COMMENTARY

Please cite this paper as: Noel SE, Millar, JA. Current state of medical thromboprophylaxis in Australia. AMJ 2014, 7, 2, 58-63. http://doi.org/10.21767/AMJ.2014.1915

Corresponding Author:
Prof J A Millar
Department of Medicine
Albany Regional Hospital
Albany, WA 6330
Australia
Alasdair.millar@health.wa.gov.au

Abstract

Background
Australia has two published national guidelines for general medical thromboprophylaxis (MT), but the two differ in detail and the basis for patient selection remains uncertain. Several aspects of current guidelines are controversial, as is the proposed design of a dedicated prescribing box in the National Inpatient Medication Chart.

Aim
To discuss and comment on the current standing of medical thromboprophylaxis in Australia.

Method
We have marshalled literature known to us from our previous published research, and have applied this knowledge to discuss shortcomings, which, in our opinion, exist in current medical thromboprophylaxis practice, and to suggest solutions.

Conclusion
Australian guidelines are flawed because they are based on unsuitable evidence (incidence of subclinical thrombotic disease) and define eligibility broadly, such that about 80 per cent of patients are considered eligible. They urge that prescribers should “consider” prophylaxis without supplying an adequate basis for doing so. They do not provide grounds for assessing the balance between hazard (in the form of major bleeds) and benefit (thrombotic events avoided). Other clinical factors promoting unnecessary use of medical thromboprophylaxis include the use of age as a risk factor and proposed inclusion of a new DVT prophylaxis section in the National Inpatient Medication Chart (NIMC), which implicitly discourages non-prescription of prophylaxis.

Key Words
Thromboprophylaxis, low molecular weight heparin, risk factor analysis, medical patients, guidelines

What this study adds:
1. What is known about this subject?
Thromboprophylaxis in medical patients is promoted actively, but the precise criteria for giving this treatment are uncertain.
2. What new information is offered in this study?
This commentary critiques the current guidelines and outlines how approaches to medical thromboprophylaxis can be improved.
3. What are the implications for research, policy or practice?
Criteria for medical thromboprophylaxis should be restricted to risk factors of reasonable weight to balance bleeding risk, and by deleting “increasing age,” because its reputation as an independent risk factor for thrombosis in medical patients has not been verified.

Introduction
Whilst there is no argument that prevention of hospital-acquired venous thromboembolism (VTE) is a worthwhile aim, several factors make its practical application in general medical patients problematic. This commentary briefly dissects the complexities of the apparently simple proposition that prophylaxis should be “considered” in all patients and given to those at “high” risk. We examine the current available guidelines, the epidemiological evidence regarding risk factor weights known to the authors from previous work, and the potential medical and economic impact of the guideline recommendations, and by doing so we address the question of how patients eligible for prophylaxis should be identified in practice.
Sources of thromboprophylaxis guidelines in Australia

An Australian prescriber wishing to obtain national guideline advice on MT has two possible sources. The first is the National Health and Medical Research Council (NH&MRC) Clinical Practice Guideline for the Prevention of Venous Thromboembolism in Patients Admitted to Hospitals in Australia.1 This guideline advises that medical patients should be “considered” for prophylaxis according to their risk of thrombosis or bleeding, but does not describe the basis for the consideration. Instead, it provides a list of risk factors of varying epidemiological significance, leaving room for subjective interpretation. Prevention of Venous Thromboembolism, the second and more didactic guideline, is from the Australia and New Zealand Working Party on the Management and Prevention of Venous Thromboembolism (ANZWP).2,3 The ANZWP is a private group of haematologists and surgeons. Its guideline has a presence on some state health department websites and is cited by the Royal Australasian College of Surgeons, but has not been endorsed by any national authority. The versions quoted in the public sources are old editions, and the most recent (5th) edition,2 which is difficult to obtain, contains substantial and indeed perplexing changes to eligibility criteria (see below). Corresponding guidelines have been published in other jurisdictions, notably in the US4 and UK.5

Overseas and Australian thromboprophylaxis guidelines in respect of medical patients have been criticised as being unscientific or overly liberal.6-13 The overall implication of these criticisms is that MT has been over-promoted, and that guideline support for MT in some medical patients is either unnecessary or potentially harmful due to the risk of bleeding.

