ORIGINAL ARTICLE

Evaluation of the frequency of venous thromboembolism prophylaxis in a selected population of patients hospitalized in nonsurgical wards

Results of the all-Poland EPID Registry

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KEY WORDS

antithrombotic prophylaxis, antithrombotic treatment, pulmonary embolism, venous thromboembolism, venous thrombosis

ABSTRACT

INTRODUCTION The results of the Prophylaxis in Medical Patients with Enoxoparin (MEDENOX) trial demonstrated the benefit of thromboprophylaxis in patients hospitalized because of acute heart failure, respiratory failure and rheumatic disease. Analysis of clinical practice shows that thromboprophylaxis is rarely used in these patients.

OBJECTIVES To assess thromboprophylaxis use in a selected population of patients hospitalized in internal departments in Poland.

PATIENTS AND METHODS Between the years 2002 and 2006, 14,707 hospitalized patients were included into the EPID Registry. The study population, selected for the purpose of this analysis, involved 5246 patients (mean age 71, 95% CI: 70.6 –71.4 years), reported by 60 internal wards, who met the entry criteria of the MEDENOX study. Patients receiving long-term antithrombotic treatment and patients with indications for initiating antithrombotic treatment were not enrolled.

RESULTS Thromboprophylaxis was administered in 63% of patients. The average duration of thromboprophylaxis was 8.1 days (95% CI: 7.8–8.4). In the group of patients admitted to the intensive care unit thromoprophylaxis was administered in 81% of cases compared with 58% in nonsurgical departments ($p < 0.0001$). Low-molecular-weight heparins were used in 93% of patients receiving prophylaxis. The risk of hemorrhage (9.5%) and lack of indications for thromboprophylaxis (27%) according to the physicians were the main reasons for not using prophylaxis. The frequency of thromboprophylaxis use varied from 35% to 89% between different regions of Poland. Hemorrhagic complications were reported in 0.8% of patients receiving prophylaxis.

CONCLUSIONS Administration of thromboprophylaxis in the MEDENOX-like population is of great importance from an epidemiological point of view because this patient group accounts for 31% of in-patients. Thromboprophylaxis is underused with large differences between regions, which should be improved by an adequate educational program for physicians from internal wards.

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INTRODUCTION Venous thromboembolism (VTE), that is venous thrombosis and pulmonary embolism, due to a high frequency of occurrence and substantial morbidity and mortality remains a serious epidemiological problem.[1] Use of primary antithrombotic prophylaxis is currently one of the important components of hospital management.[2] Results of the Prophylaxis in Medical Patients with Enoxoparin (MEDENOX) study, published in 1999, became a turning point in the approach to antithrombotic prophylaxis in patients hospitalized in nonsurgical

TABLE 1 Use of antithrombotic prophylaxis in a group of patients >40 years old admitted to the hospital because of acute internal disease according to the main reason for admission – a MEDENOX population

	n	Prophylaxis used n (%)	Prophylaxis neglected n (%)
congestive heart failure	3185	2182(69)	1003 (31)
acute respiratory disease	991	567 (57)	424 (43)
exacerbation of chronic respiratory disease	838	436 (52)	402 (48)
rheumatic or inflammatory disease + risk factor of VTE	232	135 (58)	97 (42)
altogether	5246	3320 (63)	1926 (37)

Abbreviations: VTE – venous thromboembolism

TABLE 2 Pharmacological prophylaxis frequency in particular provinces

Province	N° of centers	N° of patients included	Percentage of patients receiving prophylaxis
podlaskie	3	260	89%
mazowieckie	10	1195	80%
zachodniopomorskie	4	253	79%
wielkopolskie	5	373	77%
lubuskie	2	68	76%
opolskie	1	108	73%
kujawsko-pomorskie	1	69	71%
pomorskie	4	703	61%
dolnośląskie	4	390	60%
łódzkie	3	298	55%
świętokrzyskie	2	88	49%
małopolskie	2	77	48%
śląskie	11	617	47%
podkarpackie	4	481	37%
lubelskie	2	266	35%
warmińsko-mazurskie	0	0	
POLAND	58	5246	63%

