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Research Article

Venous Return Assist Devices for Intermittent Claudication: A Randomized Controlled Trial Utilizing a Sham Comparator

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ABSTRACT

Objectives: To determine whether an intermittent mechanical compression device (Venowave) effects walking distance in patients with intermittent claudication as compared to placebo, as well as to review the published literature on the topic.

Design: Randomized, cross-over, blinded trial of an intermittent mechanical compression device (Venowave), compared with a sham compression device.

Setting: Hamilton Health Sciences, Hamilton, Canada.

Participants: 27 patients with severe peripheral limb ischemia, as identified by at least one of: i) ABI<0.4; ii) ACD<200 m (Fontaine stage IIb); iii) toe-brachial index<0.5; or iv) toe pressure<40 mmHg or rest pain due to arterial ischemia.

Main Outcome Measures: The primary outcome measure was Absolute Claudication Distance (ACD) while walking on a treadmill. Secondary outcome measures included Initial Claudication Distance (ICD), walk time measured in minutes, and a modified version of the Walking Impairment Questionnaire (WIQ).

Results: There was no significant difference in ACD (mean difference: 14.1 m; 95% CI: -31.6 m-59.9 m; p=0.53) or ICD (mean difference: 5.9 m; 95% CI: -26.3 m-14.5 m; p=0.55) between active and sham devices. Mean walk time was identical between active and sham devices (5.6 minutes (2.1) *vs.* 5.6 minutes (2.0); p=0.99). The modified WIQ score was higher in the active group compared with the sham group (mean difference 2.1 m; 95% CI: 0.3 m-3.9 m; p=0.03).

Conclusion: In patients with moderate to severe intermittent claudication, the Venowave device did not increase walking distance when used immediately prior to and during measured effort. This is the first study to use a sham device as a comparator in this specific context.

Keywords: Intermittent Claudication; Ischemia; Placebo; Sham Comparator

INTRODUCTION

Intermittent Claudication (IC) is the most common manifestation of lower extremity Peripheral Arterial Disease (PAD). It manifests as reproducible calf, thigh or buttock pain on walking that is relieved by rest. IC results from limitation of the blood flow, generally by atherosclerotic stenosis, and an imbalance between the supply and demand of blood in the leg muscles. Three mechanisms have been proposed to improve claudication: increasing blood flow by restoring circulation in

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stenosed or occluded arteries, increasing vasodilation in distal arterioles, and improving muscle efficiency with conditioning.

Venous return assist devices act on the two former mechanisms by pumping the venous blood from the legs towards the heart, using either Intermittent Pneumatic Compression (IPC) or by mechanical compression. IPC uses pneumatic cuffs to apply pressure on the lower limbs. Hemodynamic and physiologic studies have shown that IPC can improve arterial flow, sympathetic auto-regulation, and result in the release of nitric oxide [1-4].

One of the proposed mechanisms by which IPC may work is by reducing venous pressure in the lower limbs and increasing the arteriovenous gradient, leading to improved arterial flow into the capillaries and oxygen delivery to the limb tissues. IPC has been studied in patients with PAD with multiple different devices. A Cochrane review [5] concluded that the studies of IPC in patients with critical limb ischemia are of low quality and as such do not allow a conclusion on their efficacy.

The Venowave is a lower-limb venous return assist device using mechanical compression that has been used in the treatment of post-thrombotic syndrome [6]. It acts by oscillatory mechanical calf compressions and allows patients to ambulate with the device. Prior studies have demonstrated its efficacy in prevention of deep vein thrombosis and treatment of post thrombotic syndrome [7,8]. Its mechanism of action is believed to produce a reduction in venous pressure, which may enhance arterial blood flow [9].

This hypothesis is strengthened by the observation that patients with PAD who have suffered prior deep vein thrombosis have more severe symptoms of IC highlighting the potential for enhanced venous return to improve arterial flow [10]. In this paper, we present the results of a randomized cross-over trial testing whether the Venowave device in patients with severe IC improves their absolute claudication distance.

