

# Effectiveness of Physical Counterpressure Maneuvers in Preventing Vasovagal Syncope

## The Physical Counterpressure Manoeuvres Trial (PC-Trial)

Nynke van Dijk, MD,\* Fabio Quartieri, MD,† Jean-Jaques Blanc, MD,‡ Roberto Garcia-Civera, MD,§ Michele Brignole, MD,|| Angel Moya, MD,¶ Wouter Wieling, MD, PhD,\*  
on behalf of the PC-Trial Investigators

*Amsterdam, the Netherlands; Reggio Emilia and Lavanga, Italy; Brest Cedex, France; and Valencia and Barcelona, Spain*

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<b>OBJECTIVES</b>	In this study, we assessed the effectiveness of physical counterpressure maneuvers (PCM) in daily life.
<b>BACKGROUND</b>	There is presently no evidence-based therapy for vasovagal syncope. Current treatment consists of explanation and life-style advice. Physical counterpressure maneuvers have been shown to raise blood pressure and to control or abort vasovagal episodes in laboratory conditions.
<b>METHODS</b>	We performed a multicenter, prospective, randomized clinical trial, which included 223 patients age 38.6 ( $\pm 15.4$ ) years with recurrent vasovagal syncope and recognizable prodromal symptoms. One hundred and seventeen patients were randomized to standardized conventional therapy alone, and 106 patients received conventional therapy plus training in PCM.
<b>RESULTS</b>	The median yearly syncope burden during follow-up was significantly lower in the group trained in PCM than in the control group ( $p = 0.004$ ). During a mean follow-up period of 14 months, overall 50.9% of the patients with conventional treatment and 31.6% of the patients trained in PCM experienced a syncopal recurrence ( $p = 0.005$ ). Actuarial recurrence-free survival was better in the treatment group (log-rank $p = 0.018$ ), resulting in a relative risk reduction of 39% (95% confidence interval, 11% to 53%). No adverse events were reported.
<b>CONCLUSIONS</b>	Physical counterpressure maneuvers are a risk-free, effective, and low-cost treatment method in patients with vasovagal syncope and recognizable prodromal symptoms, and should be advised as first-line treatment in patients presenting with vasovagal syncope with prodromal symptoms. (The PC-Trial; <a href="http://www.controlled-trials.com/isrctn/trial/45146526/45146526.html">http://www.controlled-trials.com/isrctn/trial/45146526/45146526.html</a> ; ISRCTN45146526) (J Am Coll Cardiol 2006;48:1652-7) © 2006 by the American College of Cardiology Foundation

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Vasovagal syncope is a common clinical condition, with an estimated life-time prevalence of 35% (1-3). Although the disorder is episodic in nature, it could be considered a chronic disorder. Often symptoms occur over many years due to recurrences of episodes of (pre)syncope (1,2) and its deleterious effects on quality of life (4,5).

Although a large variety of treatments have been proposed, evidence-based treatment options for patients with recurrent episodes are absent (6,7). Current widely accepted treatment consists of explanation of the underlying mechanism, reassurance about the benign nature of the episodes, recognition of premonitory symptoms, and avoidance of triggers, even though the effectiveness is not formally

proven. Similarly, volume expansion by means of raised water and salt intake or medication is sometimes advised (6-8). The few randomized double-blind trials on vasoactive drugs failed to show superiority over placebo (6,7,9,10). The use of pacemakers in patients with serious complaints has been of variable effectiveness (11,12).

Physical counterpressure maneuvers (PCM) have previously proven to be effective in stabilizing blood pressure in patients with autonomic failure (13,14). Recently, Krediet et al. (15) published reports on controlling or aborting impending vasovagal syncope by leg crossing and muscle tensing (16,17). Brignole et al. (18) found a comparable effect of isometric arm counterpressure maneuvers. However, these results were based on a limited number of patients in laboratory conditions. The evaluation of the effectiveness of PCM in preventing recurrent episodes of vasovagal syncope in real life was the main aim of the present trial. We assessed whether treatment of patients with vasovagal syncope with PCM reduces the yearly syncope-burden and improves time to first recurrence when compared with treatment with current conventional therapy.

