Ambulation after Deep Vein Thrombosis: A Systematic Review

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ABSTRACT

Purpose: To systematically review the effects of early ambulation on development of pulmonary embolism (PE) and progression or development of a new thrombus in patients with acute deep vein thrombosis (DVT).

Methods: Medline, PubMed, CINAHL, EMBASE, PEDro, and Cochrane Library databases were searched from inception to June 2008. Study quality was appraised using the Jadad and PEDro scales. Meta-analyses were reported as relative risks (RR) and 95% confidence intervals (CI).

Results: Four randomized trials were accepted. For development of a PE, the pooled relative risks for *ambulation and compression* versus *bed rest and compression* (RR = 0.63, 95% CI: 0.34–1.19) and for *ambulation and compression* versus *bed rest alone* (RR = 1.36, 95% CI: 0.57–3.29) were not significant. For progression of an existing thrombus or development of a new thrombus, the independent relative risks for *ambulation and compression* versus *bed rest and compression* (RR = 0.39, 95% CI: 0.13–1.14) and for *ambulation and compression* versus *bed rest alone* (RR = 0.56, 95% CI: 0.20–1.57) were also not significant.

Conclusions: Given the clinical benefits of mobility, and because there was no significant difference between ambulation and bed rest for risk of developing a PE or development and progression of a new DVT in any of the studies, clinicians should be confident in prescribing ambulation in this population.

Key Words: acute deep vein thrombosis, ambulation, pulmonary embolism, venous thrombosis, walking

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RÉSUMÉ

Objectif : Analyser systématiquement les effets du lever précoce sur la survenue d'une embolie pulmonaire (EP) ainsi que sur l'évolution d'un thrombus existant ou la formation d'un nouveau thrombus chez les patients souffrant de thrombose veineuse profonde (TVP) aiguë.

Méthodologie : On a consulté les données consignées dans les bases Medline, PubMed, CINAHL, EMBASE, PEDro et Cochrane Library depuis leur création jusqu'en juin 2008. La qualité des études a été évaluée au moyen des échelles de Jadad et de PEDro. Les méta-analyses ont été rapportées en fonction du risque relatif (RR) et d'un intervalle de confiance (IC) à 95 %.

Résultats : Quatre (4) essais avec répartition aléatoire ont été pris en compte. En ce qui concerne la survenue d'une EP, les risques relatifs combinés associés au lever et à la compression par rapport à l'alitement et à la compression (RR : 0,63 [IC à 95 % : 0,34–1,19]), de même qu'au lever et à la compression par comparaison avec l'alitement (RR : 1,36 [IC à 95 % : 0,57–3,29]) n'étaient pas significatifs. En ce qui a trait à l'évolution d'un thrombus existant ou à la formation d'un nouveau thrombus, les risques relatifs individuels associés au lever et à la compression par rapport à l'alitement et à la compression (RR : 0,39 [IC à 95 % : 0,13–1,14]), de même qu'au lever et à la compression par comparaison avec l'alitement (RR : 0,56 [IC à 95 % : 0,20–1,57]) n'étaient pas non plus significatifs.

Conclusions : Compte tenu des bienfaits cliniques de la mobilité et de l'absence d'écart significatif entre le lever et l'alitement sur les plans du risque d'EP, de l'évolution d'un thrombus existant ou de la formation d'un nouveau thrombus dans l'ensemble des études, les cliniciens ne devraient pas hésiter à recommander le lever aux patients.

Mots clés : embolie pulmonaire, lever, marche, thrombose veineuse, thrombose veineuse profonde aiguë

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BACKGROUND

Deep vein thrombosis (DVT) is described as a blood clot in the deep venous system, most commonly found in the legs. The clot may result in damage to the venous valves, causing reflux and a condition known as post-thrombotic syndrome (PTS). The blood clot or a component of it may break off and travel to the lungs, resulting in a pulmonary embolism (PE). While both PTS and PE may result in significant morbidity, PE may also be fatal. In fact, the Surgeon General of the United States has recently reported that approximately one in five individuals with PE die almost immediately and that a further 40% die within three months.¹ Together, these three conditions (DVT, PTS, and PE) are known as venous thromboembolism (VTE).

