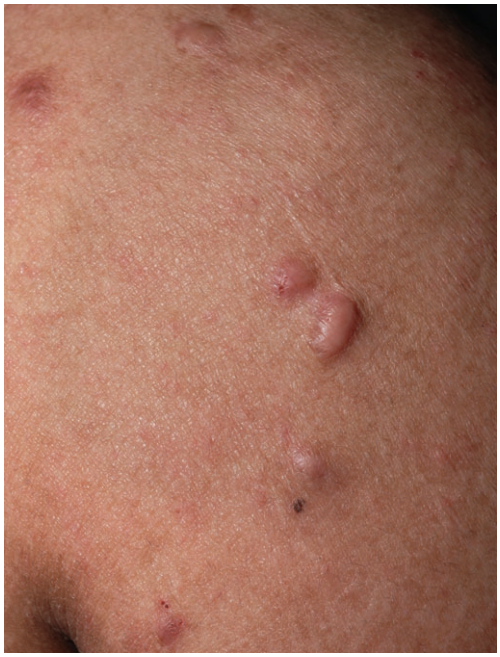

Fig. 3. Hypertrophic scars left from staples used to secure dressings.

With improved survival comes the need to take better care and attention to detail in their treatment to avoid complications associated with the disease such as synaechia and complications associated with treatment such as corneal abrasions from over-zealous glass rodding of the conjunctival fornices and hypertrophic scarring from staples used to secure dressings.

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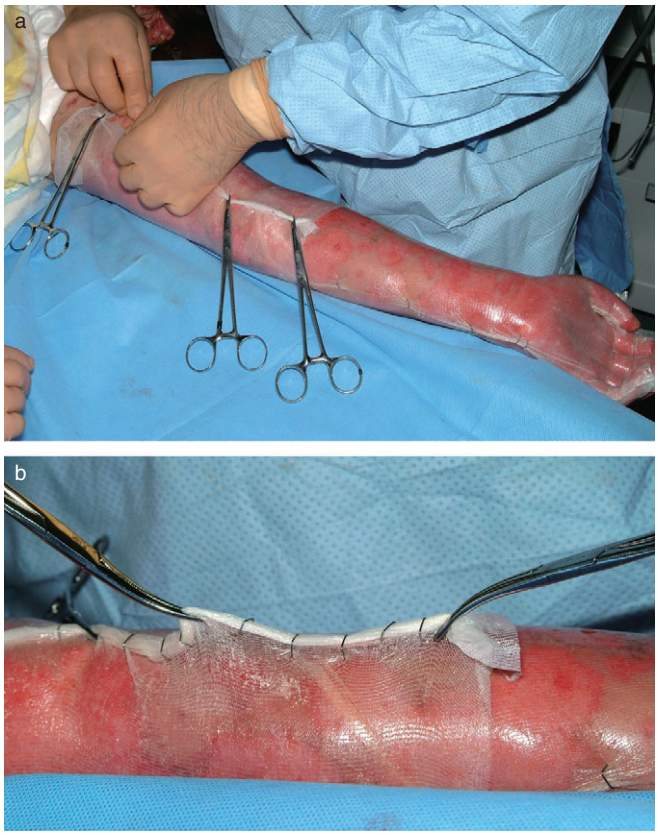

Fig. 4. A 'non-staple in skin' technique to secure biobrane to itself (a, b).

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Controversies of thrombophylaxis following knee arthroplasty surgery

Thromboembolic phenomena following major orthopaedic surgery are an ever-present risk. Because of the high venous thromboembolism (VTE) rates following surgery to the hip or knee, these interventions are described as excellent thrombophilia models and are the subject of much research in the quest for antithrombotic agents.[1] The many forms of thromboprophylaxis and their appropriateness following total knee arthroplasty surgery has been the subject of recent debate by the Arthroplasty Society of Australia. The results of this debate have led to guidelines that are now endorsed by the Australian Orthopaedic Association and are displayed on its web site.

During the last decade, low molecular weight heparin has been advocated by many groups as the preferred method of thromboprophylaxis. Aggressive marketing programs including sponsored publications have contributed to their initial popularity.[2] In 2004 the

Based on previous communications to the Arthroplasty Society and Continuing Orthopaedic Education meetings of the Australian Orthopaedic Association.

