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Research

Effectiveness of ambulation to prevent venous thromboembolism in patients admitted to hospital: a systematic review

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Abstract

Background: Patient ambulation is frequently recommended to help prevent venous thromboembolism during hospital admission. Our objective was to synthesize the evidence for ambulation as a prophylaxis for venous thromboembolism in hospital.

Methods: We conducted a systematic review. We searched MEDLINE, Embase, Scopus, Web of Science and Cochrane Central Register of Controlled Trials indexed from their inception through April 2020 for studies of adult patients admitted to hospital, in which ambulation or mobilization alone or concomitant with prophylaxis was indicated for prevention of venous thromboembolism. We searched ClinicalTrials.gov for unpublished trials. We included randomized controlled trials (RCTs) and observational studies. Two reviewers independently screened articles and assessed risk of bias using 2 validated tools. We scored studies on quality of reporting, internal and external validity and study power; combined scores determined the overall quality.

Results: Eighteen articles met the inclusion criteria: 8 retrospective and 2 prospective cohorts, 7 RCTs and 1 secondary analysis of an RCT. The intervention (ambulation or mobilized) groups varied across studies. Five studies examined exercise as a therapeutic prophylaxis for thrombosis and 9 described an ambulation protocol. Five studies attempted to quantify amount and duration of patient ambulation and 3 reported ambulation distance. In the 5 studies rated as good or excellent statistical quality, findings were mixed. Incidence of venous thromboembolism was lowest when pharmacologic anticoagulants were added as part of the prescribed prophylaxis regimen.

Interpretation: We did not find high-quality evidence supporting ambulation alone as an effective prophylaxis for venous thromboembolism. Ambulation should not be considered an adequate prophylaxis for venous thromboembolism, nor as an adequate reason to discontinue pharmacologic prophylaxis for venous thromboembolism during a patient's hospital admission.

Venous thromboembolism is a global problem, and in the United States alone, it affects up to 600 000 patients annually.[1] Prolonged immobility is a cited risk factor for developing venous thromboembolism.[2] Randomized controlled trials (RCTs) report significant reductions in venous thromboembolism events among surgical and medical patients who received pharmacological prophylaxis while in hospital.[3–5] Clinical practice guidelines describe risk-specific recommendations by patient population,[6–9] and accrediting bodies endorse prevention of venous thromboembolism as a top practice for patient safety.[10–13]

At our hospital, we significantly increased the proportion of patients who were risk assessed for venous thromboembolism and were prescribed risk-appropriate venous thromboembolism prophylaxis,[15–18] but also found up to 15% of prescribed doses were not administered to patients admitted to hospital.[19,20] Upon surveying health care providers on the wards, we discovered that based on the patient's ambulation status, many were presenting prophylaxis doses for venous thromboembolism as optional.[21,22] Several national and international clinical guidelines recommend ambulation as adequate prophylaxis for venous thromboembolism.[7,9] Further, "ambulatory patient" is ubiquitous in electronic medical records as a valid reason for not prescribing prophylaxis for venous thromboembolism.[23] To our knowledge, evidence supporting such recommendations is not provided.[24,25]

Competing interests: See the end of the article.

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Our objective was to synthesize the evidence for ambulation as a prophylaxis for venous thromboembolism among patients admitted to hospital.

Methods

We used the *Cochrane Handbook for Systematic Reviews of Interventions*[26] for guidance in designing and implementing this review.

Data sources and searches

The systematic review protocol was developed by a multidisciplinary group of clinicians, researchers and quality improvement experts focused on venous thromboembolism prevention (Appendix 1 available at www.cmajopen.ca/content/8/4/E832/suppl/DC1). A librarian with a master's degree in library sciences (S.S.) helped develop the search strategy and search terms consistent with ambulation in patients admitted to hospital (Appendix 1 and Appendix 2 available at www.cmajopen.ca/content/8/4/E832/suppl/DC1). We searched MEDLINE (1948–Apr. 28, 2020), Embase (1980–Apr. 28, 2020), Scopus (Apr. 28, 2020), Web of Science (Apr. 28, 2020) and the Cochrane Central Register of Controlled Trials (Apr. 28, 2020). We hand searched reference lists from included articles. ClinicalTrials.gov was searched for unpublished RCTs (Aug. 27, 2018).

