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Original article

The prophylaxis of venous thromboembolism in medical outpatients: results of a survey among Italian General Practitioners

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Summary. *Background:* Although the majority of venous thromboembolic events occurs in primary care, most of the studies concerning its prophylaxis investigate hospitalized patients. Therefore, in primary care, many clinical decisions have to be taken in the absence of great clinical evidence derived from studies performed directly on outpatients. The objective of our study is to evaluate the clinical approach of Italian General Practitioners to the prophylaxis of venous thromboembolism in medical outpatients. *Methods:* A web-based questionnaire was emailed to 766 Italian General Practitioners. In the questionnaire there were four exemplary clinical cases concerning hypothetical patients at venous thromboembolic risk. *Results:* Overall 232 questionnaires were returned. Approximately 40% of the participants reported to assess thrombotic and hemorrhagic risk with a risk assessment model but nevertheless only a narrow minority had recourse to a suitable and validated score for this purpose. In the chronically bedridden patient about half of the participants administered a heparin or an antiplatelet drug for long time. In acute outpatients at high venous thromboembolic risk there was a considerable underuse of heparin prophylaxis and graduated compression stockings were often considered as a first prophylactic option. Prolonged heparin prophylaxis in the post-acute setting was also the practice for half of the participants. *Conclusions:* Italian General Practitioners approach these "grey" areas of uncertainty in a significantly heterogeneous way and sometimes in sharp contrast to the recent evidence. The present findings stress the need for further targeted educational programs and new high quality studies to further deep this clinical context. (www.actabiomedica.it)

Key words: bedridden persons, family practice, outpatients, risk assessment, venous thromboembolism

Introduction

Venous thromboembolism (VTE) is one of the most important public health problems, due to its high incidence and morbidity, which has a significant impact in terms of consumption of health resources (1, 2). Antithrombotic prophylaxis may be a useful strategy to contain the problem. Despite this, thromboprophylaxis remains largely underused in many different clinical settings (3-6).

While the majority of VTE events occurs in primary care (7), almost all of the studies concerning its prophylaxis investigate hospitalized patients. Furthermore, risk assessment models (RAMs) for VTE have been validated, till now date, only for hospitalized patients. Therefore, in primary care, many clinical deci-

sions have to be taken in the absence of great clinical evidence derived from studies performed directly on outpatients.

For example, very few studies have evaluated the efficacy and safety of VTE prophylaxis both from a pharmacological and a mechanical point of view, in home-assisted non-surgical patients with acute medical problems. Despite a general perception occurrence of VTE out of hospital appears similar to in hospital both for risk factors and prognosis (8, 9). The aim of our study is therefore to evaluate the clinical approach of Italian General Practitioners (GPs) to the prophylaxis of VTE in medical outpatients. We conducted a survey among a large cohort of GPs to measure their decision orientation in some important "grey" areas of VTE prevention in the context of primary care.

Methods

Design and questionnaire

A web-based questionnaire was emailed to all 766 GPs of Local Health Authorities of Central-South Piedmont, a region in northwest Italy. Data collection was conducted from April 2018 to June 2018. All individual email addresses were obtained from the databases of Local Health Authorities of Central-South Piedmont. Emails contained a general description of the survey and an invitation to participate through a web-based link. A pilot version of the questionnaire was previously sent to 10 external GPs. They were interviewed after filling out the pilot version in order to check the correct functioning of web-based system and to assure the clarity of questions.

The definitive questionnaire consisted of a first part in which the participant's general information was collected, such as: gender, age, years of activity as GP, participation in at least a conference concerning the VTE over the last five years, assessment of thrombotic and hemorrhagic risk of a patient (whether clinically or through a RAM).

In the second part of the questionnaire, there were four exemplary clinical cases concerning hypothetical patients at VTE risk. For each of the four scenarios, three or four alternatives of choice were proposed regarding the possible optimal antithrombotic prophylaxis (Table 1).