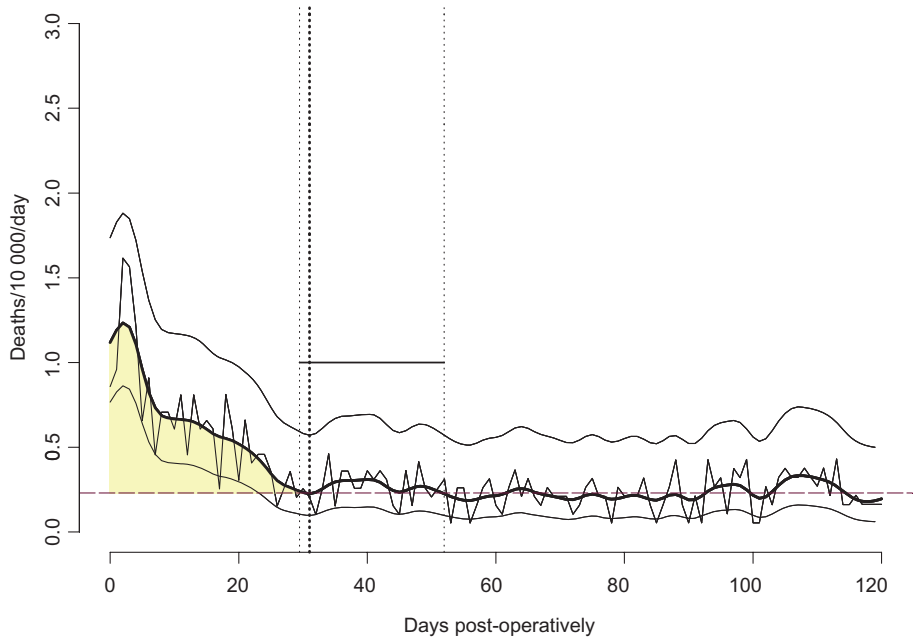

Fig. 1. Early post-operative mortality following elective hip and knee replacements recorded in the Australian and Norwegian joint replacement registry. Smoothed hazard intersection with base mortality at 31 days is the duration of risk. Shaded area is the 'operation risk'; post-operative mortality risk is 0.13%.

American College of Chest Physicians recommended guidelines for surgeons treating arthroplasty patients that universally included the addition of chemical antithrombotic agents.[3] The chest physicians made these recommendations on the basis of evidence-based studies that showed a reduction in the VTE rate in patients treated by chemical agents. It would be an easy path for surgeons to simply default and adopt these guidelines without question; however, there remain many concerns regarding the risk-benefit ratio of these agents, particularly as the holistic clinical picture includes patient survival, iatrogenic morbidity and limb outcomes.

There is no level one or level two evidence that supports the use of antithrombotic agents for the clinical outcomes of a reduction of sudden death or pulmonary embolus. However, there is abundant level one and two evidence to show a reduction of asymptomatic deep venous thrombosis. It is this evidence that has been used to recommend chemical prophylaxis for the prevention of thromboembolic disease in knee-replacement patients. Thromboembolic disease, however, is a spectrum that includes pulmonary embolus, which can be fatal or asymptomatic, as well as deep venous thrombosis, which also can be symptomatic or asymptomatic, and the sequelae, which can include the post-thrombotic syndrome (PTS) or a predisposition to further thrombotic episodes. A reduction in the incidence of asymptomatic deep venous thromboses may not necessarily lead to a similar reduction in death or limb complications.

What is the magnitude of the problem?

It is useful to define the magnitude of these problems in the quest for a logical cost/benefit analysis of treatment regimes. Pulmonary embolism will occur in approximately 4.6% of patients after total knee arthroplasty, be associated with symptoms in 0.5% and be fatal in 0.22%.[4] Most surgeons would agree that their principal concern when trying to prevent thromboembolic phenomenon is to avoid a fatal outcome, while the clinical importance of symptomatic or asymptomatic pulmonary emboli and other thromboembolic consequences is not as clear.