METHODS

Study population

We performed a placebo-controlled, double-blinded, randomized cross-over trial of patients with severe limb ischemia at the Hamilton Health Sciences, Hamilton General Hospital. Patients aged 18 years or older were eligible if they had severe limb ischemia and at least one of the following criteria: i) ABI<0.4; ii) ACD<200 m, consistent with Fontaine stage IIb; iii) toe-brachial index<0.5; or iv) toe pressure<40 mmHg or rest pain due to arterial ischemia. Patients were excluded if they: i) were using cilostazol; ii) had non-healing ulcers or sores limiting their walking; iii) had a recent lower extremity intervention (within 6 months); iv) had uncontrolled hypertension; v) had a recent coronary event; vi) had other medical conditions that limited their ability to walk; or vii) had a leg circumference greater than 40 cm. Research ethics approval was obtained on November 11, 2011 and all participants provided informed consent.

Study protocol

Eligible patients were contacted by the research team to schedule the first visit, on which baseline information was recorded, including medical history, Ankle-Brachial Index (ABI) or Toe-Brachial Index (TBI), and a treadmill test. The total schedule comprised three clinical visits. Participants were randomly allocated, via a computer generated randomizer schedule, to the order in which they would receive either the active or sham device group. Patients randomized to sequence A received the active device on Visit 2 and the sham device on Visit 3, while patients randomized to sequence B received the sham device on Visit 2, and the active device on Visit 3. Each study participant wore the Venowave (active device) or a sham device (control device) on both legs, since some patients had severe bilateral limb ischemia. Venowave is a battery-operated wave generator developed by Saringer Research Incorporated, Stouffville, ON, Canada.

It attaches to the calf *via* Velcro supports and can be worn while ambulating. It allows for adjustment to different leg sizes and leg swelling. The device generates up to 19 cycles per minute of upward wave-like compression at 16 mL/second. The sham device was identical to the Venowave in size, weight and sound. While it does compress the calf through pressure from the circumferential Velcro supports, the control device does not generate true waveform pulsations like the Venowave. Participants wore the device for 30 minutes on both legs while resting.

Then, with the device on, the subjects underwent a treadmill walk to record walk time, initial claudication distance (ICD), and absolute claudication distance (ACD). A modified version of the walking impairment questionnaire (WIQ) was administered at the end of each session. The WIQ [11] is a validated tool used to assess walking ability, specifically walking distance, speed, and stair climbing, in patients with PAD and IC.

Study end points and definitions

The primary outcome measure was ACD while walking on a treadmill. ACD was defined as the maximum total distance walked on a treadmill until stopping due to IC pain. The treadmill test used a constant workload protocol, with a 3.2 km/h speed and a progressive grade up to 12%, as defined by Gardner et al. [12].

The secondary outcome measures included walk time measured in minutes, ICD, and a modified WIQ score. ABI was measured as well. The modified WIQ was administered at baseline and at each visit, before the treadmill. The ABI was measured with a portable 10 Hz Doppler device at the posterior tibial and dorsalis pedis arteries, while inflating the cuff around the lower calf. The ABI was calculated by using the highest measurement for each lower extremity over the highest of both arms.

Statistical analyses

Continuous variables were expressed as mean (standard deviation [SD]) or medians with Interquartile Ranges (IQRs) and categorical variables as percentages. The mean change in

ACD and ICD in metres, and WIQ were compared between the active and control device with a paired T test and mixed models analysis. A minimal clinically important difference of 40 metres on ACD was considered for the calculation of the sample size.

This distance is the mean improvement in placebo groups, in studies of exercise and medical therapies for IC [13]. With information from previous studies about the standard deviation of ACD, we estimated that 25 participants would be required to detect a mean difference of 40 metres between groups with a power of 80% and a two-sided alpha of 0.05.

RESULTS

A total of 27 patients were initially enrolled in the study, with 25 completing the entire protocol (Table 1). The majority were elderly male patients. The baseline ABI (range) was 0.57 (0.24-1.00). The mean ACD (standard deviation [SD]) for baseline, and with the active and sham devices were 299.9 (132.8), 291.1 (118.1) and 276.9 (113.1) m, respectively (Table 2).

The mean ACDs in the active and sham groups were lower than the baseline mean ACD. The mean difference in ACD (SD) between active and sham devices was 14.1 m (95% CI: -31.6-59.9; p=0.53), driven by one outlier who had a difference of 446 m favouring the active device.

