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The benefit of closed loop stimulation in patients with cardioinhibitory vasovagal syncope confirmed by head-up tilt table testing: a systematic review and meta-analysis

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Abstract

Purpose A proportion of patients with vasovagal syncope (VVS) experience recurrence despite appropriate management. Closed loop stimulation (CLS) pacing is a promising treatment for a subgroup of patients with cardioinhibitory response on head-up tilt table test (HUTT). Nonetheless, its efficacy remains uncertain. We sought to assess the efficacy of CLS pacing in patients with cardioinhibitory VVS.

Methods We searched PubMed, Google Scholar, and the Cochrane Central Register of controlled trials for relevant studies (last search date April 23, 2018). Data were pooled using the Mantel-Haenszel fixed-effects model. For cohort studies, we used a Freeman-Tukey transformation to calculate the weighted summary proportion. Primary outcomes are syncope and presyncope.

Results Eight studies were included in the final analyses (two single-blinded and one double-blinded RCT, two prospective observational studies, and three retrospective observational studies). Two hundred ninety-one patients included, with an average age of 57 years. Quality of evidence is moderate. Use of CLS pacing was associated with reduced risk of syncope (OR 0.08; 95% CI 0.03–0.18; I^2 32%) and presyncope (OR 0.34; 95% CI 0.18–0.63; I^2 0.00%). Using proportion meta-analysis, the summary estimate of the proportion of cases that developed syncope during CLS pacing was similar between RCTs and prospective studies (3.2% and 3.1%), respectively. This is much lower than the rate of recurrence in the control arm of RCTs at 33.7%. Sensitivity analyses yielded similar results.

Conclusion CLS pacing is beneficial for patients with recurrent vasovagal syncope who demonstrate a cardioinhibitory response on HUTT.

Keywords Syncope · Vasovagal · Pacemaker · Closed loop stimulation

1 Introduction

Vasovagal syncope (VVS) is the most common cause of syncope accounting for at least one-fifth of the cases [1]. Although it has a benign course in most people, a subset of patients experiences recurrence despite lifestyle modifications and medical therapy.

Based on the results of head-up tilt table testing (HUTT), VVS is classified as mixed, cardioinhibitory, or vasodepressor type [2]. The bradycardic/asystolic component of the episode has long been a target for pacemaker therapy. Initial studies were promising. However, well-designed randomized controlled trials (RCT) of conventional pacing failed to demonstrate efficacy for reducing syncopal events [3]. In 2012, the ISSUE-3 trial became the first to show pacing benefit in this patient population. In this trial, patients who were ≥ 40 years old with recurrent syncope and asystole on implantable cardiac monitor had 57% relative risk reduction in syncope recurrence when randomized to dual-chamber pacing with rate-drop response algorithm compared with sensing alone [4]. Current guidelines consider pacing a reasonable option for patients with refractory vasovagal syncope if asystole is a predominant feature of the syncope [5, 6].

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Recently, a pacing algorithm called closed loop stimulation (CLS) has emerged as a new strategy to treat VVS and may be superior to conventional pacing algorithms [7]. In patients with CLS pacing, right ventricular impedance is measured with repeated subthreshold pulses during the cardiac cycle. It is hypothesized that the increased contractility and decreased filling prior to vasovagal reflex activation, the impedance increases as a greater fraction of the myocardium interferes with the lead tip. This triggers the CLS algorithm and initiates pacing even before the onset of bradycardia or asystole.

CLS by Biotronik Inc. was initially developed in the late 1980s. Since then, many studies have evaluated its efficacy in treating patients with syncope and cardioinhibitory response on HUTT. However, the evidence for CLS pacing is limited; there are conflicting recommendations by experts and a wide variation in utilization. In light of current uncertainty and the recently published SPAIN trial [8], we conducted a systematic review and meta-analysis to determine the efficacy of CLS pacing in patients with recurrent cardioinhibitory VVS confirmed by HUTT.

2 Methods

2.1 Data collection and extraction

We searched PubMed, Google Scholar, and the Cochrane Central Register of controlled trials for studies that evaluated pacemaker therapy in patients with vasovagal syncope (last search date April 23, 2018). We also searched ClinicalTrials.gov to identify any ongoing RCTs. We excluded studies that used pacing algorithms other than CLS, studies with no clinical follow-up, and studies that included patients who had bradycardia/asystole on telemetry but did not have HUTT.

The study protocol was drafted by three of the authors (M.R, M.G, and A.F) and revised by all coauthors. Two authors (M.R and M.G) independently reviewed all articles and abstracts for inclusion. They independently extracted information on sample size, follow up, and outcomes. Discrepancies were discussed and resolved by consensus.

2.2 Outcome

The primary outcomes were syncope and presyncope. We used the Cochrane risk of bias table and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system to report risk of bias in each study and quality of study outcomes, respectively.

