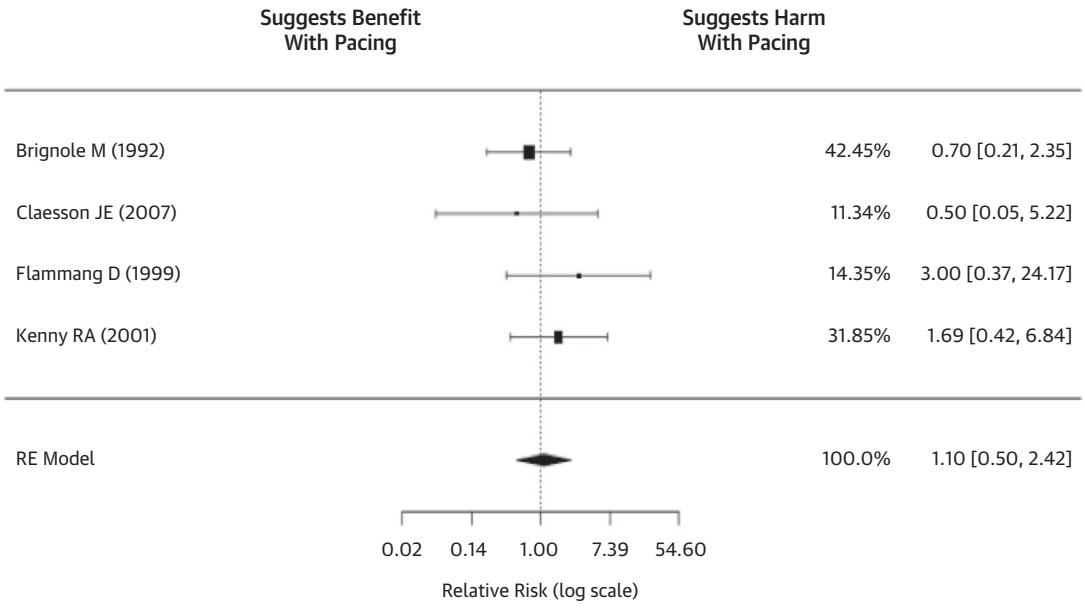


FIGURE 3 Forest Plot of Meta-Analysis of Mortality Rate



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KEY WORDS ACC/AHA Clinical Practice Guidelines, Evidence Review Committee, pacemaker, pacing, reflex syncope, syncope, syncope-diagnosis, vasovagal syncope

APPENDIX 1. EVIDENCE REVIEW COMMITTEE RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)*–PACING AS A TREATMENT FOR REFLEX-MEDIATED (VASOVAGAL, SITUATIONAL, OR CAROTID SINUS HYPERSENSITIVITY) SYNCOPE: A SYSTEMATIC REVIEW FOR THE 2017 ACC/AHA/HRS GUIDELINE FOR THE EVALUATION AND MANAGEMENT OF PATIENTS WITH SYNCOPE (MARCH 2014)

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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Amy L. Miller	Brighman and Women's Hospital, Harvard Medical School—Assistant Professor, Cardiovascular Medicine	None	None	None	None	None	None
Peter A. Noseworthy	Mayo Clinic College of Medicine—Associate Professor of Medicine	None	None	None	None	None	None
David J. Slotwiner	New York Presbyterian Queens—Chief, Division of Cardiology; Weill Cornell Medical—Assistant Professor	None	None	None	None	None	None
Venkatesh Thiruganasambandamoorthy	Ottawa Hospital Research Institute—Assistant Professor, Staff Attending Physician	None	None	None	None	None	None

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