The mean ICD (SD) for baseline, and with the active and sham devices, were 97.2 (SD 57.1), 112.9 (SD 49.9) and 118.1 (SD 48.6) m, respectively. Two participants had missing values for the "sham" measurement and were excluded from the analysis. In the remaining 23 patients, there was no significant difference in ICD between the active and sham groups (mean difference 5.9; 95% CI -26.3 m-14.5 m; p=0.55).

The mean walk time (SD) at baseline was 5.8 minutes (SD 2.5), while walking distance for active and sham devices were equal at 5.6 minutes (active SD 2.1; sham SD 2.0). The modified WIQ score was higher in the active group compared with the sham group (mean difference 2.1; 95% CI: 0.3-3.9, p=0.03).

Sensitivity analyses were performed looking for a period effect. The participants who had the active treatment first were found to perform better than those who had the sham treatment first (p=0.02), but this did not alter the effect of the intervention after adjusting for randomization sequence.

One patient had a marked difference in ACD and ICD between his baseline assessment and the assessment with the sham device, but not with the active device. This was considered atypical for IC. A sensitivity analysis was performed, excluding this individual, with the overall results unchanged. Removing the outlier reduced the mean difference in ACD to -3.9 m (95% CI -31.8 m - 24.1 m; p=0.78).

DISCUSSION AND CONCLUSION

In this analysis, application of the Venowave venous return assist device immediately before and during walking in patients with severe PAD was not associated with an improvement in walking distance. There was no significant variation in the ACD in patients wearing an active or a sham device. The ICD increased equally in both groups, but the mean difference was not significantly different between treatment groups. Interestingly, modified WIQ score as compared to those utilizing a sham device.

Table 1: Baseline characteristics of study participants in the Venowave trial. BMI: Body Mass Index; CAD: Coronary Artery Disease; SD: Standard Deviation; ABI: Ankle-Brachial Index; ACD: Absolute Claudication Distance; ACE: Angiotensin Conversion Enzyme.

Characteristic	Total eligible N=27
Age, in years (SD)	70.7 (9.8)
Male, N (%)	20 (80)
BMI (SD)	28.2 (4.1)
Current cigarette smoker (%)	7 (28)
Former cigarette smoker (%)	16 (64)
Diabetes mellitus (%)	7 (28)
Hypertension (%)	22 (88)
Previous CAD (%)	8 (32)
Previous peripheral vascular intervention (%)	9 (36)
Presence of rest pain	0
Baseline ABI, Left (SD)	0.57 (0.27)
Baseline ABI, Right (SD)	0.43 (0.28)
Reported ACD, metres (SD)	162.11 (104.3)
Concomitant drugs at randomization	
ACE inhibitors (%)	16 (64)
Beta blocker (%)	11 (44)
Calcium channel blocker (%)	9 (36)
Statin (%)	24 (96)
Other lipid lowering agent (%)	6 (24)
Diuretics (%)	14 (56)
ASA (%)	19 (76)
Other antiplatelet agents (%)	3 (12)
Anticoagulants (%)	4 (16)

Table 2: Results for Primary and Secondary Outcomes (n=24). SD: Standard Deviation; ACD: Absolute Claudication Distance; ICD: Initial Claudication Distance; WIQ: Walking Impairment Questionnaire. *Paired samples T-Test; Results expressed as mean (SD).

	Baseline	Active Device	Active Difference	Sham Device	Sham Difference	P value
ACD, metres (SD)	299.9 (132.8)	291.1 (118.1)	-8.8 (86.5)	276.9 (113.1)	-22.9 (119.6)	0.52
ICD, metres (SD)	97.2 (57.1)	112.9 (49.9)	15.7 (45.0)	118.1 (48.6)	18.0 (45.6)	0.77
Walk time, minutes (SD)	5.8 (2.5)	5.6 (2.1)	-0.2	5.6 (2.0)	-0.2	0.99
Modified WIQ score (SD)	N/A	33.0 (6.2)	N/A	30.9 (6.2)	N/A	0.03*

To place our observations in the context of other trials, we undertook a critical appraisal of prior literature. We systematically searched and screened abstracts and manuscripts for randomized trials of venous return assist devices in patients with IC. Eight papers were identified, totaling 308 patients (Table 3). The risk of bias was assessed by two authors (Caron F, Garg A) for each paper using the Cochrane risk of bias tool (Figure 1) [14].

