Author's response to reviews

Title: The Association between Statin Therapy during Intensive Care Unit Stay and the Incidence of Venous Thromboembolism: A Propensity Score-Adjusted Analysis

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Author's response to reviews: see over
Dear Nolasco,

We would like to thank the editorial board and the reviewers for their thorough review and constructive feedback which has enriched the manuscript and strengthened the discussion.

We have modified the manuscript according to the reviewers’ comments and changes are marked in RED. Below see our point-by-point replies.

Sincerely,

Yaseen Arabi, MD, FCCP, FCCM
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Reviewer 1
Comment: The prior study, while cited needs to present in more detail. Please provide some detail on the intervention / treatment allocation / outcomes in the main study and the intervention could readily influence the outcomes assessed in this study. Ideally the full manuscript would be available to reviewers of these subsequent studies and available as a full citation for any sub studies (including this current one)

Reply: Thank you for the comment. We have added the following sentences to the study design:

“This is a post-hoc analysis of a recently published cohort study of the effect of mechanical thromboprophylaxis, intermittent pneumatic compression (IPC) or graduated compression stocking (GCS), on the incidence of VTE in patients admitted to the ICU between July 2006 and January 2008 [21]. The original study included 798 patients. Inclusion criteria were age ≥18 years and expected ICU length of stay of more than 48 hours. Patients were excluded if they were on therapeutic anticoagulation with warfarin or heparin, admitted to the ICU with acute PE, DVT, or have do-not-resuscitate or brain death status on or within first 24 hours of ICU admission. Thereafter, the patients were followed for a total of 30 days from admission to ICU.” Please see attached article.

Comment: Limited data is provided or presented on the study cohort. In particular how the propensity score was arrived at and what actually was performed when providing the adjustments reported in table 1. This must be expanded in considerable detail.

Reply: Thank you for the comment. The manuscript described that

“These were derived from a logistic regression model using “pscore” program in Stata/SE version 11 for Windows (StatCorp LP, College Station, TX, USA)”
Also, it described in details the process of stratifying propensity score into 6 categories and using them as stratification factor or an adjustment variable.

“The derived propensity scores were then divided into 6 categories (blocks) and used in later analysis as stratification factor or as an adjusting covariate.

The following sentences were added expanded on the selection of variables entered in the propensity score as ordered as follows:

“Variables included in the propensity score generation model were selected according to their relationship to the outcome (VTE) rather than the exposure (statin therapy) as has been shown to reduce bias and variance of estimated exposure effect [23, 24]. Those variables were: age, APACHE II score, GCS, diagnosis of trauma, presence of femur fracture, creatinine level, INR, aPTT level, central venous line presence, history of malignancy, recent surgery, history of previous VTE, PRBC and platelet transfusion, hemodialysis catheter use, use of graduated compression stocking, use of intermittent pneumatic compression device, and unfractionated heparin or enoxaparin.”

Comment: The groups are very very different at baseline with numerous major significant differences. It is almost implausible they would in fact have similar outcomes for either DVT or mortality. I think the raw data for outcomes and the adjusted analysis would both need to be presented and significant discussions of the major limitation on interpretation of the results that such different groups may place on a post hoc non-randomized study.

Reply: Thank you for the comment. We have noticed that the coding for the outcome variable during hospital mortality analysis has been corrected. We have re-done the analysis using correct coding and updated the manuscript, tables and graphs accordingly.

We have revised table 3 and 4 to reflect crude and adjusted analysis results in addition to adding risk table to Kaplan-Meier plots. Furthermore, we have included table 2 that
represents Distribution of hospital mortality and VTE cumulative incidence according to statin use.

Table 2: Distribution of hospital mortality and VTE cumulative incidence according to statin use

<table>
<thead>
<tr>
<th>Statin Use*</th>
<th>Hospital Mortality**</th>
<th>Incident VTE**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (123, 15.4%)</td>
<td>58 (47.2%)</td>
<td>6 (7.6%)</td>
</tr>
<tr>
<td>No (675, 84.6%)</td>
<td>256 (38%)</td>
<td>51 (4.9%)</td>
</tr>
<tr>
<td>Total (798)</td>
<td>314 (39.4%)</td>
<td>57 (7.1%)</td>
</tr>
</tbody>
</table>

* Numbers between parentheses reflect counts and percentages, respectively.  
** Numbers between parentheses reflect percentage within statin category.

Table 3:

Crude and adjusted analysis of VTE risk in statin and non-statin groups

<table>
<thead>
<tr>
<th>Type of Analysis</th>
<th>HR</th>
<th>SE</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude Analysis</td>
<td>0.66</td>
<td>0.29</td>
<td>0.28 - 1.54</td>
<td>0.33</td>
</tr>
<tr>
<td>PS block-stratified analysis</td>
<td>0.63</td>
<td>0.29</td>
<td>0.25 - 1.57</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Table 4:

Crude and adjusted 30-day hospital mortality in statin and non-statin groups

<table>
<thead>
<tr>
<th>Type of Analysis</th>
<th>HR</th>
<th>SE</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude Analysis</td>
<td>1.26</td>
<td>0.18</td>
<td>0.95 - 1.68</td>
<td>0.10</td>
</tr>
<tr>
<td>PS blocks stratified Analysis</td>
<td>0.98</td>
<td>0.16</td>
<td>0.71 - 1.35</td>
<td>0.94</td>
</tr>
</tbody>
</table>
Comment: I have significant concern over the data presented in figure 1. This would suggest that no patients died in the first approx 4 days and the cohort had almost a 75% one month mortality – this should be clarified and the additional clinical detail described above may help place this in context for the reader.

Reply: Thank you for the comment. We believe this is a reflection of the inclusion and exclusion in which patients with very poor prognosis were included.

Comment: More detailed information is required regarding statin use. It is mentioned which statin but it is not clear on prior use / duration prior use / continued in ICU / commenced in ICU etc.

Reply: Thank you for the comment. We have added the following sentence to statin therapy page 6 “Data about statins use in the ICU were collected from ICU pharmacy database and were matched and combined to the original clinical study database [21]. Statins were continued if they have been prescribed in the pre-ICU period. Statin could be, however, initiated in the ICU for patients admitted with stroke or acute coronary syndrome.” Also, we have added among the limitations of our study “the lack of data on the duration of statin therapy prior to ICU admission.”

