Bed Rest versus Early Ambulation with Standard Anticoagulation in The Management of Deep Vein Thrombosis: A Meta-Analysis

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Abstract

Introduction

Bed rest has been considered as the cornerstone of management of deep vein thrombosis (DVT) for a long time, though it is not evidence-base, and there is growing evidence favoring early ambulation.

Methods

Electronic databases including Medline, PubMed, Cochrane Library and three Chinese databases were searched with key words of “deep vein thrombosis”, “pulmonary embolism”, “venous thrombosis”, “bed rest”, “immobilization”, “mobilization” and “ambulation”. We considered randomized controlled trials, prospective or retrospective cohort studies that compared the outcomes of acute DVT patients managed with early ambulation versus bed rest, in addition to standard anticoagulation. Meta-analysis pertaining to the incidence of new pulmonary embolism (PE), progression of DVT, and DVT related deaths were conducted, as well as the extent of remission of pain and edema.

Results

13 studies were included with a total of 3269 patients. Compared to bed rest, early ambulation was not associated with a higher incidence of new PE, progression of DVT, or DVT related deaths (RD = −0.03, 95% CI −0.05 to −0.02; Z = 1.24, p = 0.22; random effect model, Tau\(^2\) = 0.01). Moreover, if the patients suffered moderate or severe pain initially, early ambulation was related to a better outcome, with respect to remission of acute pain in the
affected limb (SMD 0.42, 95% CI 0.09 – 0.74; Z = 2.52, p = 0.01; random effect model, Tau² = 0.04). Meta-analysis of alleviation of edema cannot elicit a solid conclusion because of significant heterogeneity among the few studies.

Conclusions
Compared to bed rest, early ambulation of acute DVT patients with anticoagulation was not associated with a higher incidence of new PE, progression of DVT, and DVT related deaths. Furthermore, for the patients suffered moderate or severe pain initially, a better outcome can be seen in early ambulation group, regarding to the remission of acute pain in the affected limb.

Introduction
DVT is a common disease, with the incidence being up to 0.5/1000 person-years [1]. Due to its relatively high incidence and possible fatal complications, the treatment of DVT has long been a major concern for many physicians and surgeons. The first treatment of DVT can be dated back to 13th century, and both medical and surgical therapies had been studied and adopted in the following centuries [2].

Strict bed rest had been considered as the cornerstone of treatment of acute DVT for a long period, not only because of the concern of possible dislodging thrombosis, but also the confinement to bed with 24 hours unfractionated heparin infusion. However, this treatment was not evidence-based. More and more doctors began to recognize the risk of blood stasis associated with bed rest. Thanks to the introduction of low molecular weight heparin (LMWH) in 1990s, DVT patients can be treated as outpatients [2]. The tradition of immobilization therapy is being challenged by the growing evidence favoring early ambulation.

Several randomized controlled trials (RCTs) and prospective registries had investigated the outcomes of DVT patients treated with early ambulation or bed rest, including PE, progression of DVT, improvement of pain and edema [3, 4, 5]. Although the guideline of DVT treatment in China (2nd edition) [6] did not mention early ambulation for the patients, early ambulation under feasible circumstance was suggested in the 9th guideline of antithrombotic therapy by American College of Chest Physicians (ACCP) [7].

On the basis of the published studies so far, we performed this systematic meta-analysis to further demonstrate the influence of early ambulation versus bed rest on patients with acute DVT.

Materials and Methods
Eligibility criteria
(1) RCTs, prospective or retrospective cohort studies with good methodological design. (2) All participants were in the acute phase of DVT at recruitment. (3) Interventions were “bed rest” versus “early ambulation”, in addition to standard anticoagulation. (4) Endpoints were new PE (symptomatic or asymptomatic PE confirmed with CT scan or scintigraphy), progression of DVT (assessed by ultrasound or phlebography) or other DVT related parameters (e.g., extent of pain and edema).
Literature search

Literatures published up to November 2014 were searched in the following databases: Embase, Medline, PubMed, Cochrane Library, Sinomed, WanFangData and Chinese National Knowledge Infrastructure (CNKI). The last three were used to search for Chinese literatures. Key words included “deep vein thrombosis”, “pulmonary embolism”, “venous thrombosis”, “bed rest”, “immobilization”, “mobilization” and “ambulation”. The synonyms in Chinese were searched in Chinese databases. In addition, references of relative articles were also examined to make sure all the articles relative to our analysis were retrieved.