2.3 Statistical analysis

The primary analysis for studies with a control arm was performed using RevMan version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

The effect measure for outcomes was reported as odds ratios (OR) with 95% confidence interval (CI). We pooled the data using Mantel-Haenszel fixed-effects model, we then ran sensitivity analyses to ascertain the robustness of results. We quantified heterogeneity using I^2, which represents the percentage of variability in the effect risk estimate among studies that is due to heterogeneity rather than chance ($I^2 < 25\%$ considered low; $I^2 > 75\%$ considered high, and in between as intermediate).

For studies with no control arm, we used a Freeman-Tukey transformation [9] to calculate the weighted summary proportion under the fixed and random effects model. Using this method, data are transformed into new variables to create a more normal distribution and to stabilize the variance of the studied population. Transformed data are then compared with percentage points of the normal distribution to create confidence intervals [9]. This analysis was performed using MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium).

A two-sided p value < 0.05 was considered to be statistically significant.

3 Results

3.1 Qualitative synthesis

Our search identified 2719 studies, of which 12 full texts were relevant for evaluation, Diagram 1. Four full-text articles were excluded for the following reasons: one study did not contain data on clinical follow-up and three studies included patients with asystole or bradycardia on monitoring and did not require positive HUTT. Four studies were included in the meta-analysis (1 retrospective cohort study and 3 randomized trials [2 single blinded and 1 double blinded with a sham control]), and four were included in the proportion meta-analysis (two prospective and two retrospective), Table 1. A total of 275 patients received CLS pacing and 121 patients received conventional or sham pacing. ClinicalTrials.gov search identified one RCT (BIOSync CLS), randomizing patients with cardioinhibitory VVS to CLS pacing vs sham pacing (ODO) that is expected to be completed by Oct. 2019.

3.1.1 Risks of bias and quality assessment

For each of the studies, there were limitations in methodology and in outcome assessment (per Cochrane and GRADE criteria), Table 2. Patients were blinded in each of the RCTs

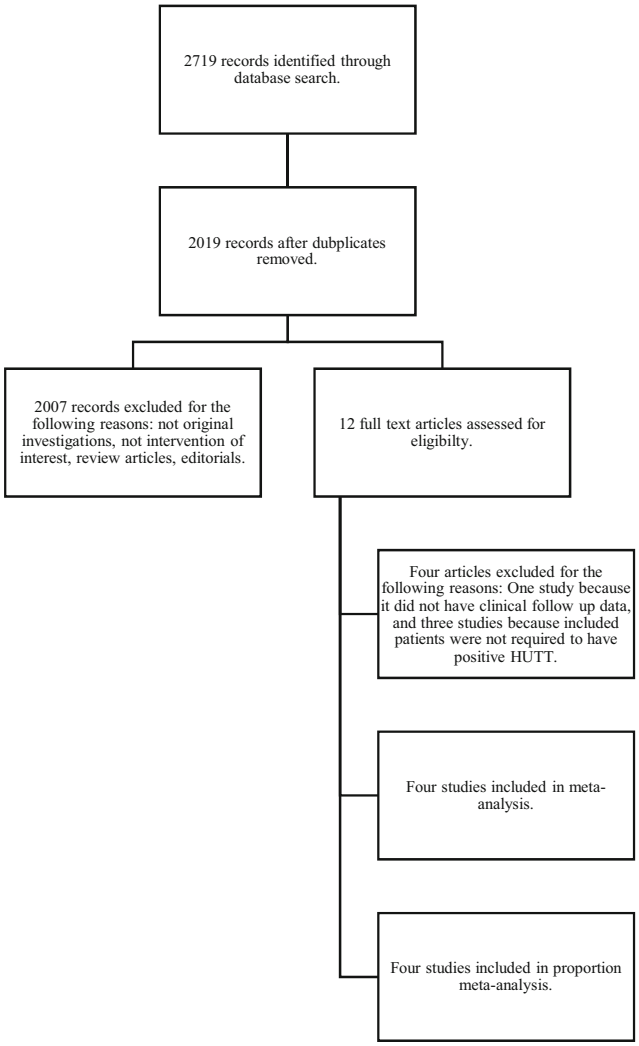

Diagram 1 Flow diagram of included studies

[8, 10, 11]. However, outcome assessment was blinded only in the SPAIN study [8]. Based on GRADE criteria, our confidence in the outcome estimates derived from pooled data was moderate, Table 3. The patient populations for each of the included studies were similar and mainly included patients with recurrent cardioinhibitory VVS who failed lifestyle modifications and medical therapy.

In the SPAIN [8] and INVASY [10] trials, recurrent syncope was defined by at least 5 previous VVS episodes (> 2 occurring within the last year). In the trial by Russo et al [11], the average number of VVS episodes was 7 ± 3. Other studies did not have a strict definition of recurrent syncope.

