Effectiveness of Ambulation to Prevent Venous Thromboembolism in Hospitalized Patients: A Systematic Review

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ABSTRACT

Background: Ambulation is frequently cited for preventing venous thromboembolism (VTE) among hospitalized patients unknown. Our objectives were to synthesize all evidence for ambulation to estimate the therapeutic regimen and effectiveness for preventing VTE.

Methods: We searched MEDLINE, EMBASE, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials indexed from inception through August 2018 for studies of adult hospitalized patients, where ambulation alone or concomitant with prophylaxis was indicated for VTE prevention. The grey literature search included ClinicalTrials.gov for unpublished trials. Two reviewers independently screened articles and assessed risk of bias using two validated tools (randomized controlled trials [RCT] and observational studies). Studies were scored on quality of reporting, internal and external validity, and study power; combined scores determined the overall quality.

Results: Sixteen articles met the inclusion criteria: 6 retrospective and 2 prospective cohorts, 1 case-control, 6 RCTs, and 1 secondary analysis of an RCT. The intervention (ambulatory/mobilized) groups varied across studies. Five studies examined exercise as a therapeutic prophylaxis for thrombosis and 9 described an ambulatory protocol. Five studies attempted to quantify amount and duration of patient ambulation and 3 reported ambulation distance. In the 4 studies rated as good/excellent statistical quality, findings were mixed. Incidence of VTE 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 VTE prophylaxis. Ambulation should not be considered an adequate VTE prophylaxis, nor an adequate reason to discontinue pharmacologic VTE prophylaxis while hospitalized.

INTRODUCTION

Venous thromboembolism (VTE) is a global problem, and in the United States alone affects up to 600,000 patients annually.[1] Prolonged immobility is a cited risk factor for developing VTE.[2] Randomized controlled trials report significant reductions in VTE with pharmacological prophylaxis,[3-5] clinical practice guidelines describe risk-specific recommendations by patient population,[6-8] and accrediting bodies endorse VTE prevention as a top patient safety practice.[9-12]

Strong evidence supports pharmacological or mechanical prophylaxis to prevent VTE, inciting interventions to improve prescription of risk-appropriate prophylaxis for hospitalized patients.[12] Since 2005, the Johns Hopkins Medicine VTE Collaborative has systematically studied and implemented interventions for preventing VTE. We first improved risk assessment[13] and prescription of risk-appropriate prophylaxis for hospitalized patients.[14-16] While successful, we found that up to 15% of prescribed prophylaxis doses were not being administered to hospitalized patients.[17,18] When nurses were surveyed, we discovered that many were presenting VTE prophylaxis doses as optional for patients based on ambulation status.[19,20] Some clinicians recommend ambulation for VTE prevention for patients deemed low risk or contraindicated for pharmacologic prophylaxis.[21] However, evidence supporting such recommendations are not provided.[22,23]

The purpose of this systematic review was to comprehensively evaluate the evidence supporting ambulation for preventing VTE among hospitalized patients. We sought to synthesize the evidence and estimate the therapeutic regimen for ambulation and its effectiveness for preventing VTE among any hospitalized patient population.

METHODS

Data Sources and Searches

A multidisciplinary group of clinicians, researchers, and quality improvement experts focused on VTE prevention developed the systematic review protocol (Appendix A). A master's prepared librarian (SS) helped develop the search strategy and search terms consistent with ambulation in the hospitalized patient population (Appendix B). We searched MEDLINE, EMBASE, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials from their respective inception through August 27, 2018. We hand-searched reference lists from included articles for additional studies, and our grey literature search included ClinicalTrials.gov for relevant unpublished trials.

Study Selection

Two reviewers (PM, AJN) independently screened titles, abstracts, and full-text articles using inclusion and exclusion criteria. Discrepancies between reviewers were resolved through third-party adjudication. We included studies published in English of adult hospitalized patients, where ambulation was indicated for VTE prevention, either as a single mode of prevention or concomitant with VTE prophylaxis (pharmacologic, mechanical, or both). Our qualitative assessment included all studies of ambulation for VTE prevention. Our quantitative assessment included all studies in which ambulation was in one or more arms. We excluded case-series reports, studies that did not specify ambulation, and those 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 VTE, we included both randomized controlled trials (RCT) and observational studies.

Data Extraction and Quality and Applicability Assessment

Using standardized forms, each reviewer independently extracted data and convened to compare and resolve any discrepancies. Data were extracted from included studies for the following variables: country of origin, study design, patient population, participant characteristics (age, gender), interventions, comparisons, and outcome and definition. We sought to assess the quality of included studies. The reviewers independently assessed risk of bias using Jadad and

colleagues criteria for RCTs,[24] and the Downs and Black tool[25] for nonrandomized trials and observational studies. 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 to 19; good, 20 to 25 and excellent, 26 to 28).