Study selection

Title and abstract review was first conducted to rule out the articles apparently mismatched to our eligibility criteria. Then the articles would be examined thoroughly to determine whether or not they should be included for the meta-analysis according to the eligibility criteria. Reviews, former meta-analyses and opinions about the disease were also kept for useful information. All the screening work was conducted independently by two authors, Liu and Tao. Disagreements were discussed and consulted until a consensus was made.

Statistical analysis

This meta-analysis was conducted with the software, Review Manager (RevMan) version 5.3, which is for Cochrane reviews. Publication bias was tested with visual inspection of funnel plot (in RevMan version 5.3), as well as Begg’s and Egger’s test (in Stata version 12.1). Quality assessment was conducted with risk of bias table for RCT in RevMan, and Newcastle-Ottawa Scale for cohort studies. Heterogeneity of included studies was tested with Chi² and heterogeneity index, I².

We performed the meta-analysis about endpoints consisting of new PE, progression of DVT and deaths, which were dichotomous, using the fixed effect model with Mantel-Haenszel method. Subgroup and sensitivity analyses were also conducted for heterogeneity exploration. Random effect model was used if a solid conclusion cannot be drawn. Risk Difference (RD) (in some studies, Risk Ratio was not applicable because no end events happened), 95% confidence interval (CI) and p value were calculated.

The meta-analysis about relief of pain (measured by change of visual analogue scales (VAS), in which patients specify their level of pain by indicating a position along a continuous line between two endpoints. General definition (10 as the highest score): mild pain, VAS < 3; moderate pain, VAS 4–6; severe pain, VAS 7–10.) and edema (measured by change of circumference of affected limb), of which the parameters were continuous, was performed with the fixed effect model and Inverse Variance method. Random effect model was used if subgroup and sensitivity analyses cannot settle heterogeneity issue. The standard mean difference (SMD, which standardizes the results of the studies to a uniform scale so that they can be combined), 95% CI and p value were calculated. p < 0.05 was considered statistically significant.

Results

Characteristics of included studies and quality assessment

The details of literature search strategy are provided in the supporting information (S1 Table). 1204 articles from English databases and 523 articles from Chinese databases were retrieved. After screening the titles and abstracts, 50 articles remained. When carefully examining the full texts, we excluded another 37 articles for reasons listed in the supporting information.
Finally we included 13 studies for the meta-analysis, with 10 in English and 3 in Chinese, and a total of 3269 patients. (Fig. 1)

All the studies were RCTs or cohort studies with reasonable design. The primary endpoints of all the recruited studies consisted of one or multiple of the followings: symptomatic PE, PE detectable by CT or scintigraphy, progression of DVT or DVT related deaths. 7 articles provided proper results of the secondary endpoints suitable for the meta-analysis pertaining to the extent of pain or edema of affected limb. The main characteristics of included studies are shown in Table 1. Patients in bed rest group were kept in bed for at least 3 days, and early ambulation group started exercising within 3 days after diagnosis of DVT. None of the studies found an increased incidence of PE or progression of DVT in the ambulation group.

Quality assessment of included studies was conducted with the Risk of bias table in RevMan 5.3 for RCTs (Fig. 2 and S3 Table) and Newcastle-Ottawa Scale for n-RCTs (Table 2).

Publication bias assessment
We assessed the publication bias by visual inspection of funnel plot (with RevMan 5.3) as well as Begg’s and Egger’s tests (with Stata 12.1). With visual inspection, there seem to be asymmetry in the funnel plot, indicating the possibility of publication bias (Fig. 3). To further address this problem, we also performed Begg’s and Egger’s tests, and found no significant publication bias ($p = 0.127$ in Begg’s test and $p = 0.320$ in Egger’s test) (Fig. 4). So it was likely that there were other sources of asymmetry (e.g., poor methodological quality, true heterogeneity, artefact, chance), which led to the false publication bias in the funnel plot, as illustrated in Table 10.4.a of the Cochrane Handbook for Systematic Reviews of Interventions [18].

