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# Carotid sinus syndrome, should we pace? A multicentre, randomised control trial (Safespace 2)

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## ABSTRACT

**Background** Cardioinhibitory carotid sinus hypersensitivity (CICSH) is highly prevalent among older people with falls.

**Objective** To assess the efficacy of dual-chamber pacing in older patients with CICSH and unexplained falls.

**Design** A multicentre, double blind, randomised controlled trial.

**Setting** Selection from emergency room, geriatric medicine and orthopaedic departments.

**Patients** Patients aged >50 years, with two unexplained falls and/or one syncopal event in the previous 12 months for which no other cause is evident apart from CICSH.

**Interventions** Patients randomised to either a 700/400 κ, rate responsive pacemaker or implantable loop recorder (Medtronic Reveal thera RDR, Medtronic, Minneapolis, Minnesota, USA).

**Main outcome measures** The primary outcome was the number falls after implantation. Secondary outcomes were time to fall event, presyncope, quality of life and cognitive function.

**Results** 141 patients were recruited from 22 centres. Mean age was 78 years and mean follow-up 24 months. The overall relative risk of falling after device implantation compared with before was 0.23 (0.15 to 0.32). No significant reduction in falls was seen between paced and loop recorder groups (RR=0.79; 95% CI 0.41 to 1.50). Data were also consistent in both groups for syncope, quality of life and cognitive function.

**Conclusions** These results question the use of pacing in CICSH. However, the study was underpowered and also patient characteristics differed from those in Safespace 1—participants were physically and cognitively frailer. Further work is necessary to assess cardiac pacing in this setting.

## INTRODUCTION

Carotid sinus syndrome is defined as recurrent syncope due to excessive bradycardia and/or hypotension in response to carotid sinus stimulation with no other apparent attributable cause of syncope. Carotid sinus hypersensitivity (CSH) is defined as the abnormal haemodynamic response without clearly attributable syncopal symptoms. In older people there is significant overlap between the symptoms of falls and syncope, this has been particularly demonstrated in CSH where older people with a reproducibly abnormal bradycardic response present with falls rather than syncope. Amnesia for loss of consciousness is often responsible for this confusion. Given that up to 70% of falls or syncopal events in older people are not witnessed, such a presentation is not uncommon.<sup>1–3</sup>

Older people with cardiovascular syncope tend to present with 'unexplained falls'—that is, no clear history of a trip and denial of loss of consciousness. In one study, 20–40% of people over the age of 65 presenting to the emergency department with unexplained falls, had cardioinhibitory (CI) CSH as a possible attributable cause of events.<sup>4–6</sup> In a single-centre randomised control trial cardiac pacing of such older people with CICSH and recurrent unexplained falls reduced subsequent fall events by 70% and injurious events by 75%.<sup>7</sup> The aim of this study was to determine whether, in a multicentre study, cardiac pacing for recurrent falls in patients with CICSH would reduce subsequent falls.

## METHODS

Participants aged >65 who had CICSH as a possible attributable cause of symptoms were recruited from five countries and 22 participating centres. Recruitment, from syncope unit referrals, selected those with a minimum of two unexplained falls and/or one syncope in the past year. All participants had in excess of 3 s of asystole in response to carotid sinus massage (CSM), a mini-mental state score >19, no evidence of neoplasm, renal or hepatic failure and at time of randomisation, no evidence of significant heart failure.<sup>8–12</sup>

Patients had no other apparently attributable cause of falls after history, clinical examination, 12-lead ECG, routine blood screen and morning orthostatic blood pressure recordings.<sup>9</sup> Ambulatory heart rate monitoring, echocardiography and cardiac electrophysiology were carried out at the doctor's discretion. Participants were capable of completing diary cards and complying with instructions for use of the implantable device.<sup>8–12</sup> Contraindications to CSM complied with international guidelines.<sup>13</sup> CSM was performed on right and left carotids while the patient was supine and repeated when upright.<sup>6</sup>

Participants were randomised to receive an implantable loop recorder or dual-chamber pacemaker according to a computer-generated randomisation. The sample was stratified by centre. All paced patients received a rate drop responsive physiological dual-chamber pacemaker (κ 700 or κ 400 system), programmed to the rate drop response algorithm, thus allowing backup pacing for patients with occasional drops in heart rate.<sup>14–16</sup> The implantable loop recorder is inserted subcutaneously, has high fidelity recordings and a solid-state memory loop of 42 min. Where possible, the device was implanted within 3 months of randomisation.