Perspective regarding the frequency of a fatal outcome following knee replacement surgery can be gained from joint replacement registries and population studies. Lie *et al*.[5] reported a daily population death rate of 0.95 deaths per 10 000 individuals in a comparable-aged normal population (standardized mortality rate). A combined study of the Australian and Norwegian registry reports the mortality rates of over 200 000 patients and demonstrated an increased mortality risk of 0.13% from all causes following knee and hip arthroplasty surgery. The period of increased risk persisted for 3 weeks and returned to baseline values thereafter.[6] (Fig. 1)

Lie *et al*.[5] reported the Norwegian Registry 60 day postoperative mortality after hip replacement. The standardised mortality rate of 0.56% increased to 0.75%. The increase in mortality was mainly due to vascular diseases that accounted for 0.60% while the broad category 'thromboembolic complications' accounted for 0.37% mortality.

The Scottish Arthroplasty Project[7] has examined a population of 44 785 hip-replacement patients, 27 503 knee replacements and 176 520 cataract patients (used as a surrogate marker of standardized mortality rate) over a 10-year period between 1992 and 2001. During this time, the 90-day mortality rate was 1.01% for cataract patients, 1.35% for hip-replacement patients and 0.81% for knee-replacement patients; the standardized mortality rate would be 0.86%. Early post-operative death was most commonly due to myocardial infarction and cerebrovascular accident (CVA) (0.36%). Pulmonary embolus accounted for only 3 of 16 deaths following knee replacement surgery (0.15%).

From the information available regarding fatal pulmonary emboli, it is estimated that a randomized controlled study to assess an agent capable of reducing the risk by 50% in hip arthroplasty patients will

require a minimum of 30 000–90 000 patients.[5,8] Currently, no such study exists for knee or hip arthroplasty patients. Strategies to assess the efficacy of agents have therefore proceeded under the presumption that most fatal pulmonary emboli progress from a deep venous thrombosis, which is often an asymptomatic finding.

Venous thromboembolic prophylaxis

There is abundant evidence examining the efficacy for the prevention of asymptomatic deep venous thrombosis. A 25-year population-based study by Silvestan *et al*. (1998), observed an annual incidence of deep venous thrombosis of 0.1% of normal individuals and 1–3% in obese individuals. Following arthroplasty surgery, symptomatic deep venous thrombosis will occur in 1–1.6% of patients[9,10], asymptomatic proximal deep venous thrombosis (DVT) in 6% and asymptomatic distal DVT in 29%.[4] Geertz *et al*.,[3] representing the American College of Chest Physicians, report a relative risk reduction of 13% of patients treated by aspirin, 42.5% of patients treated by warfarin, 45.4% of patients treated by low molecular weight heparin and 79.5% of patients treated by fondaparinux. A meta-analysis by Westrich *et al*.[11] reports similar results, but notably also a dramatic risk reduction in patients treated by a post-operative compression device. Multimodal therapy and the use of intermittent mechanical compression devices have been sparsely reviewed by the literature; two recent reviews summarize the data on intermittent compression devices with results comparable or superior to chemoprophylaxis.[12,13]

Asymptomatic deep venous thrombosis may not be an appropriate surrogate marker of the subsequent risk for pulmonary embolus and death. Fatal pulmonary embolus frequently occurs as an episode of sudden death not preceded by a DVT, a correlation between DVT and death from pulmonary embolus (PE) seems unclear. When compared with hip replacement, deep venous thrombosis is 2–3 times more common after knee replacement, but pulmonary emboli occur 2–3 times more often in total hip-replacement patients.[3] Most hip-replacement patients who develop a symptomatic PE or a late symptomatic PE after discharge will have a negative venogram.[14] Medical patients with a deep venous thrombosis will develop pulmonary emboli in some 20–30%; however, this observation does not hold for orthopaedic patients where a deep venous thrombosis will occur in 25–60% and yet pulmonary emboli occur in 0.5% and will be fatal in 0.1–0.2%. This implies that not all deep venous thrombi are equal, and perhaps should be qualified by the site and causal association, as well as whether or not they are symptom producing.

A fascinating study by Kim and Kim *et al*.[15] examined the natural history of asymptomatic deep venous thrombosis following hip arthroplasty surgery. In this study, 200 hip-replacement patients were examined by venography and lung perfusion scans. Seventy-two patients were found to have venographic evidence of deep venous thrombosis that was treated by observation without intervention. These patients were re-examined by venography 6 months later and all venographic findings had returned to normal. This questions the assumption that asymptomatic deep venous thromboses are a precursor of pulmonary emboli and that DVT require treatment at all!