Study selection

Two reviewers (P.M. and A.J.N.) independently screened titles, abstracts and full-text articles in duplicate using inclusion and exclusion criteria and resolved any discrepancies through third-party adjudication. We included studies published in English and with adult patients admitted to hospital, in which ambulation was indicated for venous thromboembolism prevention, either as a single mode of prevention or concomitant with prophylaxis. We included all studies of ambulation for prevention of venous thromboembolism even if the ambulation amount was not quantified by time, distance or frequency. Emed and colleagues found severe heterogeneity in definitions of their exposure variable, "immobility," used in studies of thromboprophylaxis among patients admitted to medical wards, re-emphasizing the problem of inconsistency in definitions when performing studies without a standard measure.[27] We excluded case-series reports, studies not specifying ambulation and studies done in outpatient, intensive care unit or rehabilitation settings. To be inclusive of all possible evidence regarding the efficacy and effectiveness of ambulation to prevent venous thromboembolism, we included both RCTs and observational studies.

Data extraction

Using standardized forms, each reviewer (P.M. and A.J.N.) independently extracted data and convened to compare and resolve any discrepancies. Data were extracted in duplicate from included studies for the following variables: country of origin, study design, patient population, participant characteristics (age, sex), interventions, comparisons, outcome and definition of ambulation.

Data analysis

DistillerSR (Evidence Partners, Ottawa, Canada) was used for screening and data extraction. We planned to conduct a meta-analysis when data were sufficient (from at least 3 RCTs) and studies were sufficiently homogeneous with respect to key variables (population characteristics, study duration and medication dosing).

Assessment of evidence

Two reviewers independently assessed the quality of the included studies and the risk of bias using the Downs and Black tool[28] for nonrandomized trials and observational studies recommended by Cochrane (version 5.1).[26] To maintain consistency of quality assessment, the Downs and Black tool was also used for assessment of RCTs. Each study was scored on the quality of reporting, both external and internal validity, and study power, and the combined scores determined overall quality (scale: poor, ≤ 14; fair, 15–19; good, 20–25; and excellent, 26–28).

The Agency for Healthcare Research and Quality evidence grading scheme for conducting comparative effectiveness reviews was adapted for use.[29]

The conclusion of this systematic review was based on a combination of both RCTs and other nonrandomized studies, as it is accepted that systematic reviews can be strengthened with observational studies after considering any study limitations. Evidence described as "high strength" probably reflected an actual effect, "moderate strength" indicated that further research may change the result and "low strength" indicated low confidence in an actual effect and that further research would be very likely to change the result. Insufficient evidence meant no evidence or that the body of evidence had unacceptable deficiencies that precluded a conclusion.

Ethics approval

As this study was solely based on literature, it was not eligible for institutional ethics approval, and none was sought.

Results

Of 20 917 titles identified from the different sources, 6545 duplicates were removed, leaving 14 372 articles. After title, abstract and full-text reviews using inclusion criteria, 14 354 articles were excluded, leaving 18 articles for analysis (Figure 1). Of the included articles, 2 studies were prospective cohort studies;[30,31] 1 was described as a case–control study, although it was a matched retrospective cohort study;[32] 7 were retrospective cohort studies involving surgical patients;[33–39] and 7 were RCTs[40–46] with an additional study of a secondary analysis of the randomized Medical Patients with Enoxaparin (MEDENOX) trial (Table 1).[47]

Study quality and heterogeneity

The studies varied in definitions of both ambulation and outcome (Table 2). The statistical quality ratings for included studies were poor (n = 3), fair (n = 10), good (n = 4) and excellent