Comment: The significant difference in sequential stocking, unfractionated heparin and enoxaparin use between the groups represents a major confounder. Perhaps one could argue you may expect from some of the demographics the statin group to have a higher incidence of DVT (older / sicker / more bed bound / etc) so that fact they are similar incidence represents an effect?

Reply: We fully agree with this statement. In fact, this was the purpose propensity score and multivariate adjustment.
Cement: Like many of the other studies in this field the end point chosen has a major limitation and inherent bias that must be acknowledged both in the way the results are presented and in the limitations section of the discussion. By design the investigators and the readers cannot know a true denominator of incidence – we are only aware of DVT in the patients it was clinically suspected rather than all patients. The study should therefore report number for both those assessed / those +ve and those not assessed rather than just DVT in 6 patients and 51 patients.

Reply: thank you for the comment. We added the following sentences to the limitation: “Due the observational nature of the study, the presence of unobserved confounders and competing risks cannot also be entirely excluded. In our pragmatic approach for case ascertainment, we did not include surveillance ultrasound to detect DVT. However, this approach represents the standard of care and it has been shown to be more cost effective than surveillance approach [35].”

Comment: Does Central venous line present – mean any location or just Femoral – it might be worth separating these in a study about DVT or acknowledge this as a limitation.
Reply: Thank you for the comment. We reported any central line

Comment: Similarly for Dialysis catheter present – femoral vs other site would be relevant
Reply: Thank you for the comment. Any location.

Comment: Does “dialysis catheter present” equate to renal replacement therapy performed – this should be made clear in the additional demographic data.
Reply: Thank you for the comment. The placement of dialysis catheter equates is a surrogate marker for renal replacement therapy.
Comment: As the primary outcome was DVT – the figure representing this should be prior to the mortality figure in the manuscript (ie Fig 1 rather than fig 2)

Reply: We have changed accordingly.

Comment: Define in methods “bedridden” – it is described in table as “3 days” – perhaps needs a bit more explanation? Had these patients been in hospital longer prior to ICU than non statin users

Reply: Thank you for the comment. We have defined “bedridden status for more than 3 days whether this was at home or in the hospital.”

Comment: Line 7 of the study design section – delete the repeated words about study approval.

Reply: We have changed accordingly.

Comment: Reference 16 mentioned in discussions– seems an odd comparison to make statin vs thyroid replacement – if mentioning this it may require some clarification for the reader about why the comparator was chosen ( in an effort to find a cohort on an agent not thought to influence DVT incidence).

Reply: Thank you for the comment. We have added the following sentence:

“In a retrospective cohort study (N= 125, 862) over 8 years, Ray et al. found that statins were associated with significant DVT risk reduction (HR 0.78, 95% CI 0.69-0.87) among outpatient individuals aged ≥ 65 years[16].”
Comment: In the 3rd sentence of the background – it might be more accurate to state the incidence in critically ill patients is “up to” 10%.

Reply: Thank you for the comment. We have added the following sentence:
“In critically ill patients, the incidence has been reported up to 10% despite thromboprophylaxis [2].”

Reviewer 2
Comment: timing of the primary outcome: it is quite understandable that the authors mean “the incidence of VTE during the hospital stay”. Yet, when they show the results of the Kaplan-Meier analysis they say to have censored the analysis at 30 days of follow up, and that might be confounding for the reader. To be more understandable, please specify for how long the patients were followed up (during the hospital stay or up to 30 days from the hospital admission independently of the length of the hospital stay, i.e. even after discharge for some patients?). Hence, how do the patients who were discharged without symptomatic VTE before 30 days enter the survival analysis? Were they censored?

Reply: Thank you for the comment. We have added the following sentences:
“The primary outcome was the effect of statin therapy on VTE incidence (lower extremities DVT, PE, or both) during the ICU stay and up to 30 days.”

We have added the following sentence to study design section:
“The patients were followed for a total of 30 days from admission to ICU.”

The following statement was added to statistical analysis section
“For hospital mortality analysis, follow-up time was censored at 30 days or at the time of hospital discharge.”
And to results section:

“The median follow-up time for statin-therapy and non statin-therapy groups were 17 days (IQR 7-30) and 14 days (IQR 7-26), respectively.”

Comment: therapy with aspirin might be a relevant variable (expected to be associated with the statin therapy and maybe with the outcomes). Why was this data not collected or included in the analysis? A similar question might be posed for a positive history of cardiovascular diseases/diabetes.

Reply: Thank you for the comment. we have added the following sentences:

“Variables included in the propensity score generation model were selected according to their relationship to the outcome (VTE) rather than the exposure (statin therapy) as has been shown to reduce bias and variance of estimated exposure effect [23, 24].”


Comment: variable for heparin: please specify in Methods that the included variable for heparin (unfractionated or at low molecular weight) corresponds to heparin for DVT prophylaxis, as stated only in the foot notes of tables 2 and 3. The authors should also clarify how they considered in their analyses the treatment with heparin for other acute reasons, for example for an acute coronary syndrome (which does not correspond to a chronic use of heparin, but either to a DVT prophylaxis).
Reply: Thank you for the comment. We actually did not include patients on therapeutic anticoagulation for all reasons. We clarified this issue by changing the sentence from “patients were excluded: patients on chronic therapeutic anticoagulation with warfarin or heparin and patients admitted to the ICU with acute PE, DVT, do-not-resuscitate order or brain death on or within first 24 hours of ICU admission. To “Patients were excluded if they were on therapeutic anticoagulation with warfarin or heparin, admitted to the ICU with acute PE, DVT, or have do-not-resuscitate or brain death status on or within first 24 hours of ICU admission.”

