Eradication of hospital-acquired venous thromboembolism

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Pulmonary embolism (PE) causes nearly 200,000 deaths annually in the United States alone. The magnitude of the risk for acquiring venous thromboembolism (VTE) in U.S. hospitals is staggering (1). About 8 million Medical Service and 4 million Surgical Service patients are at moderate or high risk for developing VTE each year (2).

The surgeon General has declared that PE is the most preventable cause of death within hospitals (3). Thus, a spotlight shines brightly on quality control and quality improvement practices within American hospitals (4) to ensure that maximum effort is exerted to prevent PE and deep venous thrombosis (DVT). A convergence of passionate advocates (5), including health care providers, patients, and governmental authorities, will transform the status quo and enable eradication of hospital-acquired VTE. Catalysts for VTE eradication are listed in Table 1.

Failure to prevent in-hospital PE and DVT will no longer be tolerated. For example, Medicare and Medicaid will have stopped reimbursing hospitals for incremental care needed to treat postoperative total hip or knee replacement patients who develop VTE (6). Whether this new policy is wise or equitable is debatable (7), but its influence in augmenting VTE prophylaxis and in decreasing the rate of postoperative VTE is undeniable.

We have entered a new era that focuses on venous disease. This contemporary heightened awareness to VTE prevention constitutes a remarkable achievement. Only a decade ago, VTE was an orphan disease which received only a modicum of attention from major cardiology, pulmonary, and haematology specialty societies. Major organisations representing these specialties were concerned about VTE but did not embrace the field as a top priority. Transformative champions who had argued in favour of paying more attention to preventing venous thrombosis had to compete with more forceful voices that favoured emphasis on more traditional core subject matter for each organisation. Examples are acute coronary syndrome for cardiologists, asthma/chronic lung disease for pulmonologists, and leukaemia/lymphoma for haematologists. Venous disease education tended to be handled as an “afterthought.” Discussion of VTE’s wide scope and potential for harm did not capture the imagination of professionals or the public. Apathy was a common response when the subject of VTE was raised. There was no unifying push toward universal protection of hospitalised patients against DVT and PE.

Failure to prescribe VTE prophylaxis

The lack of emphasis on VTE prevention is evident by reviewing the results of clinical practice surveys showing that most high risk patients have not received prophylaxis. A review of almost 200,000 discharged, high risk Medical Service patients from 227 hospitals found that appropriate VTE prophylaxis was ordered in only 34% (8). Prophylaxis is omitted more often in medical patients who, ironically, suffer PE (rather than DVT) more often than non-medical patients (9). This phenomenon has been named “Double Trouble” (9). In Canada, a survey of 1,700 acutely ill medical patients showed that only 16% received appropriate VTE prophylaxis (10). In a Swiss VTE registry, almost half of high-risk patients received no prophylaxis (11). Similar findings were observed in a multicentre study of Italian Medical Service patients (12).

The “failure-to-prophylax syndrome” is a profound problem that is global in scope. It remains uncertain why VTE prophylaxis is so frequently withheld in high-risk patients, even though rigorous clinical trials have demonstrated efficacy and safety for pharmacological prevention with low, fixed doses of anticoagulants. Only half of high-risk patients received prophylaxis in a survey of 15,000 acutely ill medical patients, enrolled from 52 hospitals in 12 countries (13). In the even larger ENDORSE Study of 68,000 patients, with 32 countries participating from six continents, only 58% of Surgical Service and 40% of Medical Service patients received prophylaxis among those at moderate or high risk for VTE (14).

Physicians as a group tend to be conservative and slow to adopt change. This might be one fundamental reason why implementation of prophylaxis has been slow. Another possibility is that physicians are so busy and overworked taking care of their patients that they do not feel they have time to deal with problems that are not immediately apparent. Preventive efforts require extra time to develop strategies that block poor clinical outcomes. Improvement will require a change in physician culture that embraces VTE prophylaxis. This transformation has now begun.