The average duration of follow up for the included studies was 33 months. The three RCTs had a similar follow-up time of 2–3 years. The follow-up time in the prospective cohort studies was variable, 4–48 months in the study by Griesbach et al [12] and 12–50 months in the study by Occhetta et al [13]. Retrospective studies had a follow-up time of 4–5 years. Funnel plots were not suggestive of publications bias, Fig. 4.

3.2 Quantitative synthesis

3.2.1 Clinical outcomes

Four studies [8, 10, 11, 14] with control arms reported syncope as an outcome (6 patients experienced syncope among 171 patients who received CLS pacing and 42 patients experienced syncope among 121 controls). Use of CLS pacing was associated with reduced risk of syncope (3.5% vs 34.7%; OR 0.08; 95% CI 0.03–0.18; I^2 32%),

Table 1 Characteristics of included studies

Author (year)	Study design	Female gender (%)	Age in years, mean (range)	Type of VVS based on VASIS	Patients with CLS pacing	Control	Follow up time
Griesbach et al. (2002)(12)	Prospective (CLS in all patients)	76.5%	63 (47–77)	Type II (14 pts) and type III (3 pts)	17	N/A	12 ± 30 months
Occhetta et al. (2003)(13)	Prospective (CLS in all patients)	23.5%	65 (33–80)	Type I or type II	34	N/A	12–50 months
Occhetta et al. (2004)(10)	Randomized, controlled, single blinded	46.0%	59 (NA)	Type II	41	9	19 ± 4 months
Palmisano et al. (2012)(14)	Retrospective cohort	56.1%	53 (NA)	Type II	25	16	4.4 ± 3.0 year
Bortnik et al. (2012)(15)	Retrospective (CLS in all patients)	NA	59 (22–80)	Type II (29 pts) and type III (6 pts)	35	N/A	61 ± 35 months
Russo et al. (2013)(11)	Randomized, single-blinded, crossover design	34.0%	53 (NA)	Type II	50	50	36 months
Anguera Camos et al. (2015)(16)	Retrospective (CLS in all patients)	44.4%	49 (27–76)	Type II	18	N/A	30 ± 6 months
Baron-Esquivias et al. (2017)(8)	Double-blind placebo-controlled	52.2%	56 (NA)	Type II	46	46	22 ± 5 months

CLS, closed loop stimulation; *HUTT*, head-up tilt table test; *NA*, not available; *N/A*, not applicable, *VVS*, vasovagal syncope

Table 2 Risk of bias table for included studies

Bias	Study	Judgment	Support for judgment
Random sequence generation (selection bias)			
	Griesbach 2002	Unknown	Prospective cohort, all patients received CLS pacing
	Occhetta 2003	Unknown	Prospective cohort, all patients received CLS pacing
	Occhetta 2004	Low risk	Computer generated randomization was used
	Palmisano 2012	Unknown	Retrospective
	Bortnik 2012	Unknown	Retrospective
	Russo 2013	Unknown	Inadequate details provided
	Anguera 2015	Unknown	Retrospective
	Baron-Esquivias 2017	Low risk	Randomization by central phone system
Allocation concealment (selection bias)			
	Griesbach 2002	High risk	All patients received CLS pacing.
	Occhetta 2003	High risk	All patients received CLS pacing.
	Occhetta 2004	Low risk	Computer generated randomization was used.
	Palmisano 2012	Unknown	Retrospective
	Bortnik 2012	Unknown	Retrospective
	Russo 2013	Unknown	Inadequate details provided
	Anguera 2015	Unknown	Retrospective
	Baron-Esquivias 2017	Low risk	Randomization by central phone system
Blinding of participants and personnel (performance bias)			
	Griesbach 2002	High risk	No blinding
	Occhetta 2003	High risk	No blinding
	Occhetta 2004	Low risk	Patients were blinded
	Palmisano 2012	High risk	No blinding
	Bortnik 2012	High risk	No blinding
	Russo 2013	Low risk	Patients were blinded
	Anguera 2015	High risk	No blinding
	Baron-Esquivias 2017	Low risk	Patients were blinded
Blinding of outcome assessment (detection bias)			
	Griesbach 2002	High risk	No blinding
	Occhetta 2003	High risk	No blinding
	Occhetta 2004	High risk	No blinding
	Palmisano 2012	High risk	No blinding
	Bortnik 2012	High risk	No blinding
	Russo 2013	High risk	No blinding
	Anguera 2015	High risk	No blinding
	Baron-Esquivias 2017	Low risk	Outcome assessment was blinded
Incomplete outcome data addressed (attrition bias)			
	Griesbach 2002	Low risk	No significant attrition
	Occhetta 2003	Low risk	No significant attrition
	Occhetta 2004	Low risk	No significant attrition
	Palmisano 2012	Low risk	No significant attrition
	Bortnik 2012	Low risk	No significant attrition
	Russo 2013	Low risk	No significant attrition
	Anguera 2015	Low risk	No significant attrition
	Baron-Esquivias 2017	Low risk	No significant attrition
Selective reporting (reporting bias)			
	Griesbach 2002	Low risk	
	Occhetta 2003	Low risk	
	Occhetta 2004	Low risk	

Table 2 (continued)

Bias	Study	Judgment	Support for judgment
	Palmisano 2012	Low risk	
	Bortnik 2012	Low risk	
	Russo 2013	Low risk	
	Anguera 2015	Low risk	
	Baron-Esquivias 2017	Low risk	

Fig. 1a. Limiting the analyses to RCTs, the results were similar (3.4% vs 34.3%; OR 0.08; 95% CI 0.03–0.20; I^2 54%), Fig. 1b.