Meta-analysis of primary endpoints
Fig. 5 shows the meta-analysis about the incidence of primary endpoints from 13 included studies. As other studies included only DVT patients, with PE patients excluded, we extracted partial data pertaining to DVT patients from Trujillo-Santos’s registry [5]. RD was employed as the effect measure, since no end events happened in 4 of the studies. The heterogeneity test ($\chi^2 = 148.16, p<0.00001, I^2 = 92\%$) indicated a significant heterogeneity among these studies. Then subgroup and sensitivity analyses were conducted to find the source of heterogeneity (Table 3).

Sensitivity analysis was carried out by leaving out one study at a time. $p_1$ evaluates the heterogeneity among included studies. $p_2$ evaluates the statistical significance level between the two interventions. If $p_1$ is less than 0.05 in a fixed effect model, it means the heterogeneity among included studies is significant and the combined result ($p_2$ value) is not solid and convincing. A random effect model should be employed to draw a more conservative and safer conclusion. According to the statistics in this table, we can draw the conclusion that compared to bed rest, early ambulation is not associated with a higher incidence of primary endpoints.

When there is significant heterogeneity among the studies, the result of a meta-analysis will not be conclusive. Subgroup and sensitivity analyses should be conducted to identify the studies that cause the heterogeneity. Or else, a random effect model should be employed to draw a more conservative conclusion. So according to Table 3, it can be elicited that compared to bed rest, early ambulation was not associated with a higher incidence of new PE, progression of DVT or DVT related death (all studies were analyzed with random effect model, $\tau^2 = 0.01$; RD-0.03, 95%CI $-0.05$ to $-0.02$; $Z = 1.24, p = 0.22$). Trujillo-Santos’s study was not the one which caused significant heterogeneity although it weighted 63.2% when using fixed effect model.
Meta-analysis of remission of pain and edema

Fig. 6 shows the meta-analysis about the remission of limb pain, measured by change of VAS during the treatment period, among the bed rest and early ambulation group. VAS is a continuous and subjective value, therefore the inverse variance method was employed. Due to the different unit system among the studies (e.g., Feng et al. used 10 as the highest score [16], while Junger et al. used 100 [3]), standard mean difference (SMD) was employed as the effect measure. Using a fixed effect model, heterogeneity test (Chi$^2 = 24.71$, df = 6, $p = 0.0004$; I$^2 = 76\%$) showed significant variance among the studies. Sensitivity analysis indicated that
Aschwanden’s study [9] was the main source of heterogeneity (Omitting this study, $\chi^2 = 5.84$, $df = 5$, $p = 0.32$; $I^2 = 14\%$, fixed effect model).

