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ARTICOLO

"THROMBOEMBOLIC RISK IN MEDICAL PATIENT: AN EXTENSIVE REVIEW AND FUTURE PERSPECTIVES"

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BACKGROUND

INTRODUCTION: Several patients affected by acute medical illnesses such as congestive heart failure, respiratory diseases, infective or inflammatory diseases, show a concrete, potential, venous thromboembolic risk.

METHODS: Many studies have proven relevant reduction of fatal pulmonary embolism due to improved medical practice aimed to provide proper thromboembolic prophylactic therapy.

RESULTS: Despite scientific efforts in clinical prevention, influence of some patients demographic variables are often underestimated (i.e. older age..) and real burden of absolute venous thromboembolic risk and thromboprophylactic efficacy remains unclear.
Moreover, establishment and development of Emergency and Acute Care Departments select a patients population that shows more complex features and comorbidities when compared to classical Medicine wards patients, thus making harder the exact choice regarding when and how to administer thromboembolic prophylactic therapy.

CONCLUSION: The simultaneous assessment of the thrombotic and haemorrhagic risk is the key for an adequate safe prophylaxis, a higher appropriateness of antithrombotic prophylaxis.
Thus it is routinely recommended to use proper tools of VTE risk evaluation in order to set the best risk/benefit therapeutic strategy in medically ill patients.

Parole chiave:
valutazione del rischio trombo-embolico, trombosi venosa profonda, embolia polmonare, emergenza

Keywords:
Medical patient, risk assessment models,
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INTRODUCTION

Venous thromboembolism (VTE) is the third most common cardiovascular illness after acute coronary syndrome and stroke and the most common preventable cause of hospital-related death.[1] [2] [3]

The critically patients ill represent a specific population of patients who are at increased risk of venous thromboembolism (VTE) which contributes significantly to their morbidity and mortality.[1]

Moreover, pulmonary embolism (PE) is associated with increased post-thrombotic syndromes as secondary pulmonary and chronic hypertension.[4]

Pathophysiology of PE is generally related to one or more elements of Virchow's triad (**FIGURE 1**) and involves many potential risk factors.[5]

Many common clinical conditions, such as immobilization, active cancer, previous VTE, chronic venous insufficiency, chronic respiratory failure, heart failure, acute respiratory infections, inflammatory bowel disease, sepsis, acute neuropathy, and estroprogestin treatment, are considered to be VTE risk factors.[5]

METHODS

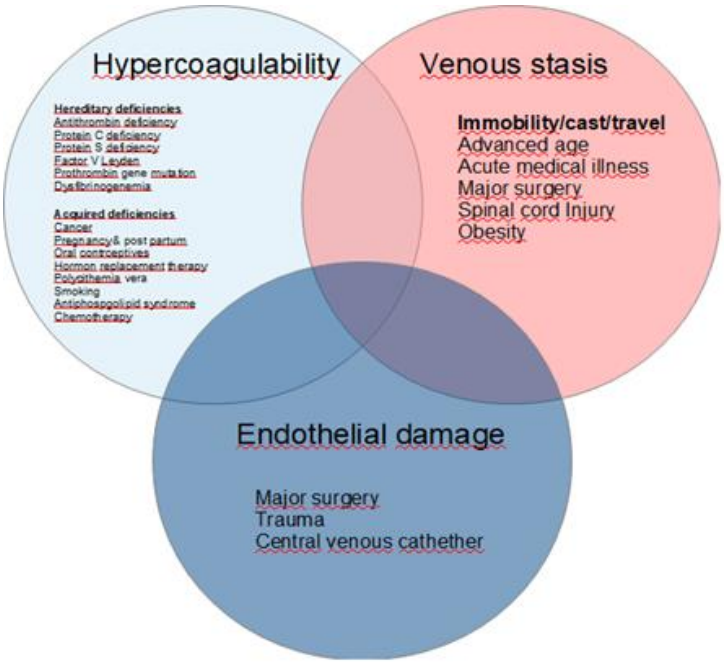
Lower limbs venous district is most frequently involved in VTE; less frequently upper limb or other venous districts are interested as well. [6]

The increased use of central vein catheters, aimed to administer chemoterapic agents or parenteral nutrition, as well as increased permanent pacemaker and cardiac defibrillator implantation in critically ill cardiac patients, are modyfing the epidemiological distribution of VTE implying more frequent cases of upper limb PE as well. [1]

About 50% patients affected by DVT o pelvic vein thrombosis is actually affected by PE as well, that is usually asymptomatic; [7] about 25% of patients affected by symptomatic PE show clinical and instrumental findings of DVT related to lower limb venous district. Clearly, PE can be definitely considered the most dangerous complication of DVT. [7]

Moreover, more than 50% of patients that undergo orthopedic surgery (mostly knee and hip surgery) and 10-40% that undergo abdominal or thoracic surgery are interested by DVT. [8]

FIG. 1 - VIRCHOW'S TRIAD OF THE THREE BROAD CATEGORIES OF FACTORS THAT ARE THOUGHT TO CONTRIBUTE TO THROMBOSIS



DVT prevalence is definitely higher in patients affected by pancreatic, lung, urogenital, gastrointestinal and mammalian neoplasia. [9]

About 10-20% of patients affected by "idiopathic" DVT is actually affected by not-diagnosed neoplasia;[9] however there are no commonly shared specific guidelines about diagnostic screening to search for hidden neoplasia in these kind of patients nowadays. [10]

Recently, hot topic about TE prevention has been highlighted.

