Disease burden and unmet needs for prevention of venous thromboembolism in medically ill patients in Europe show underutilisation of preventive therapies

Hanane Khoury¹; Sharon Welner¹; Maria Kubin²; Kerstin Folkerts²; Sylvia Haas³

¹BioMedCom Consultants inc., Montreal, Quebec, Canada; ²Bayer Schering Pharma AG, BSP-GMACS-GHEOR-GM, Wuppertal, Germany; ³Institut für Experimentelle Onkologie und Therapieforschung, Universität München, Munich, Germany

Summary
It was the aim of this review to assess the incidence of venous thromboembolism (VTE) and current practice patterns for VTE prophylaxis among medical patients with acute illness in Europe. A literature search was conducted on the epidemiology and prophylaxis practices of VTE prevention among adult patients treated in-hospital for major medical conditions. A total of 21 studies with European information published between 1999 and April 2010 were retrieved. Among patients hospitalised for an acute medical illness, the incidence of VTE varied between 3.65% (symptomatic only over 10.9 days) and 14.9% (asymptomatic and symptomatic over 14 days). While clinical guidelines recommend pharmacologic VTE prophylaxis for patients admitted to hospital with an acute medical illness who are bedridden, clear identification of specific risk groups who would benefit from VTE prophylaxis is lacking. In the majority of studies retrieved, prophylaxis was under-used among medical inpatients; 21% to 62% of all patients admitted to the hospital for acute medical illnesses did not receive VTE prophylaxis. Furthermore, among patients who did receive prophylaxis, a considerable proportion received medication that was not in accord with guidelines due to short duration, suboptimal dose, or inappropriate type of prophylaxis. In most cases, the duration of VTE prophylaxis did not exceed hospital stay, the mean duration of which varied between 5 and 11 days. In conclusion, despite demonstrated efficacy and established guidelines supporting VTE prophylaxis, utilisation rates and treatment duration remain suboptimal, leaving medical patients at continued risk for VTE. Improved guideline adherence and effective care delivery among the medically ill are stressed.

Keywords
Venous thromboembolism, thromboprophylaxis, hospitalised medically ill patients, burden, clinical practice

Introduction
Venous thromboembolism (VTE), which comprises deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a serious, potentially life-threatening, yet preventable, multifactorial disease that occurs when a blood clot forms in a vein and may be dislodged from its site of origin. Using 2004 data for six countries in the European Union, it was estimated that a substantial number of events, approximately 465,700 DVT and 296,000 PE, were diagnosed annually, resulting in over 370,000 fatalities (1). Certain patients are prone to developing VTE as a result of the combination of predisposing (i.e. age, family history) and exposing (i.e. immobilisation, acute medical illness, trauma, surgery, and certain therapies) risk factors (2). Medical illnesses that independently increase VTE risk include congestive heart failure (CHF), cancer, ischaemic stroke, renal and respiratory failure, hypertension, diabetes, chronic pulmonary disease, severe infection, and inflammatory diseases (3–6). Patients hospitalised for an acute medical illness carry multiple VTE risk factors, which have been reported to result in an eight-fold increase in VTE risk compared to the general population (3).

Medical patients account for 75% of fatal VTE cases (3, 7); 74% of all VTE events diagnosed during hospitalisation occur in patients admitted for medical reasons, compared to 26% attributed to surgical inpatients (8). Despite this considerable burden, VTE risk and preventive measures are less well defined in the medical population, leaving many high-risk patients unprotected (4). Although the efficacy of VTE prophylaxis among medically ill patients has been demonstrated in a number of clinical trials (9–14), a high proportion of medical patients at risk for VTE still do not receive appropriate prophylaxis (4).

The purpose of this review is to assess recent evidence from Europe on the clinical burden of VTE in hospitalised medically ill patients and current strategies for its prevention.

Thrombosis and Haemostasis 106.4/2011
Methods

Literature search

Literature providing evidence for the epidemiology and prophylaxis practices of VTE prevention among medical patients with acute illnesses who were hospitalised for a major medical condition was gathered, with a particular focus on cardiovascular disease (heart failure, stroke), cancer, acute infections, and acute respiratory disease.