From the \*Department of Internal Medicine, Academic Medical Center, Amsterdam, the Netherlands; †Department of Interventional Cardiology, Ospedale S. Maria Nuova, Reggio Emilia, Italy; ‡Department of Cardiology, Hospital de la Cavale Blanche, Brest Cedex, France; §Department of Cardiology, Hospital Clinico Universitario Valencia, Valencia, Spain; ||Department of Cardiology, Ospedali del Tigullio, Lavanga, Italy; and the ¶Department of Cardiology, Hospital General Vall d'Hebron, Barcelona, Spain. This study was supported by the Netherlands Heart Foundation (Grant 2003B156). For a list of the PC-Trial Investigators see the Appendix.

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#### Abbreviations and Acronyms

ESC	= European Society of Cardiology
PCM	= physical counterpressure maneuvers
PC-Trial	= Physical Counterpressure Manoeuvres Trial

## METHODS

The PC-Trial (Physical Counterpressure Manoeuvres Trial) was a multicenter, prospective, longitudinal, randomized clinical trial.

**Study population.** Patients age 16 to 70 years with recurrent vasovagal syncope and recognizable prodromal symptoms were eligible for inclusion. Patients were recruited in 15 worldwide medical centers with at least 100 to 200 patient admissions for syncope per year (Appendix).

Recurrent syncope was defined as at least 3 syncope episodes in the last 2 years or at least 1 syncopal spell and 3 pre-syncopal episodes in the last year. Furthermore, to be able to apply PCM, patients had to have recognizable prodromal symptoms for their episodes.

The diagnosis of vasovagal syncope was based on the definition of the guidelines of the European Society of Cardiology (ESC) (6,7). Pre-syncope was defined as near loss of consciousness.

The diagnosis of vasovagal syncope was based on the history taking criteria extensively described in the guidelines of the ESC (6,7). Briefly, the diagnosis was considered certain with a typical history with episodes triggered by prolonged upright position, pain, or emotional events and accompanied by lightheadedness, sweating, pallor, and/or nausea/vomiting. Patients also had to have a normal physical examination and electrocardiogram (ECG).

Either to confirm a clinical diagnosis, or to make the diagnosis in patients in whom the initial evaluation was inconclusive, tilt-table testing was performed. Tilt testing consisted of 60° passive tilting for 20 min, with an additional 15-min head-up tilt with a 0.4-mg nitroglycerin challenge when the passive tilt failed to induce syncope (6,19,20). Continuous recording of ECG and, when available, non-invasive beat-to-beat arterial blood pressure was performed by means of the Finapres (Finapres Medical Systems, Amsterdam, the Netherlands) or a similar device (6,7,21). A positive response was defined as the induction of either pre-syncope or syncope in the presence of bradycardia, hypotension, or both. Positive tilt-table testing was reported according to the VASIS (Vasovagal Syncope International Study) classification (22). Patients with a certain clinical diagnosis and patients with suspected vasovagal syncope and a positive tilt-table test with recognizable symptoms both were included in the study (23).

Exclusion criteria were: suspected or overt heart disease with a high likelihood of cardiac syncope; orthostatic hypotension; episodes of loss of consciousness different from syncope; vascular steal syndrome; patients psychologically, physically, or cognitively unable to participate; doubtful

compliance; inaccessibility to follow-up; unwillingness or inability to give informed consent; pregnancy; or a life expectancy of <1 year.

**Study design.** The recurrence risk in the conventionally treated group was estimated at 40% (24). Based on earlier experience (15,18), it was expected that PCM would halve the recurrence rate. With a power of 80% and a significance level of 0.05, a minimum of 82 patients in each group was required. To avoid underpowering because of loss of follow-up, it was decided to include 220 patients in the study.

Patients were randomized to either optimal standardized conventional therapy alone or optimal conventional therapy plus additional training in PCM. To obtain concealment of allocation, randomization was performed by an independent data manager with permuted block randomization stratified per study center. Patients were blinded for the results of the randomization and were all invited for an educational session.

Conventional therapy consisted of explanation of the mechanisms underlying vasovagal syncope and advice with regard to lifestyle modification (i.e., avoidance of triggers, lying down in case of symptoms, and increasing fluid and salt intake). A leaflet, identical for all participating centers, was used to guarantee standardized therapy. Both groups received identical counseling information.