When performing sensitivity analysis, the removal of any individual trial did not appreciably alter the point estimate or confidence interval in the results; however, removal of the INVASY trial [10], which stopped randomization after enrolling about half of the patients, had variable follow up time between the control and the intervention group, had a very high event rate in the control arm, and was judged to be at moderate to high risk of bias, led to a large reduction in heterogeneity without significant change in the treatment effect (5% vs 31.3%; OR 0.10; 95% CI 0.04–0.26; I^2 0.0%), Fig. 1c.

Additionally, syncope was reported in four studies without control arms (two prospective [12, 13] and two retrospective [15, 16]). The overall summary estimate of the proportion of cases that developed syncope during CLS pacing (including cohort studies and CLS arm of comparative studies) was 5% (95% CI 2.8–8.2, I^2 52.4%), Fig. 2a. This event rate was similar on sensitivity analysis. When excluding the study by Bortnik et al [15], which was driving up the heterogeneity, the proportion of patients who developed syncope was at 3.7% (95% CI 1.7–6.9, I^2 16.3%). In this study, 6/35 patients had vasodepressor response on HUTT, which could have led to higher syncopal rate.

When limiting analysis to cohort studies, the rate of syncope was slightly higher at 7.7% (95% CI 3.5–14.5, I^2 52.1%), Fig. 2b. When analyzing only the two prospective higher quality studies, the rate was lower at 3.1% (95% CI 0.3–11.9, I^2 0.00%), Fig. 2c. This rate of recurrent syncope was similar to the rate of 3.2% (95% CI 1–7.5%, I^2 65.9%) derived from the CLS arm of RCTs but still much lower than the rate of 33.7% (95% CI 24.8–43.4, I^2 89.1%) found in the control arm of RCTs.

Presyncope was also reduced with CLS use (12.1% vs 36%; OR 0.34; 95% CI 0.18–0.63; I^2 0.00%), Fig. 3a. The results were similar when analysis was limited to RCTs, (8.8% vs 33.9%; OR 0.26; 95% CI 0.11–0.60; I^2 0.00%), Fig. 3b.

4 Discussion

In this systematic review and meta-analysis of CLS pacing in patients with cardioinhibitory VVS confirmed by HUTT, CLS pacing was associated with a significant reduction in the odds of experiencing recurrent syncope (OR 0.08; I^2 54%) and this effect is large. The absolute reduction in recurrent syncope was found to be approximately 30% (3.5% vs 34.7%), corresponding to a number needed to treat of 3–4 patients with cardioinhibitory VVS on HUTT with CLS pacing to prevent 1 patient from experiencing recurrent syncope. The treatment effect for CLS pacing in this patient population appears to be fairly robust as it did not change with sensitivity testing and, despite moderate heterogeneity in the main analysis, exclusion of the trial leading to heterogeneity did not lead to an appreciable change in the absolute difference in events between groups, the point estimate, or confidence interval.

Table 3 Summary of findings

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (study(ies))	Certainty of evidence (GRADE)
	Risk with other pacing	Risk with CLS pacing			
Syncope	405 per 1000	49 per 1000 (24 to 101)	RR 0.12 (0.06 to 0.25)	292 (3 RCTs)	⊕⊕⊕○ moderate
Presyncope	520 per 1000	140 per 1000 (78 to 244)	RR 0.27 (0.15 to 0.47)	191 (2 RCTs)	⊕⊕⊕○ moderate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). *CI*, confidence interval; *RR*, risk ratio