A large part of the pertinent literature was retrieved from a structured Medline search of the National Library of Medicine’s PubMed. The search algorithm included combinations of the following key terms: thromboembolism (deep vein thrombosis OR Embolism OR Pulmonary Embolism OR thromboembolic events OR Thromboembolism OR Thrombosis OR Venous Thromboembolism OR Venous Thrombosis OR VTE); acutely ill medical patients (patients; acute medical* ill*; immobilised; mobility limitation; hospital* OR inpatient OR Intensive Care; heart failure OR stroke OR cancer OR acute infection OR infectious disease OR acute respiratory insufficiency OR COPD OR chronic obstructive pulmonary disease OR asthma); epidemiology (incidence OR epidemiology); prevention (prophylaxis OR prevention & control OR guidelines OR practices OR registries). International and European studies limited to human adults and published between 1999 and April 2010 were retrieved. Case reports, letters and news items were excluded.

To further capture country-specific studies, additional PubMed searches were performed combining general keywords (venous thromboembolism AND medical) to the following: UK OR France OR Germany OR Italy OR Belgium OR Spain OR Austria OR Sweden OR Norway OR Denmark OR Finland OR Greece OR Poland OR Portugal OR Ireland OR the Netherlands OR Switzerland.

In addition, the Cochrane reviews database and relevant non-Medline/Embase listed journals were searched for the keyword thromboembolism. Online abstracts from the last three annual

Table 1: Incidence of VTE among acutely ill hospitalised medical patients not receiving prophylaxis.

<table>
<thead>
<tr>
<th>Study/Region</th>
<th>Population characteristics</th>
<th>Reason for hospitalisation (% patients)</th>
<th>Outcomes definition (diagnostic tests)</th>
<th>VTE assessment timeframe</th>
<th>VTE events* % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARTEMIS trial Cohen, 2006&lt;sup&gt;12&lt;/sup&gt; International</td>
<td>Placebo group of RCT n=420 Mean age 74 Inclusion: ≥60 years; expected to be bedridden ≥4 days</td>
<td>CHF (25%) Acute infectious or inflammatory disease (25%) Acute respiratory disease (22%) More than one reason (27%)</td>
<td>Composite of objective confirmation DVT (routine bilateral venography) Symptomatic VTE confirmed symptomatic PE (high probability lung scan, pulmonary angiography, helical computed tomography, or autopsy)</td>
<td>15 days</td>
<td>10.5 (34/323)</td>
</tr>
<tr>
<td>MEDENOX trial Samama, 1999&lt;sup&gt;15&lt;/sup&gt; Alikhan, 2004&lt;sup&gt;9&lt;/sup&gt; International</td>
<td>Placebo group of RCT n=371 Mean age 73 Inclusion: &gt; 40 years; hospitalised ≥ 6 days; prior immobilisation ≤3 days</td>
<td>Acute CHF (34%) Acute infectious disease (52%) Acute respiratory failure (54%) Acute rheumatic disorder (9%)</td>
<td>Objectively confirmed DVT (systematic ascending contrast venography, venous ultrasound, PE (high probability lung scan, pulmonary angiography, helical computed tomography, or at autopsy), or both</td>
<td>14 days 110 days</td>
<td>14.9 (43/288) 17.1 (45/263)</td>
</tr>
<tr>
<td>PREVENT trial Leizorovicz, 2004&lt;sup&gt;11&lt;/sup&gt; International</td>
<td>Placebo group of RCT n=1,473 Mean age 68 Inclusion: ≥40 years; acute medical condition requiring hospitalisation ≥4 days; prior immobilisation ≤3 days</td>
<td>Acute CHF (51%) Infectious disease (38%) Acute respiratory failure (30%) Rheumatologic disorder (11%)</td>
<td>Composite of objective confirmation symptomatic DVT fatal or symptomatic non-fatal PE sudden death asymptomatic proximal DVT (systematic compression ultrasound)</td>
<td>21 days</td>
<td>4.96 (73/1473)</td>
</tr>
<tr>
<td>GEMINI study Gussoni, 2009&lt;sup&gt;16&lt;/sup&gt; Italy</td>
<td>Prospective observational cohort of consecutive patients n=4,846 Mean age 71 Inclusion: admission to internal medicine units</td>
<td>CHF (16%) COPD exacerbation (16%) Cancer (16%) Cerebrovascular disease (20%) Diabetes (22%)</td>
<td>Objectively confirmed symptomatic VTE (instrumental diagnosis)</td>
<td>Hospital stay (mean: 10.9 days)</td>
<td>3.65 (177/4846)</td>
</tr>
</tbody>
</table>

