



■ ANNOTATION: THROMBOSIS

Evidence-base for aspirin as venous thromboembolic prophylaxis following joint replacement

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The National Institute for Health and Clinical Excellence (NICE) has thus far relied on historical data and predominantly industry-sponsored trials to provide evidence for venous thromboembolic (VTE) prophylaxis in joint replacement patients. We argue that the NICE guidelines may be reliant on assumptions that are in need of revision. Following the publication of large scale, independent observational studies showing little difference between low-molecular-weight heparins and aspirin, and recent changes to the guidance provided by other international bodies, should NICE reconsider their recommendations?

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Introduction

Hip and knee replacements are highly effective procedures for the relief of pain and restoration of function in patients with end-stage arthritis. They demonstrate functional longevity, with low rates of failure and mortality.^{1,2} In England and Wales, around 150 000 such procedures are performed each year, with a 90-day mortality rate between 0.3% and 0.4%.² NICE guidelines currently recommend extended venous thromboembolic (VTE) prophylaxis for all hip and knee replacement patients (between 10 and 14 days for knee replacement and 28 to 35 days for hips) using low-molecular-weight heparin (LMWH) or newer oral agents.³ These recommendations are derived from an extensive network extrapolation of randomised trial data only. Aspirin is not recommended. We have undertaken a critical review of the NICE guidelines relating to hip and knee replacement surgery, which suggests the evidence for prophylaxis is not robust. There are a number of concerns.

Risk data. Risk data, on which the guidelines are based, are historical and may not be applicable to current orthopaedic practice. The last ten years have seen a major change in the delivery of orthopaedic services. The implementation of strategies such as day of surgery admission, the widespread adoption of regional anaesthesia, reduced operating times and fast-track analgesia, allow early mobilisation and aggressive rehabilitation, resulting in a mean length of stay in hospital

of five days.⁴ These strategies contribute to a reduction in risk of death in the peri-operative period⁵ and may reduce VTE. The papers cited by NICE⁶⁻¹⁵ to form the basis of their guidelines, are between 10 and 35 years old, when restricted ambulation and prolonged length of stay were commonplace after joint replacement. Now, patients routinely walk within 24 hours of surgery,¹⁶ and many on the same day with enhanced recovery initiatives. Results from these studies may lack relevance to modern orthopaedic practice, as they are likely to overestimate the size of the problem, and evidence of absolute VTE risk in the modern era is lacking. It is important to reflect the role of non-pharmacologic strategies upon the prevention of VTE in the production of guidelines.

Incidence of VTE after joint replacement

The incidence of VTE after joint replacement may be smaller than appreciated. Mortality within 90 days of elective hip and knee replacement performed for osteoarthritis was 2.9 per 1000 in 2011 in England and Wales. However, excess mortality attributable to the procedure (exceeding the baseline population risk) may only be 1.2 per 1000 patients.¹⁷ Based on 150 000 joint replacements per year,² the excess mortality attributable to the operation is approximately 180 cases per year. The proportion of these deaths resulting from pulmonary embolism (PE) is between

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18% and 25%,^{16,18-20} representing approximately 30 to 45 patients annually. Cardiac-related death following surgery is more common and may be more relevant, given the well-established anti-platelet effects of aspirin in secondary prevention of cardiovascular disease²¹ and the potential to reduce peri-operative mortality.²²

Given that the number of potentially preventable deaths from VTE is small, we must question the cost-effectiveness of widespread (expensive) anti-coagulant use, particularly as no anticoagulant has been proven to reduce mortality (even in the historic era of prolonged immobilisation).³ The annual cost of potent anticoagulants in these joint replacement patients across England and Wales is approximately £13 million (For example Clexane (Sanofi-Aventis Ltd, Paris, France) £3.03 per 40mg (daily) syringe, 14 days for 90 842 knee replacements and 35 days for 86 488 hip replacements),²³ and this ignores community nurse fees to administer the drug to large numbers of patients. In comparison, the estimated cost of administering aspirin is around £110 000 per year (less than 1% of the more expensive agents). One study,²⁴ which estimated the lifetime costs, quality-adjusted life-years (QALYs) and costs per QALY gained when LMWH was used instead of aspirin, found a low probability that LMWH is cost-effective for all patients undergoing hip replacement and for elderly patients undergoing knee replacement. For younger patients requiring knee replacement, the cost-effectiveness of LMWH compared with aspirin is uncertain.²⁴ The true size of the problem and the cost implications need to be more fully appreciated in any subsequent analyses carried out by NICE.

Assumptions used by NICE may need to be revised

The use of VTE prophylaxis after elective surgery is a balance of risks and benefits. However, the inclusion of only randomised controlled trials (RCTs) restricts the evidence available. Moreover, industry sponsorship is endemic within these trials. NICE state that there is no published evidence for the effects of VTE prophylaxis on fatal PE, non-fatal PE and all-cause mortality after knee replacement and no data on the effects on fatal PE and all-cause mortality after hip replacement.³ A recent systematic review of all published trials to determine the comparative effectiveness, benefits, and adverse effects of VTE prophylaxis following orthopaedic surgery concluded that, while there is a real risk of developing deep vein thrombosis (DVT), PE, and major bleeding after major orthopaedic surgery, there are inadequate data to say whether DVT causes PE, and DVT was not found to be an independent predictor of PE occurrence.²⁵ The relationship of DVT to PE is complex (and this uncertainty is described in the NICE guidelines).^{3,18,20}