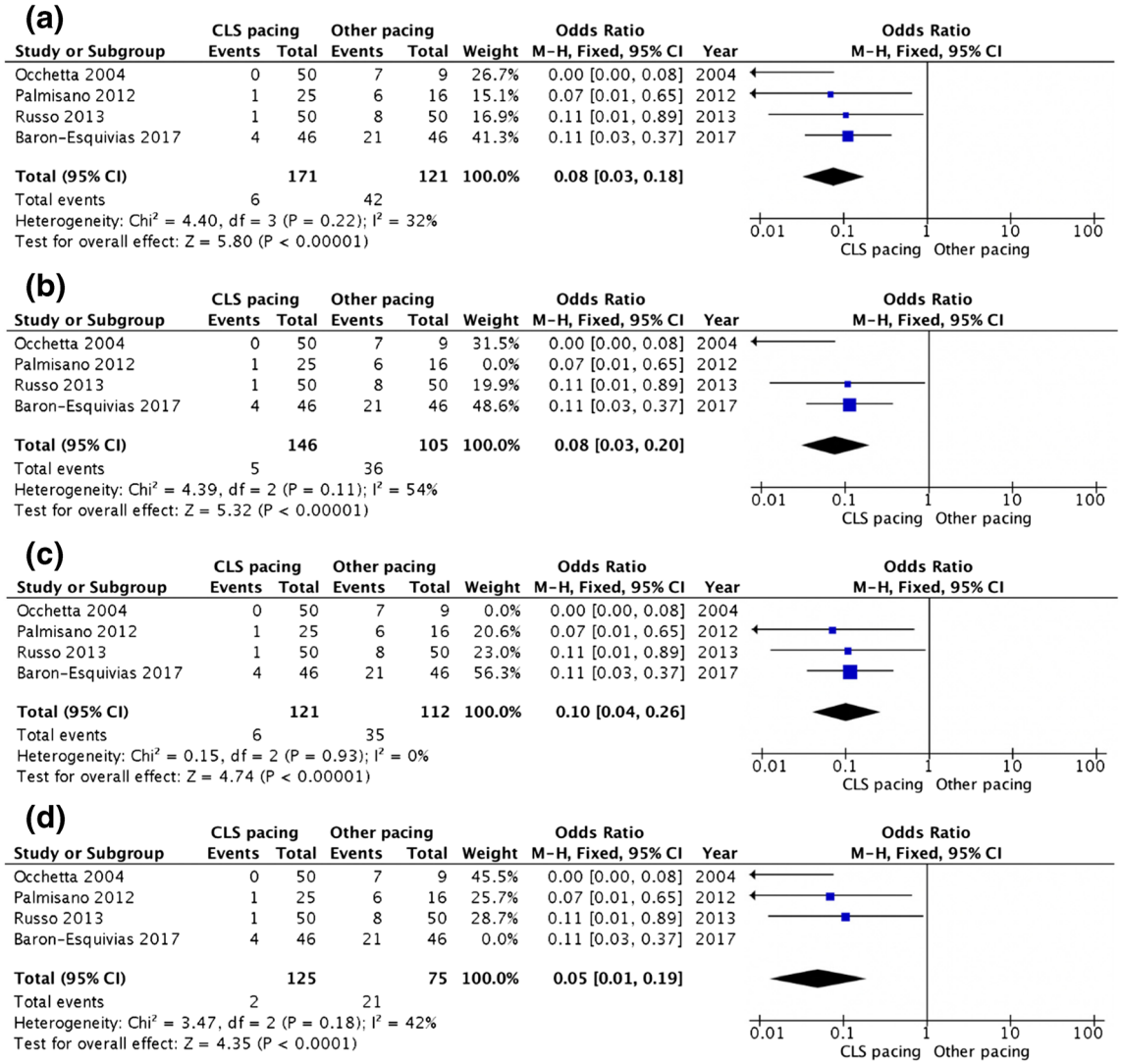

Fig. 1 Forest plot of syncope for comparative studies. **a** is a meta-analysis of all studies. **b** is the analysis after excluding the retrospective study. **c** is the analysis after excluding the study with the largest treatment effect, the INVASY trial. **d** is the analysis after excluding the SPAIN study as it has the largest weight

Furthermore, the proportion meta-analysis, which analyzed cohort studies following patients after CLS pacing but without control groups, found that the proportion of patients experiencing recurrent syncope was within range of the proportion experiencing recurrent syncope in the CLS arm of the RCTs (7.7% vs 3.2%) and was much lower than the rate of recurrence in the control arms (7.7% vs 33.7%) (Fig. 4).

The results of this analysis are consistent with the previously published meta-analysis of CLS pacing in patients with VVS [17]. The difference between this analysis and the analysis performed by Rattanawong et al [17] is that ours is focused on studies that included patients with VVS and cardioinhibitory response on HUTT. Furthermore, our analysis is more comprehensive as we also included studies that did not have a control arm, using a proportion meta-analysis.

We anticipate that a reduction in recurrent syncope to this extent with CLS pacing may improve quality of life in this patient population, and this is supported by the results of the one and only trial that systematically assessed the quality of life [10].