Patients assigned to the study arm (PCM) were trained in using maneuvers. They were advised to use leg crossing, handgrip, or arm tensing as a preventive measure in situations in which he/she is known to be prone to vasovagal syncope and immediately in case of prodromal symptoms. Leg crossing consisted of the crossing of legs combined with tensing of leg, abdominal, and buttock muscles (15). Handgrip consisted of the maximal voluntary contraction of a rubber ball, or any other available object, taken in the dominant hand. Arm tensing consisted of the contraction of the 2 arms by gripping 1 hand with the other and contemporarily abducting both arms (18). Patients were instructed to maintain the maneuver they chose for the maximum tolerated time or until complete disappearance of symptoms and to move on to a second or third maneuver if needed. The sequence of the maneuvers was left to the patients' discretion. The training session consisted of biofeedback training using a continuous blood pressure monitor (21). Each maneuver was demonstrated and explained. The maneuvers were practiced under supervision, with immediate feedback of the recordings to gain optimal performance. Patients were instructed to breathe normally during the maneuvers. Patients received a set of photos of the maneuvers, and were advised to practice the maneuvers regularly. Patients were unaware which part of the training was conventional treatment and which part was the intervention under consideration.

**Data collection.** All patients were checked by their physician with visits at 1 and 12 months. Every 3 months follow-up took place either during a regular visit or by telephone. To be able to obtain all follow-up data, physi-

cians were not blinded for the results of the randomization. The maximum follow-up period was 18 months, the minimum 6 months. All patients received a logbook for registration of symptoms. Recurrences were handled by the attending physician in each center. All data were entered into an electronic case record form made available on the internet by an independent data manager. All entered data were checked at 3-month intervals by the study coordinator. In case of incomplete or inconsistent data, the responsible study center was contacted for additional information.

**Statistical analysis.** Analysis was performed on the principle of intention-to-treat. Primary end point of the study was total burden of syncope recurrence; secondary end point was time to first recurrence.

Sociodemographic and clinical data were expressed as percentages for categorical data, mean (SD) for normally distributed numerical data, and median (quartiles) for non-normally distributed numerical data. Differences in sociodemographic and clinical data between 2 patient groups were tested using the chi-square test for categorical variables, an independent-samples *t* test for normally distributed numerical variables and a Wilcoxon signed rank test for non-normally distributed variables.

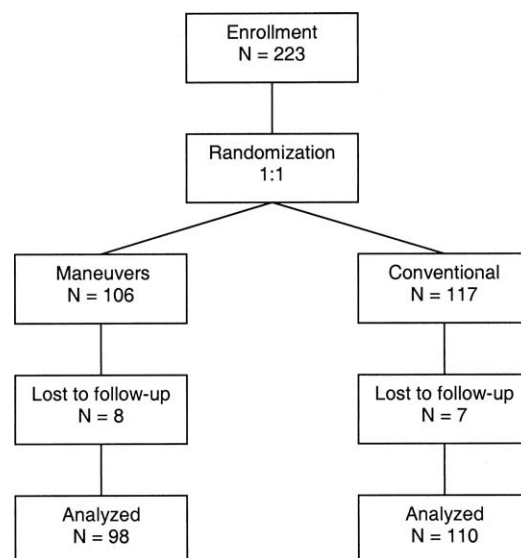
The difference in syncope burden was compared using an independent-samples *t* test. Time to first recurrence was visualized using a Kaplan-Meier survival curve and compared using a log-rank test and Cox proportional hazards analysis. The influence of personal characteristics on recurrence rate (gender, age, previous number of [pre]syncopal episodes, results of head up tilt, and use of maneuvers) was analyzed using multivariate Cox proportional hazards analysis. Relative risk reduction and hazard ratios are expressed with 95% confidence intervals.

A *p* value of <0.05 was considered to indicate a statistically significant difference.

The study was approved of by the Medical Ethical Committee of the Academic Medical Center, Amsterdam (project number 03/033). All patients gave informed consent.

## RESULTS

**Population.** From March 1, 2003 to December 15, 2004, 223 patients were included in the study. Follow-up was closed on September 1, 2005. One hundred and seventeen (52.5%) patients were randomized to conventional therapy, and 106 (47.5%) for training in PCM (Fig. 1). Seven patients randomized to conventional therapy and 8 patients in the PCM group were lost to follow-up. These patients (4 men) tended to be younger than the remaining patients (mean age  $30.6 \pm 11.5$  vs.  $38.0 \pm 15.1$  years; *p* = 0.068), less often experienced situational syncope (0% vs. 22.6%; *p* = 0.045), and less often saw black dots as a prodromal symptom (6.7% vs. 31.3%; *p* = 0.044). Otherwise, the patients lost to follow-up were similar to the remaining study population.