*among patients hospitalised. CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; DVT: deep vein thrombosis; PE: pulmonary embolism; RCT: randomised control trial; RF: risk factor; VTE: venous thromboembolism.
meetings of the American Society of Hematology (ASH), the European Hematology Association (EHA), and the International Society for Pharmacoeconomic and Outcomes Research (ISPOR) were also searched for the keyword thromboembolism, and the returned abstracts checked for relevance. Finally, titles retrieved from the “related articles” function of Medline were also perused.

Data analyses

Unless otherwise specified, data were extracted as originally reported by authors. For studies with mixed populations (medical, surgical, and general), only data relevant to non-surgical medical patients were collected. Studies reporting pooled data from mixed populations were excluded. Analysis of prophylaxis use across disease groups was conducted with a special focus on the following diseases: cardiovascular disease (heart failure, stroke), cancer, respiratory disease, and infectious disease.

Incidence data were extracted for untreated populations from control groups of antithrombotic clinical trials, prospective cohorts of at-risk patients, comparators to specific disease groups, and database studies. VTE incidence was defined as symptomatic, asymptomatic, or composite endpoint (including all symptomatic and asymptomatic events), according to the data reported for each study.

Results

Incidence of VTE in medically ill patients in Europe

To establish a baseline reference for the incidence of VTE among hospitalised medical patients with acute illness not receiving pro-

Table 2: Clinical guidelines for VTE prevention in acutely ill medical patients.

<table>
<thead>
<tr>
<th>Recommending body; Country</th>
<th>Target population</th>
<th>Recommendation</th>
<th>Duration</th>
<th>Not recommended (if explicitly stated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICE, 2007 (17); UK</td>
<td>Patients likely to be in hospital for &gt; 4 days and with reduced mobility, with either severe HF, respiratory failure (due to exacerbation of chronic lung disease or pneumonia), acute infection, inflammatory illness or cancer (with additional risk factors for VTE)</td>
<td>● All medical patients should be considered for thromboprophylaxis measures ● Heparins (UFH, LMWH preferred)</td>
<td>NS</td>
<td>● Aspirin ● Mechanical methods</td>
</tr>
<tr>
<td>Afssaps, 2010 (18); France</td>
<td>Medical patients &gt; 40 years, immobilised &gt; 3 days, or likely to be hospitalised for &gt; 3 days due to CHF, acute respiratory disease, or one of the following conditions combined to additional VTE risk factors: severe infection, acute rheumatic disease, or IBD</td>
<td>● Heparins (LMWH preferred; UFH) ● Fondaparinux ● Mechanical compressions for patients with contraindications to pharmacological prophylaxis</td>
<td>7–14 days</td>
<td>Systematic LMWH prophylaxis for cancer patients with catheters</td>
</tr>
<tr>
<td>AWMF, 2009 (19); Germany</td>
<td>Immobilised acutely ill medical patients</td>
<td>● High dose LMWH, fondaparinux ● Mechanical compressions for patients with contraindications to anticoagulants</td>
<td>6–14 days (until discharge for cancer patients)</td>
<td>NS</td>
</tr>
<tr>
<td>SIGN, 2002 (20); Scotland</td>
<td>Hospitalised patients with acute major medical illness</td>
<td>● UFH (s.c. low dose 5000 IU 8–12 hourly or 7500 IU 12 hourly), or ● LMWH</td>
<td>5 days or until discharge</td>
<td>NS</td>
</tr>
<tr>
<td>ACCP, 2008^ US</td>
<td>Acutely ill medical patients admitted to hospital with CHF or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, sepsis, acute neurological disease, or IBD</td>
<td>● LMWH, low dose UFH, or fondaparinux ● Mechanical compressions (GCS or IPC) recommended for patients with contraindications to anticoagulants (bleeding risk)</td>
<td>Until hospital discharge</td>
<td>● Aspirin alone ● Routine use of primary thromboprophylaxis for cancer patients receiving chemotherapy or hormonal therapy ● Routine use of primary thromboprophylaxis to improve survival of cancer patients</td>
</tr>
</tbody>
</table>