Data Synthesis and Analysis

We created a set of detailed evidence tables. We planned to conduct a meta-analyses when data were sufficient (from at least three trials) and studies were sufficiently homogenous with respect to key variables (population characteristics, study duration, and medication dosing).

Grading of Evidence

The Agency for Healthcare Research and Quality evidence grading scheme for conducting comparative effectiveness reviews was adapted for use. Two reviewers sequentially graded the limitations, consistency, directness, precision, and potential reporting bias for the evidence on each outcome and comparison for each study based on Downs and Black grading tool.[25] The final evidence grade and conclusion were based on the RCTs but could be strengthened using evidence from observational studies if there were few 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, with further research very likely to change the result. Insufficient evidence meant no evidence or the body of evidence had unacceptable deficiencies that precluded a conclusion.

RESULTS

Study Selection and Demographics

Of 18009 titles identified from the different sources, 5588 duplicates were removed, leaving 12421 articles. Titles and abstracts were screened and 12,405 articles that did not meet our inclusion criteria were excluded, leaving 16 articles for analysis (Figure). Two studies were prospective cohorts,[26,27] one a case-control,[28] six retrospective cohort studies of surgical

patients (mainly orthopedics),[29-34] and six RCTs[35-40] with an additional study a secondary analysis of the randomized MEDENOX trial (Table 1).[41]

Study Quality and Heterogeneity

The studies varied in definitions of both ambulation and outcome (Table 2). The overall study quality was poor to fair[25] (Table 3). The statistical quality ratings for included studies were poor (n = 3), fair (n = 9), good (n = 3), and excellent (n = 1). Only two studies performed a power calculation for the primary outcome and no study performed a power calculation to determine if the sample size was appropriate to detect a clinically meaningful difference in VTE, or appropriately powered if no difference was found. VTE event was a secondary outcome in a number of studies. The use of pharmacologic VTE prophylaxis varied: 5 studies prescribed prophylaxis for all patients, 7 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

The intervention (ambulatory/mobilized) groups varied across studies. Five studies examined exercise as a therapeutic prophylaxis for thrombosis and 11 described an ambulatory protocol (Table 2). Five studies attempted to quantify the amount and duration of ambulation[27,28,32,40,41] and 3 reported the distance of ambulation.[32,40,41] Amin had the most rigorous definition of ambulation (attain autonomous walking distance >10 meters), although they did not differentiate by time to achieve this measure.[41] De Almeida quantified ambulation, but ability to walk 3 meters independently was the primary outcome.[40] Most studies described "early mobilization" or specific prescriptions of mobility, such as twice a day physiotherapy, but failed to report adherence to the defined protocol. Two studies compared mobility with prolonged immobility. Miller 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,[35] and Lassen compared mobilization starting on post-operative day 4 to post-operative day 9.[26]

VTE Diagnosis

Most studies used clinical suspicion to test for VTE, but 7 studies used screening modalities to determine the presence or absence of VTE (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 where VTE was not the primary outcome. The majority of studies did not report on PE separately.

Ambulation as VTE Prophylaxis

The majority of studies reported a reduction in VTE with either implementation of an ambulation protocol or promotion of ambulation (Table 2). In the 4 studies rated as good/excellent statistical quality, the findings were mixed (Table 3). Sorbello targeted patients hospitalized for stroke and found no difference in VTE events between groups (randomized to very early mobilization with physiotherapy versus standard of care).[6] Cassidy conducted a retrospective analysis using the National Surgical Quality Improvement Program database and found a reduction in VTE from 3% to 0.8% after introducing a hospital wide VTE quality improvement protocol, which included risk stratification, electronic recommendations, improved adherence to pharmacologic prophylaxis, and a standardized post-operative mobilization program.[34] 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 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 meters), while VTE events were secondary outcomes, no difference was seen.[40]

The fourth study with good statistical quality best quantified the actual ambulation of medically ill patients and accurately determined the use of pharmacologic VTE prophylaxis (placebo, enoxaparin 20mg, or enoxaparin 40mg).[41] In the ambulatory group, patients achieving

autonomous ambulation >10 meters, the incidence of VTE was 8.4%, which was half the incidence of the group not achieving autonomous ambulation. When pharmacologic VTE prophylaxis (enoxaparin 40 mg) was considered with autonomous ambulation, the incidence of VTE was further reduced to 3%. In patients achieving ambulation >10 meters independently (not prophylaxis), the VTE rate was 10.6%. Two additional studies quantified ambulation/exercise. Bhatt did not report VTE events in their study of post-operative use of a pedal exerciser.[28] Chandrasekaran screened all included patients with a duplex ultrasound on post-operative day 4 and found that patients walking >5 meters did not have any PE/DVT compared to the control group (32% DVT and 6% PE).[32]