It is estimated that VTE is the third most common vascular disease, after coronary artery disease and stroke, and that the incidence of DVT in Canada is 45,000 patients per year.² In the 2007 publication *Patient Safety in Canada: An Update*, the Canadian Institute for Health Information estimated that 3.6 patients per 1,000 experience a DVT or PE following hospital admission.³ This incidence rate increases substantially with age, to 6.2/1,000 for patients 80 years or more. VTE is known as the “silent killer”; DVT may often be asymptomatic, and death from ensuing PE may occur very rapidly, before the diagnosis is suspected. Thus, incidence rates may actually underestimate the true occurrence of VTE.

In 1856, Virchow first described the pathophysiology related to the formation of a DVT. The triad of events includes venous stasis, damage to the endothelial lining of the blood vessel, and activation of circulating clotting factors. It is thought that two of these factors must be present for a DVT to develop.⁴

Physiotherapists frequently see in-patients diagnosed with a DVT. From a mobility perspective, management of such patients is controversial.^{5,6} Conservative management of DVTs using strict immobilization is based on the theoretical assumption that early ambulation and active range of motion would cause the thrombus to dislodge proximally, migrating to the pulmonary circulation and causing a PE, with potential for significant morbidity and mortality.⁷ However, this assumption has never been tested empirically.^{6,8,9}

A conservative treatment approach of bed rest can lead to secondary complications and can thus be detrimental for patients, as acknowledged by Dock in 1944.¹⁰ The impact of prolonged immobility was also noted by an English pathologist who identified an increase in the incidence of fatal PE in individuals seated in cramped underground shelters for prolonged periods during World War II.¹¹ More recently, prolonged immobility has been associated with DVT following

long airline flights and extended periods of computer work (also known as “e-thrombosis”).¹²

The overall management of DVT has witnessed considerable advances in therapies over the past several years. Traditionally, patients diagnosed with DVT were medically managed using unfractionated heparin and strict immobilization. More recently, the standard medical treatment of DVT includes pharmacological management with low-molecular-weight heparin (LMWH) and compression therapy to avoid venous stasis.^{5,13}

Early mobilization is an accepted treatment following many surgical procedures. It has been suggested recently that early ambulation following diagnosis of a DVT may provide the usual benefits of exercise with no additional risk that the DVT will migrate and cause a PE.¹⁴ It is an important clinical question to determine whether early ambulation following diagnosis of a DVT is a safe treatment approach with respect to development of a PE or development and/or progression of a thrombus. Thus, our purpose was to systematically review the effects of early ambulation, compared to bed rest, on the development of a PE and the progression of an existing thrombus or the development of a new thrombus in patients with acute DVT.

METHODS

Search Strategy

The search strategy was developed with the assistance of a university librarian. The following electronic databases were searched for materials published up to and including June 2008: MEDLINE, PubMed, CINAHL, EMBASE, Cochrane Library, and PEDro. Key words included “acute deep vein thrombosis,” “venous thrombosis,” “pulmonary embolism,” “ambulation,” and “walking.” A secondary search of the reference lists of all articles retrieved was also conducted. Papers were identified for potential review from the secondary search if their titles suggested relevance to our research purpose.

Selection of Articles

A title and abstract review of the initial search results was carried out independently by each of the three reviewers. There was unanimous agreement among the three reviewers in selecting full articles on studies judged potentially eligible for review. Studies were included in the systematic review if they met the following criteria: randomized controlled trial (RCT), acute care patients >18 years of age, English language, and standard assessment measures for the diagnosis of a PE or development or progression of a thrombus (for PE: ventilation: perfusion scans, pulmonary angiography, and spiral computerized tomography; for DVT: duplex sonography,

venography, compression sonography, and magnetic resonance imaging).

Data Extraction

Each of the three reviewers independently extracted data from all selected trials using a data-extraction and critical appraisal form modified from a previous systematic review.¹⁵ Data extracted included general study information; quality assessment, including randomization; numbers of participant dropout and withdrawals; and descriptions of participants, interventions, and outcome measures. The three reviewers were able to reach consensus regarding the data extraction for all studies.