ACCP: American College of Chest Physicians; AWMF: Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; GCS: graduated compression stockings; HF: heart failure; IBD: inflammatory bowel disease; IPC: intermittent pneumatic compression; LMWH: low molecular weight heparin; NS: not specified; s.c.: subcutaneous; SIGN: Scottish Intercollegiate Guidelines Network; UFH: unfractionated heparin; VTE: venous thromboembolism
phylaxis, the placebo groups of three large international trials (9, 11, 12, 15) and an observational cohort from one prospective observational study (16) were evaluated; results are shown in Table 1. When considering both symptomatic and asymptomatic events (determined using venography), VTE incidence was reported in 10.5% (12) and 14.9% (15) of medically ill patients over 15 and 14 days, respectively. After 110 days, the latter study showed that VTE incidence had increased to 17.1% of remaining evaluable patients (15). Studying a younger population (mean age 68 vs. 73–74 [12, 15]), the PREVENT trial reported VTE diagnosis of symptomatic and asymptomatic events (determined using ultrasound) in 4.96% of medical patients over 21 days (11). In reporting the incidence of hospital-acquired symptomatic VTE alone, a large prospective cohort study found that 3.65% of patients admitted to internal medicine departments over a mean stay of 10.9 days experienced symptomatic VTE events (16). This indicates that a substantial proportion of medical patients admitted to the hospital with acute illnesses are at risk for VTE.

Clinical guidelines for VTE prophylaxis among medically ill patients

To determine recommended treatment for VTE prophylaxis among medically ill patients in Europe, clinical guidelines pertaining to this population were sourced; major guidelines are shown in Table 2. In Europe, evidence-based recommendations for VTE prophylaxis in medical patients with acute illness are available from the National Institute for Health and Clinical Excellence (NICE) (17) and from the French Health Products Safety Agency (Afssaps) (18); country-specific recommendations from Germany (19) and Scotland (20) are also available. Summary recommendations published for Spain (21, 22) and the UK (23) further support major guidelines; they have not been tabulated. For reference, since several studies refer to the American College of Chest Physicians (ACCP) clinical guidelines for VTE risk assessment and prophylaxis use, they have been included in Table 2 (4).

Review of these publications show that European guidelines, similar to the widely used ACCP (4) recommendations, assign a moderate-to-high risk profile to hospitalised medical patients with acute illness. Thromboprophylaxis is recommended for those admitted with CHF or severe respiratory disease, and for immobilised patients with active cancer, sepsis, acute neurological disease, or inflammatory bowel disease. Heparins (preferably LMWH) and the indirect factor Xa inhibitor fondaparinux are recommended for a duration of 7–14 days or until hospital discharge (17, 18). Aspirin is not recommended for VTE prevention in medical patients (17). Mechanical compressions are not recommended in the UK (17); in France and Germany, however, they are recommended for patients for whom pharmacological prophylaxis is contraindicated (18, 19). Overall, European guidelines for VTE prevention in medical patients with acute illnesses recommend prophylaxis with heparins or fondaparinux for at least the duration of hospital stay.

Studies investigating VTE prophylaxis among medically ill patients

As indicated in Figure 1, this literature search retrieved 24 original studies reporting VTE prophylaxis among medical patients with acute illness in European populations. Table 3 shows that studies originated from France, Germany, Hungary, Italy, Poland, Spain, Switzerland, the Netherlands, and the UK, in addition to multi-country studies. Retrieved studies included randomised controlled trials, registries, chart audits, meta-analyses, and cross-sectional, retrospective, and observational studies.

Most articles reported pooled data from hospitalised medically ill patients in general; a few studies (16, 24–29) reported data stratified by disease group. Reasons for hospitalisation included cancer, cardiovascular disease (CHF, myocardial infarction, stroke, hyper-
Table 3: VTE prophylaxis use in hospitalized acutely ill medical patients*.

