

## JOURNAL CLUB CRITIQUE

# Does dalteparin PROTECT better than heparin?

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### Expanded abstract

#### Citation

The PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group: Dalteparin versus Unfractionated Heparin in Critically Ill Patients. *N Engl J Med* 2011, 364:1305-1314.

#### Background

It is unclear whether there is a clinically significant advantage to prophylactic low-molecular-weight heparin (LMWH) versus unfractionated heparin (UFH) in mixed medical/surgical critically ill adult patients.

#### Methods

**Objective:** To compare once daily dalteparin with twice daily unfractionated heparin for primary prophylaxis of proximal deep venous thrombosis in critically ill adults.

**Design:** A superiority randomized double-blinded controlled trial from 2006 to 2010 in both medical and surgical ICUs. (ClinicalTrials.gov registration number: NCT00182143)

**Setting:** Multi-center, international medical and surgical intensive care units (ICUs)

**Subjects:** Critically ill adults expected to remain in the ICU for at least 3 days.

**Intervention:** Patients were randomized to either twice daily UFH or daily dalteparin for the duration of ICU admission.

**Outcomes:** The primary endpoint was proximal leg deep venous thrombosis (DVT), at least three days after randomization, detected on twice weekly screening ultrasound. Secondary endpoints were: any DVT, pulmonary embolism (PE), venous thromboembolism (VTE), death, heparin-induced thrombocytopenia (HIT), major bleeding, and composite death/VTE.

#### Results

Three thousand seven hundred and forty-six subjects were included in the intention-to-treat analysis. Proximal leg DVT occurred in 96 of 1873 (5.1%) patients randomized to dalteparin versus 109 of 1873 (5.8%) patients randomized to UFH (hazard ratio in the dalteparin group, 0.92; 95% confidence interval [CI], 0.68 to 1.23;  $P = 0.57$ ). The incidence of PE was 1.3% in the dalteparin group compared to 2.3% in the UFH group (hazard ratio, 0.51; 95% CI, 0.30 to 0.88;  $P = 0.01$ ). There was no mortality difference and no difference in major bleeding between the two study arms. There was a statistically significant decrease in incidence of HIT in the dalteparin group in the per-protocol analysis, but not in the intention-to-treat analysis.

#### Limitations

Comparing the incidence of PE was a secondary endpoint and the study was not appropriately powered for this conclusion.

#### Conclusions

Among critically ill adult patients, dalteparin was not superior to UFH at preventing proximal lower extremity DVTs. There is a suggestion that dalteparin might be superior to UFH at preventing pulmonary embolism but a larger trial is necessary to confirm this result.

#### Commentary

Venous thromboembolism (VTE) is a significant cause of morbidity and mortality [1] and critically ill patients are at a higher risk [2] of developing deep venous thrombosis (DVT) and pulmonary thromboembolism (PE) compared to non-critically ill patients. Low molecular weight heparin (LMWH) has shown superiority and is recommended over unfractionated heparin (UFH) in certain patient populations (such as trauma, spinal cord injury, and orthopedics [3]) but has not been well studied for general ICU patients. There have been four randomized studies of VTE prophylaxis in critically patients [4-7]. These studies showed decreased VTE with UFH and LMWH prophylaxis compared to placebo, but were underpowered to determine superiority of LMWH versus UFH. The PROTECT study was the largest study

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to date comparing LMWH to UFH prophylaxis in general ICU patients.

PROTECT was a multi-center, randomized, double blinded prospective trial which enrolled adult general intensive care unit (ICU) patients who were expected to have an ICU length of stay greater than 3 days. The primary endpoint was proximal lower extremity DVT detected on twice weekly screening ultrasound. Secondary endpoints included any DVT, PE, VTE, death, heparin-induced thrombocytopenia, major bleeding, and composite of death/VTE. The study was designed to detect a 30% relative risk reduction of proximal leg DVT in the dalteparin arm compared to the UFH arm assuming a control arm incidence of 9% [8]. The study failed to show a 30% relative risk reduction in rates of proximal leg DVT in the dalteparin (5.1%) group compared to the UFH (5.8%) group. The incidence of PE was 2.3% in the UFH group compared to 1.3% in the dalteparin group (hazard ratio, 0.51; 95% CI, 0.30 to 0.88;  $P = 0.01$ ).

Strengths of this trial include multicenter recruitment, intention-to-treat analysis and randomized double blind design. The authors conducted a pilot trial of 128 patients [8] before commencing the main trial. Because of slow recruitment in the pilot trial, the authors trimmed PROTECT's exclusion criteria: they included all renal failure patients regardless of estimated glomerular filtration rate and included more patients with thrombocytopenia. These changes broadened the study group and made the PROTECT's results more generalizable.

Despite being a very large study, PROTECT may have needed more subjects to reveal a statistically significant reduction of DVTs. PROTECT's control arm event rate was less than the one used in the power calculation which may have underpowered the trial. The study failed to reject the primary null hypothesis and could not exclude a 32% benefit or a 23% harm associated with dalteparin versus UFH. Even though the incidence of DVT was similar in both arms, the study had a superiority design and therefore, we should not conclude non-inferiority between the two groups. The statistically significant reduction in incidence of PE must be taken with caution because this was a secondary endpoint and applying the results of a secondary endpoint to a general patient population has inherent uncertainty [9]. Furthermore, it is difficult to determine the clinical significance of a 1% reduction of PE without a reduced rate of proximal DVT or reduced mortality.

The PROTECT trial was negative for the primary endpoint of proximal DVT but does provide us with the best evidence to date regarding LMWH versus UFH for

critically ill adults. No firm conclusions can be drawn from PROTECT even though there is a hint dalteparin might be superior to UFH (lower rates of PE and heparin-induced thrombocytopenia), but the data are just not robust enough to answer those questions.

## Recommendation

The PROTECT study is the best data to date comparing LMWH to UFH for primary prophylaxis of proximal leg DVT in critically ill adult patients. There is no conclusive evidence supporting the use of dalteparin in lieu of UFH; however, dalteparin appears to be a safe alternative to UFH for VTE prophylaxis in general ICU patients. We would recommend dalteparin over UFH if overall healthcare costs were similar or lower.

## Competing interests

The authors declare that they have no competing interests.

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