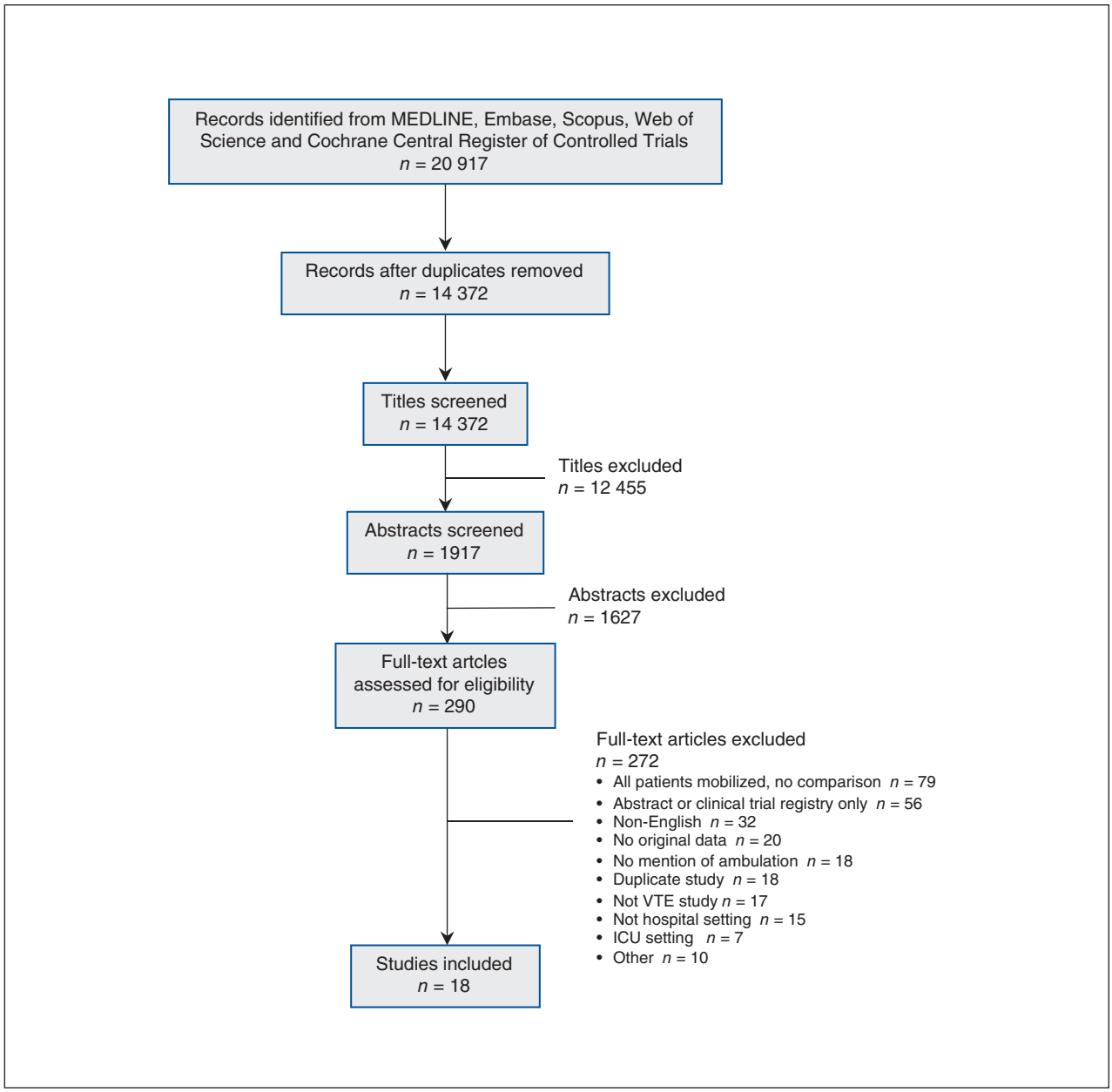

Figure 1: Selection process for studies describing ambulation as a therapy for preventing venous thromboembolism in patients admitted to hospitals. Note: ICU = intensive care unit, VTE = venous thromboembolism.

(*n* = 1) (Table 3).[28] Although 3 studies included a power calculation for the primary outcome, only 1 assessed if the sample size was appropriate to detect a clinically meaningful difference in venous thromboembolism, or appropriately powered if no difference was found.[46] A venous thromboembolism event was a secondary outcome in 7 studies.[31,32,37,39,42,43,45] The use of pharmacologic prophylaxis for venous thromboembolism varied: 6 studies prescribed prophylaxis for all patients, 8 did not report prophylaxis use, 2 did not use prophylaxis and 2 had different regimens by group. The heterogeneity of studies regarding patient populations, pharmacologic prophylaxis and ambulatory interventions precluded the aggregation of data for meta-analysis.

Ambulation definition

The intervention (ambulation) groups varied across studies. Six studies evaluated exercise (in or out of bed) as a therapeutic prophylaxis for thrombosis and 12 described an ambulatory protocol (Table 2). Five studies attempted to quantify the amount and duration of ambulation[31,32,36,45,47] and 3 reported the distance of ambulation.[36,45,47] Amin and colleagues had the most rigorous definition of ambulation (attain autonomous walking distance > 10 m), although they did not differentiate by time to achieve this measure.[47] de Almeida and colleagues quantified ambulation, where ability to walk 3 m independently was the primary outcome.[45] Most studies described "early mobilization" or specific prescriptions of mobility, such

Table 1 (part 1 of 2): Characteristics of included studies of ambulation to prevent venous thromboembolism

