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A nation-wide initiative against venous thromboembolism

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Summary

There is a gap between knowledge and recommendations regarding venous thromboembolism (VTE) on the one hand and daily practice on the other. This fact has prompted a Swiss multidisciplinary group consisting of angiologists, haematologists, internists, and emergency medicine and pharmaceutical medicine specialists interested in VTE, the SAMEX group, to set up a series of surveys and studies that give useful insight into the situation in our country. Their projects encompassed prophylactic and therapeutic aspects of VTE, and enrolled over 7000 patients from five academic and 45 non-academic acute care hospitals and fifty-three private practices in Switzerland. This comprehensive Swiss Clinical Study Programme forms the largest database surveying current clinical patterns of VTE management in a representative sample of the Swiss patient population.

Overall the programme shows a lack of thromboprophylaxis use in hospitalised at-risk medical patients, particularly in those with cancer, acute heart or respiratory failure and the elderly, as well as under-prescription of extended prophylaxis beyond hospital discharge in patients undergoing major cancer surgery. In regard to VTE treatment, planning of anticoagulation duration, administration of LMWH for cancer-associated thrombosis, and the use of compression therapy for prevention of post-thrombotic syndrome in patients with symptomatic proximal DVT require improvement.

In conclusion, this programme highlights insufficient awareness of venous thromboembolic disease in Switzerland, underestimation of its burden and inconsistent application of international consensus statement guidelines regarding prophylaxis and treatment adopted by the Swiss Expert Group.

Key words: *deep vein thrombosis; pulmonary embolism; prevention; treatment; epidemiology*

Introduction

The best estimates indicate that 350 000 to 600 000 Americans annually suffer from venous thromboembolism (VTE), and that at least 100 000 deaths may be directly or indirectly related to this disease. As stressed in a Call to Action of the US Surgeon General in 2008 [1], this is far too many, since many of these deaths could be avoided.

The US Institute of Medicine has classified the failure to provide hospitalised, at-risk patients with appropriate screening and preventive treatment as a medical error, and the US Agency for Healthcare Research and Quality has ranked the provision of such preventive treatment as one of the most important things that can be done to improve patient safety. Proven, effective measures are available to prevent and treat deep vein thrombosis (DVT) and pulmonary embolism (PE) in high-risk individuals. Yet today a substantial proportion of individuals who could benefit from such proven services do not receive them.

Obviously there is a gap between knowledge and recommendations [2] on the one hand and daily practice on the other. Thus, the global ENDORSE survey showed that 59% of hospitalised at-risk surgical patients and 40% of at-risk medical patients were given appropriate thromboprophylaxis [3].

These data prompted a Swiss multidisciplinary group consisting of angiologists, haematologists, internists, and emergency medicine and pharmaceutical medicine specialists interested in VTE – the SAMEX Group – to convene once a year between 2006 and 2011 to discuss ways of closing this gap. They did more than just discuss, since their yearly meeting ended with a series of surveys and studies that provide useful insight into the situation in our country (table 1) [4–11]. Their projects encompassed prophylactic and therapeutic aspects of VTE, and enrolled over 7000 patients from five academic, 45 non-academic acute care hospitals and fifty-three private practices in Switzerland. Overall, 76% of the patients were recruited in the German- and 24% in the French-speaking part of Switzerland, while 40% of the patients were enrolled in academic and 60% in non-academic centres.

In the present review we aim to summarise the results of the prospective comprehensive Swiss Clinical Study Programme in a meaningful conclusion which will alert and specifically advise physicians with a view to improvement of current VTE management in Switzerland.

Current consensus guidelines

According to the consensus guidelines of the American College of Chest Physicians (ACCP) [2] endorsed and commented on by the Swiss Expert Group (SEG) [12], all hospitalised medical and surgical patients should be systematically assessed for the presence or absence of VTE risk factors, and thromboprophylaxis is indicated in patients at high risk (grade 1A). Grade 1 and Grade 2 refer to the risk to benefit balance that is either clear (grade 1) or unclear (grade 2), whilst the suffixes A to C refer to the quality of evidence (A high, B intermediate, and C poor quality) [13]. After hospital discharge, extended prophylaxis for up to 35 days after surgery in patients with total hip replacement or fracture (grade 1A), knee replacement (grade 2B), and major cancer surgery (grade 2A) is recommended.