DISCUSSION

Our systematic review demonstrated a paucity of evidence to support ambulation as an adequate prophylaxis to prevent VTE. We found 16 studies since 1951 that studied ambulation to prevent VTE; only one-quarter were rated of good quality and only 1 received the highest rating of excellent. While we planned to conduct a meta-analysis, heterogeneity of the studies in our review prevented this aim. Also, ambulation definitions were diverse, and quantifying any therapeutic ambulation dose was impossible. Only 6 studies were RCTs; 3 had sample sizes below 100 and the largest trial (N = 408) defined ambulation as dorsal and plantar flexion for 1 to 2 minutes every hour. The highest quality study did quantify ambulation and conducted a secondary analysis to compare VTE rates with and without pharmacologic prophylaxis. While it is clear that the patients achieving autonomous walking in that study had a lower rate of VTE it is unclear if there were uncontrolled variables to account for this difference. The study is not an RCT, but relied on retrospective analysis of an RCT for the use of pharmacologic VTE prophylaxis, which demonstrated a substantial effect in the study. The study conclusion was that the lowest rate of VTE occurs in patients who can ambulate > 10 meters independently and receive 40 mg enoxaparin and, even then, the VTE incidence was 3.3%. Ambulation without pharmacologic prophylaxis led to a VTE rate of 10.6%.[41] The only other well-conducted RCT[40]

was primarily investigating the ability to walk after major oncologic resection, but did observe no difference in DVT events between groups.

We found that ambulation or mobilization was commonly reported as a therapeutic prophylaxis against VTE, particularly in combination with pharmacologic and mechanical VTE prophylaxis. Most concerning is that ambulation is often a cited reason to discontinue pharmacologic VTE prophylaxis. At our hospital, residents perceived that independently ambulating patients did not need pharmacologic prophylaxis for VTE.[19,20,42] The evidence for pharmacologic VTE prophylaxis is overwhelming and has been demonstrated in nearly every applicable in-patient population. To our knowledge, no group has critically examined the evidence to support ambulation as a VTE prevention tool.

Immobility is a risk factor for development of VTE; however, to our knowledge, mobility has never been shown to reduce VTE events. Many of the major guidelines recommend early ambulation for VTE prevention. For example, the American College of Chest Physicians recommend early ambulation as the only prophylactic measure needed for low-risk non-orthopedic surgical patients, as measured by the Caprini or Rogers risk assessment tool.[43] Our results challenge this recommendation and the conclusions of many studies in this review. This is not to say that ambulation in medical and surgical inpatients is useless. Immobility has many deleterious effects and hospitalized patients should be actively encouraged to ambulate. Based on our results, we caution the use of ambulation as the sole prophylaxis for VTE prevention, or as the impetus to hold pharmacologic VTE prophylaxis while patients are in a hypercoagulable state due to illness.

While diagnostic and preventative practices for VTE have changed over time, we searched decades back because the concept of ambulation is long-lived and we needed to find where the myth originated. As early as 1951, Leithauser described the “abuse of ambulation.”[15] The authors 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.” Several studies in our review described sitting or

standing as ambulatory events.[35,38] Rather, ambulation should be prescribed by the attending physician, including timing, frequency, and duration and monitored to ensure the patient undertakes it. The results of our review suggest this has never been done in a rigorous fashion. While many case-series report early ambulation is effective in preventing VTE, we specifically excluded case-series secondary to the low quality evidence they provide and the lack of external validity. Similarly, a case-control study reported that ambulating before day 2 post-surgery had a protective effect against VTE based on a multivariate logistic regression analysis; however, ambulation was not evaluated as an intervention to prevent VTE.[44]

It was challenging to conclude that most of the studies in our review qualified as describing early ambulation, or were rigorously conducted. Cassidy counted getting up to use the washroom as one of 3 required mobilization events,[34] and Sorbello failed to audit patients sitting or standing within 24 hours to ensure they were achieving it.[38] Two notable studies do attempt to quantify ambulation. Chandreasekran divided patients into sitting, walking 1-5 meters, or walking >5 meters. In the fifteen patients walking >5 meters no VTEs were seen.[32] Yet this study is a retrospective cohort and suffers from all the challenges of the study design.

While our search was comprehensive, our review was limited by the quality of the literature. We rated most of the included studies 'poor' or 'fair.' Again, the RCTs were small and devoid of rigorous methodology. Most studies failed to define the quality and quantity of ambulation. Older studies either did not report or did not use pharmacologic VTE prophylaxis. Therefore, the results must be considered in the modern practices of VTE prevention, which include pharmacologic VTE prophylaxis in most hospitalized patients.