Quality Assessment

Each reviewer independently assessed the quality of each study before the review team met to reach consensus. Reviewers considered the sources of bias that have a major influence on the magnitude of effect size in clinical trials: unconcealed randomization, blinding, and dropouts and withdrawals. The quality of each study was rated using formal quality scores based on two scales: a 0–5 scale developed by Jadad et al.¹⁶ and a 0–10 scale (PEDro) suggested by Maher et al.¹⁷ The Jadad scale scores studies based on randomization, blinding, and dropouts or withdrawals, while the PEDro scale assesses internal validity based on randomization, blinding, homogeneity of study groups, and outcome measures. The reliability of both of these scales has been established.^{17,18} The scores presented in this report represent the consensus of the three reviewers for each scale; higher scores indicate higher quality.

Analysis

Meta-analyses were conducted using a random effects model from the software package Comprehensive Meta-analysis, version 2 (Biostat, Englewood, NJ). Relative risk (RR) and 95% CI were calculated for development of a PE, progression of an existing thrombus, and development of a new thrombus. The level of significance was established as $p < 0.05$. A relative risk is the risk that an event (e.g., a DVT or PE) will occur in one group (e.g., intervention group) compared to the risk in another group (e.g., control group). Relative risk is thus expressed as a ratio. In this case, a ratio of 1.00 indicates that the risks of the event's occurring are equal in the two groups; ratios less than 1.00 indicate less risk in the intervention group; and ratios greater than 1.00 indicate greater risk in the intervention group.

The following is a simplified example of how RR is calculated. Assume that an intervention group and a control group each had 50 subjects. In the intervention group, 6 individuals developed a PE and 44 did not; in the

control group, 18 individuals developed a PE and 32 did not. The mathematical calculations are as follows:

Risk for intervention group $6/50 = 0.12$

Risk for control group $18/50 = 0.36$

Relative risk (RR) $0.12/0.36 = 0.33$

Thus the intervention group's risk of a PE is one-third that of the control group.

RESULTS

The primary literature search yielded 299 citations. After duplicates were excluded, 101 studies were screened for possible inclusion. An additional five citations from the secondary review were also screened. Four studies were finally accepted for inclusion in this review (see Table 1).^{6,8,9,19} We obtained additional data from one⁶ of two reports.^{6,20}

Quality scores for the Jadad scale for these four studies ranged from 1 to 3 of a possible 5, with a mean score of 2. All reviewers gave each paper the same score. All four studies received a score of 7/10 on the PEDro scale from each of the three reviewers. The most common internal validity error on the Jadad scale was the lack of double blinding. On the PEDro scale, the items most frequently missed were blinding of subjects, caregivers, and outcome measure assessors. It should be noted that it is difficult to double-blind studies in which the interventions are generally easily differentiated by both patients and caregivers (e.g., bed rest vs. ambulation).

Two of the studies compared *ambulation with compression* to *bed rest alone*,^{6,8} while the other two compared *ambulation and compression* to *bed rest and compression*.^{9,19} Subjects in all four studies had proximal DVT and were treated as in-patients, and all received anticoagulation therapy upon diagnosis of the DVT. Two of the four studies included only patients with symptomatic DVTs^{6,9}; the others did not indicate whether the subjects had symptomatic or asymptomatic DVTs.^{8,19} Ambulation was started immediately following randomization in three of the four studies^{6,8,19} and on the day following randomization in the fourth.⁹ The mean age for the groups in the studies ranged from 52 to 66 years (see Table 1). Three of the four studies reported the incidence of previous VTE in their subjects, ranging from 23% to 33%.^{6,8,9} Another risk factor for VTE, malignancy, ranged from 7% to 22% in the three studies that reported this condition.^{8,9,19} Interestingly, at study entry, between 47% and 70% of subjects were also diagnosed with a PE, the majority of which were asymptomatic. The follow-up evaluations for the outcome measure of PE were completed on day 4–12 in these four studies. Progression of the thrombus or presence of a new thrombus was