In patients with acute VTE, initial parenteral anticoagulation with unfractionated heparin, low-molecular-weight heparin (LMWH), or fondaparinux is indicated (grade 1A) for at least 5 days and until the target INR is reached for ≥24 hours (grade 1C), followed by administration of vitamin K-antagonist (VKA). Three-month anticoagulation with VKA is recommended for the treatment of provoked VTE (grade 1A) or first isolated distal DVT (grade 2B), and indefinite-duration anticoagulation should be considered for patients with unprovoked proximal or unprovoked recurrent VTE (grade 1A). The risk-benefit ratio of indefinite-duration anticoagulation shall be periodically evaluated (grade 1C). In patients with acute cancer-associated VTE, the recommendation mandates anticoagulation therapy for an indefinite duration or until the cancer is resolved, and the recommended modalities include LMWH for 3–6 months (grade 1A), followed by VKA or LMWH for patients with active cancer (grade 1C).

In patients with symptomatic proximal DVT, the use of elastic compression stockings or bandages is recommended for a minimum of 2 years to prevent post-thrombotic syndrome (grade 1A).

Thromboprophylactic aspects

In the Swiss ENDORSE survey [4], 2000 patients were included of whom 1153 (58%) were in surgical wards and 847 (42%) in medical wards. According to the ACCP criteria [2], the proportion of surgical patients at VTE risk was similar in Switzerland (68%, between hospital range 48–86%) in comparison with the global ENDORSE study [3] (64%) ($p = 0.296$). The rate of at-risk medical patients was lower in Switzerland (21%, range 3–44%) than in the global study (42%) ($p<0.001$). The proportion of at-risk surgical patients with ACCP-recommended VTE prophylaxis was higher in Switzerland (81%, between-hospital range 76–93%) than in the global study (59%) ($p<0.001$). Among medical patients at risk, the use of recommended thromboprophylaxis was higher in Switzerland (61%, between-hospital range 0–84%) than in the global survey (40%) ($p<0.001$). However, 56% of the patients with cancer, 41% with major trauma, and 29% undergoing vascular surgery received no prophylaxis. Briefly, in Switzerland, although the rate of recommended thromboprophylaxis was higher than in many countries it is still improvable, es-

Table 1: Studies conducted in the frame of the SAMEX initiative on VTE in Switzerland.

Study acronym	Aim of study	Publication
Swiss ENDORSE	Assessment of prevalence of VTE risk in hospitalised medical and surgical patients and of according thromboprophylaxis.	Swiss Med Wkly 2009;139:630–5
SWIVTER	Evaluation of prophylaxis use in hospitalised patients prior to VTE.	J. Thromb. Haemost. 2008;6:2082–7 Ann. Oncol. 2010;21:931–5
IMPART	Randomised comparison of various clinical decision support systems for improving thromboprophylaxis in acutely ill hospitalised medical patients.	J. Thromb. Haemost. 2010;8:1230–4
ESTIMATE	Prospective evaluation of a risk assessment model for predicting the need for thromboprophylaxis in acutely ill hospitalised medical patients.	Study completed
ESSENTIAL	Assessment of extended thromboprophylaxis in patients undergoing major orthopaedic or major cancer surgery.	Thromb. Haemost. 2009; 102:56–61
OTIS-DVT	Evaluation of practice patterns for the outpatient treatment of DVT and of planned duration of anticoagulant treatment.	Thromb. Res. 2011;127:406–10 Thromb. Haemost. 2011;105:239–44
SWIVTER II	Assessment of long-term anticoagulant prescription in cancer patients with VTE.	Thromb. Haemost. 2011;105:962-7
SWIVTER III	Evaluation of practice patterns for primary and secondary prophylaxis in cancer patients with VTE.	Study ongoing

pecially in medical patients at risk. Consequently, hospitalwide strategies for systematic risk factor assessment and implementation of practical tools to ensure appropriate use of prophylaxis in patients at VTE risk are mandatory.