In conclusion, our systematic review failed to find high quality evidence to suggest ambulation alone is an appropriate or effective VTE prophylaxis. While some studies suggest ambulation may reduce VTEs among hospitalized patients, we could not draw conclusions about how early, how much, how vigorous, or how often ambulation should occur to effectively reduce VTE events. In the context of substantial evidence for pharmacologic prophylaxis to

prevent VTE, ambulation should not be considered an adequate VTE prophylaxis, nor should ambulation be a reason to discontinue pharmacologic VTE prophylaxis while hospitalized.

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Figure legend

Figure: Selection process for studies describing ambulation as a therapy for venous thromboembolism prevention in hospitalized patients. VTE, venous thromboembolism; ICU, intensive care unit

Table 1. Characteristics of Included Studies of Ambulation to Prevent Venous Thromboembolism

Author	Year	Country	Study Design	Patient Population	Groups	N	Male n (%)	Age mean (SD), years
Moses	1951	USA	Retrospective Cohort	Surgery	Control Bicycle Exercise	74 74	NR NR	NR NR
Flanc	1969	England	Retrospective Cohort	Surgery	Control Supervised Exercise	65 67	NR NR	NR NR
Miller	1976	USA	RCT	Medicine (Acute MI and Heart Failure)	Early Ambulation Bed Rest	21 8	NR NR	NR NR
Prerovsky	1988	Amsterdam	RCT	Medicine (Acute MI)	Active Foot Flexion Heparin Control	135 133 140	109 (81%) 101 (76%) 109 (78%)	59 (9) 58 (9) 59 (8)
Lassen	1991	Denmark	Prospective Cohort	Orthopedics (THA)	POD #4 Mobilization (Gr1) POD #9 Mobilization (Gr2) Gr2 mobilization to POD #4	35 16 19	NR NR NR	NR NR NR
Pearse	2007	USA	Retrospective Cohort	Orthopedics (TKA)	Early Mobilization Control	97 98	54 (56%) 48 (49%)	69 (NR) 69 (NR)
Vioreanu	2007	Ireland	RCT	Orthopoedic (Foot and Ankle)	Cast Immobilization Early Ambulation	29 33	20 (69%) 21 (64%)	35 (16) 37 (13)

Chandrasekaran	2009	Australia	Retrospective Cohort	Orthopedics (TKA)	Before Ambulation Protocol After Ambulation Protocol	50 50	21 (42%) 24 (48%)	73 (NR) 71 (NR)
Sorbello	2009	Australia	RCT	Medicine (Stroke)	Standard of Care Early Mobilization	33 38	16 (48%) 22 (58%)	75 (10) 75 (15)
Amin	2010	France	Secondary Analysis of RCT	Medicine	Ambulatory Non-Ambulatory	607 447	317 (52%) 226 (47%)	72 (11) 75 (10)
Frantzides	2010	USA	Retrospective Cohort	General Surgery (Bypass)	Ambulation Protocol Heparin Protocol	1257 435	NR NR	NR NR
Cassidy	2014	USA	Retrospective Cohort (NSQIP)	Surgery	Before VTE QI Protocol After VTE QI Protocol	1569 1323	NR NR	NR NR
Bhatt	2015	Ireland	Case-Control	General Surgery	Control Exercise Program	30 30	18 (60%) 17 (57%)	61 (15) 61 (14)
Wang	2016	China	RCT	Orthopedics	Control Active Ankle Movements	78 96	65 (83%) 78 (81%)	54 (6) 52 (7)
Karic	2017	Norway	Prospective Cohort	Neurosurgery (Aneurysmal Repair)	Control Early Mobilization	77 94	28 (36%) 28 (30%)	54 (25-79)† 57 (25-81)†
de Almeida	2017	Italy	RCT	General Surgery	Control Early Mobilization	54 54	22 (41) 21 (39)	62 (51-68)† 61 (53-70)†

SD, standard deviation; NR, not reported; RCT, randomized control trial; MI, myocardial infarction; THA, total hip arthroplasty; POD, post-

operative day; TKA, total knee arthroplasty; NSQIP, National Surgical Quality Improvement Program; VTE, venous thromboembolism; QI, quality improvement

*Patients served as own control

†Median

Table 2. Results of Included Studies of Ambulation to Prevent Venous Thromboembolism