Patients recorded symptoms of falls or syncope in diary cards. Randomisation, data collation and

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diary card interpretation were carried out by researchers blind to the number of diaries returned by each subject.

Follow-up time was 24 months. The primary outcome measure was the number of falls during this time; participants completed falls diaries at the end of each week and received monthly telephone interviews, a process that had already been piloted with compliance rates > 80%.<sup>4</sup> Participants additionally completed Short Form-36 (quality of life measure) and Mini-Mental State Examination (MMSE; cognitive screening test) at baseline and at 12 months after device implant.<sup>17</sup>

### Statistical analyses

The primary clinical outcome was falling behaviour. Subjects were asked to complete 15 diaries, each 4 weeks long, starting from the point of randomisations. Subjects were asked to record each day whether or not they fell. The main analysis was based on all the diaries returned and undertaken on an intention-to-treat basis. For each subject the total number of falls was determined and analysed using negative binomial regression. Evidence from previous studies of falling in similar populations suggested that distribution of the number of falls would be extremely skewed. To assess the impact of the skewness, two further variables were analysed: first, the number of 4-weekly diaries to which a fall was recorded and second, the total number of falls truncated at an arbitrary threshold of 15, chosen as it corresponds to one fall per diary.<sup>18</sup> In addition to these variables, the number of reported incidents of syncope was analysed using negative binomial regression, and time to first fall was analysed using Cox regression. An explanatory analysis of the falls data was also undertaken for (a) the period following randomisation, but before their device was implanted and (b) the period following implantation of the device. This variable was also analysed using negative binomial regression.

For sample size calculation it was assumed that the number of patients who fall was likely to have a non-standard statistical distribution. Calculations described by Pocock for a binary outcome measure estimated that to detect a difference of 20% in the number of patients who fell, using a significance level of 5% with 80% power, 95 patients were needed in each experimental group<sup>19</sup>; with a 20% attrition rate, a total of 226 patients were needed. Unfortunately, only 141 patients were randomised to either loop recorder or pacemaker during the course of the study, thus allowing for a power of only 60% to detect a difference of 20%.

## RESULTS

### Baseline characteristics

One hundred and forty-one patients were recruited to the study, mean age 78±7 years; 87 women and 54 men were recruited from five countries and 22 participating centres. Seventy-one were randomised to loop recorder and 70 to pacemaker. Of those randomised to the loop recorder group, 61 received the implant; however, two later crossed over to the pacemaker group owing to a high frequency of falls. Of those who did not receive an implant, eight refused, one died before the recorder was inserted and one developed a medical condition precluding loop recorder insertion. Of those randomised to the pacemaker arm (n=71), 68 received implantation, two refused and one patient initially refused but subsequently received a pacemaker 8 months later.

Age and gender distributions were similar for both groups. Baseline clinical characteristics (such as total number of drugs, orthostatic blood pressure fall, abnormal gait and balance), drugs and key risk factors for falls were similar for both groups (table 1).

**Table 1** Baseline clinical characteristics

Variable	Loop recorder (n=71)	Paced group (n=70)	Significance (p value)
Age (SD)	77.5 (8.7)	78.0 (7.3)	0.71
Sex (% female)	56	67	0.23
Falls before randomisation - 12 months (SD)	5.7 (5.5)	4.8 (3.2)	0.14
Injury sustained (%)	62	71	0.29
Witness account (%)	38	25	0.20
IHD (%)	31	44	0.14
Stroke (%)	18	12	0.97
Hypertension (%)	35	29	0.42
Diabetes (%)	18	15	0.82
Smoker (%)	57	60	0.69
Number of medicines (SD)	3.2 (2.2)	3.1 (2.5)	0.78
Abnormal gait (%)	31	24	0.45
Abnormal balance (%)	11	15	0.47
Systolic BP mean (SD)	145 (71)	145 (23)	0.93
Diastolic BP (SD)	76.4 (13.7)	75.1 (12.4)	0.59
Resting heart rate (SD)	69.5 (11.0)	71.9 (13.4)	0.25
24 h ECG (%)	44	36	0.39
Echocardiogram (%)	21	21	1.00

BP, blood pressure; IHD, ischaemic heart disease.

