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Title: Which general medical and surgical inpatients should receive pharmacological thromboprophylaxis during hospitalisation?

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Introduction:

Venous Thrombo-Embolism (VTE) is a major global health burden. Studies conducted from 4 continents describe a consistent incidence of approximately 1-2 per 1000 individuals in the general population, increasing steeply for those over 70.[1,2] The consequences of diagnosis are serious; North American data report a 30 day case fatality rate of 10.6% and between 30 to 50% of survivors will have long term complications.[3,4]

Approximately half of all VTE episodes are classified as Hospital Acquired Thrombosis (HAT), in that they occur during or shortly after hospitalisation for surgery or acute medical illness.[5] Many of these cases are potentially preventable through patient education and pharmacological thromboprophylaxis. There is a significant body of evidence for the latter; a meta-analysis of >15,000 hospitalised trial patients has previously demonstrated a >50% risk reduction for VTE with pharmacological thromboprophylaxis, when compared to control.[6] In many elective surgical settings, routine thromboprophylaxis has become established practice.[7,8]

The balance of risk is not so clear in general medical and surgical inpatients requiring unscheduled hospitalisation. Pharmacological thromboprophylaxis can lead to adverse events in some patients and has a major bleeding rate of approximately 0.4%.[8-12] These risks can be potentially catastrophic in certain patient groups, such as those with occult bleeding on admission, or those undergoing emergency procedures. As such, the optimal use of thromboprophylaxis in this cohort may require individual evaluation of factors relating both to the patient and the hospital admission. The best way to conduct this assessment is uncertain.

Risk Assessment Models (RAMs) have been developed to address the issue, proposing individualised and reproducible evaluation of VTE risk. Such models aim to minimise unnecessary pharmacological thromboprophylaxis and reduce the associated harm/costs. A recent overview of systematic reviews identified 15 available RAMs.[13] Although many RAMs overlap regarding individual risk factors, there is significant variation between models regarding composition and threshold for high VTE risk. By example, application of different RAMs to a similar cohort of patients can result in recommendations for pharmacological thromboprophylaxis ranging from 32 to 90% of patients (figure 1).[14]

There is ongoing uncertainty regarding the optimal method of risk assessment and whether any RAM outperforms subjective clinical assessment. In addition, given the international

variability in many RAM components (such as threshold for critical care admission) it is unclear whether a validated RAM in one healthcare system will be of equal use in others.

What is the evidence of uncertainty?

Guidance from the UK National Institute for Health and Care Excellence (NICE) recently changed from advocating use of a consensus derived Department of Health (DOH) tool to recommending the use of *any* risk assessment method published by a national body, professional network or in a peer reviewed journal.[8] Recent American and Australasian guidelines also acknowledge the limited evidence both on performance and impact analysis to support use of any particular RAM.[15-18] Such guidance allows significant variation in practice.

The comparative performance of different RAMS on clinically relevant outcomes has been evaluated in several previous systematic reviews.[8,14,19] All conclude a lack of generalisability and adequate validation of currently available RAMs. In addition, variability in methods and outcome measurement preclude pooled estimates of effectiveness. An expert committee informed by systematic review data, recently concluded that 'none of the tools demonstrated sufficiently accurate performance for predicting VTE or bleeding risk based on the evidence.'[8]

A recent overview of systematic reviews, last updated in January 2020, identified five widely evaluated models which have attempted external validation; the Caprini score, the Padua prediction score, the IMPROVE models, the Geneva risk score and Kucher model.[13] Comparative characteristics and individual clinical features for these RAMs and the DOH tool (in common use within the UK), are reported in table 1.

External validation studies reporting performance for the above RAMs are summarised in table 2. These studies principally report measures of prognostic accuracy by concordance (c) statistic, regarding symptomatic VTE by 3-month follow up. In addition, several studies report summary estimates of RAM sensitivity (proportion of VTE events accurately predicted by a 'high risk' score at proposed threshold). This evidence shows overall weak prognostic performance and variable sensitivity for all RAMs, in keeping with previous systematic review findings. There is also limited evidence of safety; only 3 validation studies report estimates of major bleeding rates, ranging from 0.7 to 3.4% (table 2).

There are significant limitations to this evidence, as highlighted through risk of bias assessment (table 2). In particular, observational cohort studies commonly include patients who have received thromboprophylaxis at clinical discretion. This will likely reduce the incidence of VTE in the at-risk population and may lead to underestimation of RAM accuracy.