Table 1 Summary of RCT Studies Included

Primary Author (Year)	Description of Groups	Sample Size	Interventions* [mean age/group]	Results	Jadad Score	PEDro Score
Achwanden (2001) ⁸	Acute proximal DVT, hospitalized ≥ 4 days	N= 129	Group 1 (n= 60): Bed rest for 4 days [66 yrs] Group 2 (n= 69): Ambulation > 4 hrs/day (supervised) and compression [64 yr]	Development of new PE: • Group 1: 6/60 new PE on day 4 • Group 2: 10/69 new PE on day 4 (Not significantly different)	2	7
Blattler** (2003) ⁶	Symptomatic outpatients admitted with proximal DVT	N= 53	Group 1 (n= 18): Ambulation and compression (bandages) [60 yrs] Group 2 (n= 18): Ambulation and compression (stockings) [59 yrs] Group 3 (n= 17): Bed rest [52 yrs]	Development of new PE: • 1 new PE/group (day 9)—no difference between groups Progression of thrombus: • Groups 1 and 2: 6/27 • Group 3: 4/10 ($p < 0.01$)	1	7
Junger*** (2006) ¹⁹	Inpatients and patients admitted with proximal DVT	N= 102	Group 1 (n= 50): Bed rest $\times$ 5 days and compression [61 yrs] Group 2 (n= 52): Ambulation and compression [60 yrs]	Development of new PE: • Group 1: 8/50 new PE (day 10–12) • Group 2: 3/52 new PE (day 10–12) (Not significantly different) Progression of thrombus or new thrombus: • Group 1: 10/50 • Group 2: 4/52 ($p = 0.088$; not significantly different)	3	7
Schellong (1999) ⁹	Inpatients with symptomatic proximal DVT	N= 122	Group 1 (n= 59): Bed rest $\times$ 8 days and compression (plus elevation) [60 yrs] Group 2 (n= 63): Ambulation and compression (elevation $\times$ 2 days) [60 yrs]	Development of new PE: • Group 1: 10/59 new PE (day 8–10) • Group 2: 14/63 new PE (day 8–10) (Not significantly different)	2	7

*All patients received anticoagulation.

**Study stopped prematurely because patients did not want to be in immobilized group.

***Study stopped prematurely because centres did not want to immobilize their patients.

assessed in only two of the trials and was completed between day 9 and day 12.^{6,19}

In the first meta-analysis (see Figure 1), *ambulation and compression* was compared to *bed rest and compression* in two studies.^{9,19} The RR for development of a new PE was 0.63 (95% CI: 0.34–1.19) in favour of the ambulation and compression group; however, the result did not reach statistical significance ($p=0.16$).

Ambulation and compression was compared to *bed rest alone* in a second meta-analysis (see Figure 2), again with two studies.^{6,8} While the pooled RR for development of a new PE (1.36; 95% CI, 0.57–3.29) favoured

the bed-rest group, it was not statistically significant ($p=0.49$).

We were able to evaluate the progression of a new thrombus or the development of a new thrombus in only two of the studies (see Figure 3).^{6,19} Individual RRs for *ambulation and compression* versus *bed rest and compression* and *ambulation and compression* versus *bed rest alone* were 0.39 (95% CI: 0.13–1.14) and 0.56 (95% CI: 0.20–1.57) respectively. While favouring the *ambulation and compression* groups, the RRs were not significant ($p=0.09$ and $p=0.27$ respectively).

Figure 1 Forest plot showing the development of a new pulmonary embolus (PE): *ambulation and compression* (A) vs. *bed rest and compression* (B). The relative risk for development of a new PE (0.63; 95% CI: 0.34–1.19) favoured the *ambulation and compression* group; however, the result did not reach significance ($p=0.16$). Sample size: Junger,¹⁹ $N=102$; Schellong,⁹ $N=122$.

Figure 2 Forest plot showing development of a new pulmonary embolus: *ambulation and compression* (A) vs. *bed rest alone* (B). The pooled RR of 1.36 (95% CI: 0.57–3.29) favoured the *bed rest* group but was not statistically significant ($p=0.49$). Sample size: Blattler,⁶ $n=53$; Aschwanden,⁸ $n=129$.

Figure 3 Forest plot showing independent relative risk for progression or development of a new DVT: *ambulation and compression* (A) vs. *bed rest alone* (B)⁶ and *bed rest and compression* (B).¹⁹ Individual RRs for *ambulation and compression* vs. *bed rest and compression* and for *ambulation and compression* vs. *bed rest alone* were 0.39 (95% CI: 0.13–1.14) and 0.56 (95% CI: 0.20–1.57) respectively. These RRs were not significant ($p=0.09$ and $p=0.27$ respectively). Sample size: Blattler,⁶ $n=53$; Junger,¹⁹ $n=102$.