Thromboprophylaxis and the National Inpatient Medication Chart

The notion of “considering” patients for thromboprophylaxis has been extended to the design of a new section in the National Inpatient Medication Chart published by the Australian Commission on Safety and Quality in Healthcare.14 The published instructions for assessment of risk, to enable a prescriber to tick a box stating that prophylaxis has been considered, read: “Authorised clinician to assess individual patient’s risk for VTE based on their risk factors, including the reason for hospitalisation utilising local hospital policy.”15 This sentence does not clearly state which risk factors justify prophylaxis, alone or in combination, assumes that all hospitals have a local policy, and raises the novel concept of a clinician “authorised” to assess VTE risk. No system exists in Australia for assigning such authority. While risk factors vary markedly in the strength of their statistical association with thrombosis, the risk of anticoagulant-related bleeding applies to all patients and may exceed the risk of thrombosis endowed by a weak risk factor. The new section also calls on prescribers to state that prophylaxis is NOT required, and by so doing must generate bias in favour of the prescription, as prescribers (mainly junior medical staff) will wish to avoid making a judgement that may turn out to be wrong. Thromboprophylaxis is the only area of prescribing in which doctors are expected to nail their flag to the wind to the extent of declaring that a drug is not required. As the NIMC applies in all hospital wards (not just medical wards), the thromboprophylaxis section will apply to patient populations at widely varying VTE risk. For some patient populations at substantial risk it may be beneficial to insist on a declaration of this sort, but not in medical patients where the risk is low.

Risk of thrombosis in medical patients and validity of medical thromboprophylaxis

Though most, if not all, physicians have had the harrowing experience of a patient collapsing cyanosed and terminally breathless during an otherwise unremarkable convalescence from an unrelated condition, years can elapse between such incidents in a general medical ward. In a prospective study, we found that in-hospital clinical VTE occurs in less than 0.34 per cent of general medical inpatients.19 Most estimates are under 0.5 per cent,13,16,17 and the highest reported figure, based on a retrospective study of clinical records, is 1.59 per cent.18 The validity of prophylaxis in any area depends on the significance, cost, and incidence of the disease being prevented and the effectiveness, adverse reactions, and cost of the intervention. The essential problem of MT is that only one manifestation of the disease (pulmonary embolus) may be fatal, and the more common manifestation (venous thrombosis) is treatable, though it can carry long-term sequelae such as post-thrombotic syndrome. However, as the underlying clinical DVT rate is low in medical inpatients the chronic sequelae are also uncommon. In addition, as the relative risk reduction (RRR) of prophylaxis using low molecular weight heparin (LMWH) is of the order of 0.5–0.6, thrombotic events are not in fact totally preventable. Lastly, anticoagulant prophylaxis has a risk of major bleeding (defined as intraoculor, spinal/epidural, intracranial, or retroperitoneal bleeding; a decrease in haemoglobin of ≥2 g/dL; a need to transfuse ≥2 U of blood or for significant medical or surgical intervention, or bleeding resulting in death19) that is similar at 0.33 per cent to the reported baseline rate of thrombosis.19 Thus the simple expedient of giving LMWH to all medical patients may produce net harm,
and a reliable method of assigning prophylaxis according to risk factor weighting is essential.20

Most guidelines claim that the baseline VTE rate in medical patients is between 10 and 20 per cent. For example, both a House of Commons Select Committee Report21 and the AWP Guidelines (4th edition5) state that the incidence is 17 per cent (8 per cent is given in the AWP 5th edition9). The AWP guidelines concede1,3 that these figures include subclinical events detected by Doppler ultrasound or other imaging technique, but avoids reporting the proportion. On the basis of the above figures (0.34 per cent to 1.59 per cent clinical VTE and 17 per cent total VTE) the proportion of all VTE that is asymptomatic must range from between 90.6 per cent and 98 per cent. The House of Commons Report22 was silent in this respect and hence gave an exaggerated impression of the problem. Most sub-clinical DVT events, especially if below the knee, resolve spontaneously and may be regarded as a normal phenomenon.22 A proportion of pulmonary emboli do arise without a preceding clinical DVT. This is an interesting clinical problem, but it is irrelevant to the rationale for prophylaxis, which depends entirely on disease incidence, not pathophysiology. Thus MT cannot be justified on the frequency of asymptomatic thrombi. The importance of disease incidence on the clinical and economic performance of prophylaxis is shown in Table 1.