departments.[3] In this study a 64% relative risk reduction in VTE occurrence in the group of patients receiving 40 mg of enoxaparin compared to the placebo group, with the number needed to treat of 10, was observed. Innovative, at that time, inclusion criteria – including the population of patients with New York Heart Association III and IV heart failure, respiratory failure and acute rheumatic or inflammatory disease and an additional risk factor – became a model of antithrombotic prophylaxis in patients hospitalized in nonsurgical wards. The inclusion criteria of the MEDENOX study were subsequently used in the management guidelines indicating the necessity of antithrombotic prophylaxis with the highest level of recommendation.[4-7] In subsequent *post-hoc* analyses the benefits of prophylaxis to all subpopulations of the MEDENOX study were confirmed[8] and a beneficial outcome of pharmacoeconomic analysis of the use of antithrombotic prophylaxis was shown.[9] The effectiveness and safety of antithrombotic prophylaxis in populations similar to the MEDENOX were confirmed in subsequent trials with dalteparin,[10] fondaparinux[11] and fraxiparine.[12]

While presenting the results of the EPID Registry in previous publications[13,14], we indicated too low use of antithrombotic prophylaxis in Polish internal wards in high-risk patients. The present analysis evaluates the correctness of prophylaxis use in patients from internal medicine wards similar to the MEDENOX population.

PATIENTS AND METHODS The EPID Registry was an uncontrolled observational study involving 58 internal medicine wards from the whole Poland. 53 centers (91%) were localized in municipal or provincial hospitals and 5 in academic hospitals. In 41 centers (71%) specialist wards or separate intensive care rooms are located. Centers participating in the registry every month send information on the next 10 patients who fulfilled the study inclusion criteria. In accordance with the exclusion criteria, patients receiving chronic antithrombotic therapy because of atrial fibrillation, heart valve prothesis implantation, acute coronary syndrome or VTE do not qualify for the registry. Patients hospitalized for diagnosed *de novo* VTE who require anticoagulant therapy were also excluded from the study. Data were collected on a standardized questionnaire (Patient's Observation Card), available on the www page. Information on the main cause of admission and concomitant diseases was provided in the registry; risk factors of VTE occurrence were also evaluated. Subsequently, physicians participating in the registry provided the data on their decision about use of antithrombotic prophylaxis, its type and duration. The choice and use of the therapeutic agent were independent of the decision about the patient's qualification to the study; the used therapy is consistent with the accepted medical practice. If prophylaxis was not used, physicians participating in the registry were asked to specify reasons for such a decision. The last observation of the patient included to the registry was recorded on the day of discharge – a physician assesses occurrence of hemorrhagic events associated with antithrombotic prophylaxis. According to the rules of non-interventional study, the protocol did not suggest specific management regarding the use and type of antithrombotic prophylaxis for registry participants. The study was performed in accordance with the principles of the Declaration of Helsinki, especial-

TABLE 3 Antithrombotic prophylaxis frequency in consecutive years of the registry

Year	N° of hospitalizations	Prophylaxis administered	Prophylaxis discontinued
2002	506	333 (66%)	173 (34%)
2003	1535	906 (59%)	629 (41%)
2004	1695	1118 (66%)	577 (34%)
2005	1187	747 (63%)	440 (37%)
2006 (to May, 2006)	323	217 (67%)	106 (33%)

ly in the area of respecting the confidentiality of personal data of participants.