**Figure 1.** Flow-chart of included patients.

This resulted in 208 patients available for analysis (110 vs. 98). Patients were comparable on all personal and clinical characteristics (Table 1). Mean follow-up after randomization was  $14.1 \pm 5.1$  months in the conventional treatment group and  $14.4 \pm 5.1$  months in the PCM group (*p* = 0.734).

**Syncope burden.** During follow-up, the patients in the conventional treatment group reported a total number of 142 syncope episodes, while the patients in the PCM group reported 76 syncope episodes. The median yearly number of episodes per patient (syncope burden) was 0.6 (0.0 to 1.3) in the conventional treatment group and 0.0 (0.0 to 0.7) in the PCM group (*p* = 0.004) (Fig. 2).

**Recurrences.** Fifty-six (50.9%) patients with conventional treatment and 31 (31.6%) patients in the PCM group experienced a syncopal recurrence (*p* = 0.005), resulting in a relative risk reduction of 0.36 (95% confidence interval 0.11 to 0.53). The number of patients experiencing 1 or more pre-syncopal episodes during follow-up was similar in both groups (73.6% in conventional vs. 82.7% in PCM group; *p* = 0.118).

Time to first recurrence among the patients experiencing a recurrent syncopal episode was similar in both groups with  $6.6 \pm 5.9$  months in the conventional treatment group and  $4.8 \pm 4.5$  in the PCM group, *p* = 0.106. Overall syncope-free survival is displayed in the Kaplan-Meier curve (Fig. 3); log-rank statistic *p* = 0.018. The resulting hazard ratio was 0.59 (95% confidence interval 0.38 to 0.92).

At multivariate main effects analysis, the effectiveness of the maneuvers was independent from gender, age, previous number of (pre)syncopal episodes, results of head-up tilt, and most used maneuver. Moreover, no difference between centers was found in the effectiveness of the maneuvers, when comparing the number of patients with recurrences. Gender was an independent predictor of recurrences but did not affect the

**Table 1.** Personal and Clinical Characteristics of Patients

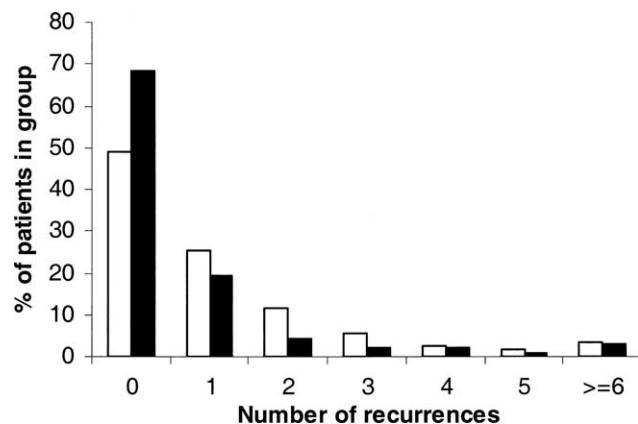
	Conventional Therapy	PCM	p Value
Number	110	98	
Gender (% male)	28.2	39.8	0.077
Age, yrs (mean [SD])	38.6 (15.4)	37.3 (14.6)	0.522
Highest educational level (%)			
None	15.5	10.2	0.698
Elementary school	27.3	26.5	
High school	31.8	35.7	
College	25.5	27.6	
No. of lifetime syncopal episodes (median [quartiles])	6 (3-12)	6 (4-12)	0.926
No. of syncopal episodes last 2 years (median [quartiles])	3 (2-5)	3 (2-6)	0.546
No. of pre-syncopal episodes last year (median [quartiles])	4 (2-7)	4 (2-13)	0.177
Period of complaints, yrs (median [quartiles])	6.8 (2.1-22.1)	7.9 (1.6-20.9)	0.851
Diagnosis by history taking (%)	94.5	99.0	0.080
Triggers (%)			
Instrumentation	9.1	7.1	0.609
Fear	10.0	8.2	0.646
Pain	17.3	15.3	0.702
Orthostatic	49.1	39.8	0.178
Situational	21.8	23.5	0.776
Prodromal symptoms (%)			
Nausea/vomiting	40.0	41.8	0.788
Sweating	63.6	65.3	0.802
Dizziness	60.9	56.1	0.484
Seeing black dots	35.5	26.5	0.166
Other	21.8	19.4	0.666
Head up tilt performed (%)	92.7	92.9	0.971
Head up tilt positive (%)	78.0	76.1	0.753
Results head up tilt test (%)			
Mixed (type 1)	46.8	43.5	0.918
Cardioinhibitor (type 2)	22.8	24.6	
Vasodepressive (type 3)	30.4	31.9	

PCM = physical counterpressure maneuvers.

treatment effect: overall women had significantly more recurrences than men (47.8% vs. 30.0%;  $p = 0.014$ ).