Efficacy and safety of pharmacological VTE prophylaxis

A meta-analysis of 20,000 hospitalized medical patients in nine studies showed that those who received pharmacological prophylaxis had a two-thirds reduction in fatal PE and a non significant increase in
major bleeding (15). Six studies used low-molecular-weight heparin (LMWH); two used unfractionated heparin (UFH); and one used fondaparinux. The LMWH regimens were: enoxaparin 40 mg daily, dalteparin 5,000 U daily, and nadroparin 7,500 U daily. The UFH regimens were 5,000 U either twice or three times daily. The fondaparinux trial used 2.5 mg once daily. A separate meta-analysis of pharmacological VTE prophylaxis in hospitalised medical patients compared LMWH versus UFH (16). LMWH was associated with a one-third lower risk of DVT and had half the risk of injection site hematoma compared with UFH. Using a hypothetical cohort of high risk medical patients in a decision analysis model, LMWH was more cost effective than UFH (17).

It has become clear that major bleeding complications in VTE prophylaxis trials constitute a strong predictor of mortality. When fondaparinux was examined in VTE prevention trials, patients who developed major bleeding were more likely to be male, have lower body weight, and have chronic kidney disease. At 30 days, the mortality rate was 8.6% among those with major bleeding versus 1.7% in those without major bleeding (18).

In addition to anticoagulants, two other pharmacological approaches appear promising for VTE prophylaxis: vitamin E supplementation (19) and rosuvastatin (29). The Women’s Health Study randomised 39,876 women to receive 600 Units of vitamin E or placebo (19). After a median follow-up of 10 years, there was a 21% reduction in VTE among women assigned to vitamin E. The reduction was most striking among women with VTE prior to randomisation and in women with either the factor V Leiden mutation or the prothrombin gene mutation.

With respect to statin therapy for VTE prophylaxis, 17,802 apparently healthy men and women with both normal low-density lipoprotein cholesterol levels of less than 130 mg/dl and elevated high-sensitivity C-reactive protein levels of 2.0 mg/dl or higher were randomised to receive rosuvastatin, 20 mg per day, or placebo (20). During a median follow-up period of 1.9 years, symptomatic VTE was reduced by 43% in the rosuvastatin group.

### Mechanical VTE prophylaxis

Mechanical VTE prophylaxis consists primarily of graduated compression stockings or intermittent pneumatic compression devices. Mechanical measures are prescribed for patients who have an absolute contraindication to anticoagulation. A meta-analysis of intermittent pneumatic compression devices was undertaken in 2,270 postoperative patients from 15 studies. In comparison to no prophylaxis, intermittent pneumatic compression devices reduced the risk of DVT by 60% (21). These mechanical devices also appear to be cost effective (22). Nevertheless, pharmacological prophylaxis appears to be much more effective than intermittent pneumatic compression for preventing VTE in general surgery patients (23). Furthermore, in a large study of patients with major, debilitating strokes, thigh-high graduated compression stockings, which were applied without pharmacological prophylaxis, did not confer any protection against the development of proximal leg DVT (24).

### Optimal duration of VTE prophylaxis

Failure to prophylax during hospitalisation has adverse effects that continue after hospital discharge (25). In a survey of 1,897 patients with VTE in the Worcester, Massachusetts area, 74% developed DVT or PE in the outpatient setting. Of the 516 who had been hospitalised within the prior three months and subsequently developed VTE, many did not receive prophylaxis, and 67% developed VTE within one month following the hospitalisation. In a separate study of middle aged women undergoing surgery, the risk of VTE was substantially increased during the first 12 postoperative weeks, especially for those undergoing hip or knee replacement or cancer surgery (26). In the large RIETE Registry of VTE, the average time elapsed from surgery to VTE was three weeks (27). These findings indicate the need to extend the duration of VTE prophylaxis in high-risk patients beyond hospital discharge.