Author	Study Size	Ambulatory Group Description	Ambulation Quantified?	Comparison Group Description	Chemical VTE Prophylaxis	Outcome and Definition	Results		Author Conclusions
Moses	148	Forced respirations and 2 min bicycle exercise qD or BID while awake	No	Standard of Care	NR	VTE Clinical	Amb Control	0% 5%	Bicycle/Deep breathing reduce thrombotic complications
Flanc	132	Supervised exercise six times a day with nursing reminders to exercise	No	Standard of Care	NR	DVT ^{125}I-Fibrinogen	Amb Control	25% 35%	Strain on hospital resources and only benefit was in the elderly
Miller	29	Sitting and standing at the bedside for 30 minutes TID; ate meals while sitting	No	Five days of bed rest with leg exercises hourly	No	^{125}I-Fibrinogen	Amb Control	10% 63%	Early mobilization program reduces the incidence of venous thrombosis in acute MI
Prerovsky	408	Dorsal and plantar flexion for 1-2 mins qHr while awake	No	Standard of Care without chemical VTE prophylaxis	No†	DVT ^{125}I-Fibrinogen	Amb Heparin Control	5.2% 9.0% 13.6%	Moderate lower limb exercise is the simplest measure to prevent VTE
Lassen	70	Mobilized from post-operative day four	No	Mobilized from post-operative	Yes	DVT	Amb	21%	Patients may lose benefit of chemical VTE prophylaxis if

		onward		day nine onward		Phlebography	Control	75%	they are not mobilized
Pearse	205	VTE prevention protocol including < 24 hr mobilization	No	Routine ambulation on POD #2	Yes	DVT Doppler	Amb Control	1% 28%	Early mobilization reduces radiographic DVT
Vioreanu	62	Custom made removable fiberglass cast with ankle exercises TID for 10 min	No	Non-removable fiberglass cast for 6 weeks	NR	VTE Clinical	Amb Control	0% 7%	Post-operative immobilization may increase DVT risk
Chandrasekaran	100	Mobilized with first 24 hr, at least BID, 15-30 min, by physiotherapists	Yes (Sitting, 1-5m, >5m)	Routine out of bed to chair and walking POD #2	Yes	VTE Doppler/Clinical	Amb Control	16% 38%	Early mobilization reduces post-operative DVT, particularly if > 5m (No VTE in 15 patients)
Sorbello	71	Sitting or standing within 24 hrs for 6 days with aid of nurse or physiotherapist	No	Standard of Care	NR	VTE NR	Amb Control	0% 0%	No difference in complications after initiation of early mobilization
Amin	1054	Ability to attain autonomous walking distance > 10 meters	Yes	Did not attain autonomous walking > 10 m	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

Frantzides	1692	VTE prevention protocol including ambulation within 2 hrs	No	Standard of Care with Enoxaparin	Yes (Control Only)	VTE NR	Amb Control	0.5% 2.7%	Early ambulation as part of a comprehensive protocol obviates need for chemical prophylaxis except in high-risk patients
Cassidy	2892	New comprehensive VTE prevention protocol including mobilization TID	No	Prior to protocol with no pre-defined practice	Yes, according to risk assessment	VTE NSQIP	Amb Control	3% 0.8%	Post-operative mobilization program, risk stratification and electronic recommendations reduce VTE
Bhatt	60	BID exercise program with pedal exerciser or POD#2 or when able to sit	Yes	Standard of Care	NR	VTE Clinical	Amb Control	0% 0%	No impact on VTE but reduced post-operative infectious complications
Wang	174	Dorsal and plantar flexion for 30x/minute, 20x/day in first 7 post-operative days	No	Standard of Care	NR	DVT Doppler/Clinical	Amb Control	7.6% 18.4%	Significant reduction in all DVTs but no difference in symptomatic DVTS (2.2% v. 3.9%)
Karic	171	Progressive mobilization from HOB elevation to sitting,	No	Standard of Care	Yes	VTE Clinical	Amb Control	4.2% 3.8%	No impact on VTE but reduced post-operative vasospasm

		standing and walking to restroom							
de Almeida	108	Twice daily exercise program based on patient's functional ability	Yes	Once daily exercise program	NR	DVT Clinical	Amb Control	1.8% 0%	Primary outcome was ability to walk but no difference in DVT

VTE, venous thromboembolism (pulmonary embolism and/or deep vein thrombosis); qD, daily; BID, twice daily; NR, not reported; Amb, ambulation; DVT, deep vein thrombosis; TID, three times daily; MI, myocardial infarction; qHr, hourly; POD, post-operative day; NSQIP, National Surgical Quality Improvement Program; HOB, Head of bed

*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 randomized to receive placebo, enoxaparin 40 mg or 20 mg once daily