Table 3: Description prior published trials of venous-return assist device and intermittent claudication. IPC: Intermittent Pneumatic Compression; IMC: Intermittent Mechanical Compression; ABI: Ankle-Brachial Index; ICD: Initial Claudication Distance; ACD: Absolute Claudication Distance; RCT: Randomized Controlled Trial; SWE: Standardized Walking Exercise; UE: Unsupervised Exercise; IQR: Interquartile Range; [a]Mean -(SD); [b]Median (range); [c]Unpublished data obtained from the author; [d]No measure of spread available.

Author and year	Study Type	Intervention groups	N	Age mean	Male Sex	Baseline ABI median (IQR)	Device	Medical Therapy	Duration (months)	ACD difference Metres (95%CI)	ICD difference metres (95%CI)
Berni et al. [24]	RCT	Group 1: Control	9	64.9	24/33	N/A	ArtAssist AA-1000 (foot and calf IPC)	Clopidogrel 75 mg	2-4	N/A	N/A
		Groups 2-5 : IPC 1h-2h OD-TID	24								
Breu et al. [17]	RCT	Group 1: IPC 1.5 h BID for 3 months +SWE	28	69.1	N/A	0.61 (0.30)[a]	ANGIOPRESS (Foot and calf IPC)	Aspirin or Clopidogrel	3	54.9 (42.63-67.17)	15.2 (-12.6-43.03)[c]
		Group 2: SWE	39			0.62 (0.27)[a]					
de Haro et al. [21]	RCT	Group 1: IMC 2 h/d	14	59	26/30	0.63 (0.09)	FM220 (IMC)	Best medical therapy +SWE	6	124.0 (97.6-150.5)	54.7 (3.4-106.0)
		Group 2: control	16			0.59 (0.02)					
Delis et al. [15]	Non-randomized	Group 1: IPC>4 h/d +UE	25	68	24/37	0.57 (0.14)	A-V Impulse System (foot IPC)	Aspirin 75 mg	4.5	126.6 (103.5-149.7)	101.7 (58.2-145.2)

		Group 2: UE	12	65		0.56 (0.08)					
		Group 1: IPC 2.5 h/d	20	66		0.59 (0.13)					
Delis et al. [16]	RCT	Group 2: Control	21	67.4	30/41	0.59 (0.16)	ArtAssist® AA-1000 (foot and calf IPC)	Aspirin 75 mg	5	281.5 (250.7-316.3)	138.2 (43.2-233.2)
		Group 1: IPC, 3 h/d	13			0.56 (0.16)					
Kakkos et al. [19]	RCT	Group 2: UE	21	67.1	27/34	0.60 (0.24)	ArtAssist® AA-1000 (foot and calf IPC)	Aspirin 75 mg Statins	6	260.0 (165.2-354.7)	30.0 (6.0-54.0)
		Group 1: IPC	12			0.46 (0.39-0.67)[b]					
Mehlsen et al. [20]	RCT	Group 2: Placebo	22	N/A		N/A	Negative pressure IPC	None	2	57[d]	38[d]
		Group 1: IPC 1 h BID+UE	15			0.64 (0.17)[a]					
Ramaswami et al. [18]	RCT	Group 2: UE	15	70.6	30/30	0.64 (0.25)[a]	ArtAssist® AA-1000 (foot and calf IPC)	None	12 months	185.8 (48.84-322.84)	81.6 (25.4-138.0)

In a nonrandomized, placebo-controlled trial, Delis et al. [15] compared the Art Assist AA-1000, an IPC device with foot and calf compressions, used four hours per day, with placebo in 25 and 12 patients with stable intermittent claudication, respectively. After 4.5 months, the mean ACD and ICD were respectively 126 m (95% CI: 103.5-149.7) and 101.7 m (95% CI: 58.2-145.2) higher in the IPC group. In another trial [16], they randomized 41 patients to the same device for 2.5 hours per day for 5 months, or placebo. The mean ACD and ICD differences were 281 m (95% CI: 250.7-316.3) and 138 m (95% CI: 43.2-233.2), respectively. In both studies, the ACD, ICD and ABI in the intervention group were significantly higher than the control group from the third month until the end of treatment.