| Study/author year | Country of study | Study design | Patients Male no./ Female no./ Mean Age ± SD (years) | Intervention | Primary endpoints | Outcome(end events/total patients) | $P$ |
|-------------------|------------------|--------------|-----------------------------------------------------|--------------|-------------------|-----------------------------------|-----|
| Schellong 1999 [8] | German           | RCT         | No details                                          | LMWH+Warfarin | 8 days /day 0     | PE assessed by serial ventilation/perfusion SPECT in 8–10 day | 0.25 |
| Washwenden 2001 [9] | Switzerland      | RCT         | 72/57/65±17                                         | LMWH+VitK antagonist | 4 days /day 0     | PE detected by scintigraphy in 3 months | 0.44 |
| Blattler 2003 [4]  | Austria          | RCT         | No details                                          | LMWH+VitK antagonist | 9 days /day 0     | Progression of DVT |
| Trujillo-Santos 2005 [9] | Spain           | Prospective | 1118/920/No details<sup>3</sup>                     | LMWH         | ≥3 days /No details | Symptomatic PE in 15 days |
| Jung 2006 [9]      | Austria          | RCT         | 57/54/60.4±14                                       | Dalteparin + phenprocoumon | ≥5 days /day 0  | Combined<sup>d</sup> |
| Romera 2006 [10]   | Spain            | RCT         | 78/68/60.7                                          | LMWH+Warfarin | 5 days /day 0     | Symptomatic PE during first 10 days |
| Isma 2007 [11]     | Sweden           | RCT         | 39/33/54±14                                         | LMWH+Warfarin | No details /immediately | Recanalization of occluded vein within 6 months | NS  |
| Romera 2008 [12]   | Spain            | RCT         | 118/101/64.2                                         | LMWH+Warfarin | 5 days /day 0     | Symptomatic PE during first 10 days | 0.54 |
| Manganaro 2008 [13]| Italy            | Retrospective case-control study | 118/134/65±17                                     | LMWH+oral anticoagulation<sup>d</sup> | 7±2 days or permanently /day 0 | Combined<sup>d</sup> at 30-day follow-up visit |
| Rahman 2009 [14]<sup>e</sup> | Turkey          | RCT         | 17/7/52.08                                          | Unfractionated heparin/LMWH +Warfarin | 7 days /day 0 | Improvement of venous outflow at day 7 |
| Huang 2010 [15]    | China            | RCT         | 21/19/61                                            | LMWH+Warfarin | 7–10 days /d 1–2 | Symptomatic PE during 3 months | 0.20 |
| Feng 2011 [16]     | China            | nRCT        | 11/21/60.5                                          | LMWH+Warfarin | 7 days /day 0     | PE(symptomatic or detectable by CT) in 7 days | 0.17 |
| Liu 2013 [17]      | China            | RCT         | 38/22/57.0                                          | Routine anticoagulation<sup>d</sup> | 7–14 days /day 1–2 | Symptomatic PE during 3 months | 0.30 |

<sup>a</sup> Favors ambulation.
<sup>b</sup> Partial data eligible for the meta-analysis was extracted. For this reason the details about mean age of these patients were not available.
<sup>c</sup> Combined endpoints: progression of DVT documented by duplex sonography or phlebography, new PE detected by scintigraphy or CT.
<sup>d</sup> No detail was mentioned in the article.
<sup>e</sup> Considering the grouping design, we only included partial data of the study (Group A and Group C).

NS not significant; RCT randomized controlled study; nRCT non-randomized controlled study; ECG electrocardiogram.

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By examining the details of these studies, we found that patients in Aschwanden’s [9] and Liu’s [17] study suffered much milder pain initially (mean VAS 2.23 ± 1.94 for the mobile and 2.82 ± 2.24 for the immobile group in Aschwanden’s study [9], 3.07 ± 0.16 for the mobile and 3.00 ± 0.95 for the immobile group in Liu’s study [17]) than in the other studies (initial mean VAS > 4 or 40). Subgroup analysis found that if the patients suffered moderate or severe pain initially, early ambulation was related to a better outcome than bed rest group, in term of reduction of acute pain in the affected limb (SMD 0.42, 95%CI 0.09~0.74; Z = 2.52, p = 0.01; random effect model, Tau² = 0.04) (Fig. 7).

Fig. 8 shows the meta-analysis about change of edema with measurement of circumference of affected limb using fixed effect model. Sensitivity analysis (S4 Table) cannot identify any
study as the main source of the significant heterogeneity ($\chi^2 = 34.70$, $df = 5$, $p < 0.00001$; $I^2 = 86$%). So random effect model was employed. Early ambulation was not associated with a better remission of edema of the affected limb (SMD 0.5, 95%CI $-0.13$ to $1.12$; $Z = 1.55$, $p = 0.12$; random effect model, $Tau^2 = 0.51$).

Discussion

The main finding of this meta-analysis was that compared to conventional bed rest treatment, early ambulation was not associated with a higher incidence of PE, progression of DVT or DVT related death in acute DVT patients with effective anticoagulation regimen. It was also associated with a better outcome in term of remission of pain, for patients suffered from moderate or severe pain initially.