According to the accepted inclusion and exclusion criteria, 14,707 patients were enrolled to the EPID Registry in the period from August 2002 to May 2006. The study group, analyzed for the purpose of this publication, consisted of 5,246 patients (mean age – 71 years, 95% CI: 70.6–71.4 years, 48% women, 52% men), which constituted 31% of hospitalizations in the EPID Registry. Patients aged >40 hospitalized because of heart failure, acute respiratory tract disease and acute infectious disease, rheumatic disease or inflammatory bowel disease, with an additional risk factor of VTE – age >75 years, malignant disease, past VTE, obesity, varicose veins, hormonal therapy, chronic respiratory insufficiency or chronic heart failure were qualified for the study. The profile of the VTE risk in the study group corresponded to the population of the MEDENOX study, which is a commonly accepted indication for pharmacological antithrombotic prophylaxis. 23% of patients were admitted to intensive care units, 77% were hospitalized in internal wards. 91% of patients were hospitalized in municipal and provincial hospitals, 9% – in academic centers. The mean duration of hospital stay was 10.1 (95% CI: 9.7–10.5) days.

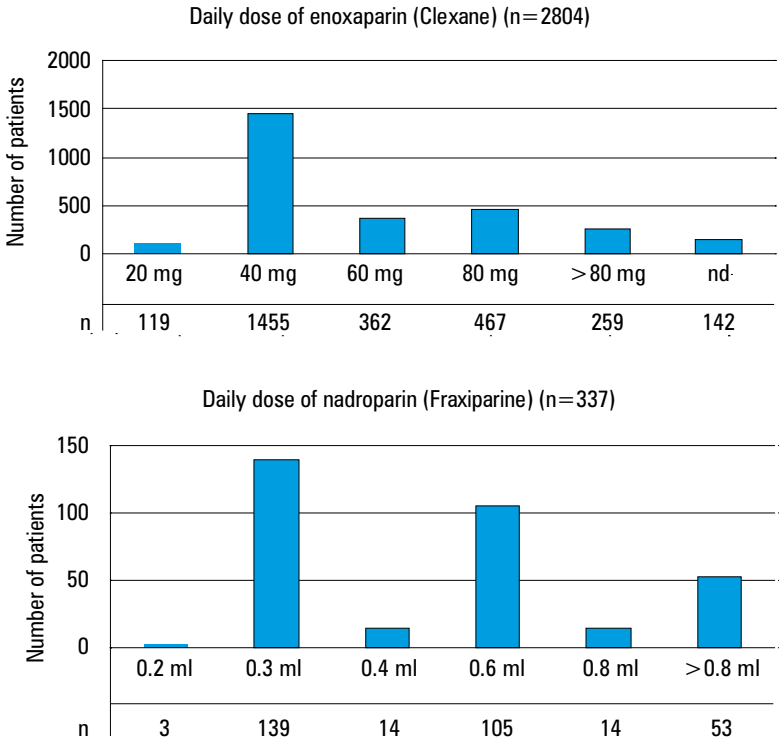

FIGURE 1 Distribution of daily doses of low-molecular-weight heparins in the antithrombotic prophylaxis group
Abbreviations:
nd – no data

The studied parameters were presented as mean and 95% confidence interval (95% CI). Qualitative variables were compared with the χ^2 test. A value $p < 0.05$ was regarded as statistically significant.

RESULTS Pharmacological prophylaxis of VTE was used in 63% of cases. Depending on the main cause of hospital admission, its frequency varied between 52–69% (TABLE 1). Prophylaxis was administered on average for 8.1 days (95% CI: 7.8–8.4), with a mean duration of hospitalization in the prophylaxis group of 10.5 days (95% CI: 10.0–11.1).

In the group of patients admitted to intensive care units, prophylaxis was administered in 81% of cases; whereas in internal departments – in 58% of cases ($p < 0.0001$). Frequency of prophylaxis in academic centers was 68%, while in municipal and provincial hospitals this percentage was 62% ($p = 0.01$).

According to the participants, prophylaxis was not administered in 495 cases (9.5%) due to a risk of hemorrhagic complications, most commonly gastrointestinal diseases (38%), central nervous system diseases (19%) and hematological disorders (14%).

From the total number of 4751 patients without contraindications to antithrombotic prophsylaxis, physicians did not see indications for its administration in 1431 patients (27% of whole population).