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However, while risk stratification has been implemented in surgical departments with consequent reduction of PE incidence, medical departments did not reach similar results and incidence of PE is currently higher in medical wards when compared to surgical ones. (11)

In "not-surgically ill" patient risk factors identification for VTE and related thrombotic prophylaxis are made harder by many different issues: medical patients are often affected by multiple comorbidities, thus involving heterogeneous pool of complex patients often associated with older age and increased haemorragic risk. (12)

In "medically-ill" patient we can also identify other intrinsic difficulties:

- early diagnosis is not always achievable
- DVT is often asymptomatic
- low sensibility of diagnostic, non-invasive tests
- PE is often the clinical outburst of concealed DVT
- complex and wide differential diagnosis

RESULTS

Clinical trials on "medical" patients are fewer than the ones focused on surgical ones.

Moreover results are often uncomparable due to heterogeneous study design, pool of patients, and diagnostic tests used to detect DVT.

Two important randomized, double blind, placebo controlled studies have validated short term PE prophylaxis (i.e. 6 to 14 days) in an in-hospital population using low molecular weight heparin. (13) (16)

A meta-analysis of nine randomized clinical studies evaluated the positive effects of VTE prophylaxis in order to reduce clinically relevant outcomes in another in-hospital population.

The patients that underwent thromboembolic prophylaxis administration showed relevant reduction in overall incidence of PE (relative risk reduction, 0,43 [95% IC 0,26-,71]; absolute risk reduction, 0,29%) and fatally-ill PE (relative risk reduction, 0,38 [95% IC 0,21-0,69]; absolute risk reduction, 0,25%), an unremarkable reduction in symptomatic DVT (relative risk, 0,47 [95% IC 0,22-1,00]), and a not-relevant increase in major haemorragic events (relative risk, 1,32 [95% IC, 0.73 a 2,37]).

These results are the stronghold that led to American College of Chest Physicians (ACCP) guidelines about heparin use in PE prophylaxis. (15)

It is important to underline that thromboprophylaxis did not have any effect on all-cause mortality, probably because of high number all-cause deaths not related to PE, if compared to relatively small number of deaths directly related to PE. (16)

In order to increase efficacy and safety of thromboprophylaxis in acutely ill patients, ACCP guidelines recommend the use of standardized risk stratification tools as the Padua score. (15)

These tools (with negative predictive value about 99%) point out that only 35-50% of medically ill population has proper PE risk needing dedicated prophylaxis, considering 1.0% of symptomatic PE as useful ACCP recommended threshold.

These datas point out that only half of medical population benefits from a pharmacological treatment actually being able to protect from bleeding risk.

Despite a more accurate and "patient -oriented" thromboembolic risk stratification, bleeding risk definition is not accurately and universally stated (ACCP, NICE). (17)
Moreover VTE prophylaxis indications remains unclear in patients affected by haemorragic or ischemic stroke.

In case of haemorragic stroke there is no clear, universal consensus statement about chronological, therapeutic steps, weighing haemorragic risk according to datas related to clinical and instrumental findings. (16)

Once stated the most relevant bleeding risk factors, besides thromboembolic risk scoring tools, it is necessary to use a score in order to assess bleeding risk in patients with acute illnesses. [18]

International guidelines currently suggest the use of IMPROVE haemorragic risk score. [17] (**FIGURE 2**).

FIG. 2 : BLEEDING RISK SCORE

VARIABLE	SCORE
Active gastric or duodenal ulcer	4.5
Prior bleeding within the last 3 months	4
Thrombocytopenia (<50x109/L)	4
Age ≥ 85 years	3.5
Liver failure (INR>1.5)	2.5
Severe kidney failure (GFR< 30 mL/min/m2)	2.5
Admission to ICU or CCU	2.5
Central venous catheter	2
Rheumatic disease	2
Active malignancy	2
Age: 40-84 years	1.5
Male	1
Moderate kidney failure (GFR: 30-59 mL/min/m2)	1
ICU: intensive care unit; CCU: critical care unit; CV central venous; GFR: glomerular filtration rate; INR: international normalised ratio.	

Fig. 2 IMPROVE Bleeding risk score considers 13 risk factors.

This scoring tool assigns specific scoring to each factor; a cumulative scoring equal to or more than 7 states hig bleeding risk.

There is evidence that VTE risk in acute phase medical patients persists after hospital discharge as well (similar evidences are shown in high risk surgical patients). [17]

In MEDENOX study 8% of venous district VTE occured in a time interval from 15 to 110 days after hospital discharge; four of these events were PE cases that ended to death. [13]

APEX study was then developed: in this study a new, direct, Xa factor inhibitor, betrixaban, was tested; the study was aimed to test efficacy and safety of the new prophylactic drug in venous tromboembolic prevention versus enoxaparin usual administration.