This information was complemented by the SWIVTER Registry [5]. In 14 Swiss hospitals, 567 consecutive patients (306 medical, 261 surgical) with acute VTE and hospital stay <30 days prior to the VTE event were enrolled. Prophylaxis had been administered in 329 (58%) patients during the previous hospital stay. Among the medical patients, 146 (48%) had received prophylaxis, and among the surgical patients 183 (70%) had received prophylaxis (p<0.001). The indication for prophylaxis was present in 262 medical patients (86%) and in 217 (83%) surgical patients. Among the patients with an indication for prophylaxis, 135 of the medical patients (52%) and 165 of the surgical patients (76%) received prophylaxis (p<0.001). Admission to the intensive care unit [odds ratio (OR) 3.28, 95% confidence interval (CI) 1.94–5.57], recent surgery (OR 2.28, 95% CI 1.51–3.44), bed rest >3 days (OR 2.12, 95% CI1.45–3.09), obesity (OR 2.01, 95% CI 1.03–3.90), prior deep vein thrombosis (OR 1.71, 95% CI 1.31–2.24), and prior pulmonary embolism (OR 1.54, 95% CI 1.05–2.26) were independent predictors of prophylaxis. In contrast, cancer (OR 1.06, 95% CI 0.89–1.25), age (OR 0.99, 95% CI 0.98–1.01), acute heart failure (OR 1.13, 95% CI 0.79–1.63) and acute respiratory failure (OR 1.19, 95% CI 0.89–1.59) were not predictive of prophylaxis. Hence, although an indication for prophylaxis was present in most patients who subsequently (within one month) suffered acute VTE, almost half did not receive any form of prophylaxis during the previous hospital stay. Future efforts should focus on the improvement of prophylaxis for hospitalised patients, particularly in patients with cancer, acute heart or respiratory failure, and in the elderly.

In the subpopulation of SWIVTER with cancer [6], 153 patients (60%) were receiving prophylaxis (49% pharmacological and 21% mechanical) before the onset of acute VTE. Outpatient status at the time of VTE diagnosis [OR 0.31, 95% confidence interval (CI) 0.18–0.53], ongoing chemotherapy (OR 0.51, 95% CI 0.31–0.85), and recent chemotherapy (OR 0.53, 95% CI 0.32–0.88) were univariately associated with the absence of VTE prophylaxis. In multivariate analysis, intensive care unit admission within 30 days (OR 7.02, 95% CI 2.38–20.64), prior deep vein thrombosis (OR 3.48, 95% CI 2.14–5.64), surgery within 30 days (OR 2.43, 95% CI 1.19–4.99), bed rest >3 days (OR 2.02, 95% CI 1.08–3.78), and outpatient status (OR 0.38, 95% CI 0.19–0.76) remained the only independent predictors of thromboprophylaxis. Thus, although most hospitalised cancer patients were at high risk, 40% received no prophylaxis before the onset of acute VTE, a situation which clearly calls for improvement, particularly in the presence of recent or ongoing chemotherapy.

In the frame of IMPART [7], we compared various tools aiming at improving the adequacy of thromboprophylaxis among hospitalised acutely ill medical patients. We randomly assigned medical services across Switzerland to a pocket digital assistant programme (PDA), pocket cards (PC), and no clinical decision support system (CDSS) as controls. In centres using an electronic chart, an e-alert system (eAlerts) was developed. After 4 months we compared post-CDSS with baseline thromboprophylaxis adequacy for the various CDSS and control groups. Overall, 1085 patients were included (395 controls, 196 PC, 168 PDA, 326 eAlerts), 651 pre- and 434 post-CDSS implementation: 472 (44%) presented a risk of VTE justifying thromboprophylaxis (32% pre, 61% post) and 556 (51%) received thromboprophylaxis (54% pre, 47% post). The overall adequacy of pre- and post-CDSS implementation was 56% and 51% for controls (P = 0.29), 67% and 45% for PC (P = 0.002), 66% and 65% for PDA (P = 0.99), 51% and 56% for eAlerts (P = 0.37) respectively, eAlerts limited over-prescription (56% pre, 31% post, P = 0.01). Hence, while pocket cards and handhelds did not improve thromboprophylaxis adequacy, eAlerts had a modest effect, particularly in reducing overprescription. This effect only partially contributes to improvement of patient safety, and more work is needed towards institution-tailored tools.