**Maneuvers.** Of the patients randomised to PCM, 82 (77.4%) used 1 or more maneuvers during follow-up. Of the patients that used maneuvers, arm tensing was the maneuver of first choice in 36.0%, hand grip in 25.8%, and leg crossing in 23.6%. The remaining 14.6% of the patients did not prefer any maneuver above the other.

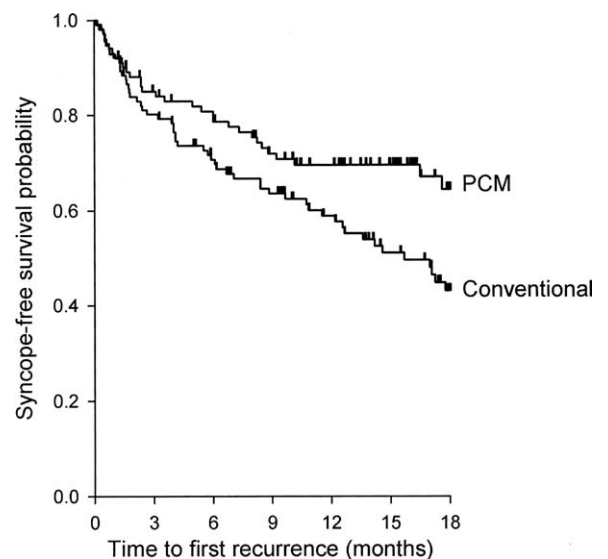
Of the remaining 16 patients in the PCM group who never used maneuvers, 1 patient experienced syncope during



**Figure 2.** Number of recurrences during follow-up. Black columns = maneuvers; white columns = conventional therapy.

follow-up. Two others did experience pre-syncope during follow-up, but did not apply PCM.

Of the 31 patients that experienced syncope recurrence in the PCM group, 11 patients (35%) had not used maneuvers during 1 or more recurrent episodes because of either



**Figure 3.** Kaplan-Meier syncope-free survival curve of time to first syncopal recurrence. Log-rank statistic  $p = 0.018$ ; hazard ratio 0.59 (0.38 to 0.92). PCM = physical counterpressure maneuvers.



absence of warning at all or too short duration of the prodromal symptoms.

**Safety.** During follow-up, no patient experienced any adverse clinical outcomes related to syncope.

## DISCUSSION

**Effectiveness.** This is the first randomized controlled trial providing an evidence-based treatment modality for vasovagal syncope (6,7). Physical counterpressure maneuvers are an effective evidence-based treatment for patients with recurrent vasovagal syncope and recognizable prodromal symptoms. After training in PCM, patients experience fewer syncopal episodes, and training in PCM reduces the number of patients with a recurrent syncopal episode by 36% during a mean follow-up period of 14 months. The number of patients needed to treat to prevent 1 patient from experiencing a syncope recurrence episode is 5 (quartiles 3 to 17). Our results advocate training in PCM to be first-line therapy in patients presenting with vasovagal syncope with recognizable prodromal symptoms. The lifetime number of episodes and the prolonged period of complaints patients have (mean over 7 years) (Table 1) indicate that vasovagal syncope in our study population can be considered a chronic condition that warrants this specific treatment (3).

Although maneuvers are not effective in all episodes in trained patients, the majority of patients show a reduction in the number of recurrences. The variable presentation of episodes probably causes the recurrences in these patients. Although recognizable prodromal symptoms were an inclusion criterion, some patients did not experience or recognize prodromal symptoms in every recurrent episode. Others had too short prodromal symptoms to apply the maneuvers. Carotid sinus massage has not been performed in all patients. Especially in elderly patients, the presence of complex neurally mediated syncope, with a combination of vasovagal and carotid sinus syndrome, could be an explanation for the variation in presentation and the ineffectiveness of the maneuvers on some occasions. Furthermore, although not reported by patients in this study, patients could forget to apply the maneuvers due to panic at the moment of syncope or not remember the maneuvers. Practicing the maneuvers regularly at home, therefore, should be advised to all patients. Although patients were instructed to breathe normally during the maneuvers, straining, causing a high intrathoracic pressure, and thereby reducing the blood flow to the thorax could also have diminished the effectiveness of the maneuvers in some patients (25).