In short, the first scenario described a patient suffering from Parkinson's disease and chronically bedridden. The second case was a cancer patient with a severe renal insufficiency and an acute urinary tract infection. The third scenario analyzed the situation of a patient with an acute heart failure relapse with respiratory failure treated at home. Finally, the last clinical case described a diabetic patient, previously hospitalized for an exacerbation of chronic obstructive pulmonary disease (COPD), discharged to his home to continue antibiotic therapy.

Statistical analysis

All the obtained answers were inserted into an anonymous database and subsequently analyzed. Continuous variables were expressed as mean and standard deviation (SD); categorical data and qualitative variables instead as counts and percentages. Subgroup analyses were performed including only physicians with clinical experience longer than ten years and doctors who have attended at least one conference concerning VTE in the last five years. Statistical analyzes were performed using the SPSS program version 23.0.

Results

Overall 232 questionnaires were returned (30.3% of the whole sample). Baseline characteristics of responders are summarized in Table 2; 130 GPs (56.0%) were male. Responders' mean age was 52.4±13.1 years with an average service length of 21.5±14.6 years; 136 GPs (58.6%) attended at least one conference regarding the topic of VTE n the last 5 years; 96 participants (41.4%) claimed to use a specific RAM for thromboembolic risk. The scores used were: CHA2DS2-VASC (42 participants, 18.1% of the total sample), PADUA (20 participants, 8.6%), WELLS (19 participants, 8.2%), CAPRINI (2 participants, 0.9%) and GENEVA (1 participant, 0.4%).

The risk of hemorrhagic complications was assessed through the use of a RAM by 95 participants (40.1%). The scores adopted were: HASBLEED (78

Table 1. The four exemplary clinical cases

Case 1
91-years-old woman
Past medical history: Parkinson's disease;
History of the present illness: In the last year the patient has gradually lost autonomy in the activities of daily life and at the present time is chronically bedridden.
Which of the following prophylactic therapies do you consider appropriate?
1. LMWH at prophylactic dosage for long-term;
2. The patient does not need VTE prophylaxis;
3. Antiplatelet drug (e.g. acetylsalicylic acid 100 mg/day);
4. Oral anticoagulant therapy with VKA.

Case 2
66-years-old man
Past medical history: Prostatic carcinoma with bone metastases treated with hormonal therapy, chronic renal failure IV stage (CrCl = 28 ml/min);
History of the present illness: For one day the patient has a high fever (>38°C) with shiver accompanied by dysuria and pyuria. Antibiotic therapy is started In the strong suspicion of infection of the lower urinary tract. The patient moves independently at home.
Which of the following prophylactic therapies do you consider appropriate?
1. The patient does not need VTE prophylaxis;
2. LMWH at prophylactic dosages for 10±4 days;
3. Prophylactic doses of UFH;
4. Antiplatelet drug (e.g. acetylsalicylic acid 100 mg/day).

Case 3
82-year-old woman
Past medical history: Heart failure with reduced ejection fraction (NYHA class II), previous transient ischemic attacks, polymyalgia rheumatica, moderate obesity, previous deep venous thrombosis (2 years ago);
History of the present illness: for about 3 days increase in peripheral edema with worsening of dyspnea (NYHA class III). In agreement with the family, heart failure relapse is treated at home. Intravenous diuretic therapy is initiated and oxygen supplementation by nasal cannula too. The patient is not currently bedridden and he retains autonomy in the activities of daily living.
Which of the following prophylactic therapies do you consider appropriate?
1. The patient does not need prophylaxis;
2. LMWH at prophylactic dosages;
3. Graduated compression stockings.

Case 4
77-year-old man
Past medical history: Type 2 diabetes mellitus, essential arterial hypertension, COPD stage 3C;
History of the present illness: The patient was hospitalized for 8 days in the department of internal medicine for bronchitic exacerbation. It has been treated with intravenous antibiotics, oxygen supplementation by nasal cannula and prophylactic-dose of LMWH. He was discharged with indication to continue oral antibiotic therapy for another 3 days and provided with home oxygen for the persistence of mild respiratory failure. The patient performs bed-chair passages and goes to the bathroom with the help of a caregiver.
Which of the following prophylactic therapies do you consider appropriate?
1. LMWH at prophylactic dosage until the complete resumption of walking or in any case for a period not exceeding 35 days;
2. LMWH at prophylactic dosage up to the 14th day from the beginning of the hospital;
3. The patient does not need VTE prophylaxis;
4. Antiplatelet drug (e.g. acetylsalicylic acid 100 mg/day).