Trials of conventical pacing in patients with VVS have mixed results [3, 4, 18]. In the Third International Study on Syncope of Uncertain Etiology (ISSUE-3) trial [4], patients ≥ 40 years, who had severe asystolic VVS (syncope with ≥ 3 s asystole or ≥ 6 s asystole without syncope), had significant

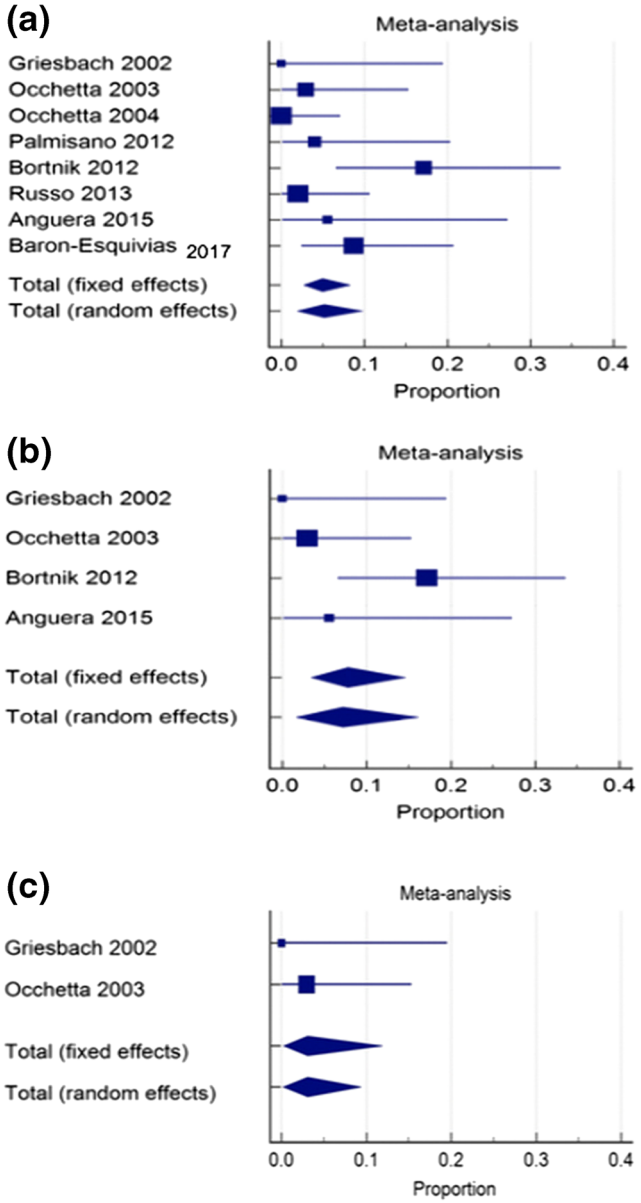

Fig. 2 Forest plot of syncope for proportion meta-analysis. **a** is the analysis for all studies. **b** is the analysis of the cohort studies. **c** is the analysis of the two prospective studies

reduction in syncope recurrence with dual-chamber pacing. Observational studies showed that CLS pacing reduces syncope recurrence in this population as well [19].

The difference in the results between the negative VPS II [3], SYNPACE [18] trials and the positive ISSUE-3 [4] trial could be related to patients selection. While the former two trials recruited patients based on the results of HUTT, the ISSUE-3 trial recruited patients with asystolic VVS based on the results of an implantable cardiac monitor. Although HUTT was not mandatory in the ISSUE-3 trial, it was performed in the majority of patients. To further support this hypothesis, a post hoc analysis of the ISSUE-3 trial demonstrated that patients who had positive HUTT with cardioinhibitory response did not have significant reduction in syncope with pacing [20]. In contrast to conventional pacing trials, CLS pacing trials had more strict inclusion criteria based on the results of HUTT. The findings of the conventional pacing trials and our analysis support the superiority of CLS pacing over conventional pacing in patients with VVS and positive HUTT, whether or not they demonstrate asystolic episodes on long-term monitoring.

This meta-analysis has several limitations. Firstly, a limited number of studies and a relatively small number of subjects may result in an overestimation of the treatment effect. Secondly, pharmacological interventions were not systemically used or reported. However, no treatment is universally effective in treating this patient population. Thirdly, expectation effect [21] among the majority of the studies (those without blinding) may have affected their results. Finally, programmers cannot see what the device has done during an event and data on optimal device programming are lacking.

Despite the fact that our analysis contains a relatively small number of patients, large numbers are not required to reliably conclude that a large effect of an intervention is present. The recurrence rate in this patient population is high (~35%) in the included studies and the risk reduction is large (~90%). The low-intermediate heterogeneity found across comparative studies is diminished by exclusion of a single study that leads to no appreciable change in the treatment effect, and thus our confidence in the results of this analysis is high.

Current guidelines classify pacemakers as a class IIb recommendation for patients with VVS and documented asystole [5]. Guidelines do not specifically comment on the use of CLS pacing. Nonetheless, based on the results of this analysis, the authors believe that CLS pacing should be considered a class IIa recommendation for patients with recurrent VVS and cardioinhibitory response on HUTT.

5 Conclusion

For patients with recurrent cardioinhibitory syncope confirmed by HUTT, CLS pacing reduces recurrent syncope and may improve quality of life. Based on the findings of this analysis, "it should be considered" for patients who meet this condition. The ongoing "Benefit of Dual-chamber Pacing with Closed Loop Stimulation (CLS) in Tilt-induced Cardioinhibitory Reflex Syncope (BIOSync CLS) trial, NCT02324920" will provide more information on the role of this treatment for patients with cardioinhibitory VVS.