In the majority of cases where pharmacological antithrombotic prophylaxis was used low-molecular-weight heparins were administered (93%); standard heparin (2%), acenocoumarol (3%) and physical methods (2%) were implemented with a lower frequency. Amongst low-molecular-weight heparins, enoxaparin was administered in 89% of patients and nadroparin in 10%. In the group of 2804 patients who received enoxaparin, 52% received a dose of 40 mg/day, 44% – a higher dose, and 4% of patients received a dose of 20 mg/day. Daily dose distribution of low-molecular-weight heparins used as primary prevention of VTE is presented in FIGURE 1.

Significant differences in the frequency of antithrombotic prophylaxis use between particular provinces were observed – the percentage of patients receiving prophylaxis varied between 35–89% (TABLE 2 and FIGURE 2). However, unequivocal time trend findings in the frequency of antithrombotic prophylaxis use in subsequent years of the registry were not observed (TABLE 3).

22 cases of hemorrhagic complications (0.8%) were noted in the group receiving antithrombotic prophylaxis. Intracranial bleedings and deaths from bleedings were not observed. However, 3 patients from the bleeding group died, including – 1 because of heart failure, 1 of lung cancer and 1 because of suspected pulmonary embolism. Autopsy was not performed in any of the cases. Gastrointestinal bleeding was observed in 8 cases, hematuria – in 5, and hemoptysis in 4 patients. Hematoma involving the abdominal wall

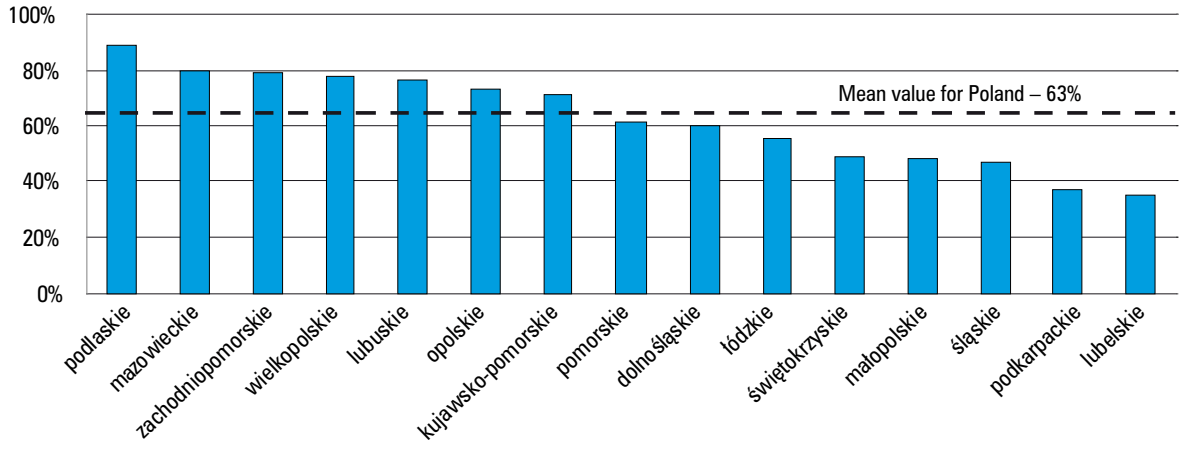

FIGURE 2 General thromboprophylaxis frequency in particular provinces. Data from warmińsko-mazurskie province were not received

and retroperitoneal space was observed in 1 case. Bleedings at sites of intravenous injections were reported twice. There was one subcutaneous hematoma at the site of injection. Epistaxis and gingival bleeding were also observed only in 1 subject.

DISCUSSION Despite unequivocal expert guidelines and its confirmed unquestionable medical and pharmacoeconomic benefits antithrombotic prophylaxis is rarely used in the population of patients hospitalized in nonsurgical wards.[15] On the basis of evaluation of 708 patients from internal medicine departments in Paris, Bergman et al. demonstrated that only 33% of them received antithrombotic prophylaxis with low-molecular-weight heparins.[16] Ageno et al. showed that in a small group of 112 patients from 2 Italian internal medicine departments, only 46% of subjects from the high-risk group received prophylaxis.[17] Among 1894 patients at increased risk of throboembolic complications hospitalized in nonsurgical departments, 23% of subjects received some form of prophylaxis; only 16% of them were given prophylaxis concordant with the guidelines.[18] Similarly, a small percentage of patients receiving prophylaxis – 31%, was noted by Stark and Kilzer in the retrospective review of medical records of 100 patients.[19]