There had been 2 English meta-analysis on this topic in 2009, conducted by Aissaoui et al. [19] and Anderson et al. [20] respectively. Aissaoui et al. included 5 studies [3, 5, 8, 9, 21], one of which [21] was interim analysis by Partsch and Blattler published in 2003. Aissaoui et al. did not mentioned quality assessment in the article. Anderson et al. included 4 studies [3, 4, 8, 9], all of which were included in our meta-analysis. Compared to their analysis, ours included more studies, which made subgroup analysis more feasible. Understandably, our findings were consistent with them, as well as several former reviews [22, 23, 24]. Additionally, we focused
on not only PE and prognosis of DVT, but also remission of pain and edema. We also explored whether ambulation could improve recanalization of vessels and reduce Post-thrombotic syndrome (PTS), as discussed in the following paragraphs. In 1996, Koopman reported that treatment with LMWH at home was feasible, effective, and safe for patients with proximal vein thrombosis [25]. Included in this meta-analysis, Romera’s study consisted of 2 consecutive RCTs with 365 patients enrolled from January 2002 to December 2007, and proved that it was safe to treat acute DVT at home with early walking, in addition to standard anticoagulation [10, 12]. Hence, it is proper to treat DVT patients as outpatients. Liu et al. [17] compared ambulation therapy versus bed rest for acute DVT after stroke among 60 patients, and reported no PE happened in both groups during a 3-month follow-up period. Conversely, Kiser et al. [26] and Jiang et al. [27] recommended to immobilize the affected limb at least 48–72 hours before an effective anticoagulation was reached. However, their studies were retrospective and thus less convincing.

The meta-analysis also found a better remission of acute pain in the affected limb in the early ambulation group, for the patients suffered moderate or severe pain initially. Although it was theoretically reasonable for avoiding one factor of Virchow’s triad, this conclusion should
be taken carefully because of the small sample size of each study. In addition, Kahn et al. came up with the theory that there was a possibility that exercise may exacerbate pain and edema due to active hyperemia and venous obstruction, which could increase capillary pressure and promote fluid transfusion from capillaries into interstitial space [28]. Isma et al. [11] reported that no benefit of early exercise was seen regarding faster remission of pain or swelling. However, there were also other studies that found the opposite. Partsch et al. [21] reported that the rate of remission of pain was significantly faster when the patients ambulated with compression. Ratiu et al. [29] conducted a RCT with 32 pregnant women diagnosed with proximal

**Table 3. Summary of subgroup and sensitivity analyses of primary endpoints.**

| Number of studies | Heterogeneity | RD (95% CI) | Effect size | $p_2$ |
|-------------------|---------------|-------------|-------------|-------|
|                   | Chi$^2$(for FE*) or Tau$^2$(for RE**) | I$^2$ | $p_1$ |       |
| Total studies (FE) | 13 | 148.16 | 92% | $< 0.00001$ | -0.003 ($-0.005$, $-0.002$) | 4.79 | $< 0.00001$ |
| Total studies (RE) | 13 | 0.01 | - | *** | -0.03 ($-0.05$, $-0.02$) | 1.24 | 0.22 |
| Omitting Manganaro’s study [13] (FE) | 12 | 6.30 | 0% | 0.85 | -0.00 ($-0.02$, 0.01) | 0.69 | 0.49 |
| Omitting Trujillo’s study [5] (FE) | 12 | 94.76 | 88% | $< 0.00001$ | -0.09 ($-0.12$, $-0.05$) | 4.77 | $< 0.00001$ |
| Omitting Trujillo’s study [5] (RE) | 12 | 0.01 | - | - | -0.094 ($-0.12$, 0.03) | 1.18 | 0.24 |

Subgroup analysis

| RCTs (FE) | nRCTs (FE) | nRCTs (RE) |
|-----------|-----------|-----------|
| 10 | 3 | 3 |
| 6.42 | 203.30 | 0.25 |
| 0% | 99% | - |
| 0.70 | $< 0.00001$ | - |
| -0.01 ($-0.04$, 0.03) | -0.04 ($-0.06$, $-0.03$) | -0.14 ($-0.71$, 0.42) |
| 0.44 | 6.64 | 0.49 |
| 0.66 | <0.00001 | 0.62 |

*FE fixed effect model

**RE random effect model.

***In a random effect model, Tau$^2$ should be employed to indicate the heterogeneity rather than I$^2$ and $p_1$ value.

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deep vein thrombosis and found pregnant women also benefited from leg compression and early mobilization for a faster alleviation of the signs and symptoms of DVT.