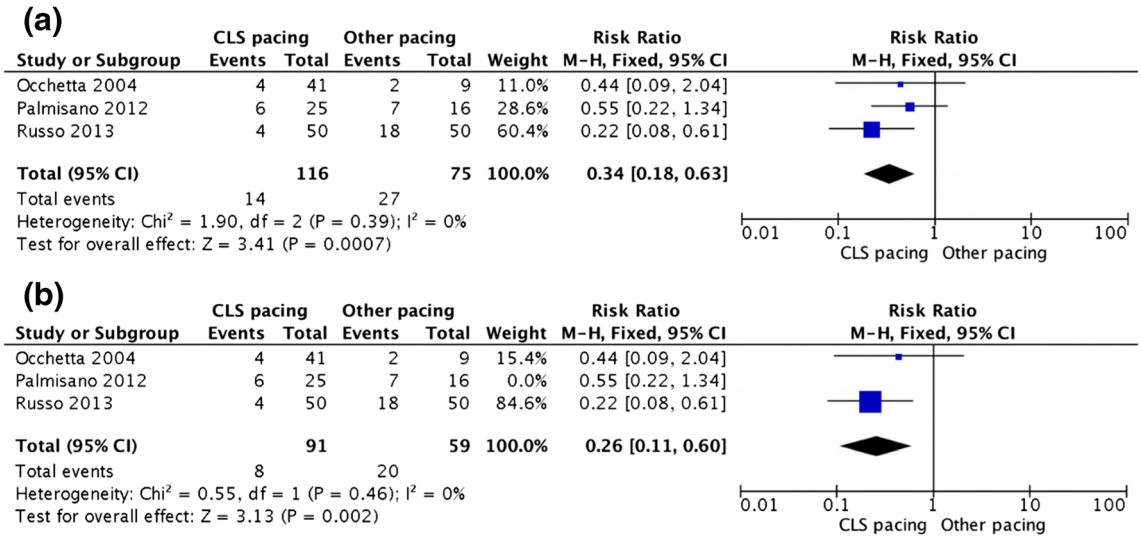

Fig. 3 Forest plot of presyncope for all studies with control arm (**a**) and after excluding the retrospective study (**b**)

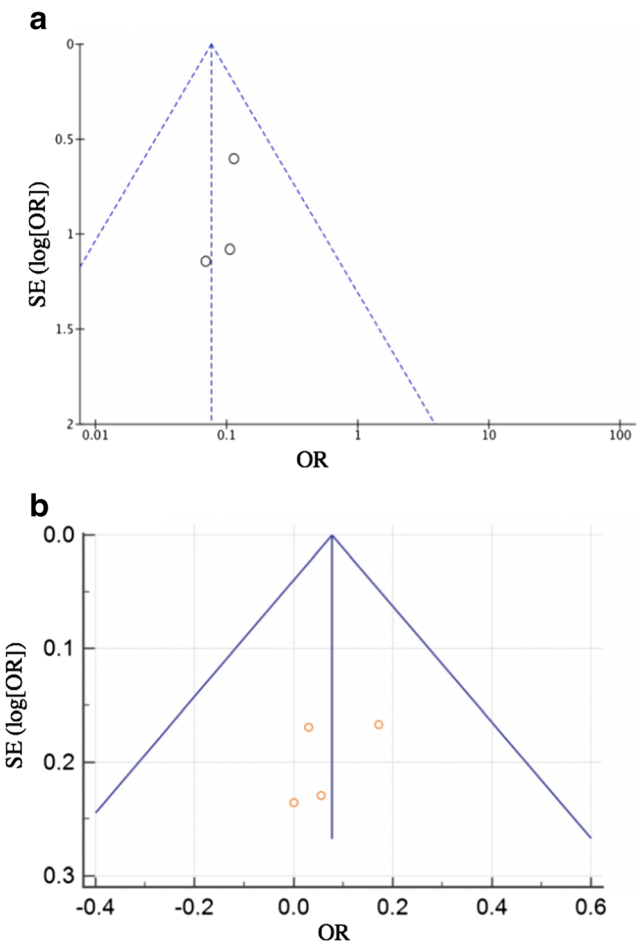

Fig. 4 Funnel plot for studies with control arm (**a**) and for retrospective and prospective observational studies (**b**)

