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Title	Effectiveness of ambulation to prevent venous thromboembolism in hospitalized patients: a systematic review
Authors	Brandyn D. Lau MPH, Patrick Murphy MD, Anthony J. Nastasi MHS, Stella Seal MLS, Peggy S. Kraus PharmD, Deborah B. Hobson MSN, Dauryne L. Shaffer MSN, Christine G. Holzmueller MS, Jonathan K. Aboagye MBChB, Michael B. Streiff MD, Elliott R. Haut MD
Reviewer 1	Catherine Moltzan
Institution	
General comments (author response in bold)	<p>This paper dispels the myth that ambulation is good prophylaxis against DVT for hospitalized patients. It should encourage the use of pharmacologic prophylaxis unless there is a specific contraindication to same. The quality of the studies is poor and a proper study will never be done, so this is likely the best evidence we will get.</p> <p>Thank you for your comments. We agree that pharmacologic prophylaxis should be considered the primary prophylaxis for VTE. The data, although poor, do not support ambulation as primary prophylaxis.</p>
Reviewer 2	Susan Kahn
Institution	Medicine, SMBD Jewish General Hospital, Montréal, Que.
General comments (author response in bold)	<p>Solid systematic review; unfortunately as is often the case, the number and quality of underlying studies is so poor there is nothing to meta analyze and conclusions are weak.</p> <p>We agree with your assessment of the generally poor quality of literature. We have responded to this issue in the manuscript. Please see comment 5 to the editors for details. While our conclusions are weak (based on weak data), the importance of publishing papers such as this is critical.</p> <p>1) Please provide PROSPERO registration number of this systematic review. We did not register this systematic review in PROSPERO. While this is recommended by some journals, this is not a required step (as is registration for clinical trials) that we saw in the CMAJ instructions.</p> <p>2) Abstract, Background: Sentence 1 is illogical-rewrite please. Sentence 2- unclear use of "therapeutic regimen"-reword please. Thank you for your comments. We have revised the Abstract Background (page 3) as follows: Page3: "Patient ambulation is frequently recommended to help prevent venous thromboembolism (VTE) while hospitalized. Our objective was to synthesize the evidence for ambulation as VTE prophylaxis."</p> <p>3) Abstract, results: 'ambulatory' should be ambulation Thank you. We have changed ambulatory to ambulation in sentences 2 and 3.</p> <p>4) Introduction, 1st paragraph: Sentence 3 beginning RCTs report...: in which patient populations? I think you mean hospitalized medical and surgical patients-add this please. References 6-8 are outdated and do not correctly reference the guidelines mentioned in that sentence- replace with the most recent guidelines (eg ASH 2018 guidelines for medical patients, and Chest 2012 or ASH 2019 guidelines for surgical patients, and NICE guidelines.</p>

**Thank you for your guidance. We have revised the Introduction as follows:
Page 4, Paragraph 1, sentence 3: “Randomized controlled trials report significant reductions in VTE among hospitalized medical and surgical patients administered pharmacological prophylaxis.”**

Page 4, References 6-8: We have updated the references with the following 4 newer ones:

Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. Blood Adv. 2018 Nov 27;2(22):3198-3225.

Falck-Ytter Y, Francis CW, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e278S-e325S.

Anderson DR, Morgano GP, Bennett C, Dentali F, Francis CW, Garcia DA, Kahn SR, Rahman M, Rajasekhar A, Rogers FB, Smythe MA, Tikkinen KAO, Yates AJ, Baldeh T, Balduzzi S, Brozek JL, Ikbaltzeta IE, Johal H, Neumann I, Wiercioch W, Yepes-Nuñez JJ, Schünemann HJ, Dahm P. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Adv. 2019 Dec 10;3(23):3898-3944.

Venous Thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. NICE guideline [NG89]. National Institute for Health and Care Excellence London, UK; 2018. <https://www.nice.org.uk/guidance/ng89>

Also comment 4) Paragraph 2 has too much text on Johns Hopkins previous initiatives that have nothing to do with this paper- please remove or shorten.

Thank you, we were trying to show the progression of our research that led us to discover that clinicians were using ambulation in place of prescribed dose of prophylaxes. We cut some content as follows:

Page 4, Paragraph 2, starting sentence 2: Since 2005, the Johns Hopkins Medicine VTE Collaborative has systematically studied and implemented interventions for preventing VTE. We first Our hospital improved risk assessments (13) and prescription of risk-appropriate prophylaxis, for hospitalized patients (14-16) While successful, we but also found that up to 15% of prescribed prophylaxis doses were not being administered to hospitalized patients.(17,18) When nurses were Upon surveying nurses, we...”