ASA=acetylsalicylic acid, COPD=chronic obstructive pulmonary disease, CrCl=clearance of creatinine, LMWH=low-molecular-weight heparin, n=number, NYHA class=New York Heart Association functional classification of heart failure, UFH=unfractionated heparin, VKA=vitamin K antagonists, VTE=venous thromboembolism

Table 2. Baseline characteristics of responders

Male gender, n (%)	130 (56.0)
Mean age, years, m±ds	52.4 ± 13.1
Mean length of service, years, m±ds	21.5 ± 14.6
Attendance at least one conference concerning VTE in the last 5 years, n (%)	136 (58.6)
Thromboembolic risk evaluation with a RAM, n (%)	96 (41.4)
CHA2DS2–VASC score, n (%)	42 (18.1)
PADUA score, n (%)	20 (8.6)
WELLS score, n (%)	19 (8.2)
Not specified, n (%)	12 (5.2)
CAPRINI score, n (%)	2 (0.9)
GENEVA score, n (%)	1 (0.4)
Bleeding risk evaluation with a RAM, n (%)	95 (40.1)
HASBLEED score, n (%)	78 (33.6)
Not specified, n (%)	12 (5.2)
IMPROVE score, n (%)	4 (1.7)
HEMORR2HAGES score, n (%)	1 (0.4)

ds=deviation standard, m=mean, n=number, RAM=risk assessment model, VTE=venous thromboembolism

participants, 33.6% of the total sample), IMPROVE (4 participants, 1.7%) and HEMORR2HAGES (1 participant, 0.4%).

Result of four clinical scenarios are summarized in Table 3 and Table 4. In the first scenario almost half of the participants (47.0%) abstained from prescribing any prophylactic therapy, while about one third (29.3%) would have added an antiplatelet drug in therapy; 19.0% of responders adopted a low-molecular-weight heparin (LMWH) at prophylactic dose and 4.7% an oral anticoagulant therapy with a vitamin K antagonists (VKA).

In the second case, the majority of GPs (71.6%) did not prescribe any prophylactic therapy, whereas only 18.5% adopted a prophylactic dose of LMWH. The percentages of those who administered a prophylactic dose of unfractionated heparin (UFH) (6.0%) or of an antiplatelet drug (3.9%) were low.

In the third scenario, participants almost equally choose to abstain from any therapy (34.5%) or to use a prophylactic dose of LMWH (32.3%) or a graduated compression stockings (GCS) (33.2%).

In the last clinical case, the majority of responders (59.1%) preferred to continue a prophylactic dose of LMWH at until complete resumption of walking or for a period not exceeding 35 days; 19.0% prescribed LMWH prophylaxis for a period of 14 day. The percentages of those who did not prescribe any prophylaxis (14.6%) or administer an anti-aggregation (7.3%) were low.

Table 3. Results of first and second clinical scenarios and analysis of the subgroups

	case 1				case 2			
	1	2	3	4	1	2	3	4
All (232), n (%)	44 (19.0)	109 (4.0)	68 (29.3)	11 (4.7)	166 (71.6)	43 (18.5)	14 (6.0)	9 (3.9)
Clinical experience > 10 years (144), n (%)	25 (17.4)	60 (41.6)	52 (36.1)	7 (4.9)	101 (70.1)	28 (19.4)	6 (4.2)	9 (6.3)
Attendance at one conference concerning VTE in the last 5 years (136), n (%)	28 (20.6)	61 (44.9)	41 (30.1)	6 (4.4)	93 (68.4)	29 (21.4)	7 (5.1)	7 (5.1)
	LMWH	nothing	ASA	VKA	nothing	LMWH	UFH	ASA