The mean of prophylaxis use in Poland was 63%. This appears to be a better (but still not ideal) result than the findings presented in available data. With the frequency of contraindications of 10%, the optimal level of prophylaxis use should amount to about 90%. The percentage of patients receiving prophylaxis in intensive care units is close to the optimal level. A prospective study which assessed the frequency of antithrombotic prophylaxis use in 142 French and Canadian intensive care units confirmed that 92% of patients with indications and without contraindications received prophylaxis.[20] This is an important observation because patients hospitalized in intensive care units are a high risk group for VTE and simultaneously derive greater benefits from the antithrombotic prophylaxis.[21] The extent of observance of the guidelines among teams working in intensive care units does not differ from those observed in France and Canada and could serve as an example for conservative medicine departments.

The geographical diversity of the frequency of antithrombotic prophylaxis use is striking– some provinces approach optimal values, whilst in others only a $^1/_3$ of patients with indications receive prophylaxis according to the guidelines.

Difficulties in reliable evaluation of the effectiveness and direct results of prophylaxis discontinuation are registry limitations. However, extrapolating data from the MEDENOX study, where the frequency of proximal lower extremity deep venous thrombosis was 5% and the frequency of episodes of pulmonary embolism was 1% in the placebo group, it can be expected that in the group of 1431 patients without indications for prophylaxis 71 cases of venous thrombosis and 14 cases of pulmonary embolism occurred. Assuming that mortality for pulmonary embolism is about 19%, it can be supposed that 2 patients could have died from this.

In Poland, antithrombotic prophylaxis is performed using low-molecular-weight heparins. This is in line with clinical practice in the European countries, but different from the management in the USA, where standard heparin is subcutaneously injected 2 or 3 times a day.[22] Meta-analysis of randomized studies comparing prophylaxis with low-molecular-weight heparins and standard heparin showed a similar effectiveness, but greater safety, manifested by a lower rate of serious bleedings in the former group.[23] Recently published retrospective effectiveness analysis of prophylaxis with enoxaparin and standard heparin showed a 74% risk reduction in thromboembolic complications during use of enoxaparin compared to standard heparin.[24] Moreover, prophylaxis with low-molecular-weight heparins have a better safety profile, especially in elderly patients.[25] Prophylaxis with low-molecular-weight heparins is in general calculation less expensive for a hospital, despite higher costs of these agents.[26]

Looking critically at the number of doses taken by the registry participants it can be suspected that in some cases VTE prophylaxis is mistaken with antithrombotic therapy or systemic embolism prophylaxis. An indirect indication for this

is that in the group of patients hospitalized because of heart failure there is a significantly higher percentage of patients using prophylaxis. If true, this should be improved by appropriate education. This is of great importance as low doses of heparins used in VTE prophylaxis provide an optimal compromise between the effectiveness and the risk of hemorrhagic complications. Higher doses may unfavorably shift this balance towards an increased risk of bleedings. On the other hand, too low doses (i.e. 20 mg of enoxaparin daily) appeared to be ineffective in antithrombotic prophylaxis in the MEDENOX population.

It is interesting that hemorrhagic complications occurred in <1% of patients receiving antithrombotic prophylaxis. This number is closer to the frequency of severe (massive) bleedings observed in randomized clinical studies with low doses of low-molecular-weight heparins; however, it is definitely less common than all bleedings, which range from 7 to 9%.[27] Practicing physicians may take a situation requiring performance of additional tests, blood transfusion or medical intervention for "hemorrhagic complication", which would approximately correspond to the definition of severe hemorrhagic complication in clinical studies. Less severe bleedings (i.e. epistaxis) are rarely recognized as complications by practicing physicians. However, it should be remembered that the reporting method of hemorrhagic complications in the registry was completely different from that commonly used in controlled clinical trials.