Study	Year	Country	Study design	Patient population	Groups	*n*	Male no. (%)	Age, yr; mean ± SD
Miller et al[39]	1976	US	RCT	Medicine (acute MI and heart failure)	Early ambulation	21	NR	NR
					Bed rest	8	NR	NR
Prerovský et al[40]	1988	Amsterdam	RCT	Medicine (acute MI)	Active foot flexion	135	109 (81)	59 ± 9
					Heparin	133	101 (76)	58 ± 9
					Control	140	109 (78)	59 ± 8
Vioreanu et al[41]	2007	Ireland	RCT	Orthopedics (foot and ankle)	Cast immobilization	29	20 (69)	35 ± 16
					Early ambulation	33	21 (64)	37 ± 13
Sorbello et al[42]	2009	Australia	RCT	Medicine (stroke)	Standard of care	33	16 (48)	75 ± 10
					Early mobilization	38	22 (58)	75 ± 15
Amin et al[46]	2010	France	Secondary analysis of RCT	Medicine	Ambulatory	607	317 (52)	72 ± 11
					Nonambulatory	447	226 (47)	75 ± 10
Wang et al[43]	2016	China	RCT	Orthopedics	Control	78	65 (83)	54 ± 6
					Active ankle movements	96	78 (81)	52 ± 7
de Almeida et al[44]	2017	Italy	RCT	General surgery	Control	54	22 (41)	62 (51–68)*
					Early mobilization	54	21 (39)	61 (53–70)*
Guo et al[45]	2019	China	RCT	Gynecology (surgical oncology)	Control	53	0 (0)	52 ± 13
					Functional exercises	62	0 (0)	48 ± 11
Lassen and Borris[29]	1991	Denmark	Prospective cohort	Orthopedics (THA)	POD #4 mobilization (Gr1)	35	NR	NR
					POD #9 mobilization (Gr2)	16	NR	NR
					Gr2 mobilization to POD #4	19	NR	NR
Karic et al[30]	2017	Norway	Prospective cohort	Neurosurgery (aneurysmal repair)	Control	77	28 (36)	54 (25–79)*
					Early mobilization	94	28 (30)	57 (25–81)*

Table 1 (part 2 of 2): Characteristics of included studies of ambulation to prevent venous thromboembolism

Study	Year	Country	Study design	Patient population	Groups	*n*	Male no. (%)	Age, yr; mean ± SD
Moses[32]	1951	US	Retrospective cohort	Surgery	Control	74	NR	NR
					Bicycle exercise	74	NR	NR
Flanc et al[33]	1969	England	Retrospective cohort	Surgery	Control	65	NR	NR
					Supervised exercise	67	NR	NR
Pearse et al[34]	2007	US	Retrospective cohort	Orthopedics (TKA)	Early mobilization	97	54 (56)	69 (SD NR)
					Control	98	48 (49)	69 (SD NR)
Chandrasekaran et al[35]	2009	Australia	Retrospective cohort	Orthopedics (TKA)	Before ambulation protocol	50	21 (42)	73 (SD NR)
					After ambulation protocol	50	24 (48)	71 (SD NR)
Frantzides et al[36]	2012	US	Retrospective cohort	General surgery (bypass)	Ambulation protocol	1257	NR	NR
					Heparin protocol	435	NR	NR
Cassidy et al[37]	2014	US	Retrospective cohort (NSQIP)	Surgery	Before VTE protocol	1569	NR	NR
					After VTE QI protocol	1323	NR	NR
Bhatt et al[31]	2017	Ireland	Retrospective cohort	General surgery	Control	30	18 (60)	61 ± 15
					Exercise program	30	17 (57)	61 ± 14
Silver et al[38]	2020	US	Retrospective cohort	Medical (ischemic stroke)	Control (24 h bed rest)	203	97 (52)	72 ± 16
					12 h bed rest	189	87 (46)	72 ± 16

Note: Gr = Grade of mobilization, MI = myocardial infarction, NR = not reported, NSQIP = National Surgical Quality Improvement Program, POD = postoperative day, QI = quality improvement, RCT = randomized controlled trial, SD = standard deviation, THA = total hip arthroplasty, TKA = total knee arthroplasty, VTE = venous thromboembolism.
*Median (interquartile range).

as twice daily physiotherapy, but failed to report adherence to the defined protocol.

Three studies compared mobility with prolonged immobility. Miller and colleagues compared sitting and standing at the bedside for 30 minutes 3 times a day, starting the first day following myocardial infarction, to 5 days of bed rest,[40] Lassen and Borris compared mobilization starting on postoperative day 4 to postoperative day 9,[30] and Silver and colleagues compared 12-hour versus 24-hour bed rest following stroke.[39]

Venous thromboembolism diagnosis

Most studies used clinical suspicion to test for venous thromboembolism, but 8 studies used screening modalities to determine the presence or absence of venous thromboembolism (Table 2). The most common screening modalities were ^{125}I-fibrinogen and phlebography. Most studies failed to clarify the diagnostic modality used to confirm the clinical suspicion, particularly studies in which venous thromboembolism was not the primary outcome. Most studies did not report on pulmonary embolism separately.