ASA=acetylsalicylic acid, LMWH=low-molecular-weight heparin, n=number, UFH=unfractionated heparin, VKA=vitamin K antagonists, VTE=venous thromboembolism

Table 4. Results of third and fourth clinical scenarios and analysis of the subgroups

	case 3			case 4			
	1	2	3	1	2	3	4
All (232), n (%)	80 (34.5)	75 (32.3)	77 (33.2)	137 (59.1)	44 (19.0)	34 (14.6)	17 (7.3)
Clinical experience > 10 years (144), n (%)	46 (31.9)	57 (39.6)	41 (28.5)	85 (59.0)	34 (23.6)	12 (8.4)	13 (9.0)
Attendance at one conference concerning VTE in the last 5 years (136), n (%)	42 (30.8)	47 (34.6)	47 (34.6)	80 (58.9)	32 (23.5)	13 (9.5)	11 (8.1)
	nothing	LMWH	GCS	LMWH for 35 d	LMWH for 14 d	nothing	ASA

ASA=acetylsalicylic acid, d=days, GCS=graduated compression stockings, LMWH=low-molecular-weight heparin, n=number, UFH=unfractionated heparin, VKA=vitamin K antagonists, VTE=venous thromboembolism

The analysis of the subgroups comprising only participants with clinical experience over ten years and those who attended at least one conference concerning VTE over the last five years, showed similar and overlapping results to those observed in the main analysis.

Discussion

The results of this survey conducted among Italian GPs reflect a substantial heterogeneity in the clinical management of medical outpatients at risk of VTE. About 40% of participating GPs reported that they assess the risk of VTE and bleeding in their patients with the use of a RAM. However, the vast majority reported to use score developed and validated in other clinical settings and less than 10% of physicians reported to use the Padua Prediction Score (10) and the IMPROVE Bleeding Score (11), to evaluate the thrombotic and hemorrhagic risk as suggested by the most recent guidelines from the American College of Chest Physicians (ACCP) (12).

There is an open debate on whether to consider chronically bedridden patients at high risk of VTE (first scenario). Clinical data indicate that prolonged immobility represents a risk factor for VTE in the first thirty days of immobility and then its weight in terms of risk is reduced in the absence of intercurrent risk factors such as acute non-surgical disease (such as sepsis, exacerbated COPD, heart failure relapse, stroke). Therefore, in the absence of overlapping intercurrent risk factors, prolonged immobility beyond thirty days should not be considered a risk factor for VTE (13). This is in accordance with the latest guidelines of the ACCP that in chronically bedridden patients residing at their home or in a nursing home, recommended against the routine use of thromboprophylaxis (12). Nevertheless, in our study only less than half of the sample adopted this clinical behavior, and about one out of five GPs prescribed a prophylaxis with LMWH and almost one out of three GPs prescribed an antiplatelet agents which are not recommended for antithrombotic prophylaxis in medical patients due to their limited efficacy in this setting (14-16).

Evidence on the appropriate antithrombotic prophylaxis in patients with severe renal failure is lacking and evidence on the risk of bleeding associated with the use of these drugs in this setting is not compelling (12). Pharmaceutical company recommends a reduced daily dose of enoxaparin for patients with a clearance of creatinine (CrCl) less than 30 ml/min. Anti-factor Xa levels appeared slightly increased in a small cohort of patients with renal failure treated with prophylactic dose of this drug (17). Data on other LMWH are even more limited and it is not clear if the use of UFH is associated with a better efficacy and safety tradeoff in comparison to LMWH. Answer to the second scenario seem to be driven by the fear of bleeding complication and use of a prophylactic dose of heparin was suggested by approximately 25% of GP, with only a minority of participants choosing UFH.

In the international literature there is not convincing scientific evidence on the effectiveness of the use of mechanical devices in the prophylaxis of VTE in medical patients (18-20). The latest guidelines of the ACCP underline how mechanical devices are therefore an alternative for the prevention of VTE in medical patients at high risk of bleeding in which pharmacological prophylaxis is contraindicated or the benefit is not clear (12). Nevertheless the use of GCS in the third clinical case was considered by almost one third of the participants. In this circumstance, furthermore, they could promote venous return damaging the cardiac preload and aggravating heart failure disease.