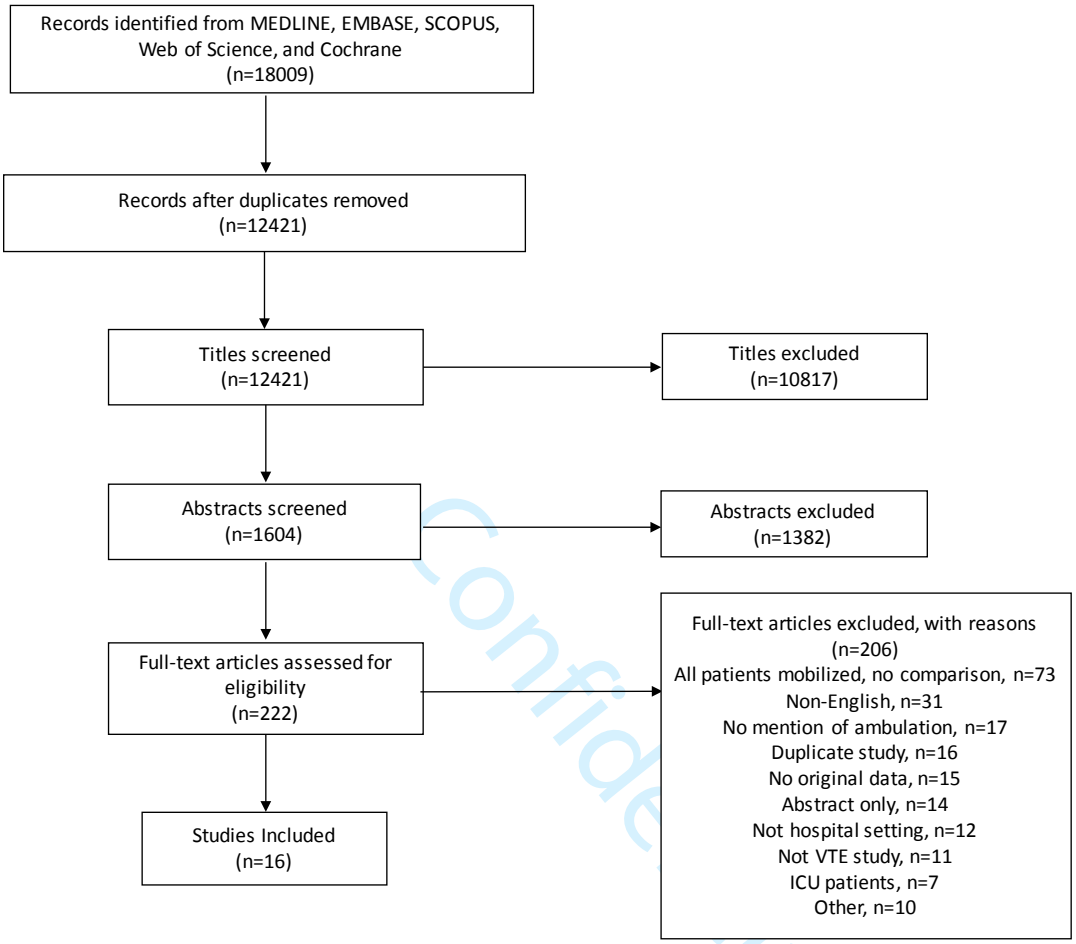
Table 3. Quality of Included Studies and Assessment of Bias

Author	Year	Study Design	Measure				Score	Overall Quality[a]
			Quality of Reporting	External Validity	Internal Validity	Power		
Moses	1951	Retrospective Cohort	2	1	1	0	4	Poor
Flanc	1969	Retrospective Cohort	7	2	6	0	14	Fair
Miller	1976	RCT	5	1	6	0	12	Poor
Prerovsky	1988	RCT	6	2	6	0	14	Fair
Lassen	1991	Prospective Cohort	3	1	4	0	8	Poor
Pearse	2007	Retrospective Cohort	9	0	6	0	15	Fair
Vioreanu	2007	RCT	7	3	6	0	16	Fair
Chandrasekaran	2009	Retrospective Cohort	8	1	8	0	17	Fair
Sorbello	2009	RCT	10	3	7	0	20	Good
Amin	2010	Secondary Analysis of RCT	11	3	9	0	23	Good
Frantzides	2010	Retrospective Cohort	7	3	4	0	14	Fair
Cassidy	2014	Retrospective Cohort (NSQIP)	8	3	8	0	19	Good
Bhatt	2017	Case-Control	8	2	6	0	16	Fair
Wang	2016	RCT	8	1	9	0	18	Fair
Karic	2017	Prospective Cohort	8	3	6	1	18	Fair
de Almeida	2017	RCT	11	3	11	1	26	Excellent

RCT, randomized control trial; NSQIP, National Surgical Quality Improvement Program

[a] Scale for quality scores: poor: ≤ 14; fair: 15 to 19; good: 20-25; excellent: 26-28

Figure. Study Selection Flow Diagram



Ambulation and VTE Prevention in Hospitalized Patients: A Systematic Review

APPENDIX A. Study Protocol

BACKGROUND

Venous thromboembolism (VTE), comprised of deep venous thrombosis (DVT) and pulmonary embolism (PE), is the formation of blood clots in the large veins of the lower limbs, pelvis, or lungs obstructing blood flow (1). It is diagnosed clinically, blood d-dimer levels and confirmed with a Doppler ultrasound. If left untreated, thrombi can propagate and embolize to distant sites, with the highest risk posed on pulmonary arteries, a life-threatening complication. An estimated 900,000 Americans are affected by VTE annually (2), and 10-30% die within a month of diagnosis (2). In addition to many well-established modifiable and non-modifiable risk factors for thrombosis development, patients who are hospitalized are particularly known to be at a great risk of morbidity and mortality due to thrombosis (3,4).

