



# THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

## Routine VTE prophylaxis Is there a net health benefit?

**P**rophylaxis of venous thromboembolism (VTE) with low molecular weight heparin (LMWH) is now common for hospitalized non-surgical patients in British Columbia and much of North America. This includes patients who are at very low risk for a VTE. VTE events include deep vein thrombosis (DVT), usually in the legs, which can be either symptomatic or asymptomatic, as well as pulmonary embolism (PE).

Routine VTE prophylaxis for non-surgical patients in hospital (~85%)<sup>1,2</sup> is driven by two assumptions: a) VTE risk is high, and b) unfractionated heparin (UFH) and LMWH are effective in preventing VTE events.<sup>3,4</sup>

Because of the inclusion of asymptomatic VTE events in trials, and flaws in interpreting evidence for heparin prophylaxis, a rethink is needed in our efforts to reduce VTE-related morbidity and mortality.<sup>5</sup>

### What is the incidence of VTE in non-surgical hospitalized patients?

Some VTE guidelines warn of very high risks of DVT and PE amongst hospitalized medical patients,<sup>3,4</sup> while other guidelines are more conservative.<sup>6,7</sup>

VTE occurs in less than 2% of medical patients, mostly in hospital or within three months of hospital discharge.<sup>8-10</sup> Among the 15,000 patients enrolled in the International Medical Prevention Registry on VTE (IMPROVE) study, the 90-day incidence of symptomatic VTE was 1.2%. Symptomatic DVT, non-fatal PE and fatal PE were 0.44%, 0.32%, and 0.18% respectively.<sup>10</sup> These observational findings mirror randomized clinical trials (RCTs), which found similar incidences in medical patients not receiving heparin.<sup>11-13</sup>

### Evidence for thromboprophylaxis

A 2014 Cochrane systematic review (N=27,998) concluded that heparin prophylaxis (UFH or LMWH) versus placebo reduces the risk of DVT but increases the risk of bleeding, without reducing all-cause mortality. It considered the effects on non-fatal and fatal PE "imprecise".<sup>13</sup> Our detailed concerns about this Cochrane review are published as comments in the current version.<sup>14,15</sup>



The review did not analyze **symptomatic** DVT. The more frequently detected **asymptomatic** DVT is of debatable clinical importance.<sup>5</sup> Another major failure in this review concerns missing outcomes and other data not reported. (Table) For example, the two largest RCTs lacked data for 889 (16%) of all randomized patients.<sup>11,12</sup> DVT outcomes from three large RCTs comprising over 22,000 patients were not included in the Cochrane analysis because the RCTs did not report DVT as an outcome.<sup>16-18</sup> The two RCTs that contribute the most data to the Cochrane review reported PE incidence based on a denominator of only 3% of all patients randomized (i.e. trials only reported PE for people who died and underwent autopsy).<sup>17,18</sup>

The assumption for all patients who were missing from these analyses is that they did not have a DVT or PE. This approach most often exaggerates treatment effect estimates.<sup>19</sup> We have greater confidence in the Cochrane review conclusion that heparin prophylaxis does not reduce all-cause mortality, as 8 of the 10 largest trials reported on this outcome. Post-thrombotic syndrome is another morbidity arising from DVT, but no RCT reported on this outcome.

The Cochrane authors report that heparins increase the incidence of bleeding. Unfortunately, it is not possible to estimate the true magnitude of the increase because the review lacks data on bleeding from 42% of all patients randomized in RCTs.<sup>18</sup> For PREVENT, a large trial of dalteparin



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that represents 13% of all patients randomized in all RCTs, we were able to confirm that total serious adverse events (including deaths, VTE and major bleeds) were not reduced despite a reported reduction in VTE.<sup>12,20</sup>

A 2018 American Society of Hematology guideline also notes that mortality is not reduced by VTE prophylaxis of medical patients.<sup>7</sup> The authors report that any prevention of symptomatic VTE is counter-balanced by increased bleeding. Yet this guideline makes a “conditional recommendation” in favour of LMWH with “low certainty in the evidence of effects.”

### Real world evidence from the US and British Columbia

A state-wide evaluation of over 20,000 medical patients in Michigan found that hospitals with high rates of prophylaxis (>86% of patients) did not achieve a lower 90-day rate of VTE compared with hospitals using less frequent prophylaxis (>55% of patients).<sup>21</sup> Another analysis of 140,000 medical patients concluded that in-hospital thromboprophylaxis had no impact on the burden of VTE in the community.<sup>9</sup>

Currently the majority of hospitalized medical patients receive prophylaxis, even though 70 to 80% are considered “low risk” for VTE.<sup>1,22</sup>

In British Columbia, an analysis of hospitals within Fraser Health and Vancouver Coastal Health found that of all the medical patients who received VTE prophylaxis, at least 70% were considered low risk when prophylaxis was started,<sup>22</sup> basing “risk” on the predictive model derived from the IMPROVE study.<sup>10</sup> This suggests that many patients at low risk of VTE now receive prophylaxis, despite its uncertain effect on VTE and an increased risk of harm.

### Can we better identify people at risk?

The current flawed approach to routine VTE prophylaxis in medical patients risks overtreatment of low risk patients. Risk assessment tools such as the IMPROVE model are externally validated and could be used in clinical practice.<sup>9,10</sup> The “IMPROVE RAM” quickly discriminates “low risk” patients from “higher risk” patients (previous VTE, current cancer, known thrombophilia, lower limb paralysis or immobilization for more than 7 days).<sup>9,10,23,24</sup>

### Conclusions

- The risk of symptomatic VTE in hospitalized medical patients is less than 2%.
- Prophylaxis with low molecular weight heparins does not reduce all-cause mortality.
- **Prophylaxis has unknown effects on PE/DVT (due to missing outcome data), but increases the risk of major bleeds.**
- Risk assessment tools for DVT (such as IMPROVE RAM) can identify patients at low risk of VTE.

**Table: Data used in the Cochrane meta-analysis versus amount of missing data from RCTs**

Outcome	Heparin (LMWH or UFH) Events / denominators reported for putative absolute differences in Cochrane meta-analysis	Placebo Events / denominators reported for putative absolute differences in Cochrane meta-analysis	% of randomized patients on whom meta-analytic results are based
DVT (asymptomatic or symptomatic)	112 / 2,931	172 / 2,580	DVT not reported in 23,363 of 27,988 randomized patients (83%). Putative difference of 60 DVT derives from only 17% of all randomized patients.
PE (non-fatal and fatal)	33 / 14,100	50 / 13,871	PE not reported in 13,661 of 27,988 randomized patients (49%). Putative difference of 17 PE derives from only 51% of all randomized patients.
Major bleed (trial definitions vary)	44 / 7,094	24 / 6,710	Major bleeds not reported for 11,693 of 27,988 randomized patients (42%). Putative difference of 20 major bleeds derives from only 58% of all randomized patients.

For the complete list of references go to: <https://ti.ubc.ca/letter120>