The average number of falls during the year before randomisation was 5.7±5.5 and 4.8±3.2, respectively, for loop recorder and pacemaker patients (p=0.14). Sixty-two per cent and 71% of patients had sustained a notable injury—either a fracture or laceration which required sutures (p=0.31). Sixty-nine loop patients and 67 pacemaker patients had also complained of syncope before implants—a mean of 0.3±0.6 and 0.5±1.2 syncopal episodes in the 12 months before randomisation (p=0.22). The cardioinhibitory and hypotensive responses to CSM were similar for both groups.

### Outcome

One hundred and twenty-eight subjects (91%) returned at least one diary. In all, 1416 diaries were returned (66% of the total possible from all subjects; 74% of the total possible from the 128 who returned at least one). Forty-six subjects (36%) returned all 15 diaries.

Analysis of primary outcome data relating to falling behaviour showed that when the total number of falls was analysed, the relative risk of falling (those with the pacemaker device compared with loop recorder) was 0.79 (95% CI 0.41 to 1.50). One subject, randomised to the loop recorder group, however, fell a very large number of times (159). Outliers like this would have had a detrimental impact on the normal distribution of the data (range of falls 0 to 159 with a median of 1). For this reason further analyses were carried out, in which the number of falls by each person was truncated to an arbitrary threshold of 15, chosen as it corresponds to one fall per diary.<sup>18</sup>

When the total number of falls each participant reported was truncated to a threshold of 15, the relative risk increased to 1.38 (implying that the risk of falling is slightly greater in the group that was paced than in the group that received the loop recorder). The relative risk of recording a fall in a diary was 1.30 (95% CI 0.80 to 2.12). Of note, the number of 4-weekly diaries which reported a fall, a non-truncated variable, was also consistent for both groups. Mean time to first fall was 31.9 weeks in the loop recorder group and 25.7 weeks in the paced group with an HR of 1.34 (95% CI 0.84 to 2.12). In each case the difference between experimental groups was not

significant. There is no evidence that subjects in one group had better outcomes than subjects in the second (table 2).

A secondary explanatory investigation was undertaken to investigate the impact of the following factors: (a) not all subjects who were randomised actually had a device implanted; (b) some subjects crossed over from one arm of the trial to the other (two participants in the loop recorder arm fell multiple times and crossed over to the pacemaker arm); (c) there was variation between subjects in the time between randomisation and their surgical procedure (table 3).

### Comparison of data before and after implant

Patients were much less likely to report a fall or syncopal event after the device implant than before. The relative risk of reporting a fall after implantation of a device compared with before was 0.23 (95% CI 0.15 to 0.37). The number of fall events was significantly less after implant than before implant 0.23 (CI 0.15 to 0.37). Participants were much less likely to report syncope after implant 0.47 (95% CI 0.26 to 0.86). The number of syncopal events was also significantly less after implant, 0.52 (95% CI 0.29 to 0.95).

### Loop recorder

In total there were 55 activations of which 48 were successful recordings, seven did not record. The loop recorder was activated because of a fall in 19 cases, dizziness in 17 and syncope in 4. In the remainder, reasons for activation were palpitations,<sup>1</sup> breathlessness,<sup>1</sup> routine check,<sup>5</sup> inability to recall reason<sup>6</sup> and others.<sup>2</sup> Thirty-eight were in sinus rhythm at the time. One person had atrial flutter, one premature ventricular beats, six had premature supraventricular beats and two had bradycardia.

### Quality of life and cognitive function data

In general, quality of life and cognitive function were broadly similar across the two groups. The mean Short Form-36 physical component score at baseline was 28.7 and 29.6 in the loop recorder and pacemaker groups, respectively and 30.3 and 33.2, respectively, at 12 months' follow-up. Mean Euroqol at baseline was 0.64 and 0.68 in the loop recorder and pacemaker groups, respectively, and 0.57 and 0.66 at 12-month follow-up. No statistical difference was observed in either.