There are also concerns regarding the manner in which major bleeding complication data were handled. In the NICE analysis, bleeding risk associated with aspirin (based on data from ten knee replacement studies) was not thought plausible, as the risk was low. It was therefore

disregarded, fundamentally changing the cost-effectiveness analysis (in which aspirin was most cost-effective) and, as a result, altering the prophylaxis recommendations for knee replacement patients. In a recent study on apixaban, bleeding complications occurred around ten times more frequently (10% to 11%) than major VTE, including symptomatic or asymptomatic proximal DVT, non-fatal PE and death from VTE (0.7% to 1.5%).²⁵

Although symptomatic and asymptomatic DVT are commonly used as outcome measures in prophylaxis trials, the long-term impact of these on patients' perceived quality of life has never been evaluated. NICE assume that longer-term complications of VTE following joint replacement surgery, such as post-thrombotic syndrome and chronic pulmonary hypertension, are a major cause of morbidity³; there is no supporting data for this in the literature. However, there is published evidence that venous ulceration is found equally amongst those with and without a history of VTE following joint replacement,²⁶ and when those who underwent joint replacement without chemical thromboprophylaxis were compared with the general population.²⁷

Other clinically relevant effects of potent anticoagulants as randomised trials have not routinely reported the incidence of wound complications, return to theatre and deep joint sepsis. An observational study of over 17 000 procedures found "an etiological relationship between the administration of LMWH and the ensuing risk related to surgical site infections".²⁸ There is also evidence of higher wound complications with rivaroxaban compared with LMWH.^{29,30} Prolonged wound ooze and surgical site complications cause distress to patients, delay discharge and can necessitate additional surgical interventions. Surgical site infection (SSI) is a serious complication of joint replacement. The Health Protection Agency in England reports an incidence of 6 per 1000 but the true figure may be higher.⁴ This can necessitate prolonged antibiotics, repeat operations and revision surgery as well as occasional fusion of the joint or, rarely, amputation. Each infection costs over £20 000 to treat and across the NHS, SSI costs approximately £92 million per year.³¹ Patients who develop SSI and undergo revision surgery have poorer functional outcomes and satisfaction when compared with uncomplicated primary replacements, even when the infection has been eradicated.^{23,32} The financial and emotional costs incurred when treating the side effects of potent anti-coagulants are considerable, and need to be factored into future recommendations. As there is a trade-off between increased efficacy and increased bleeding, any harm caused (such as bleeding resulting in transfusion, infection, readmission or re-operation) should be determined in all cases. However, few trials report these harms.³³

Cohort studies

Large, contemporary cohort studies show little difference in terms of efficacy and safety between aspirin and LMWH. Randomised trials have thus far been underpowered to detect differences in rare events such as PE and

mortality after joint replacement. However, observational studies are well suited to the evaluation of this type of data. An article³⁴ in *The Lancet* by Professor Sir Michael Rawlins, Chair of NICE, states:

Decision makers need to assess and appraise all the available evidence irrespective of whether it has been derived from randomised controlled trials or observational studies; and the strengths and weaknesses of each need to be understood if reasonable and reliable conclusions are to be drawn.

Furthermore: “decision makers need to avoid adopting entrenched positions about the nature of evidence; and accept that the interpretation of evidence requires judgment”. This would seem to conflict with the approach used by NICE for the current VTE guidance. The inclusion of large-scale, non-randomised, contemporaneously-controlled observational studies should be considered, including joint registry data.³⁵⁻³⁷ Such registry reports have documented the outcome in many hundreds of thousands of patients. Although they provide lower levels of evidence, these studies are important when it is not feasible to conduct RCTs to answer the questions posed. Observational analyses reflect the real effect of VTE prophylaxis in a contemporary setting, without the artificial environment of a RCT.

Comparative effectiveness research

The comparative effectiveness research initiative approach is specifically designed to generate and synthesise evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition, or to improve the delivery of care. It appreciates the importance of combining evidence from a variety of sources, including both RCTs and observational sources, to reach a conclusion that has direct application within clinical practice.³⁸ The subject has recently been awarded USD \$1.1 billion of funding by United States Congress. One of the first 100 projects to be commissioned using this funding is a comparison of the effectiveness of different anticoagulant therapies (e.g. warfarin, aspirin, injectable anticoagulants) for patients undergoing hip and knee arthroplasty surgery.³⁹ This suggests an appreciation for the need to combine both RCT and observational approaches across a range of anti-coagulant agents when evaluating their efficacy following hip and knee replacements.

International guidelines differ from those of NICE

Both the American College of Chest Physicians (ACCP) and the American Academy of Orthopaedic Surgeons (AAOS) now recommend aspirin as a method of VTE prophylaxis after elective hip and knee replacement in their revised guidelines.^{40,41} These guidelines state that the goal of prophylaxis continues to be the prevention of venous thromboemboli and pulmonary emboli, but the risks of prophylaxis must be considered. The revised

guidelines give clinicians more autonomy in choosing a prophylactic agent (including aspirin), with greater emphasis placed on dialogue between the surgeon and patient as to the choice of prophylaxis when balancing the risks and benefits of prophylaxis.⁴² The ACCP and AAOS guidelines differ from NICE, despite consideration of the same available evidence. Major guideline bodies should not present conflicting advice based on the same available evidence.

Conclusion

There is a case for revision of the NICE guidelines for the prevention of VTE after elective hip and knee replacement. The size of the problem may be much smaller in the modern era, assumptions linking DVT with PE/death may not be valid and there is an under-appreciation of the number of wound problems, infective complications and bleeding events the potent anticoagulants are causing. All of these factors are likely to have an effect on the cost-benefit of expensive anti-coagulants when compared with agents such as aspirin, which is cheaper, safer and equally efficacious.

We strongly recommend that NICE consider all the evidence for VTE prophylaxis (including lesser levels of evidence where trial data is not sufficient), given the lack of a clear benefit from the use of potent anticoagulants, as well as the concerns expressed within the orthopaedic community regarding unmeasured risks of prophylaxis and cost implications.

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