**Table 1: The effect of varying baseline event rate for DVT at 17 and 0.5 per cent**

|     | 17%   | 0.5%   |
|-----|-------|--------|
| RRR | 0.6   | 0.6    |
| Incidence treated | 6.8%  | 0.2%   |
| NNT | 15    | 500    |
| $/event avoided   | $1500 | $50,000 |

Illustration of the effect of varying baseline event rate for DVT at rates of 17 and 0.5 per cent, on both the number needed to treat (NNT) to avoid 1 episode of thrombosis and the cost per event avoided by prophylaxis. The calculations assume that the same relative risk reduction applies to both subclinical and clinical thromboses, and use an arbitrary unit cost/patient for prophylaxis and treatment of thromboembolic disease of $100. The NNT is given by the equation  

\[ NNT = \frac{100}{I \times RRR} \]

where \( I \) is the baseline (untreated) disease incidence, expressed as a percentage.

The reason for publication of misleading incidence data is complex. The US Food and Drug Administration has insisted that treatment trials of anticoagulants should use objective and sensitive diagnostic methodology. The disadvantage of this ruling is that the trials to which it applies inevitably report an incidence that, on the basis of the above figures, is 20 to 50 times that of the clinical disease. Appropriately powered trials based on clinical thrombotic endpoints would be prohibitively large and costly. Thus emerges the odd situation in which we have excellent efficacy data using end-points that are of little clinical relevance. These data are then used to promote application of prophylaxis, without secure information on whether the RRR for asymptomatic VTE events also applies to clinical disease.

**Practical application of risk factors**

Wisely, given the rarity of the event in medical patients, no guidelines recommend medical prophylaxis in all medical patients. However, the AWP guidelines (under which 84 per cent of patients are eligible23) and unrestricted application of the NH&MRC provisions (89 per cent eligible)13 come close. With such percentages it is inevitable that many patients are treated unnecessarily. The guidelines list risk factors for thrombosis and in general imply or explicitly state that the presence of any one risk factor renders a patient at “high” risk and hence eligible for prophylaxis. This is questionable, for several reasons. First, “high” is undefined and the absolute level of risk that justifies deployment of prophylaxis (now almost universally LMWH) is not stated. This is important because prophylactic treatment carries its own risk, is uncomfortable for patients, and frequently causes minor bruising at injection sites. A balancing of risks and benefits is required. The guidelines do not refer to the statistical weighting of individual risk factors; therefore, it is difficult to know whether the incremental risk of thrombosis resulting from the presence of a given factor is sufficient to compensate for the added haemorrhagic risk of prophylaxis. Secondly, some of the pro-thrombotic factors described in guidelines may not be risk factors at all. The most important of these is advancing age, widely touted as a risk factor, but not found to be so in medical patients on multivariate analyses.24,25 Indeed, increasing age is a risk factor for bleeding when anticoagulants are deployed for therapeutic purposes.26-28 Whether this applies to prophylactic use is uncertain. This is of great importance because age above a certain value (which differs in the two national guidelines: > 40 in the NH&MRC and > 60 in the ANZWP) is the “risk factor” that makes the majority of medical patients “eligible” for thromboprophylaxis, since the average age of medical inpatients is about 75. Thirdly, the risk factors themselves are described vaguely and this places a need for interpretation on the part of the doctor “considering” whether prophylaxis should be prescribed. For example, heart failure is a risk factor, but the absolute risk depends on the grade of failure.29,30 The “consideration” for...
prophylaxis to be assigned to a risk factor whose risk is variable depending on disease severity is no simple task.