Study limitations In the following study only a subgroup of patients with, according to international guidelines, indications for antithrombotic prophylaxis was analyzed. As a result evaluation of the frequency of overuse of antithrombotic prophylaxis in patients without indications was impossible.

In evaluation of the frequency of prophylaxis use in particular provinces, a potential falsification of the real situation may arise from different numbers of centers participating in the registry within particular provinces and resulting from this various numbers of patients enrolled in the registry.

An appropriate use of antithrombotic prophylaxis in the MEDENOX population is of crucial epidemiological importance, as this group constitutes about 31% of all patients hospitalized in internal medicine departments. The VTE prophylaxis is still rarely used in the group of non-surgical department patients, especially in general medicine departments. Disparities in the frequency of prophylaxis use between particular provinces are striking. Administered doses are in many cases different from those recommended by the guidelines.

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List of centers participating in the registry is presented in Appendix.

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APPENDIX The list of hospitals with internal medicine wards which provided the questionnaires (number of questionnaires in parentheses)

Regional Hospital in Strzelno (240), Municipal Hospital in Gdynia (235), State Tuberculosis and Lung Diseases Research Institute in Warsaw (231), The Wolski Hospital in Warsaw (221), Provincial Hospital in Gdańsk (208), Provincial Hospital in Suwałki (172), The Falkiewicz Hospital in Wrocław (170), Provincial Hospital in Przemyśl (157), The Dr. Troczewski Independent Public Health Care Facility in Kutno (153), State Clinical Hospital No.2 in Szczecin (146), Independent Public Health Care Facility in Chojnice (140), Independent Public Health Care Facility in Chełm (140), The Health Care Facility Municipal Hospital in Garwolin (139), District Hospital in Leżajsk (137), Independent Public Health Care Facility in Świdnik (126), District Hospital in Wołomin (122), Specialist Hospital in Gdańsk (120), The Praski Hospital in Warsaw (119), Municipal Hospital in Głogów (112), Complex Hospital in Kędzierzyn-Koźle (108), Municipal Hospital in Ruda Śląska (102), District Hospital in Mielec (98), Railway Hospital in Pruszków (92), Municipal Hospital in Piekary Śląskie (91), Municipal Hospital in Rzeszów (89), Sonnenberg 1st Municipal Hospital in Łódź (89), Municipal Hospital in Bolesławiec (87), Provincial Complex Hospital in Płock (86), Central Clinic Hospital in Katowice (81), Municipal Hospital No.1 in Sosnowiec (77), Specialist Provincial Hospital No.1 in Tychy (76), Regional Hospital in Racibórz (75), Municipal Hospital in Bydgoszcz (69), Municipal Hospital in Ostrowiec Świętokrzyski (2 internal medicine wards – total 69), Regional Hospital in Turek (67), Health Care Facility in Gryfice (66), The Żeromski Hospital in Kraków (65), Provincial Hospital in Siedlce (65), District Hospital in Nowa Sól (60), The Knights Hospitallers' Hospital in Łódź (56), Provincial Specialist Hospital in Radom (54), The Tytus Chałubiński Hospital in Częstochowa (54), 108 Military Hospital in Ełk (51), Provincial Complex Hospital in Białystok (37), Specialist Hospital in Puławy (37), Municipal Hospital in Słupca (33), Municipal Hospital in Rawicz (32), Municipal Hospital in Kielce (29), 106 Military Hospital in Gliwice (28), State Clinical Hospital No. 2 in Szczecin (25), Specialist Complex Hospital in Wałbrzych (21), Provincial Comlpex Hospital in Częstochowa (21), Municipal Hospital in Golub-Dobrzyn (16), Independent Public Health Care Facility in Szczecinek (16), The Rydgier Hospital in Kraków (12), Oncologic Hospital in Bielsko (12), Provincial Hospital in Zielona Góra (8), Municipal Hospital in Ostrzeszów (3), Municipal Hospital in Poznań (1)