### MMSE

Fourteen per cent (n=16) of patients demonstrated a significant deterioration in MMSE of three or more units after 12 months. For 118 patients where both baseline and 12-month data were available, MMSE was 27.9 (95% CI 27.4 to 28.3) at baseline and 27.1 (95% CI 26.4 to 27.9) at 12 months. Across the entire sample there was a statistically significant deterioration in MMSE score of 0.87 (p<0.001) but this reduction did not differ between treatment groups. This deterioration is equivalent to that observed in patients with mild to moderate Alzheimer's disease and would imply that our subject group demonstrated significant cognitive decline during the study period.<sup>20</sup>

## DISCUSSION

There was no difference in falling behaviour between patients randomised to loop recorder and pacemaker in this multicentre randomised control trial. Analysis of the falls variables gave reasonably consistent results. In none of the analyses was the difference between experimental groups significant. Analysis of the total number of falls without making any special allowance for the extreme outlier gave a point estimate of the relative risk of falling that was substantially different from that obtained from the other analyses. The method of truncating the total number of falls, as suggested by Davies *et al*<sup>5</sup> would seem to be a sensible way of handling these data. The estimate of the relative risk of falling was consistent with the analyses of other measures of the level of falling. In the explanatory analysis there appeared to be a trend towards a larger risk of falling in the pacemaker group relative to the loop recorder group. This would be consistent with those subjects in the loop recorder group who fell the most crossing over into the other arm but continuing to fall after implantation of the second device.

The data are at variance with those previously reported for pacing in fallers with CICSH in Safespace 1. The seminal study was carried out at a single centre<sup>7</sup> with a long-established clinical facility and healthcare pathways for referral, evaluation and management of older people with syncope and falls. The technique of carotid sinus massage is operator dependent and it was not possible to standardise it in this multicentre trial. This possibly influenced recruitment. Recruitment itself was also more challenging when the study was rolled out to a multicentre design and used centres without systems in place for managing older patients with falls and syncope. Thus the study may have been underpowered to show a significant difference between groups.

Difficulty in recruitment may be one reason why the patients in Safespace 2 were older and frailer than in the previous study. Recruitment for Safespace 1 consisted of systematic screening of 24 539 fallers over age 50 presenting to accident and emergency. Screening was carried out by dedicated research staff present 24 h a day, 7 days a week, for the 12-month recruitment period. Screening in Safespace 2 was more ad hoc. Most centres, at the time, did not have an extant systematic screening service for falls which incorporated a cardiovascular assessment. The patient characteristics for both studies differed.

In the first instance, patients in this study were older; 78 years in Safespace 2 versus 73 in Safespace 1 (p<0.001). More participants had ischaemic heart disease (p<0.001). In fact, the OR for ischaemic heart disease in patients recruited to Safespace 2 was 3.8 compared with Safespace 1. Patients in Safespace 2 were more likely to take  $\beta$  blockers (p<0.001) and ACE inhibitors (p=0.03). Hypertension approached significance (p=0.06). Therefore, patients in Safespace 2 were older and had more comorbid cardiovascular disease.

When extreme outliers are removed, falls were more common in the prerandomised period for Safespace 2 than Safespace 1, though those in Safespace 2 reported fewer syncope episodes

**Table 2** Primary outcome: falling behaviour by treatment group (intention to treat analysis)

Variable	Loop recorder	Pacemaker	Difference	95% CI
Any fall recorded during study period	Yes= 33 (53%)	Yes=44 (67%)	RR=1.25	0.93, 1.67
Number of falls	Mean=6.52, Median=1	Mean=4.33 Median=1	RR= 0.79	0.41, 1.50
Number of falls (truncated at 15)	Mean=2.63, Median=1	Mean=3.42, Median=1	RR=1.38	0.80, 2.12
Number of diaries in which a fall was reported	Mean=1.87 Median=1	Mean=2.50, Median=1	RR=1.30	0.80, 2.12
Time to first fall in weeks	Mean=31.9 Median=33.1	Mean=25.7 Median=15.3	HR=1.34	0.84, 2.12
Number of episodes of syncope	Mean=0.66 Median=0	Mean=0.42 Median=0	RR=0.87	0.30, 2.48

RR; Relative risk and HR= Hazard ratio.

**Table 3** Explanatory analysis (falls behaviour, syncope and diaries returned after implantation of either loop recorder or pacemaker)