Comment: covariates adjustment: please clarify what the authors mean when they say that “Multivariate Cox regression was also used to control for any residual confounding not taken [into] account for by propensity score adjustment or blocks stratification”. Do they mean that they include again all the variables used to build the propensity score as covariates in the Cox, together with the propensity score? If so, there is no technical reason to do that, also because in this way the advantage of using a propensity score (i.e. to avoid the concern about the over-parameterization) is lost. Usually, and not necessarily, only a subset of variables believed “major”, or for which the balancing property after adjusting for the propensity score is not satisfied, is included again as covariates.

Reply: Thank you for the comment. Three separate models were used but yielded similar results, only one was reported in the table, the statement in results section was modified as following:

Statistical analysis section:
“Cox-proportional hazard regression was used to evaluate the effect of statins on the incidence of VTE. In addition to crude model, propensity score block-stratified, propensity score-adjusted and multivariate-adjusted models were assembled for verification. Hazard ratios (HR) were derived and presented with their 95% confidence intervals (CI). All tests were considered significant at 0.05 alpha level.”
The following sentences were added to the result section:

“In univariate analysis, statins were not associated with reduced VTE incidence (HR 0.66, 95% CI 0.28-1.54, P= 0.33) (Table 3 and Figure 1). Propensity score block-stratified analysis showed identical results (HR 0.63, 95% CI 0.25-1.57, P= 0.32) to the analysis using propensity score as an adjustment variable and similar to multivariate analysis (HR 0.63, 95% CI 0.25 -1.57, P= 0.32).”

Comment: was there any missing data? If so, how did the authors manage them? They may represent a limit when the STATA command pscore is used.

Reply: Thank you for the comment. There were no missing data.

Comment: Results. In Methods the authors state that they performed 3 different Cox analyses with propensity score: a block stratification, a propensity score adjustment and an additional propensity score and covariates adjustment. Why did they report only the HR for one of those analyses (block-stratification) and did not mention at all the results for the other analyses?

Reply: Thank you for the comment: The results were similar. The manuscript was adjusted to reflect these separate analyses as described in the previous question.

Comment: The authors should clarify in the abstract, as well in the main text, the timing for the primary outcome: “incidence of VTE”, when? The reviewer also suggests the authors specify in the Methods section of the Abstract that a survival analysis, and in particular a Cox regression, was performed.

Reply: We have added the following sentence: “The primary endpoint was the incidence of VTE during ICU stay and up to 30 days.”
Comment: Abstract, page 3, line 3: please change “if they reduce the odds” with “if it reduces the odds”.

Reply: Thank you for the comment. We have added the following sentence:

“Studies have shown that statins have pleiotropic effects as well as on inflammation and coagulation; which may affect the risk of developing VTE.”

Comment: Background, page 4, line 8: please change “for both primary and secondary indications” with “when administered for both primary and secondary indications”

Reply: Thank you for the comment. We have added the following sentence:

“Statins (Hydroxy-3- methylglutaryl conenzyme A reductase inhibitors) have demonstrated efficacy in reducing cholesterol levels and improving cardiovascular outcomes when administered for both primary and secondary indications.”

Comment: Results. Like for the occurrence of VTE, please provide the percentage of patients died in hospital, overall and in the statin and non-statin groups.

Reply: Thank you for the comment. We have added the following sentence:

“During the study, there were 58 (47.2%) deaths in statin-therapy group and 256(38%) deaths in no-statin therapy group (Table 2).”

Comment: Results, page 8, lines 3-5: please rephrase “Similarly (...) blocks-stratified analysis (...)”, which is not grammatically clear.

Reply: We have changed accordingly.

Comment: Discussion: in Background (page 4, lines 20-21) the authors state that there are “limited studies” examining the association between statins and VTE in critical patients, whereas in Discussion (page 10, line 22) they write that the study described is “the first study” on this topic. Please clarify.

Reply: we have added the following sentences:

“Several other studies have shown that statin therapy reduces VTE incidence but in outpatient settings.”

“These studies, which showed benefit of statin therapy in reducing VTE risk, share long-term intervention in a low VTE risk outpatient population, and therefore are not
applicable to ICU patients. Our study differs as it evaluates the effect of statin therapy on the short-term occurrence of VTE in a high-risk population.”

Comment: Along the manuscript there are several small typos/grammatical errors: please carefully revise it.

Reply: we have changed accordingly.

Comment: Background. How the background is framed in the main text is inconsistent with how the Background is framed in the abstract. Indeed, in the abstract, the statins’ property of modulating inflammation is advocated as the possible biological link with the development of VTE, whereas, in the main text, their antithrombotic properties on the venous side are primarily presented as the driving mechanism (in fact, in part by the interaction with the inflammatory system, but this is a mechanism not explicitly mentioned in the text). The reviewer would suggest the authors slightly reorganize the first part of the Background in order to make the structure of the manuscript more consistent.

Reply: Thank you for the comment. we have added the following sentences:

“Statins (Hydroxy-3- methylglutaryl conenzyme A reductase inhibitors) have demonstrated efficacy in reducing cholesterol levels and improving cardiovascular outcomes when administered for both primary and secondary indications. Additionally, through their effects on inflammation and coagulation [5], statins may have antithrombotic properties that can affect not only arterial but also venous thrombosis.”

Comment: Methods. The choice of the variables to include in the propensity score might be commented and the type of variables described, for example distinguishing those which were really confounders (associated both to the treatment with statin and to the outcomes), those which were only associated to the treatment with statin, those associated only to the outcomes, those eventually not associated either to the treatment or to the outcomes.

Reply: Thank you for the comment. We have added the following sentence to statistical section:

“Variables included in the propensity score generation model were selected according to their relationship to the outcome (VTE) rather than the exposure (statin therapy) as has been shown to reduce bias and variance of estimated exposure effect [23, 24].”

Comment: Discussion. The authors report extensively the existing evidence in the literature on the association between statins and VTE. This part might be synthesized and/or the authors should at least emphasize the difference in the
setting between the study here prescribed and most of the cited evidence (population-base cohorts, long term follow up, outpatients).

Reply: we have changed accordingly.

Comment: Discussion. The reviewer suggests the authors to rephrase the sentence “However, we have adjusted for those imbalances using multivariate and propensity score analysis” (page 11, lines 17-18), making clearer that they adjusted for some putative confounding variables but not all (i.e., to completely overcome the imbalance” in an observational setting is not possible).