In terms of edema in acute DVT patients, we found that early ambulation was not associated with a better remission of edema of the affected limb. Several studies [4, 9, 15, 16, 17, 29] reported a positive effect while others [11, 30] did not. However, it should be noticed that no exacerbation of edema was ever reported with early ambulation.

PTS of the leg arose in one third of patients with first occurred proximal deep vein thrombosis who received standard treatment with anticoagulants [1]. Partsch et al. [30] followed up 53 patients with DVT for 2 years, assessing the PTS-score with the Villalta-Prandoni-scale. A significantly better outcome could be found in the mobile group (mean score was 5.1) than in the bed rest group (mean score was 8.2), p<0.01. However, this result could be controversial. In Partsch’s study, patients in bed rest group wore no compression stockings while the mobile patients did. It had been reported that the incidence of PTS in patients with first proximal deep vein thrombosis can be reduced by a below-knee graduated elastic compression stocking [1].
Isma et al. [11] explored if physiotherapist supervised exercise lasting for 6 months could improve recanalization of thrombotic veins. No benefit of early exercise was seen regarding the degree of recanalization during the 6 months follow-up period in their study.

In addition, ambulation could reduce discomfort of patients, e.g., back pain and constipation [3], as well as costs if treated as outpatients.

By now, we can affirm that early ambulation in acute DVT patients with standard anticoagulation regimen is not associated with a higher incidence of PE, progression of DVT or DVT related deaths. It seems that early ambulation is better for relieving the limb pain, edema as well as PTS condition according to current studies, which is also consistent with the Virchow’s theory.

Study limitations

Our analysis has several limitations mainly because of the small number and sample size of studies on this topic, as well as the variability among them which led to heterogeneity. Firstly, the Trujillo-Santos’s registry had the largest sample size and counted as much as 63.2% of the total weight. These patients were allocated to bed rest group or ambulation group according to his/her doctor’s advice, which definitely affected the matching of risk factors (e.g., age, malignancy, surgery) [31] between the two groups and could lead to significant bias. Nevertheless, as the authors pointed out, their population-based sample reflected the effects in “real-world” clinical care and enhanced the generalizability of the findings [32]. Secondly, protocols of ambulation were not the same among different studies, e.g., Junger et al. [3] instructed patients to move around the ward, while Romera et al. [12] treated patients as outpatients and instructed them to establish normal in-house activity and walk 2 to 3 hours a day. Thirdly, the choices about when to begin ambulation were not identical, varying from day 0 to day 3 after the DVT diagnosis. The immobilization duration varied from 3 to 14 days and the follow-up period varied from 7 days to 6 months among the studies. Fourthly, the primary endpoints were symptomatic PE in 4 studies, equipment detectable PE in 6 studies and progression of DVT in another 3 studies. The incidence of symptomatic PE was much lower than asymptomatic PE [23]. Thus studies with symptomatic PE as the endpoints had a lower detectable rate which may lead to a false negative result. Fifthly, nearly all the studies excluded PE patients detectable by CT or scintigraphy at inclusion. While PE occurred in up to 50% of patients with proximal DVT [33]. So the result of this meta-analysis cannot be applied to all acute DVT patients, especially for proximal DVT patients.

Conclusions

Compared to bed rest, early ambulation of acute DVT patients with standard anticoagulation regimen is not associated with a higher incidence of new PE, progression of DVT, and DVT related deaths. Furthermore, a better outcome can be seen with early ambulation, regarding to
remission of acute pain in the affected limb, for those suffered moderate or severe pain initially. Still, more studies are needed to confirm the benefit with respect to reduction of edema, incidence of PTS, as well as extent of recanalization of thrombotic veins.

**Supporting Information**

S1 PRISMA Checklist. PRISMA 2009 (bed rest vs. ambulation for DVT).

(S1) Table. Literature search strategies and results.

(S2) Table. Reasons for article exclusion.

(S3) Table. Quality assessment of included studies.

(S4) Table. Sensitivity analysis of remission of edema.