As a follow-up study ESTIMATE was set up to prospectively validate the Geneva Risk Assessment Model (RAM) [14] through evaluation of the relationship between the combined rate of fatal and non-fatal symptomatic VTE (primary endpoint) and bleeding events at 90 days after hospital admission on the one hand, and the calculated risk score provided by the Geneva RAM at hospital admission on the other. The study will include at least 1000 patients, a goal that is about to be reached.

Because a substantial proportion of venous thromboembolic events do occur after hospital discharge as initially reported in a large retrospective study from Geneva University Hospital [15], extended prophylaxis has been recommended in high-risk patients undergoing major orthopaedic surgery or major cancer surgery [2]. In ESSENTIAL [8] we prospectively investigated thromboprophylaxis in 1046 consecutive patients undergoing major orthopaedic (70%) or major cancer (30%) surgery in 14 Swiss hospitals. Appropriate in-hospital prophylaxis was used in 1003 patients (96%). At discharge, 638 patients (61%) received prescription for extended pharmacological prophylaxis: 564 (77%) after orthopaedic surgery, and 74 (23%) after cancer surgery (p<0.001). Patients with knee replacement (94%), hip replacement (81%), major trauma (80%), and therapeutic arthroscopy (73%) had the highest prescription rates for extended VTE prophylaxis; the lowest rates were in patients undergoing major surgery for thoracic (7%), gastrointestinal (19%), and hepatobiliary (33%) cancer. Thus, approximately one quarter of the patients with major orthopaedic surgery and more than three quarters of the patients with major cancer surgery did not receive prescription for extended VTE prophylaxis.

Therapeutic aspects

The SWIVTER II and the OTIS-DVT registries [9–11] focused on therapeutic aspects of venous thromboembolism. Among 1247 patients with acute VTE enrolled in the prospective Swiss Venous Thromboembolism Registry (SWIVTER) II from 18 hospitals, 315 (25%) had cancer of whom 179 (57%) had metastatic disease, 159 (50%) ongoing or recent chemotherapy, 83 (26%) prior cancer surgery, and 63 (20%) recurrent VTE. Long-term anticoagu-

lation treatment for >12 months was more often planned in patients with vs. without cancer (47% vs. 9%; p<0.001), with recurrent cancer-associated vs. first cancer-associated VTE (70% vs. 41%; p<0.001), and with metastatic vs. non-metastatic cancer (59% vs. 31%; p<0.001). In patients with cancer, recurrent VTE (OR 3.46; 95%CI 1.83–6.53), metastatic disease (OR 3.04; 95%CI 1.86–4.97), and no acute infection (OR 3.55; 95%CI 1.65–7.65) were independently associated with the intention to maintain anticoagulation for >12 months. In conclusion, long-term anticoagulant treatment for more than 12 months was planned in less than half of the cancer patients with acute VTE, which is at variance with the ACCP recommendations [16].