DISCUSSION

The debate around whether to walk a patient with a DVT has gone on for many years. Therapists must weigh the risk that ambulation will cause a PE against the alternate treatment of bed rest, which is not without its own risks: bed rest can result in loss of aerobic capacity and decreases in strength, range of movement, and general function. How can clinicians use the evidence presented in this systematic review to aid their clinical practice? We begin by reviewing the results in more detail.

Whether *ambulation and compression* was compared to *bed rest and compression* or to *bed rest alone*, there was no significant difference in the risk of developing a PE. There was a trend favouring decreased risk from *ambulation and compression* compared with *bed rest and compression* (RR=0.63). Conversely, the trend for decreased risk appears to favour the bed-rest group in the second comparison, *ambulation and compression* versus *bed rest alone* (RR = 1.36). The latter finding may be at least partly attributed to baseline differences between the groups in the study by Aschwanden et al.⁸ Aschwanden et al. list eight risk factors for thromboembolism, including malignancy, being in bed for three or more days, and use of estrogen; of these, seven were more common among the mobility group. The exception was a history of previous thromboembolism, which was more common among the immobile group. While there was no significant between-group differences for any of the eight risk factors, the greater overall number of risk factors among the mobility group may have contributed to an increased risk of developing thromboembolism.²¹

The RRs for the progression of an existing DVT and for developing a new DVT did not reach significance, but these RRs (0.39 and 0.56 respectively) did suggest a trend favouring *ambulation and compression* over either *bed rest alone* or *bed rest with compression*.

Given that there were no statistically significant differences for development of a PE, progression of a thrombus, or development of a new thrombus between ambulation and bed rest in any of the studies, and given the well-recognized physiological benefits of mobility, it seems appropriate to suggest to clinicians that mobilizing the patient with DVT would be the better option. This idea is supported by a number of studies with lower levels of evidence.^{22–26}

In a large prospective observational registry study of 2,650 patients with acute DVT or PE, Trujillo-Santos et al. reported patient outcomes for bed rest compared to early ambulation.²² They found no difference in the incidence of PE when patients were ambulated (9 of the 1,435 patients on bed rest and 6 of the 1,215 early ambulators developed a new PE). One limitation of their study was that the patients prescribed bed rest tended to be sicker at baseline.

More recently, Manganaro et al. retrospectively examined the evolution of DVT in patients with a DVT on bed rest or mobilization.²³ All patients were on LMWH, and those who were mobilized were encouraged to walk as much as possible at least three times per day. Manganaro et al. found that the bed-rest group had a higher incidence of PE and progression of thrombotic disease at 30 days, with a hazard ratio (estimate of RR) of 4.39 (95% CI: 2.44–9.33; $p < 0.0001$). Immobilization was also an independent predictor of these clinical endpoints (hazard ratio = 2.41, 95% CI: 1.11–5.22; $p = 0.026$).

Henke et al. compared the outcomes of patients who developed a primary DVT while hospitalized to those of outpatients with a DVT who had no antecedent risk event in the previous 30 days.²⁴ Ambulation was associated with freedom from PE with an odds ratio (a method of comparing the probability of an event, in this case freedom from PE, between groups) of 2.3 (95% CI: 1.1–5.0; $p = 0.04$).

In a prospective cohort study of patients ($N = 1289$) with acute DVT treated with LMWH, compression, and immediate ambulation, Partsch reported that approximately 50% of the patients had PE on admission; two-thirds of these were asymptomatic.²⁵ Ventilation: perfusion scans repeated after 10 days identified new perfusion defects in 77 (6.0%) of the patients.

In addition, management of DVT has recently shifted from the acute care setting to treatment at home using LMWH.²⁶ The use of outpatient LMWH for the initial treatment of DVT, rather than the use of unfractionated heparin in hospital, was recommended (grade 1C recommendation) in both the seventh and eighth American College of Chest Physicians (ACCP) antithrombotic therapy guidelines.^{27,28} It is now believed that patients with DVT can be safely treated at home, with the following exceptions: massive DVT, concurrent symptomatic PE, high risk of anticoagulant-related bleeding, and presence of acute comorbid conditions that require hospitalization.² It is reasonable to assume that if patients are treated for DVT as outpatients, they will not be on strict bed rest and thus are likely doing some ambulation. Since this treatment regimen for DVT is now considered safe according to the most recent evidence-based guidelines,²⁸ it also seems reasonable that hospitalized patients with a diagnosis of DVT should be able to ambulate safely.