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**Author Contributions**

Conceived and designed the experiments: YL ZL XT. Performed the experiments: ZL XT. Ana-
lyzed the data: ZL XT YC ZF YL. Wrote the paper: ZL XT YC ZF YL.

**References**

1. Kyrle PA, Eichinger S. Deep vein thrombosis. Lancet. 2005; 365(9465):1163–1174. PMID: 15794972
2. Galanaud JP, Laroche JP, Righini M. The history and historical treatments of deep vein thrombosis. J Thromb Haemost. 2013; 11:402–11. doi: 10.1111/jth.12127 PMID: 23297815
3. Junger M, Diehm C, Stonko H, Hach-Wunderle V, Heidrich H, Karasch T, et al. Mobilization versus im-
mobilization in the treatment of acute proximal deep venous thrombosis: a prospective, randomized,
open, multicentre trial. Curr Med Res Opin. 2006; 22(3):593–602. PMID: 16574042
4. Blatterl W, Patsch H. Leg compression and ambulation is better than bed rest for the treatment of
acute deep venous thrombosis. Int Angiol. 2003; 22(4):393–400. PMID: 15153824
5. Trujillo-Santos J, Perea-Milla E, Nez-Puente AJ, Nchez-Cantalejo ES, Toro JD, Grau E, et al. Bed Rest
or Ambulation in the Initial Treatment of Patients With Acute Deep Vein Thrombosis or Pulmonary
Embolism*Findings From the RIETE Registry. Chest. 2005; 127:1631–6. PMID: 15888839
6. Vascular Surgery Group of Chineses Medical Association. Guideline for diagnosis and treatment of
deep vein thrombosis. Chin J Surg. 2013; 50(7):611–614.
7. Kearon C, Akk EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic
Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American
College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2):
e419S–e494S. doi: 10.1378/chest.11-2301 PMID: 22315286
8. Schellong SM, Schwarz T, Kropp J, Prescher Y, Beuthien-Baumann B, Daniel WG. Bed rest in deep
vein thrombosis and the incidence of scintigraphic pulmonary embolism. Thromb Haemost. 1999; 82
(suppl 1):127. PMID: 10695503
9. Aschwanden M, Labs K, Engel H, Schwob A, Jeanneret C, Mueller-Brand J, et al. Acute deep vein
thrombosis: early mobilization does not increase the frequency of pulmonary embolism. Thromb Hae-
most. 2001; 85(1):42–46. PMID: 11204585
10. Romera-Villegas A, Cairós-Castellote MA, Perez-Piqueras A, Martí-Mestre X, Bonell-Pascual A, Lapiedra-Mur O. Early mobilisation of patients with acute deep vein thrombosis does not increase the risk of a symptomatic pulmonary embolism. Angiologia. 2006; 58(2):127.
11. Isma N, Johansson E, Bjork A, Bjorgell O, Robertson F, Mattiasson I, et al. Does supervised exercise after deep venous thrombosis improve recanalization of occluded vein segments? A randomized study. J Thromb Thrombolysis. 2007; 23(1):25–30. PMID: 17186396
12. Romera-Villegas A, Cairós-Castellote MA, Vila-Coll R, Gomez AP, Martí-Mestre X, Bonell-Pascual A, et al. Early mobilisation in patients with acute deep vein thrombosis does not increase the risk of a symptomatic pulmonary embolism. Int Angiol. 2008; 27(6):494–499. PMID: 19078912
13. Manganaro A, Ando G, Lembo D, Sardo SL, Buda D. A retrospective analysis of hospitalized patients with documented deep-venous thrombosis and their risk of pulmonary embolism. Angiology. 2008; 59(5):599–604. doi: 10.1177/0003319707309655 PMID: 18388030
14. Rahman A, Colak MC, Ustunel L, Koc M, Kocakoc E, Colak C. A comparison of different treatment managements in patients with acute deep vein thrombosis by the effects on enhancing venous outflow in the lower limb. Med Sci Monit. 2009; 15(11):CR588–CR593. PMID: 19865059