Reply: Thank you for the comment. We have added the following sentence:

“Due the observation nature of the study, the presence of unobserved confounders and competing risks cannot also be entirely excluded.”

Comment: Among the limits of the analyses, the "competing" nature of the two outcomes, which would have required a specific survival method for competing risk, and which may be particularly relevant in a patient population at high in hospital mortality, might be mentioned.

Reply: Thank you for the comment. We have added the following sentence:

“Due the observational nature of the study, the presence of unobserved confounders and competing risks cannot also be entirely excluded.”

Comment: Figures. The reviewer suggests the authors invert the order of figure 1 and 2 according to the “order” of the outcomes.

Reply: We have changed accordingly.
Use of Intermittent Pneumatic Compression and Not Graduated Compression Stockings Is Associated With Lower Incident VTE in Critically Ill Patients

A Multiple Propensity Scores Adjusted Analysis

Yaseen M. Arabi, MD, FCCP; Mohammad Khedr, MD, FCCP; Saqib I. Dara, MD, FCCP; Gousia S. Dhar, MBBS; Shaila A. Bhat, MBBS; Hani M. Tamim, MPH, PhD; and Lara Y. Afesh, RN, MSN

Background: A limited amount of data exist regarding the effect of intermittent pneumatic compression (IPC) and graduated compression stockings (GCS) on the incidence of VTE in the ICU setting. The objective of this study was to examine the association of mechanical thromboprophylaxis with IPC or GCS with the risk of VTE and hospital mortality among critically ill medical-surgical patients.

Methods: In this prospective cohort study of patients admitted to the ICU of a tertiary-care medical center between July 2006 and January 2008, we used multiple propensity scores adjustment to examine the association of IPC and GCS with VTE. The primary outcome was incident VTE, including DVT and pulmonary embolism. The following data were collected: patient demographics, admission physiologic data, VTE risk factors, pharmacologic thromboprophylaxis, and mechanical thromboprophylaxis.

Results: Among 798 patients enrolled in the study, incident VTE occurred in 57 (7.1%). The use of IPC was associated with a significantly lower VTE incidence compared with no mechanical thromboprophylaxis (propensity scores adjusted hazard ratio, 0.45; 95% CI, 0.22-0.95; P = .04). GCS were not associated with decreased VTE incidence. No significant interaction was found between the mechanical thromboprophylaxis group and the type of prophylactic heparin used (P = .99), recent trauma (P = .66), or recent surgery (P = .07) on VTE risk.

Conclusions: The use of IPC, but not GCS, was associated with a significantly lower VTE risk. This association was consistent regardless of the type of prophylactic heparin used and was not modified by trauma or surgical admission.

Abbreviations: ACCP = American College of Chest Physicians; ACP = American College of Physicians; aHR = adjusted hazard ratio; CLOTS = Clots in Legs or Stockings after Stroke; GCS = graduated compression stockings; HR = hazard ratio; IPC = intermittent pneumatic compression; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; RCT = randomized controlled trial; UFH = unfractionated heparin
condition and will not pay for the expenses associated with it.6

Pharmacologic prophylaxis has been recommended as the thromboprophylaxis of choice in critically ill patients; however, VTE continues to occur. For example, in one study, VTE occurred in 5.1% and 5.8% of patients with critical illness not related to trauma receiving dalteparin or unfractionated heparin (UFH), respectively.7

Unlike for pharmacologic thromboprophylaxis, limited data exist on the efficacy of mechanical thromboprophylaxis, including intermittent pneumatic compression (IPC) and graduated compression stockings (GCS).8,9 These observational studies were limited by small sample sizes, heterogeneous patient populations, and variation in end points. Existing randomized controlled trials (RCTs) and a subsequent meta-analysis compared mechanical devices to pharmacologic thromboprophylaxis10,11 as the primary prophylactic regimen, a question of little clinical relevance at present. To our knowledge no study has reported the effect of IPC and GCS on incident VTE in a mixed medical-surgical ICU setting in which pharmacologic thromboprophylaxis is used. The lack of clear evidence is reflected by the wide variability in the use of these devices in surveys from Canada, France, Australia, and Germany10,12-15 and, more importantly, in the current practice guidelines. The American College of Physicians (ACP) guidelines for nonsurgical patients recommend against the use of GCS and suggest that IPC be used as an alternative to pharmacologic thromboprophylaxis but made no recommendation about its adjunct use with pharmacologic thromboprophylaxis.8 The eighth edition of the American College of Chest Physicians (ACCP) guidelines recommended that GCS or IPC be used as an alternative or adjunct to pharmacologic thromboprophylaxis.16 The recent, ninth edition of the ACCP guidelines recommend the use of GCS or IPC (although preference is given to IPC) as an alternative, but not as an adjunct, to pharmacologic thromboprophylaxis in nonsurgical critically ill patients.3 In surgical, nonorthopedic patients (presumably critically ill included), the ACCP guidelines recommend that mechanical thromboprophylaxis (preferably with IPC) be used as an alternative or adjunct to pharmacologic thromboprophylaxis.17 However, in general orthopedic patients (presumably critically ill patients included), the ACCP recommends IPC as an alternative or adjunct, but no recommendation is made regarding GCS.18

With consideration of the limited data and the differences in clinical practice guidelines, we studied the association between the use of mechanical thromboprophylaxis with IPC or GCS and the risk of VTE and hospital mortality among critically ill medical-surgical patients.

Materials and Methods

Subjects and Setting

This prospective, observational, cohort study was conducted in the adult medical-surgical ICU at King Abdullah Medical City, a tertiary-care academic medical center in Riyadh, Saudi Arabia. Consecutive patients admitted to the ICU from July 2006 to January 2008 were enrolled in the study if they were aged ≥ 18 years with an expected ICU length of stay of > 48 h. The following patients were excluded: those with a do not resuscitate order or brain death, those receiving long-term therapeutic anticoagulation with warfarin or heparin, and those admitted to the ICU with acute PE or DVT diagnosed on or within the first 24 h of ICU admission. The study was approved by the institutional review board of the hospital (IRB/016/2006), and informed consent was not required.