Furthermore, the use of complex RAMs appears to compare unfavorably against simple, reproducible criteria. In a secondary analysis of 14,910 patients prospectively recruited to the PREVENU study across 25 French Hospitals, Moumneh *et al* compared the performance of age ≥70 as a single variable against the Padua, Caprini and IMPROVE RAMs for predicting VTE risk.[20] No significant difference in performance was seen between groups, with the c statistic between 0.60 and 0.64 for all, indicating weak prognostic performance.

Despite these limitations in prognostic accuracy, several RAMs have undergone impact analysis and demonstrated improved rates of appropriate pharmacological thromboprophylaxis prescribing.[14,21-24] One well conducted randomized controlled trial also showed a reduction in VTE event rates in patients at high risk.[23] This data supports use of any RAM within a clinical pathway, to encourage risk assessment and increase appropriate use of thromboprophylaxis.

Is ongoing research likely to provide relevant evidence?

Further external validation research on current RAMs is challenging, given the development of national VTE prevention programs and subsequent contractual requirements.[25,26] Derivation and validation of any new RAM through prospective research would necessitate withholding pharmacological prophylaxis from patients identified at risk of VTE, which would be unethical. In addition, the widespread use of pharmacological thromboprophylaxis would inevitably reduce the number of VTE events in any observational study and confound the association between risk factors and VTE events. However, it may be reasonable and ethical to compare RAMs to modern clinical gestalt, given the recent international focus on prevention and education. It may also be useful to compare alternative RAMs in a cohort of patients identified at lower risk for VTE, given the significant uncertainty about which models (and thresholds) are optimal.

We searched EU Clinical Trials Register, ISRCTN Registry and ClinicalTrials.gov and identified several actively recruiting studies attempting to prospectively compare existing risk models, bleeding risk scores and clinical judgement to improve VTE prevention strategies

(table 3). [27,28] The RICO study is a multicenter cluster randomized controlled trial looking to compare the performance of thrombosis and bleeding risk assessment using objective RAMs (the Padua score and IMPROVE bleeding tool) against clinical judgement. This study is currently recruiting and will provide patient level randomized evidence on the clinical effectiveness of objective RAMs compared to standard clinical judgement. In addition, a further cluster randomized study aims to compare the use of an embedded risk assessment process within an electronic healthcare record, using the IMPROVE RAM, to usual medical care for VTE prevention.[29]

The UK National Institute for Health Research has also recently commissioned a project assessing the cost effectiveness of VTE risk assessment tools for hospital inpatients (NIHR127454).[30] This project will use decision analysis modelling to determine how the cost effectiveness of thromboprophylaxis varies for different thresholds of risk from a UK National Health Service perspective and which factors contribute most to current uncertainty about the optimal threshold for thromboprophylaxis. It will also explore the feasibility of using efficient methods to compare alternative RAMs in a large future study.

Finally, several recent studies have investigated the use of additional biomarkers to improve current RAMs. In a retrospective analysis of the MAGELLAN trial, Spyropoulos *et al* used a modified IMPROVE score with the addition of a raised D-dimer (more than twice the upper limit of normal) to identify a threefold higher VTE risk in a subgroup of hospitalised acutely ill medical patients.[31] In a subsequent well conducted systematic review and meta-analysis of prognostic factors for VTE in hospitalized medical patients, Darzi *et al* report moderate certainty evidence from 14 studies of a probable association between VTE risk and elevated C-reactive protein, D-dimer and fibrinogen levels.[32] This recent work has not yet been prospectively validated or assessed via implementation studies.

What should we do in light of the uncertainty:

The revision of recent national guidelines to include multiple options for risk assessment suggest that clinicians and patients recognise the limitations of current evidence. However, this uncertainty should not necessarily lead to national variation in clinical practice, or outcomes. NHS England has used a single recommended risk assessment tool and supporting guidance to achieve a consistent reduction in HAT and mortality from VTE.[25,26] These results undoubtedly

owe as much to the use of a nationally endorsed RAM, coordinated metrics, local quality improvement practice and new contractual obligations as they do to original research.