<table>
<thead>
<tr>
<th>Country</th>
<th>Study design</th>
<th>Medical population: n, mean age</th>
<th>Patients at VTE risk, n (%) risk criteria</th>
<th>Prophylaxis use, n (%)**</th>
<th>Prophylaxis duration, mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>International</td>
<td>Cross-sectional survey – ENDORSE study N=37,356 Age 70</td>
<td>15,487 (41.5) – ACCP</td>
<td>7,419 (47.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>International</td>
<td>Cross-sectional chart audit – ENDORSE study N=37,356 Age 67 (median)</td>
<td>15,487 (41)</td>
<td>6,119 (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>International</td>
<td>Observational – IMPROVE registry N=15,156 Age 68 (median)</td>
<td>7,640 (50)</td>
<td>5–7 days (correlates with hospital stay)</td>
<td>Post-discharge (12%)</td>
<td></td>
</tr>
<tr>
<td>International</td>
<td>Multicountry survey – Oncologists Cancer patients</td>
<td>NS (&lt; 5)</td>
<td>Duration of hospital stay</td>
<td>90 days for patients on chemotherapy</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>Retrospective observational N=89 inpatients Age 66.4</td>
<td>42 (47) – MEDENOX</td>
<td>40 (95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>Prospective cross-sectional N=812 Age 82 (median)</td>
<td>409 (49)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>Cross-sectional N=1,032 Age 67.6</td>
<td>330 (32)</td>
<td>188 (57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>Multicenter cross-sectional N=852 Age 82</td>
<td>NS (56)</td>
<td>33.8 days (median 25) (correlates with hospital stay)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>Prospective observational N=334 Age 72.5</td>
<td>NS (56)</td>
<td>&gt; 10 days (27% patients) (correlates with hospital stay)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>Cross-sectional survey N=1,194 Age 60</td>
<td>High: 18 (6) Moderate: 160 (56)</td>
<td>284 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>Sub-analysis – ENDORSE N=1,160 Age 74 (median)</td>
<td>479 (41.3) – ACCP</td>
<td>370 (77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td>Sub-analysis – ENDORSE N=865 Age 71 (median)</td>
<td>266 (31) – ACCP</td>
<td>89 (33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>Multicenter prospective observational – GEMINI N=4,846 Age 71</td>
<td>40.9%</td>
<td>NS (58)</td>
<td>11.4 ± 10.1 days (correlates with hospital stay)</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>Meta-analysis N=1,184</td>
<td></td>
<td>5 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td>Observational – EPIID registry N=5,246 Age 71</td>
<td>100% (MEDENOX population)</td>
<td>3,320 (63)</td>
<td>8.1 days</td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td>Sub-analysis – ENDORSE N=1,581 Age 73 (median)</td>
<td>514 (32) – ACCP</td>
<td>239 (46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>Hospital chart review N=6,460 Age 55</td>
<td>303 (9.7) – PRE-TEMED</td>
<td>149 (49)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
tension), infectious disease (other than pulmonary), respiratory disease (chronic obstructive pulmonary disease exacerbation, respiratory failure, pulmonary infection), diabetes, rheumatoid arthritis, inflammatory disease, kidney or liver disease.

Overall, where reported, the average patient age was approximately 69 years, ranging from 55 years (30) to 84 years (31) (Table 3). The proportion of patients at risk for VTE was roughly 40% of study populations, and ranged from 9.7% (30) to 86% (27).

It should be noted that criteria used to assess patients at risk varied among studies, and was based on ACCP guidelines, the thromboembolic risk factors (THRIFT) I Consensus, the prevention of thromboembolic venous disease in medical patients (PRETEMED), or the Geneva risk score.

**Rates of VTE prophylaxis**

A number of studies reported that the proportion of hospitalised medical patients with acute illnesses for whom pharmacological prophylaxis was contraindicated did not exceed 10% (16, 24, 26, 28, 29, 32). Based on this information, it was assumed that 90% of hospitalised medical patients at risk for VTE should receive prophylactic medication. However, the majority of studies captured in this search reported suboptimal prophylaxis rates, which were below 90% (Table 3) (16, 24–46). Figure 2 shows that rates varied between 42% and 77% among the medically ill patients in general (disease not specified), and between 38% and 79% among patients hospitalised due to cancer, cardiovascular, respiratory, or infectious disease (16, 24, 26–29). Consequently, 21% to 62% of hospitalised medical patients who would benefit from VTE prophylaxis were not offered any preventive treatment.