The same device was tested in three other trials. One trial [17] randomized patients with IC stage IIb to five groups: a control group and four groups with IPC for 1 to 2 hours, one to three times per day. Compliance varied from 33% to 100% in the intervention groups, with the best compliance in the once daily group. The ABI increased by 18% to 26%, and the ACD increased by 83% to 101% in the intervention groups, while it did not change in the control group. Ramaswami et al. [18] randomized 30 patients with intermittent claudication to the Art Assist AA-1000 device or a control group with unsupervised exercise. After twelve months of treatment, the mean ACD and ICD differences were 185.8 m (95% CI: 48.8 m-322.8 m) and 81.6 m (95% CI: 25.4 m-138.0 m), respectively. However, there was a high rate of dropout, with only 11 patients left for the 1-year analysis. Kakkos et al. [19] randomized 34 patients with stage IIb IC to IPC (n=13), supervised exercise (n=12) or unsupervised exercise (n=9). Both IPC and supervised exercise showed a significant increase in median ACD at 6 month compared to baseline values (265 m and 75 m [p<0.01], respectively). The median ICD was also significantly improved, in a lesser proportion, in the IPC (10 m, p=0.02) and supervised exercise (30 m, p=0.04) groups.

Breu et al. [17] tested the Angiopress device, a foot-and-calf IPC device. 67 patients were randomized to the IPC for 1.5 hours twice daily (n=28) or to the control group (n=39). Both groups received maximal medical treatment and supervised walking exercises. After three months of treatment, the mean ACD and ICD differences (95% CI) were 54.9 m (42.6 m-67.2 m; p=0.0287) and 15.2 m (12.6 m-43.0 m; p>0.05), respectively. There were no changes in ABI between the intervention and control groups.

One of the trials [20] used a negative pressure device consisting in a pair of felt boots wrapped in an airtight plastic bag connected to a suction pump adjusted to provide a pressure 30% lower than the atmosphere. Patients were randomized to receive 25 active treatments (n=22) or 25 placebo treatments (n=12). The mean difference in ACD and ICD between the intervention and placebo groups were 57 m and 38 m (p value not reported).

Only one trial [21] tested an intermittent mechanical compression device similar to the Venowave, but used a different schedule. Thirty patients with IC were randomized to use the device 2 hours per day (n=14) or to a control group. Both groups had the best medical therapy and supervised

walking exercises. After 6 months, the mean ACD and ICD difference (95% CI) were 124 m (97.6 m-150.5 m) and 54.7 m (3.4 m-106.0 m).

Altogether, the eight previous trials of venous return assist devices in patients with intermittent claudication stand in contrast to the results of the Venowave trial.