Ambulation as prophylaxis

Most studies reported a reduction in venous thromboembolism events with either implementation of an ambulation protocol or promotion of ambulation (Table 2). In the 5 studies rated as good or excellent statistical quality, the findings were mixed

Table 2 (part 1 of 2): Results of included studies of ambulation to prevent venous thromboembolism

Study	Ambulatory group description	Ambulation quantified?	Comparison group description	Pharmacological VTE prophylaxis	Outcome (definition)	Group sizes	Results		Study conclusion
Miller et al[39]	Sitting and standing at the bedside for 30 min 3 times/d; ate meals while sitting	No	Five days of bed rest with leg exercises hourly	No	DVT (^{125}I-fibrinogen)	21 8	Amb Control	10% 63%	Early mobilization program reduces the incidence of venous thrombosis in acute MI
Prerovský et al[40]	Dorsal and plantar flexion for 1–2 min every hour while awake	No	Standard of care without chemical VTE prophylaxis	No*	DVT (^{125}I-fibrinogen)	135 133 140	Amb Heparin Control	5.2% 9.0% 13.6%	Moderate lower limb exercise is the simplest measure to prevent VTE
Vioreanu et al[41]	Custom made removable fiberglass cast with ankle exercises 3 times/d for 10 min	No	Non-removable fiberglass cast for 6 weeks	NR	VTE Clinical	29 33	Amb Control	0% 6%	Postoperative immobilization may increase DVT risk
Sorbello et al[42]	Sitting or standing within 24 h for 6 d with aid of nurse or physiotherapist	No	Standard of care	NR	VTE (NR)	33 38	Amb Control	0% 0%	No difference in complications after initiation of early mobilization
Amin et al[46]	Ability to attain autonomous walking distance > 10 m	Yes	Did not attain autonomous walking > 10 m	Yes†	VTE (clinical)	607 447	Amb Control	8.4%‡ 16.2%	In the prevention of VTE, reaching ambulatory status may not be a reason for stopping pharmacological prophylaxis
Wang et al[43]	Dorsal and plantar flexion 30 times/min, 20 times/d in first 7 postoperative days	No	Standard of care	NR	DVT (doppler or clinical)	78 96	Amb Control	7.6% 18.4%	Significant reduction in all DVTs but no difference in symptomatic DVTs (2.2% v. 3.9%)
de Almeida et al[44]	Twice daily exercise program based on patient's functional ability	Yes	Once daily exercise program	NR	DVT (clinical)	54 54	Amb Control	1.8% 0%	Primary outcome was ability to walk but no difference in DVT
Guo et al[45]	Active ankle motions, calf massage and deep breathing	No	Standard of care	Yes	DVT (clinical or ultrasonography)	53 62	Amb Control	1.9% 1.6%	Because of the sample size limitation, the authors could not draw any conclusion about the effects of exercise on the prevention of VTE
Lassen and Borris[29]	Mobilized from postoperative day 4 onward	No	Mobilized from postoperative day 9 onward	Yes	DVT (phlebography)	35 35	Amb Control	21% 75%	Patients may lose benefit of pharmacological VTE prophylaxis if they are not mobilized
Karic et al[30]	Progressive mobilization from HOB elevation to sitting, standing and walking to restroom	No	Standard of care	Yes	VTE (clinical)	77 94	Amb Control	4.2% 3.8%	No impact on VTE but reduced postoperative vasospasm

Table 2 (part 2 of 2): Results of included studies of ambulation to prevent venous thromboembolism