5) Page 5, 1st para-what is a “master’s prepared librarian”? As an example of grey literature, searches of clinicaltrials.gov are mentioned. How does this help identify published literature? Did you contact the authors of trials found on clinicaltrials.gov ? What was the result? Were other grey lit sources searched e.g. theses, other?
You raise some good questions. We revised “master’s prepared librarian” to “librarian with a Masters in Library Science” (Page 5, paragraph 1, sentence 2). We also reviewed the references of included studies to ensure we performed a comprehensive search.

6) Page 10, para 3: Re: “For example, the American College of Chest Physicians

	<p>recommend early ambulation as the only prophylactic measure needed for low-risk nonorthopedic 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”.</p> <p>-I don't think your results “challenge” the ACCP12 recommendation- even if ambulation is not conclusively effective, it may be that not giving prophylaxis is the correct recommendation in low risk populations, as the risk of VTE is so low. Your findings should not be interpreted that ambulation should be replaced with pharmacoprophylaxis in low risk groups. Please reword.</p> <p>Thank you. We have reworded the manuscript as follows:</p> <p>Page 10, paragraph 3, sentence 4: “Our results challenge early ambulation as appropriate VTE prophylaxis. A patient’s risk should be assessed and evidence-based treatment given, considering the risks and benefits.”</p> <p>7) page 10 last para: suggest replace “myth” with concept or tenet. We appreciate your suggestion and have replaced myth with concept (Page 11, paragraph 2, line 3).</p> <p>8) Page 11: “It was challenging to conclude that most of the studies in our review qualified as describing early ambulation, or were rigorously conducted.” Awkward overly complex sentence, please reword You raise a good point, thank you. We have revised the sentence as follows:</p> <p>Page 11, Paragraph 3, sentence 1: “Most studies in our review did not qualify as early ambulation despite our rigorous literature search. Moreover, most studies were not rigorously conducted.”</p> <p>9) throughout, I feel there is an overemphasis on pharmacoprophylaxis which in fact may be unnecessary (and overused) in very low and low risk medical and surgical patients We agree that chemical VTE prophylaxis may not be required in all patients. Our study did not investigate the potential for overuse of chemical VTE prophylaxis in very low / low risk patients but rather aimed to determine whether ambulation was effective as VTE prophylaxis regardless of risk stratification. We hope that our response to comment 6) tempers our recommendations in low risk patients. However, the over-reliance on ambulation without any data to support its benefit may also be harmful to patients.</p>
Reviewer 3	Andrew Kouri
Institution	Division of Respiriology, University of Toronto, Medicine, Toronto, Ont.
General comments (author response in bold)	<p>This paper review by Lau and Murphy et al. seeks to establish the evidence base for the notion that ambulation in hospitalized patients may be effective at reducing the risk for VTE. They accomplish this through a systematic review of the literature, which identified 16 studies (RCTs and observational studies). These studies were highly heterogeneous, covering a range of patient populations, ambulation intervention types, and outcome measures. They conclude that they were unable to find high-quality evidence supporting the use of ambulation alone as effective prophylaxis for VTE, and that pharmacologic prophylaxis for VTE should not be discontinued solely based on patient ambulation.</p> <p>The primary strength of this study is its methodological rigour. They broadly searched the literature, and were transparent throughout their reporting about</p>

important steps of their systematic review. They seemed to follow PRISMA reporting guidelines for systematic reviews, and in particular, they dutifully acknowledged their inability to perform meta-analysis based on the clinical heterogeneity present in the identified studies.

Elements that could be improved further:

- Their rationale for the systematic review cites local evidence/care gaps (i.e. nurses not providing VTE prophylaxis based on ambulation status) only, and doesn't discuss the broader literature to make the case that this is a more systemic care gap that needs to be addressed

We have bolstered the second paragraph in our introduction to frame the broader context. While there is a paucity of literature on the topic, anecdotally, the authors get asked questions on this topic on a routine basis from clinicians across the country and around the world.

Page 4, bottom part of paragraph 2: "Indeed, this recommendation is widespread in national guidelines.(7,9) used by physicians and hospitals. Further, "ambulatory patient" is ubiquitous in electronic medical records as a valid reason for not prescribing VTE prophylaxis.(22) To our knowledge, evidence supporting..."