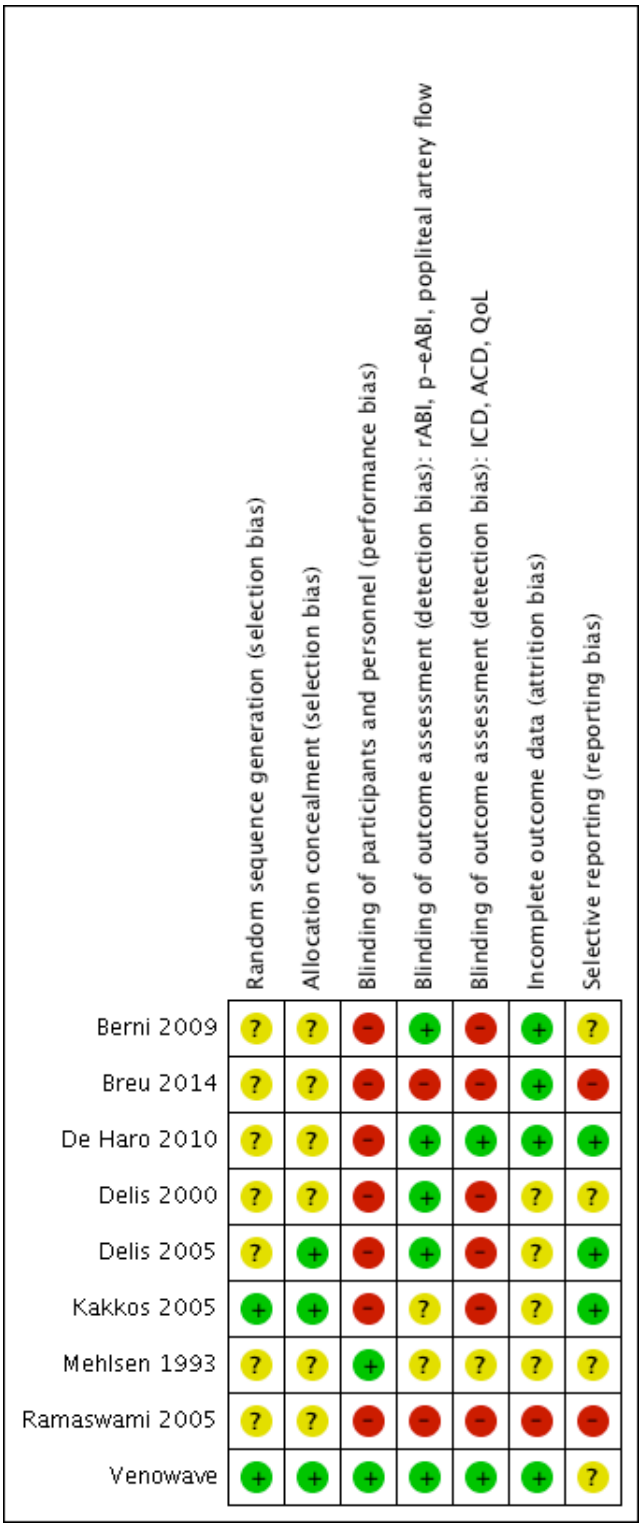

Figure 1: Risk of bias table for included studies. +: Low risk of bias, -:High risk of bias, ?: Unknown risk of bias.

Technical differences and timing of device application may account for this disparity. First, in our study the Venowave was applied 30 minutes before, and until the end of study test, whereas in other trials, they were used at rest, on a daily schedule, for multiple months. Next, the Venowave device used mechanical compression, while most previous trials assessed pneumatic devices. The benefit of compression devices is presumably attributable to their increase in the arteriovenous gradient, [3] resulting from the emptying of leg veins, but possibly also to a decrease of sympathetic regulation and to nitric oxide release by shear stress [22,23]; the latter two would be anticipated to cause vasodilation and to reduce exercise-induced muscle ischemia.

It is a prudent consideration however, that no previous trials have utilized a comparable placebo or sham device. The Venowave trial is the first randomized trial of venous compression to use a sham control. An isolated analysis of the active treatment group shows a reduction of ACD by 7.3 m (95% CI: -45.2-29.4; p=0.665), whereas ICD was increased modestly by 16.2 m (95% CI: -3.16-35.62; p=0.097). This suggests that the presence of a sham group did not change the result of our analysis.

Collectively, our observations suggest that the clinical benefit observed in prior trials may be attributable to longer usage of the device, whereas wearing a device only while walking does not have a significant impact on walking distance in patients with IC. However, the trials conducted to date have been small and heterogeneous. Moreover, as our investigation marks the first use of a convincing sham device, the placebo effect of compressive devices should be considered as a potential explanation for the discrepant results. Finally, other trials with neutral results may not have been published leading to publication bias in the existing literature.

In patients with moderate to severe intermittent claudication, the Venowave device did not increase walking distance when used immediately prior to and during measured effort. Future trials of such devices should be randomized, recruit a larger sample of PAD patients with moderate to severe IC, utilize convincing sham devices, and test the impact of a venous return device like the Venowave, worn for a longer duration such as a minimum of 2 hours per day for at least 3 months.

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Venous return assist devices were received from Springer incorporated. No other formal funding was received.

ETHICAL APPROVAL

The Hamilton Integrated Research Ethics Board approved this study (REC number: 11-591).

CONTRIBUTORSHIP

Aleksova N and Nowacki B conducted and supervised the study visits. Aleksova N drafted the study protocol and first abstract. Caron F and Garg A conducted the systematic review. Caron F Revised content and wrote the first draft of the manuscript.

Kaplovitch E updated the search strategy and revised the final draft of the manuscript. Neupane B conducted the statistical analyses. Ginsberg J, Hirsh J and Eikelboom J provided content expertise, critical review and edited the manuscript. de Souza R advised the group on search strategy and systematic review, as well as edited the manuscript. Anand SS supervised all aspects of the study protocol, conduct and development of the manuscript. All authors approved the final version of the manuscript.

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