The ICU is run as a closed unit by on-site, critical care, board-certified intensivists.19 In 2004, the hospital created a multidisciplinary task force chaired by the primary author (Y. M. A.) to develop hospital-wide guidelines for thromboprophylaxis. The guidelines were based on the seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy.20 Implementation of the guidelines included several educational awareness days directed to all physicians and nurses in the hospital along with the distribution of posters and pocket-sized summaries of the guidelines. In the ICU, a checklist for thromboprophylaxis was incorporated in the admission order set and in the template of the daily progress notes.

Interventions

The IPC devices used during the study period were sequential and multichamber (Kendall SCD Response and SCD Express Compression System Controllers; Covidien). The consumption records indicated that the sleeves used were below knee in 94% of the patients, with the rest being thigh length. The GCS used were primarily below knee (85.4%). The length of IPC sleeves and GCS was determined by the bedside nurse. Fitting instructions from the manufacturers were used to select and apply GCS. GCS were discontinued during ICU stay only if the patient declined to wear them or there was concern about skin integrity.

Measurements

The following data were collected: patient demographics, including age and sex; admission physiologic data; VTE risk factors; pharmacologic thromboprophylaxis; and mechanical thromboprophylaxis (IPC and GCS) (Table 1). Of the 798 enrolled patients, 389 did not receive mechanical thromboprophylaxis, 211 received IPC, 153 received GCS, and 45 received both modalities. Of the patients receiving both modalities, 18 were assigned to the IPC group and 27 to the GCS group on the basis of which device was
Table 1—Characteristics of the Patient Cohort and the Study Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (N = 798)</th>
<th>IPC (n = 229)</th>
<th>GCS (n = 180)</th>
<th>No Mechanical Thromboprophylaxis (n = 389)</th>
<th>Crude P Value</th>
<th>Propensity Score</th>
<th>Adjusted P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50.2 ± 11.2</td>
<td>47.4 ± 21.6</td>
<td>49.0 ± 21.5</td>
<td>52.3 ± 20.7</td>
<td>.15</td>
<td>1.00</td>
<td>.00</td>
</tr>
<tr>
<td>Female sex</td>
<td>263 (33.0)</td>
<td>71 (31.0)</td>
<td>50 (27.8)</td>
<td>142 (36.5)</td>
<td>.09</td>
<td>.67</td>
<td>.80</td>
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<tr>
<td>Time in hospital prior to enrollment, d</td>
<td>10.6 ± 29.6</td>
<td>9.3 ± 24.7</td>
<td>7.6 ± 25</td>
<td>12.8 ± 33.7</td>
<td>.0001</td>
<td>.20</td>
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</tr>
</tbody>
</table>

Admission physiologic data

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (N = 798)</th>
<th>IPC (n = 229)</th>
<th>GCS (n = 180)</th>
<th>No Mechanical Thromboprophylaxis (n = 389)</th>
<th>Crude P Value</th>
<th>Propensity Score</th>
<th>Adjusted P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II score</td>
<td>24.0 ± 9.0</td>
<td>24.2 ± 9.3</td>
<td>23.3 ± 8.5</td>
<td>24.2 ± 9.1</td>
<td>.53</td>
<td>.99</td>
<td>.99</td>
</tr>
<tr>
<td>Glasgow coma score</td>
<td>8.6 ± 4.1</td>
<td>7.4 ± 3.8</td>
<td>8.4 ± 3.9</td>
<td>9.4 ± 4.2</td>
<td>.001</td>
<td>1.00</td>
<td>.00</td>
</tr>
<tr>
<td>Creatinine, μmol/L-1</td>
<td>158.9 ± 144.7</td>
<td>142.5 ± 119.3</td>
<td>151.9 ± 153.1</td>
<td>171.9 ± 153.1</td>
<td>.04</td>
<td>1.00</td>
<td>.00</td>
</tr>
<tr>
<td>Platelets, ×10^9/L</td>
<td>244.4 ± 155.6</td>
<td>225.0 ± 131.3</td>
<td>277.3 ± 127.7</td>
<td>253.0 ± 162.3</td>
<td>.18</td>
<td>.98</td>
<td>.98</td>
</tr>
<tr>
<td>INR</td>
<td>1.4 ± 0.7</td>
<td>1.4 ± 0.8</td>
<td>1.4 ± 0.7</td>
<td>1.4 ± 0.7</td>
<td>.65</td>
<td>1.00</td>
<td>.65</td>
</tr>
<tr>
<td>PTT, s</td>
<td>42.4 ± 60.2</td>
<td>43.3 ± 51.9</td>
<td>43.3 ± 54.8</td>
<td>41.4 ± 66.8</td>
<td>.90</td>
<td>1.00</td>
<td>.90</td>
</tr>
</tbody>
</table>