- Ideally, the protocol should have been registered (i.e. with PROSPERO) prior to beginning the systematic review, and if this was done, it should be mentioned

Thank you for mentioning, we did not register the protocol in PROSPERO.

- Looking at Figure 1, a very large number of titles were screened and excluded without reviewing the full abstracts. Given that many of the included studies looked at effects of ambulation on VTE rates as a secondary outcome, important studies may have been missed through excluding so many based on title alone

This is an excellent point. We intentionally kept our search broad given the lack of studies with ambulation as a primary intervention. We performed a title and abstract review based on the best available methodology for performing systematic reviews, however acknowledge the potential to miss important studies. We have added this point to our limitation section.

Page 12, paragraph 2, line 6: "Further, we intentionally kept our search broad and, therefore, eliminated the majority of studies at the title and abstract phase. As such, we may have missed studies that included ambulation as a secondary intervention or VTE as secondary outcome."

- Publication bias potential could be discussed, with presentation of a funnel-plot as well

I do not believe a funnel plot is possible without performing a meta-analysis. In addition, a funnel plot to look for publication bias is often looking for null studies that may not have been published to counter the projects that do find an effect. This issue does not apply directly.

- It would be interesting to see sub-group analyses based on patient-population or risk-stratification profiles

We agree this would be very interesting. We are, again, limited by study quality and the fact that most studies did not risk stratify. We added an additional table (Table 4) reflecting only higher quality studies.

The main limitation of this article is the disconnect between their research question and the clinical scenario where ambulation alone as a means of prophylaxing for

VTE would ever be considered appropriate. In the guidelines the authors reference, holding pharmacologic or mechanical VTE prophylaxis (and encouraging early ambulation) is only recommended in medical and surgical patients with very-low risk for VTE or high-risk of bleeding (Guyatt 2012). For example, in non-orthopedic surgical patients, this is only recommended in patients with a VTE risk of <0.5%. The studies they reviewed did not appear to focus solely on this low-risk patient population, for example, in the Amin 2010 study (one of the few with good statistical quality that also quantified ambulation), patients in the ambulation alone arm had a VTE rate of 10.6%. Based on current guidelines, there is not a question of clinical equipoise around the idea of whether or not hospitalized patients with a VTE risk/rate of greater than 10% should receive pharmacological VTE prophylaxis, and thus the question of the effectiveness of ambulation alone in this patient population as a means of prophylaxis for VTE is moot. If this group of patients is not receiving appropriate pharmacologic VTE prophylaxis, it rather represents a failure of guideline-based medical practice, and I do not find evidence in this article that points to this being primarily due to a misjudgment in the effectiveness/role of ambulation as a alternative means of VTE prophylaxis.

The reviewer makes an excellent point and we are not advocating chemical VTE prophylaxis for all patients. We have tempered our discussion to advocate for an accurate assessment of risk and evidence based VTE prophylaxis (see response to Reviewer 2, comment 6). Ambulation is ubiquitous in guidelines and practice as an acceptable intervention to prevent VTE prophylaxis either in conjunction with chemical VTE prophylaxis or not. Our review challenges this notion. We don't want clinicians to erroneously believe that ambulation prevents VTE and, therefore, not prescribe other approaches (i.e. pharmacologic prophylaxis) that have strong data showing their clinical benefit to prevent VTE. We clarified this in the Introduction as well (see our response to your first comment).

While this systematic review does an excellent job of highlighting the lack of strong evidence for the effectiveness of ambulation alone as a means of DVT prophylaxis in medical and surgical patients in general, the rationale and justification to provide pharmacologic and/or mechanical DVT prophylaxis in all but very low-risk medical and surgical hospitalized patients is already well established in current guidelines. A more compelling focus would be to answer the question of how effective ambulation alone is vs. no ambulation in very low-risk patients who are not recommended to receive pharmacologic/mechanical DVT prophylaxis, though I suspect that the rate of DVT might be so low in these patients that this would be a difficult question to answer.

Similar to other reviewer's points we agree the role of ambulation in very low risk patients would be challenging to answer and, unfortunately, given the quality of studies we are unable to perform a sub-group analysis based on risk. Our goal was to examine the evidence of ambulation in all-comers and hope this may prompt additional studies and/or modification of existing guidelines. We revised the Objective statement in the Abstract and manuscript to make this clear.

Page 4, last sentence: "Our objective was to synthesize the evidence for ambulation as a VTE prophylaxis among any hospitalized patient population."