Along the same lines, in the prospective Outpatient Treatment of Deep Vein Thrombosis in Switzerland (OTIS-DVT) registry [10] of 502 patients with acute, objectively confirmed lower extremity DVT (59% provoked or first distal DVT; 41% unprovoked proximal, unprovoked recurrent, or cancer-associated DVT) from 53 private practices and 11 hospitals, we investigated the planned duration of anticoagulation at the time of treatment initiation. The decision to administer limited-duration anticoagulation therapy was made in 343 (68%) patients with a median duration of 107 days (interquartile range 91–182) for provoked or first distal DVT, and 182 days (interquartile range 111–184) for unprovoked proximal, unprovoked recurrent, or cancer-associated DVT. Among patients with provoked or first distal DVT, anticoagulation was recommended for <3 months in 11%, ≥3 months in 63%, and for an indefinite period in 26%. Among patients with unprovoked proximal, unprovoked recurrent, or cancer-associated DVT, anticoagulation was recommended for <6 months in 22%, 6–12 months in 38%, and for an indefinite period in 40%. Overall, there was more frequent planning of indefinite-duration therapy from hospital physicians as compared with private practice physicians (39% vs. 28%; p = 0.019). Obviously, considerable inconsistency in planning the duration of anticoagulation therapy mandates an improvement in risk stratification of outpatients with acute DVT.

In the same study [9], diagnosis of DVT was done in 95% of the cases, preceded by D-dimer testing in 53%. Low-molecular-weight heparin (LMWH) was prescribed for a median (IQR) duration of 7 (5–12) days in 83% of patients, and vitamin K-antagonists for 163 (92–183) days in 81%. Mechanical measures to prevent post-thrombotic syndrome were prescribed in 83%; compression stockings or bandages for a median (IQR) duration of 364 (101–730) days from hospital physicians, and 92 (45–183) days from private practice physicians (p<0.001). Among patients with symptomatic proximal DVT, mechanical measures were prescribed for at least 2 years in 24% patients; 55% in hospital, and 6% in private practice (p<0.001). Among patients with cancer-associated DVT, the median (IQR) duration of LMWH therapy was 16 (8–45) days, and 35% received LMWH for less than 90 days. In summary, the use of mechanical measures in patients with symptomatic proximal DVT and the administration of LMWH for a long-term therapy of cancer-associated DVT require improvement to comply with current guidelines.

Conclusions

This comprehensive Swiss Clinical Study Programme forms the largest database surveying current clinical patterns of VTE management in a representative sample of the Swiss patient population. Overall, the programme shows a lack of thromboprophylaxis use in hospitalised at-risk medical patients, particularly those with cancer, acute heart or respiratory failure and the elderly, as well as underprescription of extended prophylaxis beyond hospital discharge in patients undergoing major cancer surgery. In regard to VTE treatment, planning of anticoagulation duration, administration of LMWH for cancer-associated thrombosis, and the use of compression therapy for prevention of post-thrombotic syndrome in patients with symptomatic proximal DVT require improvement. The main conclusions of the SAMEX initiative are summarised in table 2.

Even though one might argue that many of the observations made and conclusions reached are far from original, the studies and surveys performed over a 6-year period by a multidisciplinary group of physicians across Switzerland point to insufficient awareness of venous thromboembolic disease, underestimation of its burden and inconsistent application of international consensus statement guidelines regarding prophylaxis [2] and treatment [15] adopted by the Swiss Expert Group [12]. Consequently, implementation tools to improve compliance with current recommendations have been or are still being studied. It is worth noting that the network around this initiative fostered interest in and awareness of VTE in the participating university and regional hospitals and, anecdotally, also produced slide kits to disseminate the new knowledge in CME forums.

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Table 2: Main conclusions of the SAMEX initiative on VTE in Switzerland.

– Acutely ill hospitalised at-risk medical patients are given thromboprophylaxis in only 61% of cases.
– In patients diagnosed with acute VTE who had been hospitalised within 30 days prior to the event, 70% of surgical patients but only 48% of medical patients had been given thromboprophylaxis during hospital stay; in cancer patients, the figure was as low as 60%.
– In high-risk patients undergoing major orthopaedic surgery or major cancer surgery, extended thromboprophylaxis was given in only 77% or 23% of the cases respectively.
– Long-term anticoagulant treatment was planned in less than half of cancer patients with VTE.
– There is considerable inconsistency in the prescribed duration of anticoagulant treatment in outpatients diagnosed with acute DVT.
– Mechanical compression as adjunctive treatment of symptomatic proximal DVT is prescribed for at least two years in only 24% of patients.

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