Specific risk factors for VTE

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (N = 798)</th>
<th>IPC (n = 229)</th>
<th>GCS (n = 180)</th>
<th>No Mechanical Thromboprophylaxis (n = 389)</th>
<th>Crude P Value</th>
<th>Propensity Score</th>
<th>Adjusted P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>226 (28.3)</td>
<td>85 (37.1)</td>
<td>61 (33.9)</td>
<td>80 (20.6)</td>
<td>&lt;.001</td>
<td>.98</td>
<td>.98</td>
</tr>
<tr>
<td>Femur or pelvic fracture</td>
<td>52 (6.5)</td>
<td>11 (4.8)</td>
<td>11 (6.1)</td>
<td>30 (7.7)</td>
<td>.36</td>
<td>1.00</td>
<td>.36</td>
</tr>
<tr>
<td>and hip or knee replacement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bedridden status &gt;3 d</td>
<td>394 (49.4)</td>
<td>104 (45.4)</td>
<td>73 (41.7)</td>
<td>215 (55.3)</td>
<td>.004</td>
<td>1.00</td>
<td>.00</td>
</tr>
<tr>
<td>Malignancy</td>
<td>94 (11.8)</td>
<td>32 (14.0)</td>
<td>24 (13.3)</td>
<td>38 (9.8)</td>
<td>.22</td>
<td>1.00</td>
<td>.22</td>
</tr>
<tr>
<td>Recent surgery</td>
<td>243 (30.5)</td>
<td>91 (39.7)</td>
<td>49 (27.2)</td>
<td>103 (26.5)</td>
<td>.001</td>
<td>.92</td>
<td>.001</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>12 (1.5)</td>
<td>3 (1.3)</td>
<td>2 (1.1)</td>
<td>7 (1.9)</td>
<td>.79</td>
<td>.93</td>
<td>.79</td>
</tr>
<tr>
<td>Sepsis</td>
<td>168 (21.1)</td>
<td>45 (21.0)</td>
<td>34 (18.9)</td>
<td>86 (22.1)</td>
<td>.68</td>
<td>.88</td>
<td>.68</td>
</tr>
<tr>
<td>Use of vasopressors</td>
<td>408 (51.1)</td>
<td>127 (55.5)</td>
<td>96 (53.3)</td>
<td>185 (47.6)</td>
<td>.13</td>
<td>.87</td>
<td>.13</td>
</tr>
<tr>
<td>PRBC transfusion</td>
<td>390 (48.9)</td>
<td>132 (57.6)</td>
<td>74 (41.1)</td>
<td>184 (47.3)</td>
<td>.003</td>
<td>.94</td>
<td>.003</td>
</tr>
<tr>
<td>Central venous catheter</td>
<td>595 (74.6)</td>
<td>178 (77.7)</td>
<td>147 (81.7)</td>
<td>270 (69.4)</td>
<td>.003</td>
<td>1.00</td>
<td>.003</td>
</tr>
<tr>
<td>Hemodialysis catheter</td>
<td>158 (19.8)</td>
<td>45 (19.7)</td>
<td>32 (17.8)</td>
<td>81 (20.8)</td>
<td>.70</td>
<td>1.00</td>
<td>.70</td>
</tr>
<tr>
<td>Prophylactic UFH</td>
<td>411 (51.5)</td>
<td>97 (42.4)</td>
<td>80 (44.4)</td>
<td>234 (60.2)</td>
<td>.00</td>
<td>1.00</td>
<td>.00</td>
</tr>
<tr>
<td>Prophylactic enoxaparin</td>
<td>137 (17.2)</td>
<td>45 (19.7)</td>
<td>38 (21.1)</td>
<td>54 (13.9)</td>
<td>.00</td>
<td>1.00</td>
<td>.00</td>
</tr>
<tr>
<td>Botha</td>
<td>91 (11.4)</td>
<td>35 (15.3)</td>
<td>27 (15.0)</td>
<td>29 (7.5)</td>
<td>.000</td>
<td>.87</td>
<td>.000</td>
</tr>
<tr>
<td>No pharmacologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>thromboprophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic anticoagulation</td>
<td>67 (8.4)</td>
<td>19 (8.3)</td>
<td>7 (3.9)</td>
<td>41 (10.5)</td>
<td>.03</td>
<td>.03</td>
<td>.03</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or No. (%). Concomitant use of prophylactic UFH and enoxaparin is shown among the three groups of mechanical thromboprophylaxis used. APACHE = Acute Physiology and Chronic Health Evaluation; GCS = graduated compression stockings; INR = international normalized ratio; IPC = intermittent pneumatic compression; PRBC = packed RBC; PTT = partial thromboplastin time; UFH = unfractionated heparin.

To convert conventional units to mg/dL, divide by 88.4.

aBoth refers to the administration of UFH and enoxaparin at different periods of the ICU stay.

Study End Points

The primary end point was incident VTE (lower extremities DVT, PE, or both) during the ICU stay and up to 5 days after ICU discharge. Diagnostic tests were performed at the discretion of the treating team and included Doppler ultrasonography for the diagnosis of DVT and spiral CT scan of the chest and ventilation-perfusion scanning of the lungs for PE. Hospital mortality was the secondary end point.

Statistical Analysis

Continuous variables are reported as mean ± SD and categorical variables as counts and proportions. Comparison among groups (IPC, GCS, and no mechanical thromboprophylaxis) was done with analysis of variance, Kruskal-Wallis test, multinomial logistic regression, or χ² test, as appropriate. Because of the observed imbalances in baseline characteristics, the multiple propensity scores adjustment approach was used as detailed elsewhere. Three investigators (Y. M. A., M. K., S. I. D.) selected variables for the final model to drive propensity scores, which was done according to the findings of Brookhart et al. These variables were age, sex, time spent in the hospital prior to enrollment, APACHE (Acute Physiology and Chronic Health Evaluation) II score, Glasgow coma score, creatinine level, international normalized ratio, partial thromboplastin time level, recent trauma, recent femur or pelvic fractures or knee or hip replacement, bedridden status, presence of malignancy, recent surgery, packed RBC transfusion, presence of central venous or hemodialysis catheter, presence of sepsis, use of vasopressors, use of prophylactic UFH or enoxaparin, and use of therapeutic anticoagulation after enrollment. Because mechanical device categories (IPC, GCS, and no mechanical thromboprophylaxis) numbered more than two (the dependent variable), multinomial logistic regression analysis was carried out with the aforementioned selected variables as independent variables. The likelihood ratio test for the model, compared with the empty model, was assessed.

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Original Research

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Independence of irrelevant alternatives assumption and goodness of fit were checked with the Hausman and McFadden generalized goodness-of-fit tests, respectively. Three separate propensity scores were then derived from the model. Overlap of different propensity scores was checked visually with the box plot method. To check the balancing effect of propensity scores, two of three multiple propensity scores and their mutual interactions were used as covariates in an analysis of covariance for continuous variables and in multinominal logistic regression for categorical variables.

Finally, Cox regression analysis was done to estimate the crude and adjusted associations of IPC and GCS (compared with no mechanical thromboprophylaxis) on the occurrence of VTE. Three different adjusted models were performed including the two propensity scores, the selected variables mentioned earlier, or both. Results are reported as hazard ratios (HRs) with corresponding 95% CIs and associated P values. Wald test was used to investigate the presence of a significant interaction between the use of a mechanical device (IPC, GCS, or no mechanical thromboprophylaxis) and the type of prophylactic heparin used (UFH, enoxaparin, or none), recent trauma, and admission as a surgical patient. All tests were considered significant at the <.05 a level. Stata version 11 SE for Windows (StatCorp LP) was used in all analyses.