The NHS results also likely arise from use of a RAM which has a low threshold for recommending pharmacological thromboprophylaxis. The recent pandemic has drawn further attention to this issue.[33,34] UK national guidance has subsequently lowered the bar further in this cohort and now recommends pharmacological thromboprophylaxis for *all* patients hospitalized with COVID-19, unless contraindicated by bleeding risk.[35] Studies attempting to retrospectively validate RAMs in hospitalised patients with COVID-19 continue to be subject to significant confounding; the vast majority of patients (90%) receive some form of pharmacological thromboprophylaxis.[36]

As the risk of VTE with hospitalization increases, the requirement for a complex RAM to guide individualised decision making is significantly reduced. Decision analytic modelling of the benefits, harms and costs of pharmacological thromboprophylaxis suggest it is likely to be cost effective from a United States healthcare perspective, for an average medical patient with a VTE risk of ≥1% and a low risk of bleeding.[37] Previous estimates suggest the risk of DVT for hospitalized medical patients without pharmacological thromboprophylaxis exceeds 10%.[7,38] These data create a compelling rationale to switch the focus of risk assessment from selecting 'in' those at risk, to advocating broader use and using a RAM to identify those patients at low risk where pharmacological thromboprophylaxis can potentially be withheld. RAMs may also be helpful to identify high risk of bleeding, where potential harm may outweigh any benefits.[39,40]

Current research and international benchmarking initiatives may allow refinement and further comparison of prognostic accuracy, reliability and cost effectiveness between RAMs. Until such data is available, repeated risk assessment and patient education are crucial. Current evidence strongly supports the use of pharmacological thromboprophylaxis in hospitalised general medical and surgical patients identified at risk of VTE. In the absence of definitive evidence, patients identified at lower risk of VTE using a RAM should be individually counselled. In addition, supporting information and clear safety netting throughout hospital stay and on discharge, remain vital.

Box 1 - “What you need to know”

- Hospital Acquired Thrombosis is responsible for approximately half of all diagnosed Venous thromboembolism. Many cases are potentially preventable, through patient education and pharmacological thromboprophylaxis.
- Different risk assessment models (RAMs) are used in different countries and patient groups to help clinicians decide who should be offered pharmacological thromboprophylaxis, resulting in wide variations in care and patient experience.
- It remains uncertain as to which RAM is optimal and whether any complex RAM definitively outperforms simple criteria or subjective clinical opinion.

Box 2 – “Search Strategy”

- Potentially relevant studies were identified through searches of 5 electronic databases including MEDLINE (with MEDLINE in-process and Epub ahead of print), EMBASE and the Cochrane Library. The search strategy used free text and theasaurus terms and combined synonyms relating to the condition (e.g VTE in medical inpatients) with risk prediction modelling terms. No language restrictions were used. However, as the current review updated three previous systematic reviews, searches were limited by date from 2017 (last search date from earlier reviews) to March 2021. Searches were supplemented by hand searching the reference lists of all relevant studies (including existing systematic reviews); forward citation searching of included studies; contacting key experts in the field; and undertaking targeted searches of the world wide web using the google search engine.

Box 3 - “How patients were involved in the creation of this article”

- Patient representatives from Thrombosis UK and the Sheffield Emergency Care Forum have been integral to the funding, development and progress of NIHR127454.
- The patient author on this article made several suggestions to emphasise the importance of repeated patient education, advice on individualised risk reduction and safety netting alongside routine clinical risk assessment.

Box 4 – "What patients need to know"

- Any hospital admission for more than 24h or major surgical procedure can increase your risk of developing a blood clot. This increased risk can persist for up to 90 days after hospital discharge.
- Blood clots can be one of the most serious complications associated with an operation and/or hospital stay. Many patients can reduce this risk substantially once they are properly informed, through increased fluid intake, early mobilisation and regular use of preventative therapies.
- All patients admitted to hospital should undergo a risk assessment for blood clots and be offered blood thinning medication if appropriate. This risk assessment can be repeated when the clinical situation changes and at the point of hospital discharge. Every risk assessment should be accompanied by patient education and supporting information to describe the signs and symptoms of blood clots, so that patients know when and how to seek help if required.

Box 5 – Recommendations for further research

Future research should determine whether it is safe to withhold pharmacological thromboprophylaxis in hospitalized medical and surgical patients identified at low risk by a

validated Risk Assessment Model. Such research could also compare the clinical and cost effectiveness of different models

- P – Hospitalised medical and surgical patients identified at low risk of VTE
- I – Withholding of routine pharmacological thromboprophylaxis
- C – Standard care (including pharmacological thromboprophylaxis at the discretion of the treating clinician, or as advised by the local RAM).
- O – Symptomatic VTE events up to 90 days following hospital discharge, including objectively diagnosed VTE and/or fatality attributable to VTE. Safety outcomes to include major bleeding and clinically relevant non-major bleeding, by international definition.[41,42]

Box 6 - “Education into practice”

Reflective question: how do you perform a VTE risk assessment for patients you admit to hospital and why do you use that particular method? Think about the last time you talked to a patient about their VTE risk, to what extent did you counsel them regarding the signs and symptoms of VTE, irrespective of risk? How might you alter your discussion next time?

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