Study	Ambulatory group description	Ambulation quantified?	Comparison group description	Pharmacological VTE prophylaxis	Outcome (definition)	Group sizes	Results		Study conclusion
Moses[32]	Forced respirations and 2-min bicycle exercise every day or twice daily while awake	No	Standard of care	NR	VTE (clinical)	74 74	Amb Control	0% 5%	Bicycle or deep breathing reduce thrombotic complications
Flanc et al[33]	Supervised exercise 6 times/d with nursing reminders to exercise	No	Standard of care	NR	DVT (^{125}I-fibrinogen)	65 67	Amb Control	25% 35%	Strain on hospital resources and only benefit was in older patients
Pearse et al[34]	VTE prevention protocol including < 24 h mobilization	No	Routine ambulation on POD #2	Yes	DVT (Doppler)	97 98	Amb Control	1% 28%	Early mobilization reduces radiographic DVT
Chandrasekaran et al[35]	Mobilized with first 24 h, at least twice daily, 15–30 min, by physiotherapists	Yes (sitting, 1–5 m, > 5 m)	Routine out of bed to chair and walking POD #2	Yes	VTE (Doppler or clinical)	50 50	Amb Control	16% 38%	Early mobilization reduces postoperative DVT, particularly if > 5 m (no VTE in 15 patients)
Frantzides et al[36]	VTE prevention protocol including ambulation within 2 h	No	Standard of care with enoxaparin	Yes (control only)	VTE (NR)	1257 435	Amb Control	0.5% 2.7%	Early ambulation as part of a comprehensive protocol obviates need for pharmacological prophylaxis except in high-risk patients
Cassidy et al[37]	New comprehensive VTE prevention protocol including mobilization 3 times/d	No	Prior to protocol with no predefined practice	Yes (according to risk assessment)	VTE (NSQIP)	1569 1323	Amb Control	3% 0.8%	Postoperative mobilization program, risk stratification and electronic recommendations reduce VTE
Bhatt et al[31]	Twice daily exercise program with pedal exerciser or POD#2 or when able to sit	Yes	Standard of care	NR	VTE (clinical)	30 30	Amb Control	0% 0%	No impact on VTE but reduced infectious complications postoperatively
Silver et al[38]	Bedrest for ≥ 24 h	No	At least 12 h of bedrest	No	DVT (clinical)	203 189	Amb Control	0.5% 1.5%	No effect on VTE but reduction in pneumonia and LOS

Note: Amb = ambulation, DVT = deep vein thrombosis, HOB = head of bed, LOS = length of stay, MI = myocardial infarction, NR = not reported, NSQIP = National Surgical Quality Improvement Program, POD = postoperative day, RCT = randomized controlled trial, VTE = venous thromboembolism.
*Ambulation and Enoxaparin 40 mg once daily had the lowest rate of VTE at 3.3%.
†Heparin was used in a third group but not ambulatory or control group.
‡Patients in both groups were randomly assigned to receive placebo, enoxaparin 40 mg or 20 mg once daily.

(Table 4). Sorbello and colleagues targeted patients admitted to hospital for stroke and found no difference in events among groups (randomized to very early mobilization with physiotherapy v. standard of care).[43] Cassidy and colleagues conducted a retrospective analysis using the National Surgical Quality Improvement Program database and found a reduction in events from 3% to 0.8% after introducing a hospital-wide quality improvement protocol for venous thromboembolism.[38] The protocol included a standardized risk-stratification protocol combined with a postoperative mobilization program.[38] This mobilization program required the patient to be out of bed at least 3 times a day starting the day of surgery and "early ambulation" was encouraged.

de Almeida and colleagues compared twice daily graduated exercise protocols to once daily in surgical oncology patients to determine if increased mobility improved functional capacity (ability to walk 3 m), and although events were secondary outcomes, no difference was seen.[45] Guo and colleagues evaluated prescribed "functional exercises" including deep breathing, active ankle mobility and calf

Table 3: Quality of included studies and assessment of bias, as evaluated by Downs and Black[28]

Study	Year	Study design	Measure				Score	Overall quality*
			Quality of reporting	External validity	Internal validity	Power		
Moses[32]	1951	Retrospective cohort	2	1	1	0	4	Poor
Flanc et al[33]	1969	Retrospective cohort	7	2	6	0	14	Fair
Miller et al[39]	1976	RCT	5	1	6	0	12	Poor
Prerovský et al[40]	1988	RCT	6	2	6	0	14	Fair
Lassen and Borris[29]	1991	Prospective cohort	3	1	4	0	8	Poor
Pearse et al[34]	2007	Retrospective cohort	9	0	6	0	15	Fair
Vioreanu et al[41]	2007	RCT	7	3	6	0	16	Fair
Chandrasekaran et al[35]	2009	Retrospective cohort	8	1	8	0	17	Fair
Sorbello et al[42]	2009	RCT	10	3	7	0	20	Good
Amin et al[46]	2010	Secondary analysis of RCT	11	3	9	0	23	Good
Frantzides et al[36]	2012	Retrospective cohort	7	3	4	0	14	Fair
Cassidy et al[37]	2014	Retrospective cohort (NSQIP)	8	3	8	0	19	Good
Bhatt et al[31]	2017	Retrospective cohort	8	2	6	0	16	Fair
Wang et al[43]	2016	RCT	8	1	9	0	18	Fair
Karic et al[30]	2017	Prospective cohort	8	3	6	1	18	Fair
de Almeida et al[44]	2017	RCT	11	3	11	1	26	Excellent
Guo et al[45]	2019	RCT	11	2	11	1	25	Good
Silver et al[38]	2019	Retrospective cohort	9	3	5	0	17	Fair