The strongest risk factors for VTE in medical inpatients are malignancy (especially during chemotherapy), previous history of DVT or a proxy thereof (varicose veins or post-thrombotic syndrome), and recent surgery. Other risk factors are of modest statistical weight. On the other hand, the presence of multiple risk factors, even of modest statistical weighting, or likely but undocumented risk from rare conditions, may be high. For this reason, routine adoption of thromboprophylaxis in medical intensive care units is justified. Application of a weighted risk-factor approach is implied by the proposal that the need for prophylaxis should be “considered” in all patients. What does this mean if not that there should be an assessment of absolute risk? This approach has been suggested by several authors and is embodied in computer algorithms that assist in the decision for or against thromboprophylaxis. However, the presence of multiple risk factors is unusual and most patients whose risk of prophylaxis is commensurate with the risk of major bleeding are captured in a simple algorithm consisting of systemic malignancy and previous history of DVT, plus some special conditions known to have high risk such as severe sepsis and acute inflammatory bowel disease.

The difficulty with a qualitative risk factor solution, in which risk factors are considered without regard to their statistical weight, is exemplified in the differences in risk factor analysis proposed in the 4th and 5th editions of the AWP guideline, shown in Table 2.

Several important points can be made:

- None of the changes between the editions are explained, given literature citations, or otherwise justified.
- In the 5th edition the dichotomous division of risk groups (“HIGH” and “LOWER”) is grammatically inept.
- The 5th edition introduces complementary and nested risk factors in the “HIGH” risk group and no clear distinction between the groups owing to the presence of quite strong risk factors in the “LOWER” risk group. This makes it difficult to apply in practice and is likely to result in unnecessary use.
- The changes in group risk factor content must be associated with a change in the absolute level of risk in each group, but the quantitative aspects of this consequence are unknown.

- Patients with mild degrees of some risk factors with little likely impact on VTE risk, for example, “heart failure” are not excluded.

Table 2: Comparison of the eligibility criteria for thromboprophylaxis in the 4th and 5th editions of the Australia and New Zealand Working Party (ANZWP) recommendations for medical inpatients.

| Risk groups: | 4th edition | 5th edition |
|--------------|-------------|-------------|
| HIGH and LOW | Any one of: ischaemic stroke, VTE history, acute cancer, decompensated heart failure, acute on chronic lung disease, acute on chronic inflammatory disease, age > 60 | A OR B, where A is: Admission due to heart failure or severe respiratory disease; and B is: Reduced mobility for 3 days or more PLUS ANY OF prior VTE, active cancer, acute neurological disease, inflammatory bowel disease, age > 60 |
| Risk factors requiring prophylaxis | NONE | Thrombophilia, oestrogen therapy, pregnancy or puerperium, active inflammation, strong family history, obesity |
| Risk factors suggestive of prophylaxis, non-high-risk group | NONE | “Consider” prophylaxis in the presence of the above factors |
| Action to be taken in the non-high-risk group | NONE | “Consider” prophylaxis in the presence of the above factors |

## Cost effectiveness

Drug therapy in many countries including Australia is usually subject to satisfaction of cost-effectiveness criteria. The primary group for that purpose in Australia is the Pharmaceutical Benefits Advisory Committee (PBAC), but the PBAC has not considered MT. Though several publications have concluded that thromboprophylaxis with LMWH is cost effective, these conclusions are suspect since they rely mainly on the incidence data for sub-clinical events reported in the MEDENOX Study. When cost effectiveness is measured according to clinical disease, it is found to vary inversely with the size of the eligible population defined by the risk factors of variable statistical weight. When eligibility is restricted to strong risk factors, drug acquisition costs and toxicity (major bleeding) are minimised, and most clinical events are prevented. But there is a price to pay, because events also occur at low rates in non-eligible patients. Not all prescribers will agree on the level of risk that justifies prophylaxis to overcome...
the risk of bleeding on the one hand yet allows DVT events in non-prophylaxed individuals. In fact, not many will have the insight and knowledge of the various risk factors to be able to come to a rational conclusion in this regard. This circumstance makes MT a complex issue. Several factors such as promotion by pharmaceutical manufacturers and potential bias arising from the design of the proposed section in the NIMC further increase this intrinsic complexity.