**Prescribing patterns of VTE prophylaxis**

In these studies, low-molecular-weight heparin (LMWH) was the most widely prescribed anticoagulant prophylaxis (up to 96% of all prescriptions) (16, 24–46), followed by unfractionated heparin (UFH) and oral anticoagulants (OAC). Although not recommended by guidelines in the majority of cases, mechanical prophylaxis was used by 8.2% to 41.6% of patients to whom prophylaxis was prescribed, either alone or in combination with pharmacological therapy (25, 27, 29, 33, 34, 36, 43).

---

Table 3: Continued

<table>
<thead>
<tr>
<th>Country</th>
<th>Study (reference)</th>
<th>Study design</th>
<th>Medical population: n, mean age</th>
<th>Patients at VTE risk, n (%)</th>
<th>Prophylaxis use, n (%)**</th>
<th>Prophylaxis duration, mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>Nieto Rodriguez, 2009 (46)</td>
<td>Sub-analysis – ENDORSE</td>
<td>N=2,069 Age 71 (median)</td>
<td>1,140 (55) – ACCP</td>
<td>731 (64)</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>Villar Fernandez, 2004 (41)</td>
<td>Prospective</td>
<td>N=394 Age 68–77</td>
<td></td>
<td>NS (43)</td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>Chopard, 2009 (32)</td>
<td>Sub-analysis – ENDORSE</td>
<td>N=847</td>
<td>179 (21)</td>
<td>109 (61)</td>
<td></td>
</tr>
</tbody>
</table>
| Switzerland | Kucher, 2008 (27) | Prospective registry – SWIVTER | N=306 Age 62 ± 16 | 262 (86) – Geneva risk score | 146 (56) | Pharmacological ● 8 days, median (range 5–12)  
Mechanical ● 10 days (range 8–13) |
| Switzerland | Augesky, 2002 (42) | Retrospective chart review | N=227 Age 69 | 153 (67) – THRIFT I Consensus | 101 (66) | Until discharge – 11 ± 5 days (33[22%] patients) |
| UK       | South, 2007 (31) | Medical records audit | N=601 Age 84.6 | 117 (19.5) | 34 (29) | |
| UK       | Rashid, 2005 (43) | Prospective observational | N=1,062 | 429 (40.4) – THRIFT | NS (29) | |

* unless otherwise specified, patients were acutely ill medical patients in general (mixed diseases).  
** among patients at risk for VTE. NS: not specified.
Prophylaxis duration

In general, when VTE prophylaxis was given, it was done so until hospital discharge (16, 24, 26, 27, 34, 35, 38, 40, 42), consistent with clinical recommendations. One observational study reported extended prophylaxis beyond hospital discharge only in a small proportion of the study patients (12%) (34). Mean prophylaxis duration varied across studies for the most part between five days (from a meta-analysis) (40) and 11 days (16, 42). In France, VTE prophylaxis was extended to 33.8 days among elderly patients (mean age 82 years) in hospital or in rehabilitation departments, coincident with an extended hospital stay (24). Further, in a multi-country study of cancer patients, VTE prophylaxis was stated to continue most commonly up to 90 days for patients on chemotherapy (35).

Inadequate use of prophylaxis

Not only was the rate of VTE prophylaxis in hospitalised medically ill patients less than optimal, as shown above, but among those who did receive prophylaxis, a considerable proportion received VTE preventive treatment that was not in agreement with clinical guidelines (inadequate prophylaxis) (27–29, 31, 32, 36, 42, 44–46). Reasons for disagreement with guidelines included insufficient anticoagulation duration, reported for 44% of patients on prophylaxis (42), treatment of patients for which prophylaxis was not indicated (i.e. patients with low VTE risk; 21%-38%) (36, 42); and use of inappropriate dose or type of prophylaxis (e.g. the use of mechanical prophylaxis only).