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

1. Soteriades ES, Evans JC, Larson MG, Chen MH, Chen L, Benjamin EJ, et al. Incidence and prognosis of Syncope. N Engl J Med. 2002;347:878–85.
2. Mosqueda-Garcia R, Furlan R, Tank J, Fernandez-Violante R. The elusive pathophysiology of neurally mediated syncope. Circulation. 2000;102:2898–906.
3. Connolly SJ, Sheldon R, Thorpe KE, Roberts RS, Ellenbogen KA, Wilkoff BL, et al. Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope: second vasovagal pacemaker study (VPS II): a randomized trial. JAMA. 2003;289:2224–9.
4. Brignole M, Menozzi C, Moya A, Andresen D, Blanc JJ, Krahn AD, et al. Pacemaker therapy in patients with neurally mediated syncope and documented asystole. Circulation. 2012;125:2566–71.
5. Shen W-K, Sheldon RS, Benditt DG, Cohen MI, Forman DE, Goldberger ZD, et al. 2017 ACC/AHA/HRS guideline for the evaluation and Management of Patients with Syncope: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines, and the Heart Rhythm Society. Circulation. 2017;136:e60–e122.
6. Brignole M, Moya A, de Lange FJ, Deharo J-C, Elliott PM, Fanciulli A, et al. 2018 ESC guidelines for the diagnosis and management of syncope. Eur Heart J. 2018;39:1883–948.
7. Ruzieh M, Ammari Z, Dasa O, Karim S, Grubb B. Role of closed loop stimulation pacing (CLS) in vasovagal syncope. Pacing Clin Electrophysiol. 2017;40:1302–7.

8. Baron-Esquivias G, Morillo CA, Moya-Mitjans A, Martinez-Alday J, Ruiz-Granell R, Lacunza-Ruiz J, et al. Dual-chamber pacing with closed loop stimulation in recurrent reflex vasovagal syncope:the SPAIN study. J Am Coll Cardiol. 2017;70:1720–8.
9. Freeman MF, Tukey JW. Transformations related to the angular and the square root. Ann Math Stat. 1950;21:607–11.
10. Occhetta E, Bortnik M, Audoglio R, Vassanelli C. Closed loop stimulation in prevention of vasovagal syncope. Inotropy controlled pacing in vasovagal syncope (INVASY): a multicentre randomized, single blind, controlled study. Europace. 2004;6:538–47.
11. Russo V, Rago A, Papa AA, Golino P, Calabrò R, Russo MG, et al. The effect of dual-chamber closed-loop stimulation on syncope recurrence in healthy patients with tilt-induced vasovagal cardioinhibitory syncope: a prospective, randomised, single-blind, crossover study. Heart. 2013;99:1609–13.
12. Griesbach L, Huber T, Knote B, HÄRTEL J. Closed loop stimulation: therapy for malignant neurocardiogenic syncope. Prog Biomed Res. 2002;7:242–7.
13. Occhetta E, Bortnik M, Vassanelli C. The DDDR closed loop stimulation for the prevention of vasovagal syncope: results from the INVASY prospective feasibility registry. Europace. 2003;5:153–62.
14. Palmisano P, Zaccaria M, Luzzi G, Nacci F, Anaclerio M, Favale S. Closed-loop cardiac pacing vs conventional dual-chamber pacing with specialized sensing and pacing algorithms for syncope prevention in patients with refractory vasovagal syncope: results of a long-term follow-up. Europace. 2012;14:1038–43.
15. Bortnik M, Occhetta E, Dell'Era G, Secco GG, Degiovanni A, Plebani L, et al. Long-term follow-up of DDDR closed-loop cardiac pacing for the prevention of recurrent vasovagal syncope. J Cardiovasc Med (Hagerstown). 2012;13:242–5.
16. Anguera Ramos I, Rodrigeus F, Di Marco A, Dallaglio P, Sebate X, Cequier A. Effectiveness of closed loop stimulation pacing in preventing disabling cardioinhibitory vasovagal syncope. A single-center experience. Eur Heart J. 2015;36(223):SUPPL. 1.
17. Rattanawong P, Riangwiwat T, Chongsathidkiet P, Vutthikraivit W, Limpruttidham N, Prasitlumkum N, et al. Closed-looped stimulation cardiac pacing for recurrent vasovagal syncope: a systematic review and meta-analysis. J Arrhythm. 2018;34:556–64.
18. Raviele A, for the Vasovagal S, Pacing Trial I, Giada F, et al. A randomized, double-blind, placebo-controlled study of permanent cardiac pacing for the treatment of recurrent tilt-induced vasovagal syncope. The vasovagal syncope and pacing trial (SYNPACE). Eur Heart J. 2004;25:1741–8.
19. Yu S, Kanjwal K, He W, Ren K, Cooper E, Karabin B, et al. A long-term follow-up on the use of closed-loop cardiac pacing in patients with refractory neurocardiogenic syncope. The Journal of Innovations in Cardiac Rhythm management. 2015;6:1982–5.
20. Brignole M, Donateo P, Tomaino M, Massa R, Iori M, Beiras X, et al. Benefit of pacemaker therapy in patients with presumed neurally mediated syncope and documented asystole is greater when tilt test is negative. Circ Arrhythm Electrophysiol. 2014;7:10–6.
21. Sud S, Massel D, Klein GJ, Leong-Sit P, Yee R, Skanes AC, et al. The expectation effect and cardiac pacing for refractory vasovagal syncope. Am J Med. 2007;120:54–62.