Note: NSQIP = National Surgical Quality Improvement Program, RCT = randomized controlled trial.
*Scale for quality scores: poor: ≤ 14; fair: 15–19; good: 20–25; excellent: 26–28.

massage, and although ultrasonography screening was used, there was no difference in the rates of deep venous thrombosis among groups.[46]

Amin and colleagues' study best quantified the actual ambulation of medically ill patients and accurately determined the use of pharmacologic prophylaxis for venous thromboembolism (placebo, enoxaparin 20 mg or enoxaparin 40 mg).[47] In the ambulatory group, with patients achieving autonomous ambulation more than 10 m, the incidence of venous thromboembolism was 8.4%, which was half the incidence of the group not achieving autonomous ambulation. When pharmacologic prophylaxis (enoxaparin 40 mg) was considered with autonomous ambulation, the incidence of venous thromboembolism was further reduced to 3%. In patients achieving ambulation more than 10 m independently (but not receiving pharmacologic prophylaxis), the event rate was 10.6%.

Two additional studies at higher risk of bias quantified ambulation or exercise. Bhatt and colleagues did not report any venous thromboembolism events in their study of postoperative use of a pedal exerciser.[32] Chandrasekaran and colleagues screened all included patients with a duplex ultrasonography on postoperative day 4 and found that patients walking more than 5 m did not have any deep venous thrombosis or pulmonary embolism compared with the control group (32% v. 6% pulmonary embolism, respectively).[36]

Interpretation

Our systematic review showed a paucity of evidence to support ambulation as an adequate prophylaxis to prevent venous thromboembolism. We found 18 studies over a 69-year span that studied ambulation, most indirectly, to prevent venous thromboembolism; only one-quarter were rated good or excellent quality. We planned a meta-analysis, but the heterogeneity of studies and the varied ambulation definitions made it impossible to quantify any therapeutic ambulation dose.

Four of the 7 RCTs had fewer than 100 patients, and the largest RCT (n = 408) defined ambulation as dorsal and plantar flexion for 1 to 2 minutes every hour.[41] The highest quality study did quantify ambulation and conducted a secondary analysis to compare venous thromboembolism rates with and without pharmacologic prophylaxis.[47] Although patients achieving autonomous walking in that study had a lower rate of venous thromboembolism events, it is unclear if there were uncontrolled variables to account for this difference. Moreover, the study was designed to investigate the effect of pharmacological prophylaxis on events, which showed a substantial effect in the study. The authors concluded that patients who ambulated more than 10 m independently and received 40 mg enoxaparin had fewer venous thromboembolism events,

Table 4: Results of included studies rated "good" or "excellent" quality

Study	Study size	Study population	Study quality*	Ambulation quantified?	Pharmacological VTE prophylaxis	Outcome (definition)	Results		Study conclusion	Notes
Sorbello et al[42]	71	Medicine	Good	No	NR	VTE (NR)	Amb Control	0% 0%	No difference in complications after initiation of early mobilization	Physiotherapy-directed OR physiotherapist-directed ambulation early in admission did not change VTE rates compared with standard of care
Amin et al[46]	1054	Medicine	Good	Yes	Yes†	VTE (clinical)	Amb Control	8.4%‡ 16.2%	In the prevention of VTE, reaching ambulatory status may not be a reason for stopping chemical prophylaxis	The best study to quantify ambulation (> 10 m walking). Reinforces need for chemical VTE prophylaxis
Cassidy et al[37]	2892	Surgery	Good	No	Yes, according to risk assessment	VTE (NSQIP)	Amb Control	3% 0.8%	Postoperative mobilization program, risk stratification and electronic recommendations reduce VTE	Large study with definition of VTE used widely. Wide implementation of a 3 times/d regimen failed to show a reduction in VTE
de Almeida et al[44]	108	Surgery	Excellent	Yes	NR	DVT (clinical)	Amb Control	1.8% 0%	Primary outcome was ability to walk but no difference in DVT	VTE events were a secondary outcome. More ambulation (≥ 2 times/d compared with ≤ 1 time/d) did not reduce VTE events
Guo et al[45]	115	Surgery	Good	No	Yes	DVT (clinical or ultrasonography)	Amb Control	1.6% 1.9%	Because of the sample size limitation, the authors could not draw any conclusion about the effects of exercises on the prevention of VTE	Similar to other lower quality studies, ankle exercises do not seem to reduce risk of DVT

Note: Amb = ambulation, NR = not reported, NSQIP = National Surgical Quality Improvement Program, VTE = venous thromboembolism (pulmonary embolism or deep vein thrombosis [DVT])
*Assessed using the Downs and Black tool.[28]
†Patients in both groups were randomly assigned to receive placebo or enoxaparin 40 mg or 20 mg once daily.
‡Ambulation and enoxaparin 40 mg once daily had the lowest rate of VTE at 3.3%.