A number of thrombosis prevention measures for hospitalized patients such anticoagulation and pneumatic calf compressors have been widely used due to evidence of effectiveness. Moreover, ambulation remains the first and most recommended step for thrombosis prevention, even in hospitalized patients and post-operative patients in particular. This is based on the association of VTE with long distance travel, first identified in the 1950's, that was attributed to venous stasis; a component of Virchow's classic triad in the pathogenesis of thrombus formation (5). For a traveler, who is otherwise healthy without any risk factors for thrombosis development, ambulation may be sufficient (6). However, this remains questionable for hospitalized patients who are likely to have multiple risk factors for thrombosis. Moreover, the hospitalized population is at a risk of falls with serious consequences during ambulation. Therefore, weighting of risks and benefits of ambulation for thrombosis prevention in hospitalized patients is essential prior to recommending it.

In the era of evidence based medical practice, and given the high prevalence of thrombosis in hospitalized patients, the complexity of thrombosis pathogenesis and the variability of risk factors in different populations, it is imperative to identify and assess the level of evidence that supports ambulation as a preventive measure against thrombosis in hospitalized patients. Up to our knowledge, there are currently no published systematic reviews that assess this.

OBJECTIVES

The objective of this systematic review is to assess the comparative effectiveness of ambulation compared to other commonly used measures/ standards of care (namely; anticoagulation or calf compressors) as a preventive measure for thrombosis prevention in all hospitalized patients using evidence from both observational studies and randomized controlled clinical trials (RCTs).

METHODS

Ethical approval is not required and will not obtained.

a. Criteria for considering studies for this review

Types of studies:

Both observational studies and RCTs published in English will be considered for review. Studies must compare ambulation to either no preventive measure or any other prevention modality such as anticoagulation or pneumatic calf compressors in an acute care setting. Case-series reports, studies that do not specify ambulation, and those done in outpatient, intensive care unit or rehabilitation settings will be excluded. We will not limit our studies to any publication year.

Types of participants:

We will include studies that enrolled hospitalized patients of any age group. We will not limit our selection based on indication of hospital admission, disease process, or length of hospital stay. Both surgical and medical patients will be included. Patients with known risk factors such as obesity or thrombophilas will be included for subgroup analysis.

Types of intervention:

Any indicator of movement (ambulation, exercise, physiotherapy) with the intention of thrombosis prevention will be considered. Ambulation for any distance, duration, frequency, assisted or not, will be included. Further, for surgical patients, studies with both early and late ambulation will be included.

Types of outcome measures:

Primary outcomes: Reported in-hospital or post discharge venous thrombosis in any site will be included in the review. Any diagnostic criteria or diagnostic modality (clinical, d-dimer, Doppler, spiral CT) will be accepted if well described in the study.

Secondary outcomes: We will include mortality, and falls or any associated complication of ambulation as secondary outcomes.

b. Search methods for identification of studies

Electronic searches will be conducted in MEDLINE using PubMed, EMBASE, Cochrane, Web of Science, and Scopus. Additionally, hand searching for articles and reference lists will be used. We will not search the gray literature. The concepts, "Ambulation," "Thrombosis," and "Prevention" will be used to build our search strategy with the help of an informationist.

c. Search strategies by database

See Appendix B.

d. Data collection and analysis

Selection, Data extraction and management

All yielded articles from all databases will be imported into DistillerSR, where 2 independent reviewers will complete title and abstract screening to identify relevant articles. Full text articles will be retrieved for agreed upon articles to assess for eligibility. DistillerSR forms will then be used for data abstraction.

Assessment of risk of bias in included studies

Selected observational studies will be assessed for risk of bias and confounding using the Newcastle-Ottawa instrument, and RCTs will be assessed using the tool provided in the Cochrane Handbook for Systematic Reviews of Interventions.