**Results**

**General**

The baseline characteristics and main VTE risk factors are shown in Table 1. The mean age was 50.2 ± 21.2 years. The first day mean APACHE II score was 24.0 ± 9.0. Of note, 28% of patients were admitted because of trauma, 31% had recent surgery, and 51% were receiving a vasopressor. Central venous catheterization was common either for IV access (75%) or hemodialysis (20%).

**Exposures**

The IPC group comprised 229 patients (28.7%), the GCS group comprised 180 patients (22.6%), and the no mechanical thromboprophylaxis group comprised 389 patients (48.7%). Concomitant pharmacologic thromboprophylaxis with UFH or enoxaparin is shown in Table 1.

**Propensity Scores**

The balancing effect of the generated propensity scores is shown in Table 1. When adjusted to propensity scores, all baseline characteristics were balanced. The only exception was the use of therapeutic anticoagulation after enrollment. This variable was also included from the multivariate model and showed no impact on effect estimates of the association of IPC or GCS with VTE. Box plots for the overlap of the three propensity scores among the three study groups are shown in Figure 1.

**Outcomes**

Incident VTE occurred in 57 patients (7.1%), with 11 in the IPC group (4.8%), 18 in the GCS group (10.0%), and 28 in the no mechanical thromboprophylaxis group (7.2%) (Table 2). A crude analysis showed that IPC use was associated with a significantly lower VTE risk (HR, 0.48; 95% CI, 0.24-0.97; P = .04). No significant change in this estimate was observed with propensity score adjustment (adjusted hazard ratio [aHR], 0.45; 95% CI, 0.22-0.95; P = .03), multivariate adjustment (aHR, 0.45; 95% CI, 0.21-0.94; P = .04), or both combined (aHR, 0.45; 95% CI, 0.22-0.95; P = .04). No significant association between the use of GCS and VTE was noticed in either crude (HR, 1.15; 95% CI, 0.64-2.08; P = .64), propensity score adjustment (aHR, 1.09; 95% CI, 0.59-2.04; P = .76), multivariate adjustment (aHR, 1.13; 95% CI, 0.60-2.12; P = .7), or both propensity score and multivariate adjustment combined (aHR, 1.24; 95% CI, 0.66-2.34; P = .5) (Fig 2, Table 3). No significant interaction was found between the mechanical thromboprophylaxis groups and the type of prophylactic heparin used (P = .99), recent trauma (P = .66), or recent surgery (P = .07).

The association of mechanical thromboprophylaxis with hospital mortality was not significant on crude or adjusted analyses for either IPC (propensity score aHR, 0.92; 95% CI, 0.68-1.24; P = .59) or GCS (propensity score aHR, 0.86; 95% CI, 0.62-1.21; P = .40) (Table 3). In addition, no significant interaction was observed between the mechanical thromboprophylaxis groups and type of prophylactic heparin used (P = .08), recent trauma (P = .47), or recent surgery (P = .07).

**Discussion**

We found that the use of IPC but not GCS was associated with a significantly decreased risk of incident VTE. This effect was consistent whether the patient was receiving concomitant prophylactic UFH or enoxaparin and whether the admission was related to trauma or surgery.
The effectiveness of IPC and GCS in preventing VTE has not been evaluated in RCTs in medical-surgical patients in the ICU\(^1\) as reflected in two systematic reviews.\(^{10,26}\) A systematic review by the Clinical Guidelines Committee of the ACP evaluated mechanical thromboprophylaxis as a group (GCS and IPC) in hospitalized nonsurgical patients.\(^{27}\) The review included three trials\(^{28-30}\) of which two studied GCS and one IPC. The results were influenced mainly by the largest trial, which used GCS and found no significant difference in risk for mortality, symptomatic DVT, or PE but did report an increased risk for lower-extremity skin damage compared with no thromboprophylaxis.\(^{30}\) Another systematic review by Limpus et al\(^{46}\) included two RCTs that compared IPC to low-molecular-weight heparin (LMWH) in patients with critical illness related to trauma\(^{11,31}\) and found IPC to be less effective. As such, the ACP clinical practice guidelines recommend that IPC use be reserved for patients with a contraindication to pharmacologic thromboprophylaxis.\(^8\) Systematic reviews and clinical practice guidelines\(^{3,16,17}\) combined IPC and GCS together in their meta-analyses and recommendations. The present study demonstrates that the effect of these two modalities on VTE is different and possibly opposing. Therefore, the two modalities should be analyzed and reported separately.

IPC is a mechanical method of delivering compression to the lower extremities.\(^{32}\) The thromboprophylaxis effect is believed to be related to enhanced venous blood flow in the legs, increase in endogenous fibrinolysis, stimulation of vascular endothelial cells, and reduction in the caliber of veins.\(^{32}\) Previous studies of IPC effectiveness yielded inconsistent findings. Existing studies have limitations related to sample size and study design. Additionally, the two existing RCTs were conducted in patients with trauma and used LMWH as a comparator.\(^{11,31}\) Such a comparison has little relevance at present because current clinical practice guidelines recommend pharmacologic thromboprophylaxis as the first choice. The present study demonstrates lower incident VTE with the use of IPC. This association was consistent regardless of the use and type of prophylactic heparin and the type of admission being trauma or surgical related. These findings suggest that the association of lower VTE risk with the use of IPC is not only significant if used as an alternative to UFH or enoxaparin but also significant if used as an adjunct to pharmacologic thromboprophylaxis. Considering the significantly lower risk observed with IPC (aHR, 0.45; 95% CI, 0.22-0.95), the combined strategy of pharmacologic thromboprophylaxis with IPC may be optimal in medical-surgical patients in the ICU.