Variable	Statistic	Group		Difference	p Value
		Loop recorder (n=61)	Pacemaker (n=68)		
Number of people who returned at least one diary after device implanted	n	55	63	RR=1.01 (0.91 to 1.12)	1.00
	%	90.2	92.6		
Number of diaries returned	Mean	9.4	10.9	RR=1.16 (0.94 to 1.43)	0.18
	SD	4.4	4.3		
Number of falls	Mean	1.4	3.4	RR=2.43 (1.28 to 4.62)	0.07
	SD	2.1	6.6		
	Median	0	1		
	Range	0-9	0-36		
Number of syncope episodes	Mean	0.35	0.32	RR=1.38 (0.80 to 2.39)	0.25
	SD	1.08	0.82		
	Median	0	0		

before randomisation (syncope episodes: mean 0.35 in Safespace 2 vs 5.59 in Safespace 1,  $p<0.001$ ). Furthermore, the cardioinhibitory response observed in Safespace 2 was shorter than that for Safespace 1. The maximum R-R interval in Safespace 1 was 4.37 s while the R-R interval in Safespace 2 was 3.12 s supine or upright. This suggests that patients recruited to Safespace 2 had less severe carotid sinus hypersensitivity, although they fell more often. The cause of falls is generally multifactorial and it is likely that factors other than CSH were causal in Safespace 2.

Patients in Safespace 2 were a frail cohort as evidenced by the deterioration in cognition noted on follow-up. Although the overall MMSE scores did not differ between groups, the overall decline in cognitive function at end of follow-up (MMSE=27.1, 95% CI 26.4 to 27.9) compared with baseline (27.9, 95% CI 27.8 to 28.3) was significant. MMSE score deteriorated by 0.87 ( $p<0.001$ ), a rate of decline that is indicative of progressive neuropathological disease.<sup>20</sup> No follow-up MMSE data are available for Safespace 1 (table 4).

Therefore, it would appear that the Safespace 2 patients were older, physically (higher falls rates) and cognitively frailer, had less syncope and a more moderate heart rate response to carotid sinus pressure. It is conceivable that earlier intervention in patients with more evidence of autonomic dysfunction targets respondents in whom carotid sinus hypersensitivity is a more likely attributable cause of falling.

In a recent study of R-R interval duration in response to CSM among community-dwelling patients with and without syncope,

the author suggests that an abnormal response may be of longer duration than indicated by guidelines.<sup>6</sup> If so, the shorter cardioinhibitory response in Safespace 2 may have biased results. Although international guidelines were used for the purpose of recruitment, review of these recommendations may be indicated if supported by further research.

In a recent publication in this journal, Parry *et al* failed to demonstrate significant reductions in falls (crossover study design), alternating between pacing on mode and off mode during a 12-month period (RR=0.82; CI 0.62 to 1.10), although the study was underpowered owing to high attrition rates.<sup>21</sup> Furthermore, they reported an overall reduction in falls, highlighting the effect of placebo in this group. Placebo effect of pacing in vasovagal syncope has been reported in several randomised double blind placebo trials.<sup>22 23</sup> Vasovagal syncope shares a number of clinical and pathophysiological characteristics with carotid sinus syndrome, both described as neurally mediated syncope. VPS2 (Vasovagal Pacemaker Study), for example, demonstrated a non-statistically significant benefit of pacing in vasovagal syncope compared with its placebo arm.<sup>22</sup> This is in contrast to its preceding study—VPS, with no blinded placebo arm which demonstrated an 85.4% benefit of pacing ( $p=0.000022$ ).<sup>24</sup> SYNPACE, too has demonstrated similar findings to VPS2.<sup>23</sup>

## CONCLUSION

In this multicentre study pacemaker implantation had no independent effect on the number of falls or syncopal episodes. The population studied was older, frailer with less severe CSH than in the previous single-centre study and there were a higher than normal proportion of patients with significant cognitive decline following intervention. It may be that earlier detection of fallers with CISH is necessary before irreversible physical and cognitive decline is established.

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**Competing interests** None.

**Ethics approval** This study was conducted with the approval of the Multicentre trial. Local ethics committee approval sought.

**Patient consent** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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**Table 4** A comparison of patient characteristics in Safespace 1 and Safespace 2

	Safespace 2	Safespace 1	p Value
Baseline characteristics:			
Age	78	73.2	<0.001
Gender (% female)	61.5	59.4	0.088
Mean syncope events in year before the implantation	0.35	5.59	<0.0000001
Comorbid disease:			
Ischaemic heart disease (%)	25.4	9.1	<0.001
Hypertension (%)	30.8	25.7	0.06
Diabetes (%)	17.7	9.1	0.012
Medication:			
$\beta$ Blockers (%)	8.5	0.6	<0.01
ACE inhibitors (%)	16.2	8.0	0.03
Diuretic therapy (%)	26.2	21.1	0.06

No MMSE (mini-mental state) 12-month follow-up data available for Safespace 1.

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