though the incidence was still 3.3%, and the ambulation-only group had an event rate of 10.6%.[47] The only other RCT receiving an excellent quality rating primarily investigated the ability to walk after major oncologic resection, but observed no difference in deep venous thrombosis events among groups.[45]

Ambulation or mobilization remains a commonly reported approach, often as the sole prophylaxis, against venous thromboembolism. Most concerning is that ambulation is often a cited reason to discontinue pharmacologic prophylaxis for venous thromboembolism. At our hospital, nurses and residents perceived that independently ambulating patients did not need pharmacologic prophylaxis for venous thromboembolism.[21,22,48] However, there is overwhelming evidence supporting pharmacologic prophylaxis in nearly every applicable population admitted to hospital.

Immobility is a risk factor for development of venous thromboembolism. However, our systematic review found that mobility, ambulation or mobilization have not been shown to reduce VTE events. Many of the major guidelines recommend early ambulation for prevention of venous thromboembolism. For example, the American College of Chest Physicians recommends early ambulation as the only prophylactic measure needed for low-risk nonorthopedic surgical patients, as measured by the Caprini or Rogers risk assessment tool.[49] Our results challenge early ambulation as appropriate prophylaxis for venous thromboembolism. A patient's risk should be assessed and evidence-based treatment given, considering the risks and benefits. We are not suggesting that ambulation in medical and surgical inpatients is useless. Immobility has many deleterious effects and patients admitted to hospital should be actively encouraged to ambulate. Based on our results, however, we caution the use of ambulation as the sole prophylaxis for prevention of venous thromboembolism or as the impetus to hold pharmacological prophylaxis when ill patients are in a hypercoagulable state.

Although diagnostic and preventive practices for venous thromboembolism have evolved, we searched decades back because the concept of ambulation is long-lived and we needed to find where the concept originated. As early as 1951, Leithauser and colleagues described the "abuse of ambulation."[50] They suggest, and we agree, that early ambulation is not having the patient "dangle the feet over the edge of the bed or sit in a chair."[50] Several studies in our review described sitting or standing as ambulation.[40,43] Cassidy and colleagues counted walking to the washroom as 1 of 3 required mobilization events,[38] and Sorbello and colleagues defined ambulation as sitting or standing within 24 hours.[43] Rather, the attending physician should prescribe ambulation therapy, including timing, frequency and duration, and the prescribed ambulation should be monitored to ensure the patient undertakes it. The results of our review suggest that such a program has not been studied.

Limitations

While comprehensive, our review was limited by the quality of the literature. The RCTs were small and often rated as low quality, and most were negative studies. Most studies failed to define the quality and quantity of ambulation. Older studies did not report or did not use pharmacologic prophylaxis for venous thromboembolism. Therefore, the results must be considered in the modern practices of prevention, which include pharmacologic prophylaxis for venous thromboembolism for most patients admitted to hospital.

We considered only studies published in English and only the ClinicalTrials.gov registry for unpublished studies; it is possible that we failed to identify a relevant study.

Further, most studies were eliminated after title or abstract review, and we may have missed studies with ambulation as a secondary intervention or venous thromboembolism as a secondary outcome. Systematic reviews that find little to no evidence are still important to perform and publish. This key step is critical to delineate clear gaps in the published literature for several reasons. First, researchers can plan new studies to address these concerns.[51] Second, concepts about the robustness of the evidence can be combatted. This is particularly true for ambulation, which is now ubiquitous as a preventive measure for venous thromboembolism despite a lack of evidence. Third, clinical practice might change, in particular using the concepts of implementation or de-implementation science.[52,53] Although we used a study protocol, it was not registered with PROSPERO (https://www.crd.york.ac.uk/prospero/).

Conclusion

Our systematic review failed to find high-quality evidence to suggest that ambulation alone is an appropriate or effective prophylaxis for venous thromboembolism. Although some studies suggest that ambulation may reduce venous thromboembolism events among patients admitted to hospital, we could not draw conclusions about how early, how much, how vigorous or how often ambulation should occur to reduce events effectively. In the context of substantial evidence for pharmacologic prophylaxis to prevent venous thromboembolism, ambulation should not be considered an adequate prophylaxis, nor should ambulation be a reason to discontinue pharmacologic prophylaxis during hospital admission. Our findings point to an important function of systematic reviews, which is to evaluate existing evidence. We rigorously evaluated data from studies over a 69-year span and can conclude that research is needed to assess prescribed therapies for ambulation and determine whether any are effective in preventing venous thromboembolism events.

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