REFERENCES

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APPENDIX B. Search Strategies by Database

The following search strategy will be used for MEDLINE:

1	Search ("prevention and control" [Subheading] OR "Secondary Prevention"[Mesh] OR "Primary Prevention"[Mesh:noexp] OR prevent* [tiab] OR reduc* [tiab])
2	Search Venous thrombosis [mh] OR thromboembolism [mh] OR thrombosis [mh:noexp] OR pulmonary embolism [mh:noexp] OR thromboprophyla* [tiab] OR thrombus*[tiab] OR thrombolic* [tiab] OR thromboemboli* [tiab] OR thrombos* [tiab] OR embol* [tiab] OR dvt* [tiab] OR vte [tiab] OR “pulmonary embolism” [tiab] OR “blood clot” [tiab] OR “vein thrombosis” [tiab] OR “deep vein thrombosis” [tiab] OR “venous thromboembolism” [tiab] OR phlebothrombosis [tiab] OR emboli* [tiab]
3	Search "Early Ambulation"[Mesh] OR "Rehabilitation"[Mesh:NoExp] OR "Exercise Therapy"[Mesh] OR "Walking"[Mesh] OR "Exercise"[Mesh] OR walk* [tiab] OR exercis* [tiab] OR ambulat* [tiab] OR rehabilit* [tiab]
4	Search animals [mh] NOT humans [mh]
5	Search (#1 AND #2 AND #3) NOT #4

The following search strategy will be used for EMBASE:

1	'deep vein thrombosis'/exp OR 'deep vein thrombosis' OR 'vein thrombosis'/exp OR 'vein thrombosis' OR 'thrombosis'/exp OR 'thrombosis' OR 'thromboembolism'/exp OR 'thromboembolism' OR 'lung embolism'/exp OR 'lung embolism' OR thromboprophyla*:ab,ti OR thrombus*:ab,ti OR thrombolic*:ab,ti OR thromboemboli*:ab,ti OR thrombos*:ab,ti OR embol*:ab,ti OR dvt*:ab,ti OR vte:ab,ti OR ((pulmonary NEAR/3 embolism):ab,ti) OR 'blood clot':ab,ti OR ((vein NEAR/3 thrombosis):ab,ti) OR 'deep vein thrombosis':ab,ti OR 'venous thromboembolism':ab,ti OR phlebothrombosis:ab,ti OR emboli*:ab,ti
2	'mobilization'/exp OR 'walking'/exp OR 'kinesiotherapy'/exp OR 'rehabilitation'/de OR walk*:ab,ti OR ambulat*:ab,ti OR exercis*:ab,ti OR rehabilit*:ab,ti
3	'prevention and control'/exp OR 'primary prevention'/exp OR 'secondary prevention'/exp OR prevent*:ab,ti OR reduc*:ab,ti
4	#1 AND #2 AND #3
5	'animal'/exp NOT 'human'/exp
6	#4 NOT #5

The following search strategy will be used for Cochrane:

#1	MeSH descriptor: [Primary Prevention] explode all trees
#2	MeSH descriptor: [Secondary Prevention] explode all trees
#3	#1 or #2 or prevent* or reduc*
#4	MeSH descriptor: [Venous Thrombosis] explode all trees
#5	MeSH descriptor: [Thromboembolism] explode all trees
#6	MeSH descriptor: [Thrombosis] this term only

#7	MeSH descriptor: [Pulmonary Embolism] this term only
#8	"deep vein thrombosis" or "vein thrombosis" or thromboprophyla* or thrombus* or thrombolic* or thromboemboli* or thrombos* or emboli* or dvt* or vte or pulmonary near/3 embolism or vein near/3 thrombosis or "blood clot" or phlebothrombosis or "venous thromboembolism"
#9	#4 or #5 or #6 or #7 or #8
#10	MeSH descriptor: [Early Ambulation] explode all trees
#11	MeSH descriptor: [Rehabilitation] explode all trees
#12	MeSH descriptor: [Exercise] explode all trees
#13	MeSH descriptor: [Walking] explode all trees
#14	#10 or #11 or #12 or #13 or walk* or exercis* or abmulat* or rehabilit*

The following search strategy will be used for Web of Science:

TS=("deep vein thrombosis" OR "vein thrombosis" OR thromboprophyla* OR thrombus* OR thrombolic* OR thromboemboli* OR thrombos* OR emboli* OR dvt* OR vte OR pulmonary NEAR/3 embolism OR vein NEAR/3 thrombosis OR "blood clot" OR phlebothrombosis OR "venous thromboembolism")

AND

TS=(ambulat* OR walk* OR exercis* OR rehabilitat* OR mobiliza*)

AND

TS=(prevent* OR reduc*)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC

The following search strategy will be used for Scopus:

(((TITLE-ABS-KEY ("deep vein thrombosis" OR "vein thrombosis" OR thromboprophyla* OR thrombus* OR thrombolic* OR thromboemboli* OR thrombos* OR emboli* OR dvt* OR vte) OR TITLE-ABS-KEY (pulmonary W/3 embolism OR vein W/3 thrombosis OR "blood clot" OR phlebothrombosis OR "venous thromboembolism")))

AND

(TITLE-ABS-KEY (ambulat* OR walk* OR exercis* OR rehabilitat* OR mobiliza*)))

AND

(TITLE-ABS-KEY (prevent* OR reduc*))