### Modifying physician behaviour to improve VTE prophylaxis

There is a wide gap between clinical trial evidence favouring prophylaxis and physicians’ ordering preventive measures among hospitalised patients at risk for VTE. Computerised decision support can improve implementation of prophylaxis (28) and has applications for quality improvement in other areas of medicine, such as dyslipidaemia treatment (29). In the United States, there have been low levels of adoption of electronic health records (30). However, it is clear that hospitals with automated notes, records, order entry, and clinical decision support have fewer complications, lower mortality rates, and lower costs (31). With the passage of the 2009 American Recovery and Reinvestment legislation, there exists new impetus in the United States to provide incentives for

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**Table 1: Catalysts for VTE eradication.**

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<th>Catalysts for VTE eradication</th>
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<td>Evidence favouring pharmacological VTE prophylaxis in rigorous clinical trials</td>
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<td>Surgeon General’s Report on pulmonary embolism as #1 preventable cause of death</td>
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<td>Hospital Quality Improvement Committees</td>
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<td>Peer pressure</td>
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<td>Advocacy, with groups such as the North American Thrombosis Forum (<a href="http://www.NATFonline.org">www.NATFonline.org</a>)</td>
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<td>Computerised Electronic Alerts if physician omits VTE prophylaxis</td>
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<td>Multiscreen alerts, with default VTE prophylaxis ordered by the computer for high-risk patients (allowing physician to “opt out”)</td>
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<td>“Human” Alerts</td>
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<td>Lack of Medicare reimbursement for VTE after total hip or knee replacement</td>
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<td>Expanded educational programming on VTE prevention</td>
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<td>Extended prophylaxis that continues after hospital discharge</td>
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adoption of electronic medical records (32).

At Brigham and Women’s Hospital, we have used electronic alerts to prevent VTE among hospitalised patients. In a randomised trial of 2,500 high-risk patients, we showed that institution of a computer alert program increased physicians’ use of VTE prophylaxis and reduced the rate of symptomatic DVT and PE by more than 40% (33). After completing this randomised trial, we discontinued the control group, and we implemented the computer alert for all patients who were at high risk but not receiving orders for VTE prevention. Over time, the hospital “culture” and practice evolved so that ordering VTE prophylaxis within the hospital became a universal expectation. Therefore, the gap between clinical trial evidence and “real-world” practice narrowed. And physicians’ orders for preventive measures in hospitalised high-risk patients became the norm. In a subsequent observational study, only 9% of high-risk patients did not receive prophylaxis orders and required computerised electronic alerts to their physicians (34).

We have upgraded our computer alert from the initial single screen version to a multi-screen set of alerts. Our new advanced algorithm increases the use of VTE prophylaxis among physicians who have declined an initial, traditional single screen alert reminder (35). Our multi-screen alert also provides a “default option” that automatically orders prophylaxis unless the physician specifically “opts out” (36). It appears that electronic alert systems for VTE prevention will maintain effectiveness over time, without physicians succumbing to “alert fatigue” (37).

For those hospitals without the capability to target computer reminders to physicians caring for patients at high risk of VTE, an alternative strategy uses a human alert. This system consists of a direct page from a hospital staff member to the attending physician when high-risk hospitalised patients are not receiving prophylaxis. In a multicentre randomised trial, we found that this program of direct notification of the physician by a staff member increased prophylaxis use and reduced the rate of symptomatic DVT and PE by about 20% (38).

**Extended beneficial effects of VTE prophylaxis**

The benefits of universal prophylaxis of high-risk hospitalised medical patients are profound. Based upon data from the U.S. Healthcare Cost and Utilization Project Nationwide Inpatient Sample database, VTE related events afflict two of every 100 acutely ill hospitalised medical patients. Most frequently affected are patients with heart failure, respiratory failure, pneumonia, and cancer. With probability modelling, symptomatic DVT, PE, and deaths from VTE will be halved if universal prophylaxis is utilised (39). Furthermore, long-term benefits will extend at least five years by drastically reducing the number of cases of delayed complications, such as postthrombotic syndrome and chronic thromboembolic pulmonary hypertension (40).

**Conclusions**

In summary, eradication of most hospital-acquired VTE is within our reach. We have the evidence-based clinical trials with which we can formulate and implement VTE prophylaxis policy. We have achieved a consensus that preventing in-hospital death from PE is a top priority. And by combining educational efforts with behaviour modifying tools such as computerised and “human” alerts to physicians, we can maximise implementation of proven preventive strategies. By extending VTE prophylaxis at hospital discharge for patients who remain at high risk, we can start an aggressive program to minimise out-of-hospital PE and DVT that occurs in the community setting.

**References**

19. Glynn RI, Ridker PM, Goldhaber SZ, et al. Effects of random allocation to vitamin E supplementation