Conclusion

MT is a complex issue. Provisions in Australian guidelines (and corresponding guidelines overseas) and proposed changes to the NIMC are likely to promote overuse. The new 5th edition ANZWP guidelines contain substantial and unexplained changes, which are confusing and hence potentially unsafe. To maintain cost effectiveness and achieve a benefit:hazard ratio that exceeds unity, MT has to be administered under an algorithm that takes account of the statistical weights of individual risk factors in a way that identifies not more than 20–40 per cent of the medical inpatient population as being at sufficiently high risk. This is the challenge facing prescribers in Australia and overseas. One simple way of approaching this ideal would be to remove age as a risk factor in medical patients.

References

1. National Health and Medical Research Council. Clinical practice guideline for the prevention of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to Australian hospitals. Melbourne: National Health and Medical Research Council; 2009. http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/guideline_prevention_venous_thromboembolism.pdf. Accessed 5 August 2013.

2. The Australia and New Zealand Working Party on the Management and Prevention of Venous Thromboembolism. Prevention of venous thromboembolism (4th Edition). Best Practice Guidelines for Australia and New Zealand. Health Education & Management Innovations Pty Ltd, 2007.

3. The Australia and New Zealand Working Party on the Management and Prevention of Venous Thromboembolism. Prevention of venous thromboembolism (5th Edition). Best Practice Guidelines for Australia and New Zealand. Health Education & Management Innovations Pty Ltd, 2010.

4. Geerts WH, Bergqvist D, Pineo GP, Heit JA, Samama CM, Lassen MR et al. Prevention of Venous Thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133 (6 suppl 3):815–4535.

5. Anon. Venous thromboembolism: reducing the risk. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. National Institute for Health and Clinical Excellence, London, UK, 2010. http://www.nice.org.uk/nicemedia/live/12695/47195/47195.pdf

6. Welfare M. NICE’s recommendations for thromboembolism are not evidence based. BMJ 2011;343:d6452.

7. D’Costa DF. Time to reconsider NICE guidance on heparin prophylaxis in medical patients. BMJ 2011;343:d7886.

8. Lederle FA, Zylla D, MacDonald R, Wilt TJ. Venous thromboembolism in hospitalized medical patients and those with stroke: A background review for an American College of Physicians Clinical Practice Guideline. Ann Int Med 2011;155(9):602–615.

9. Allareddy RR. Venous thromboembolism prophylaxis. Ann Int Med 2012;156(4):324–325.

10. Herzig SJ, Rothberg MB. Prophylaxis rates for venous thromboembolism and gastrointestinal bleeding in general medical patients: too low or too high? BMJ 2012;344:e3248 doi: 10.1136/bmj.e3248.

11. Millar JA. Rational thromboprophylaxis with low molecular weight heparin in medical inpatients: not quite there yet. Med J Aust, 189; 504-506.

12. Millar JA. Australasian guidelines for medical thromboprophylaxis are flawed. Thromb J. 2011. http://www.thrombosisjournal.com/content/9/1/7/comments#495685

13. Millar JA, Lett JE, Bagley LJ, Densie IK. Eligibility for medical thromboprophylaxis are flawed. Thromb J 2011. http://www.thrombosisjournal.com/content/9/1/7/comments#495685

14. Australian Commission on Safety and Quality in Healthcare. New NIMC. Medication Safety Newsletter, July 2013. www.safetyandquality.gov.au/wp-content/uploads/2012/01/Medication-Safety-Update-10-Jul-2013.pdf. Accessed 8 August 2013.

15. Australian Commission on Safety and Quality in Healthcare. Your guide to the NIMC VTE prophylaxis section. http://www.safetyandquality.gov.au/wp-content/uploads/2012/02/NIMC-VTE-Brochure-PDF-706KB.pdf. Accessed 8 August 2013.
16. Millar JA, Lee GE, Ienco R. Prevalence of venous thromboembolism in medical inpatients. Med J Aust. 2010;192(12):724–725.