In the conventional treatment group, the number of patients with late recurrences (i.e., after 1 year of follow-up) is large (Fig. 2), which is comparable to earlier findings (26). An explanation for this finding can be that patients treated conventionally avoid situations in which they are prone to vasovagal episodes and lie down in case of symptoms. After a symptom-free period, they may try to test these situations again. In the trained patients, the opposite might occur.

Knowing that they have an effective method to prevent episodes from occurring they will try the maneuvers in situations in which they fainted at earlier occasions.

**Population.** The study population consisted of more women than men (66.8% vs. 33.2%). This adequately reflects the higher prevalence of vasovagal syncope in women (2,3). Recurrence was also more prevalent in women, which is in agreement with the earlier results reported by Sheldon *et al.* (24). However, PCM were not more effective in women than in men. Number of episodes before presentation was, however, no predictor for recurrences, which is in contrast with the results of Sheldon *et al.* (24).

**Study limitations.** A limitation of the study is that only patients were blinded to the outcome of the randomization. This study design was chosen to be able to perform the training of the maneuvers and assess the use of the maneuvers in case of symptoms. Although earlier laboratory findings proved the possibility to stop or postpone syncopal episodes (15,18,25), this design might have biased the results. To assess the true reduction in recurrences from using the maneuvers, a double-blind study with a “placebo” arm could be performed, although the currently found effect seems large enough to accept there is a true benefit of the maneuvers above conventional therapy alone. Additionally, we feel that both blinding of the doctors as well as a placebo therapy may be almost impossible to perform in this kind of study.

In the earlier studies by Krediet *et al.* (15) and Brignole *et al.* (18), training in PCM resulted in even fewer syncopal recurrences. A possible explication for this difference could be the intensity of the training during an impending faint in their studies.

In this study, patients were trained in the maneuvers using biofeedback with a continuous blood pressure monitor. This method is effective in many patients and allows the patient to select the most effective of the various maneuvers in a non-threatening situation.

The additional attention and confidence gained by the visual effects during the training session would have provided an additional psychological treatment effect. Patients randomized to conventional therapy, however, also received an explanation of the diagnosis and life-style advice. Not knowing the existence of additional treatment with maneuvers, this might have had a similar effect. Furthermore, it is known that vasovagal syncope can be triggered by a complex combination of physical and psychological stimuli (27). Any beneficial effect of training in maneuvers, psychological or physical, is, therefore, inherent to the treatment and equally useful.

No difference between centers was found in the effectiveness of the maneuvers. It could be that the results are dependent on the trainer instructing the patient. The participation of 15 worldwide centers in the study ruled out this possibility. It can, therefore, be assumed that the maneuvers are effective in patients trained in any center.

**Conclusions.** Physical counterpressure maneuvers are a risk-free, effective, and low-cost treatment method in patients with vasovagal syncope with prodromal symptoms, and should be advised in combination with current conventional therapy as first-line treatment in patients presenting with this syndrome.

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**Reprint requests and correspondence:** Dr. Nynke van Dijk, Department of Internal Medicine, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands. E-mail: n.vandijk@amc.uva.nl.

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## APPENDIX

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*PC Trial steering committee:* W. Wieling, C. Menozzi, J.J. Blanc, R. Garcia-Civera, M. Brignole, A. Moya.

*PC-Trial investigators:* N. van Dijk, W. Wieling, C. Menozzi, F. Quartieri, G.M. Francese, M. Gulizia, J.J. Blanc, M.L. Borel, G. Baron-Esquivias, R. Garcia-Civera, R. Sanjuan, R. Pozzi, F. Rabaioli, M. Brignole, F. Croci, A. Del Rosso, D. Hachul, B. Oliveira, C. Morillo, C. Alonso, A. Moya, R. Pedretti, S. Sarzi Braga, P. Alboni, M. Dinelli, R. Garcia, J.C. Guzman-Orduz.

*Database development and management:* Y. le Bras.

For a full list of the PC-Trial Investigators and their affiliations, please see the online version of this article.