Furthermore, the ACCP guidelines on antithrombotic and thrombolytic therapy now recommend “early ambulation in preference to initial bed rest when this is feasible” with greater confidence.^{28(p.456S)} This recommendation, graded as 1B in the 2004 guidelines, has been raised to a 1A recommendation in the most recent guidelines.^{27,28}

There have been two previous systematic reviews examining bed rest versus early mobilization.^{20,29} The first was published in Spanish in 2003;²⁰ we attempted

to contact the author to see if the complete review was available in English, but we were not successful. Trujillo-Santos et al. included three studies in this review, two of which were also included in our systematic review.^{8,9} However, Trujillo-Santos et al. also included an interim analysis by Partsch and Blattler,³⁰ while we included the complete data set published by Blattler and Partsch in 2003.⁶ The authors of this first review concluded in their English abstract that “treatment of DVT with early mobilization rather than bed rest neither increases the rate of PE nor increases the complication rate,”^{20(p.641)} a conclusion very similar to the one we reached in the present review.

The second review was conducted more recently by Aissaoui et al.²⁹ This group included three of the four studies included in our systematic review,^{8,9,19} as well as the interim analysis by Partsch and Blattler.³⁰ In addition, Aissaoui et al. included data from the RIETE registry,²² an ongoing record of management of patients with VTE in Spanish hospitals. We did not include non-randomized designs in our meta-analysis, as recommended in the Cochrane Handbook.³¹ Despite the differences in the pool of included papers, however, Aissaoui et al. concluded that “compared with bed rest, early ambulation of patients with DVT, PE or both, was not associated with a higher risk of progression of DVT, new PE or death.”²⁹ It is interesting to see that Aissaoui et al. reached the same conclusion we did, even though they included these two different studies. And it is certainly encouraging that three independent groups, each using slightly different literature pools, have all reached the same conclusion: that there is no difference in development of new PE or progression of DVT with early ambulation compared to bed rest.

One of the limitations of our review is the small number of studies and subjects included. The methodological quality of the four RCTs was only moderate (scores of 1/5 to 3/5 on the Jadad scale, and 7/10 on the PEDro scale). However, it should be recognized that it is difficult to double-blind studies in which the interventions are easily differentiated by both patients and caregivers, and, as a result, quality scores are lower for these types of studies.

While some of the studies in our review included individuals admitted to hospital with a DVT, some also included patients who developed a DVT while in hospital. The studies do not make it clear how long the former group of subjects had their DVT prior to hospital admission; therefore, the results are difficult to generalize to patients who develop a DVT postoperatively.

A final limitation is the lack of detail in the description of factors such as ambulation and compression in the included studies. It would be preferable to have more information regarding amount of ambulation, type of compression garment, and duration of application.

CONCLUSION

Physiotherapists should use the best available evidence in designing treatment programmes for their patients. Historically, the practice has been to place patients with DVT on bed rest to reduce the risk that the thrombus will progress to a PE. The information presented in our systematic review and meta-analysis provides physiotherapists with the best available evidence on this long-standing clinical question, evidence that suggests no harm associated with early ambulation in patients diagnosed with a DVT. It should still be recognized that clinical judgment is always necessary in weighing the pros and cons of ambulation for such cases, and these patients should also be closely monitored for changes in status when being ambulated during the initial acute phase. Nevertheless, clinicians should be confident that ambulating patients with DVT does not appear to increase the risk of developing a PE, progression of an existing DVT, or developing a new DVT.

KEY MESSAGES

What Is Already Known on This Subject

There has been controversy for many years as to whether physiotherapists should walk patients who have been diagnosed with a deep vein thrombosis. The concern has been that ambulation may cause a portion of the clot in the deep venous system in the legs to break away and travel to the lung, resulting in a pulmonary embolus. Two previous systematic reviews have examined this issue, but both have methodological shortfalls and have not included complete data sets from the existing randomized control trials.

What This Study Adds

This paper presents the best available evidence on the safety of ambulating patients with DVT. This evidence suggests that in such patients, there is no difference in risk between ambulation and bed rest for development of a PE, progression of an existing DVT, or development of a new DVT.

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