The use of GCS in critically ill patients is common.\(^{13}\) GCS is believed to work by reducing the cross-sectional area of the veins and, thus, increasing blood velocity.\(^{32}\)

### Table 2—Number of Incident VTE Events According to Mechanical Thromboprophylaxis Used

<table>
<thead>
<tr>
<th>Occurrence of VTE</th>
<th>IPC (n = 229)</th>
<th>GCS (n = 180)</th>
<th>No Mechanical Thromboprophylaxis (n = 389)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>11 (4.8)</td>
<td>18 (10.0)</td>
<td>28 (7.2)</td>
</tr>
<tr>
<td>No</td>
<td>218 (95.2)</td>
<td>162 (90.0)</td>
<td>361 (92.8)</td>
</tr>
</tbody>
</table>

Data are presented as No. (%). See Table 1 legend for expansion of abbreviations.

Figure 2. Kaplan-Meier curves for VTE probabilities of the three categories of mechanical devices. See Figure 1 legend for expansion of abbreviations.
The present study demonstrates that GCS was not associated with lower VTE risk. The findings are consistent with previous evidence showing no reduction of VTE with GCS. In the Clots in Legs or Stockings after Stroke (CLOTS) I trial, 2,518 hospitalized patients with stroke were randomized to thigh-length GCS or to avoidance of GCS. GCS resulted in a nonsignificant difference in DVT risk of 0.9% (95% CI, 0.4-1.8%) but with increased skin complications (OR, 4.4; 95% CI, 2.4-7.8). In the CLOTS II trial, 3,114 hospitalized patients with stroke were randomized to thigh-length or below-knee stockings. DVT occurred less frequently with thigh-length stockings than with below-knee stockings (absolute difference, 2.5 percentage points; 95% CI, 0.7-4.4 percentage points) but with increased skin complications (OR, 4.18; 95% CI, 2.40-7.27). The present findings, the use of GCS, especially below-knee stockings, in critically ill patients needs to be explored further. Furthermore, in light of the present findings, the use of GCS, especially below-knee stockings, in critically ill patients needs to be reconsidered.

The interpretation of different studies on mechanical thromboprophylaxis should take into consideration the effect of context. Our hospital launched an institution-wide thromboprophylaxis campaign with implementation of clinical practice guidelines that recommend pharmacologic thromboprophylaxis as the primary mode of therapy. This campaign explains the fact that around 80% of the patients in our study were receiving both mechanical and pharmacologic thromboprophylaxis. This high rate of pharmacologic prophylaxis contrasts, for example, with the CLOTS I and II trials, in which the concomitant use of prophylactic UFH or LMWH during the study period was documented in around 12% to 14% of patients who were not receiving therapeutic anticoagulation. The higher use of pharmacologic thromboprophylaxis seen in the present study is likely to reduce the baseline risk of VTE and may underestimate the potential benefit of IPC or GCS.

The effectiveness of mechanical therapeutic interventions such as IPC or GCS is best examined in RCTs because they provide the best assurance that the observed differences in outcomes are unlikely to be related to confounders. Propensity scores in observational studies have been used to adjust for imbalances in baseline differences. Because investigators have no control over treatment assignment, the differences in the observed covariates between treated and control groups may explain all or part of the observed differences in the outcome and, in turn, may avoid biased estimates of treatment effect. The propensity score attempts to reduce biased estimates of treatment effect by balancing the observed effect of the covariates in one or more variables and is a more practical method than matching on several covariates, which may not always be possible.

The present study should be interpreted in terms of its strengths and limitations. Its clinical relevance stems from reflecting real-life practice. The VTE rate is consistent with other studies. The diagnostic approach for VTE is consistent with standard practice, being based on clinical suspicion rather than on surveillance. Although this approach might be less sensitive than the surveillance-based approach, it is more specific and clinically applicable in medical practice. Other strengths are the prospective inclusion of patients and the use of multiple propensity scores. To our knowledge, this study is the first to specifically address the impact of mechanical devices on VTE risk among medical-surgical patients in the ICU, and the results

| Table 3—Association of IPC and GCS Use With Outcomes |
|-----------------------------|---|---|---|---|
| Outcome                     | Crude Estimates | Propensity Score Adjusted Estimates |
|                             | HR (95% CI)     | P Value     | aHR (95% CI) | P Value     |
| VTE                         |                |             |              |             |
| IPC                         | 0.48 (0.24-0.97) | .04         | 0.45 (0.22-0.95) | .03         |
| GCS                         | 1.15 (0.64-2.08) | .64         | 1.04 (0.59-2.04) | .76         |
| Hospital mortality          |                |             |              |             |
| IPC                         | 0.84 (0.63-1.11) | .22         | 0.92 (0.68-1.24) | .59         |
| GCS                         | 0.73 (0.54-1.03) | .07         | 0.86 (0.62-1.21) | .40         |

Comparisons are made with the no mechanical device group as the reference group. aHR = adjusted hazard ratio; HR = hazard ratio. See Table 1 legend for expansion of other abbreviations.
may be generalizable to a wider population. In terms of limitations, the study was not an RCT; as such, the findings only highlight associations, and cause-and-effect relationships cannot be inferred. However, the various comparison groups were generally comparable, as confirmed by the propensity score analysis. Additionally, given the possible effect of unknown confounders and other issues attendant to an observational study, the observed treatment effect might be larger than the true effect.

CONCLUSIONS

In this single-center observational study of 1.5 years duration, we found that the use of IPC was associated with a lower risk of incident VTE, irrespective of concurrent administration of prophylactic UFH or enoxaparin. Furthermore, this association was not specific to admission category. On the other hand, the use of GCS was not associated with lower VTE risk. The study suggests that IPC may have an additive protective effect to pharmacologic thromboprophylaxis in critically ill medical-surgical patients.

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Author contributions: Dr Arabi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dr Arabi: contributed to the study conception and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and supervision and final approval of the version to be published.

Dr Khedr: contributed to the analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and final approval of the version to be published.

Dr Dara: contributed to the analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and final approval of the version to be published.

Dr Bhat: contributed to the acquisition of data, critical revision of the manuscript for important intellectual content, and final approval of the version to be published.

Dr Tanum: contributed to the analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and final approval of the version to be published.

Ms Afsh: contributed to the acquisition of data, critical revision of the manuscript for important intellectual content, and final approval of the version to be published.

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REFERENCES