Although we did not collect information about the logical reasoning of the responses, we can hypothesize that acute ill patients in third scenario were perceived to be at low risk of thromboembolic complications, also thanks to his apparently preserved mobility. However, it must be emphasized that the concept of reduced mobility does not exclusively define the patients confined to bed or armchair for the whole day but it must also be extended to those who perform, autonomously or with help, only modest movements from a room to another one at home (21). Furthermore, as underlined by the PADUA score, the risk of VTE is generally increased also during an acute cardiac (22), respiratory (23), infectious (24) and rheumatic (25) disease or for the presence of a thrombophilia (26) or an active cancer disease (27, 28).

The duration of pharmacological prophylaxis of VTE in the medical patient (fourth clinical case) remains uncertain (29). Despite the lack of clear evidences to support this strategy, most GPs considered the possibility of extending anticoagulant prophylaxis for a significant period beyond hospitalization in patients who potentially remain at higher risk for VTE. This would appear to be in contrast with the latest guidelines of the ACCP, where prolonged routine prophylaxis is discouraged beyond the period of immobilization or acute hospitalization of the patient (12). These recommendations are based on the negative results of three large RCTs, who compared respectively enoxaparin (30) and the direct oral inhibitors apixaban (31) and rivaroxaban (32) with placebo after an initial period of prophylaxis of up to 14 days. In all these studies, the potential benefit of prolonged prophylaxis was compromised by an increased risk of major bleeding complications.

The results of our survey suggest that Italian GPs approach the prophylaxis of VTE in medical outpatients in a heterogeneous way and sometimes deeply in contrast to current international recommendations. This would seem to follow the information obtained from previous similar studies concerning the clinical behaviors of Italian Internist Physicians (33). Both the poor familiarity with the published guidelines and the lack of clear evidence from studies specifically oriented to the world of primary care could explain these behaviors in clinical practice. Unfortunately, as previously pointed out, the structure of this survey don't allow, however, to gather various motivations and explanations regarding the different answers. Nevertheless, these results allow us to evaluate the current knowledge of a large group of GPs on the topic of VTE prophylaxis and provide us useful information on their attitude in different medical scenarios.

It is also interesting to note that almost 60% of GPs declared they have participated in at least one conference concerning the VTE over the last 5 years. However, the specific analysis of the data of this subgroup didn't show significant variability in comparison to the total sample questioning its effective impact on clinical practice. The information obtained from our survey could therefore be used as a starting point to plan future more targeted educational programs and new quality studies aimed at further deepening this clinical context.

Our study has some limitations. The response rate we have observed (30.3%) seems to be modest, but it is similar to results of most surveys performed among GPs. Actually, GPs' response rates to surveys are lower than those of the general population and often lower than 30% (34, 35). Moreover, response rates to web and email surveys are known to be lower than those of postal surveys (36). Most studies have found time and workload pressure, negative attitudes toward research, concerns about the researchers' motivations and lack of interest in the research as the main self-reported reasons for low participation (37, 38). Furthermore, our survey includes only Italian GPs and therefore the extrapolation to different foreign health systems can be questionable. In addition, physicians may have misin-

terpreted the questions and we cannot be sure that the participants gave reproductive answers to their clinical behavior in daily practice. To avoid these potential biases we have tried to structure the survey in the simplest and least equivocal form possible and collected the answers in a totally anonymous way.

Conclusion

In conclusion, the results of our survey provide real data on the current clinical management of antithrombotic prophylaxis in the context of Primary Care. Italian GPs approach these "grey" areas of uncertainty in a significantly heterogeneous way and sometimes in sharp contrast to the recent evidence of international scientific literature. All this reinforces the need for further targeted educational programs and new high quality studies to further deep this clinical context.

Authors' contributions

All the authors participated in the conception and realization of the study. All the authors contributed in data interpretation and drafted the article and approved the final version to be published.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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