Discussion

This literature review shows that although hospitalised medical patients with acute illnesses are particularly at risk for developing VTE, there is a gap between clinical recommendations for VTE prophylaxis and the use of available therapies in Europe. The majority of studies reported that more than half, and up to 79%, of high-risk hospitalised medical patients received no VTE preventive treatment. Among patients who received prophylaxis, inadequate duration or type of therapy was prescribed in up to 44% of cases (42).

Many possible reasons for prophylaxis underuse among hospitalised medical patients with acute illnesses have been proposed in studies from different regions of the world (31, 43, 47–51). The lack of physician awareness of and adherence to treatment guidelines is an important barrier to identifying high-risk populations, and subsequently to implementing optimal prophylaxis (31, 43, 50). Several strategies have been adopted to increase adequate prophylaxis use (52). Risk assessment models have been developed to facilitate clinical decision-making (2, 53). Electronic alert programs based on programmed risk models have been implemented, resulting in improved prophylaxis use to a certain extent (6, 54–56). One study showed that physician alert reduced VTE incidence from 4.13 to 2.23 events per 1,000 patients (odds ratio [OR] 0.54; 95% confidence interval [CI] 0.20–1.33) (30). In another study, guideline implementation decreased DVT incidence and the rate of inadequate prophylaxis use significantly (57). In either example, however, there was still a considerable proportion of alerted physicians who opted against the use of prophylaxis, suggesting that other factors may be involved, such as fear of bleeding risk and other adverse events associated with pharmacological
prophylaxis (58, 59). Another level of complexity in the identification of target populations for prophylaxis is that risk factors vary from one person to another (6), emphasising the need for risk assessment on an individual basis.

At the patient level, limitations with currently available treatment options, such as inconvenience of injectable formulations, may negatively affect adherence to therapy. Inefficient transfer of medical information between health care providers and ineffective care delivery following hospital discharge may result in prophylaxis underuse, which could lead to increased medical incidents such as myocardial infarction and cardiac death among discharged patients (60, 61). Programs designed to facilitate information transfer and continued patient counselling after hospital discharge should improve patient outcomes (62).

Insufficient duration of prophylaxis may result in inadequate prevention of VTE or increased risk of recurrence. In this review, several studies reported prophylaxis use for the duration of hospital stay, in agreement with the clinical guidelines for a moderate-risk patient population, while reports of shorter prophylaxis duration were noted in up to 44% of patients (42). Although prolonged prophylaxis duration (38 days to several months) was shown to be beneficial in the elderly (> 75 years), in cancer patients and those with prior VTE (53, 63–65), extended anticoagulant use may be associated with increased risk of bleeding in susceptible patients (66). Further assessment of extended prophylaxis is warranted. Some limitations to assessing the results of this review should be noted. In general, a wide heterogeneity was noticed throughout studies in terms of population characteristics, data reporting and analysis, making comparison across studies difficult. For example, patient populations varied and different risk assessment criteria were used to identify patients eligible for VTE prophylaxis (e.g. ACCP [4], THRIFT [5], PRETEMPED [21]); regardless of the criteria used, however, prophylaxis underuse was consistently reported in these studies. Incidence data were reported over different time frames, and could not be annualised because it is not necessarily linear. In addition, many cases of incomplete data reporting were evident in the studies retrieved. For example, duration of prophylaxis was not always explicitly stated; neither were the proportion of patients at risk for VTE and those with contraindication to anticoagulants.

In summary, this review shows that VTE prophylaxis utilisation is suboptimal among the hospitalised acutely ill medical patients who are at risk for VTE, emphasising the need for improved guideline adherence and effective care delivery within this population.

Acknowledgements
The authors wish to thank Bill O’Neil for assistance with original data extraction. This study was funded by Bayer Schering Pharma AG.

Conflict of interest
Hanane Khoury and Sharon Welner received consultancy fees from Bayer Schering Pharma AG to conduct the study. Maria Kubin and Kerstin Folkerts are Bayer Schering Pharma AG employees. Sylvia Haas received honoraria from Bayer Schering Pharma AG for advisory board and speakers bureau activities.

References