15. Huang ZJ, Qu LF, Jing ZP, Liu AF, Yuan XL. A randomized controlled prospective study on ambulation versus bed rest for the initial treatment of patients with acute deep venous thrombosis. Chin J Gen Surg. 2010(9): 737–739.
16. Feng XF. Early walking for treatment of acute deep vein thrombosis. Gems of Health. 2011(8):74,51.
17. Liu J, Liu T, Wan Y, Zou XM, Liu QQ. Effect of early functional training on acute deep venous thrombosis of patients with stroke. Chin J Rehabil. 2013; 28(2):117–119.
18. Sterne J, Matthias E, Moher D. Chapter 10: Addressing reporting biases. In: Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011. p. 10.13.
19. Aissaoui N, Martins E, Mouly S, Weber S, Meune C. A meta-analysis of bed rest versus early ambulation in the management of pulmonary embolism, deep vein thrombosis, or both. Int J Cardiol. 2009; 137:37–41. doi: 10.1016/j.ijcard.2008.06.020 PMID: 18691773
20. Anderson CM, Overend TJ, Godwin J, Sealy C, Sunderji A. Ambulation after Deep Vein Thrombosis: A Systematic Review. Physiother Can. 2009; 61(3):133–140. doi: 10.3138/physio.61.3.133 PMID: 20514175
21. Partsch H, Blattler W. Compression and walking versus bed rest in the treatment of proximal deep venous thrombosis with low molecular weight heparin. J Vasc Surg. 2000; 32(5):861–9. PMID: 11054217
22. Qi H, Zhang F. Should early ambulation be recommended in deep vein thrombosis? Chin J Surg. 2012; 50(8):688–690.
23. Partsch H. Ambulation and compression after deep vein thrombosis: dispelling myths. Semin Vasc Surg. 2005; 18(3):148–52. PMID: 16168890
24. Kahn SR, Shrier I, Kearon C. Physical activity in patients with deep venous thrombosis: A systematic review. Thromb Res. 2008; 122:763–773. PMID: 18079881
25. Koopman MMW, Prandoni P, Piovella F, Ockelford PA, Brandjes DPM, van der Meer J, et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. The Tasman Study Group. N Engl J Med. 1996; 334(11):682–7. PMID: 8594426
26. Kiser TS, Stefans VA. Pulmonary embolism in rehabilitation patients: relation to time before return to physical therapy after diagnosis of deep vein thrombosis. Arch Phys Med Rehabil. 1997; 78(9):942–5. PMID: 9305265
27. Jiang P, Liu J, Jia W, Tian X. Clinical Report on Lower Limb Deep Venous Thrombosis Complicated with Pulmonary Embolism in 45 Cases. Chin J Bases Clin General Surg. 2012; 19(11):1179–81.
28. Kahn SR, Azoulay L, Hirsch A, Haber M, Strulovitch C, Shrier I. Acute effects of exercise in patients with previous deep venous thrombosis: impact of the postthrombotic syndrome. Chest. 2003; 123(2):399–405. PMID: 12578357
29. Ratiu A, Motoc A, Pascaud D, Crisan DC, Anca T, Pascaud M. Compression and walking compared with bed rest in the treatment of proximal deep venous thrombosis during pregnancy. Rev Med Chir Soc Med Nat Iasi. 2009; 113(3):795–798. PMID: 20191834
30. Partsch H, Kaulich M, Mayer W. Immediate mobilisation in acute vein thrombosis reduces post-thrombotic syndrome. Int Angiol. 2004; 23(3):206–212. PMID: 15765034
31. Tapson VF. Acute Pulmonary Embolism. N Engl J Med. 2008; 358:1037–52. doi: 10.1056/NEJMra072753 PMID: 18322885
32. Lozano F, Trujillo-Santos J, Barron M, Gallego P, Babalis D, Santos M, et al. Home versus in-hospital treatment of outpatients with acute deep venous thrombosis of the lower limbs. J Vasc Surg. 2014; 59 (5):1362–7. doi: 10.1016/j.jvs.2013.11.091 PMID: 24439322

33. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. Lancet. 2012; 379 (9828):1835–1846. doi: 10.1016/S0140-6736(11)61904-1 PMID: 22494827