The study included a population of 7513 in-hospital patients affected by acute medical illnesses.

Patients in betrixaban group were administered 160 mg dosage per os once daily on the first day of hospitalization, followed by 80 mg dosage once daily for a time period between 35 to 42 days; a once daily placebo dose was concurrently administered for a time between 6 to 14 days.

Patients in enoxaparin group received a 40 mg once daily subcutaneous dosage for a time period from 6 to 14 days and a concurrent once daily oral placebo for a time period between 35 to 42 days.

Efficacy was measured considering a composite outcome including deep vein, symptomatic or asymptomatic, proximal limb thrombosis, non-fatal PE, or VTE related death.

Betrixaban assigned patients group showed less of the above mentioned events (4,4%) when compared to enoxaparin assigned patients group (6%), with a relative risk equal to 0,75 and confidence interval equal to 95% (0,61 – 0,91). [18]

Food and Drug Agency then approved use of betrixaban in VTE prophylaxis in in-hospital, acutely ill, medical patients, with concrete TE risk, validating its use after hospital discharge as well.

Nowadays, TE prophylaxis in medical wards is often underused mainly because of bleeding risk overestimated perception or because of delay in prophylactic treatment. [16] (**FIGURE 3**).

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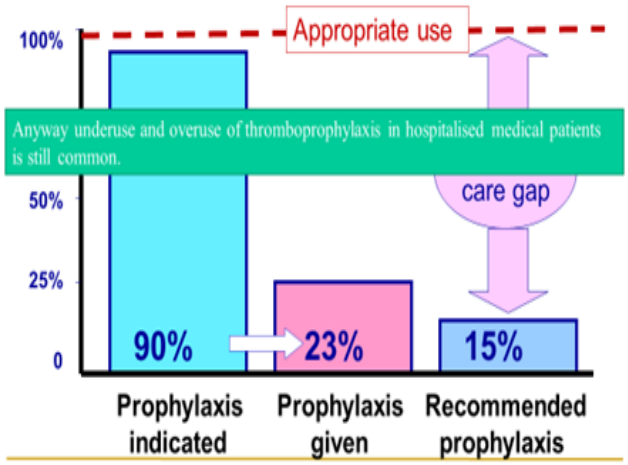
FIG. 3 - TE PROPHYLACTIC TREATMENT IN MEDICAL PATIENT



Differently than surgical wards, a remarkable dissimilarity in medical treatment risk stratification was reported in medically ill patients, particularly concering patients admitted to Emergency Departments. [19]

A recent Italian study, TEVere, was then developed in order to accurately assess risk stratification for PE. This study included more than 1200 patients, all over 20 Italian hospitals, and led to a new PE assessment tool: ***TEVere Score***.

This score assesses VTE risk considering specific, clinical aspects and associating specific scoring to each variable evaluating potential VTE global risk with consequent thromboprophylaxis need.

TEVere score was tested and applied to Emergency Department patients as well.

This is a new feature for a VTE assessement score as the majority of well-known VTE risk scores do not consider Emergency Departments patients.

The score then evaluates the complexity of acutely ill patient affected by multiple morbidities avoiding underestimation of thrombotic risk that can occur in patient usually admitted to Medicine wards. [20] (**TABLE 1**)

TAB.1 : TEVERE SCORE: A SCORING EQUAL TO OR MORE THAN 4 POINTS VALIDATES USES OF TE PROPHYLATIC TREATMENT

Cancer	3
Previous VTE	3
Thrombophilia	3
Major Surgery (<60 Days)	2
Drug That Stimulate Hematopoiesis, CVC	2
BMI > 30 Kg/M2	1
Immobilization (<30 Minutes/Day Of Walking For 3 Or More Days)	1
Hormone Therapy	1
Age > 70 Aa	1
Recent Hospitalization (≥2 days in the preceding 90 days)	1
Varicose veins	1
Respiratory Failure	1

Results deriving from this study show that considering also environmental risk factors, coagulation variables, comorbidities informations lead to a more accurate evaluation of VTE risk in medically ill patient.

CONCLUSIONS

In Medicine wards, difficulties in providing accurate and proper VTE prophylactic treatment arise because of different aspects: first, homogeneous VTE risk stratification due to complex, polipathological, older patients, is not always easy; second, in medically ill patients concurrent high bleeding risk is often associated.

Moreover other intrinsic factors have to be considered: early diagnosis of thrombotic condition is often difficult, VTE are largely asymptomatic, low sensibility of non-invasive diagnostic tests is a remarkable matter, wide range of clinical features in diffrential diagnosis have to be considered. In conclusion while waiting for the "ideal" RAM or strategy to best identify the individual VTE risk, the thrombotic/haemorrhagic risk profile of medical patients should be routinely assessed, and the use of prophylaxis be tailored to individual thrombotic/haemorrhagic risk.

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