17. National Institute for Clinical Studies. The incidence and risk factors of venous thromboembolism in West Australian hospitals 1999 to 2001. Report commissioned from the School of Population Health, University of Western Australia. Canberra, Australia: National Institute for Clinical Studies; 2005. Available from: http://www.nhmrc.gov.au/nics/materialresources/resources/incident_risk.htm. Accessed September 18, 2012.

18. Edelsberg J, Hagiwira M, Taneja C, Oster G. Risk of venous thromboembolism in hospitalised medically ill patients. Am J Health-Syst Pharm 2006; 63 (20 Suppl. 6):S16–21.

19. Leizorovicz A, Cohen AT, Turpie AGG, Olsson C-G, Vaitkus PT, Goldhaber SZ for the PREVENT Medical Thrombosis Study Group. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation 2004;110:874–879.

20. Millar JA. Selection of medical patients for prophylaxis of venous thromboembolism based on analysis of the benefit:hazard ratio. Int Med J 2009;39(9):606–610.

21. House of Commons Health Committee. The prevention of venous thromboembolism in hospitalized patients (HC99). London, The Stationery Office, 2005.

22. Singh K, Yakoub D, Giangola P, DeCicca M, Patel CA, Marzouk F et al. Early follow-up and treatment recommendations for isolated calf deep venous thrombosis. Journal of Vascular Surgery. 2012;55:136–40.

23. Gibbs H, Fletcher J, Blombery P, Collins R, Wheatley D. Venous thromboembolism prophylaxis guideline implementation is improved by nurse directed feedback and audit. Thrombosis Journal 2011;9:7 (5 April).
http://www.thrombosisjournal.com/content/9/1/7

24. Alikhan R, Cohen AT, Combe S, Samama MM, Desjardins L, Eldor A et al. Risk factors for venous thromboembolism in Hospitalised Patients with acute medical illness: Analysis of MEDENOX Study. Arch Int Med 2004;164:963–968.

25. Kobbervig CE, Heit JA, Petterson TM, Bailey KR, Melton LJ. The effect of patient age on the incidence of idiopathic vs secondary venous thromboembolism: a population-based cohort study. Blood 2004;104:957a.

26. Hughes M, Lip GY. Risk factors for anticoagulation-related bleeding complications in patients with atrial fibrillation. Quart J Med 2007;100:599.

27. Kadakia MB, Desai NR, Alexander KP, Chen AY, Foody JM, Cannon CP et al. Use of anticoagulant agents and risk of bleeding among patients admitted with myocardial infarction. J Am Coll Cardiol 2010;3:1166–77.

28. Mikkola KM, Patel SR, Parker JA, Goldhaber SZ. Increasing age is a major risk factor for haemorrhagic complications after pulmonary embolus thrombolysis. Am Heart J 1997;134:69–72.

29. Alikhan R, Cohen AT, Combe S, Samama MM, Desjardins L, Eldor A et al. Prevention of venous thromboembolism in medical patients with enoxaparin: a subgroup analysis of the MEDENOX Study. Blood Coagul Fibrinolysis 2003; 14:341–346.

30. Howell MD, Geraci JM, Knowlton AA. Congestive heart failure and outpatient risk of venous thromboembolism: a retrospective, case-controlled study. J Clin Epidemiol 2001;54:810–816.

31. Hippisley-Cox J, Coupland C. Development and validation of risk prediction algorithm (QThrombosis) to estimate future risk of venous thromboembolism: prospective cohort study. BMJ 2011;343:d4656 doi: 10.1136/bmj.d4656.

32. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C et al for the Prophylaxis in Medical Patients with Enoxaparin Study Group. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. The Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med 1999;341:793–800.

33. Millar JA. Validity of medical prophylaxis guidelines assessed from a health-economics perspective. In preparation.

34. Millar JA. Genesis of guidelines for thromboprophylaxis in Australia: a need for transparency and standardization in guideline development. MJA 190;446–450.

PEER REVIEW
Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST
The authors declare that they have no competing interests.