In the context of clinically evident thromboembolic disease, the information is less clear. The Scottish Arthroplasty Project[7] reports a clinical thromboembolic rate of 2.08% that remained virtually unchanged throughout the 10-year period of study between 1992 and 2001 despite the evolving practice where chemical prophylaxis was administered in less than 50% of arthroplasty patients at the commencement of the study and more than 80% at the completion.

PTS following a deep venous thrombosis is a significant clinical entity. In medical patients, asymptomatic DVT will lead to recurrent DVT in approximately 30% and to the PTS in 30%. Mueller *et al*.[16] identified PTS in 8.67% of knee-replacement patients that compared with an aged-matched control of 9.6–12.6%. This was not associated with the presence of a positive venogram. Ginsberg *et al*.,[17] demonstrated an ultrasound confirmed PTS in 4% of patients who had a proximal DVT, 6.1% of patients with a distal DVT and 4.3% of patients who had no venous thrombosis, which further questions the relationship between a previous DVT and the community prevalence of this disorder. Wille-Jorgensen *et al*.[18] performed a meta-analysis on seven studies of 1655 orthopaedic and abdominal surgery patients and report an association with asymptomatic post-operative DVT leading to an overall reduction in the risk of developing PTS of 8% if one can prevent an asymptomatic DVT. We identified a further five studies including 1189 patients following hip or knee replacement surgery; four studies[16,19–21] reported no significant difference between PTS symptoms in patients with asymptomatic DVT and one study[22] reported increased symptoms in 132 patients at a mean follow-up period of 18 months.

VTE risk management

Surgeons need to be wary of the therapeutic ratio of these chemoprophylactic drugs. Antithrombotic agents are associated with haemorrhagic sequelae, which have not insignificant mortality and morbidity rates. Colwell *et al*.[23] defined a major bleeding event as a retroperitoneal, intracranial, or intraocular haemorrhage, a life threatening event, or those believed to require more than two units of transfusion. Long-term warfarin use has been associated with major bleeding in 1.2–8.1% of patients during each year of long-term warfarin therapy[24,25]. Most surgeons would be alarmed to discover that these serious complications are identified in 0.4–7.9% of patients enrolled in trials with antithrombotic agents.[26] The most frequently used agents, low molecular weight heparins and warfarin, are typically associated with major bleeding complications in 0.4–4.4% of patients. Predictably, there is an association between the efficacy of thrombotic agents and their associated haemorrhagic complication rate.

Sharrock *et al*.[27] have recently published a meta-analysis examining whether the all-cause mortality and pulmonary embolism rates in patients undergoing total joint arthroplasty differ with currently used chemical and multimodal thromboprophylactic protocols. This study found that the all-cause mortality was double (0.4%) in patients receiving potent anticoagulants (including low molecular weight heparin (LMWH), ximelagatran, fondaparinux, Rivaroxaban and warfarin) versus patents receiving multimodal prophylaxis (regional anaesthesia, aspirin and pneumatic compression) (0.2%). The incidence of clinical pulmonary embolus was also significantly higher in

those treated with potent anticoagulant agents versus multimodal treatment by a factor of up to 75% (0.6% versus 0.35%). The inescapable conclusion to be drawn is that pulmonary embolism will occur despite potent anticoagulant agents and that these agents may well expose patients to a higher mortality risk post-surgery.

The adverse local effect of antithrombotic agents on the perioperative progress of the knee is poorly defined in the literature. Although most orthopaedic surgeons report an anecdotal association of impaired outcomes since the introduction of chemical antithrombotic treatments, there is a paucity of literature to support this observation. The swollen, blistered and bruised leg we have all seen since the introduction of low molecular weight heparins is surprisingly absent in clinical trials. This is most likely due to a loophole in definition that allows such an outcome to be recorded as a 'minor' bleeding event in studies. Keays *et al*.[28] demonstrated prolonged, but not persisting stiffness following the arthroplasty in patients treated by enoxaparin compared with aspirin. Sach *et al*.[29] compared patients treated with low-dose warfarin compared with placebo in 1742 knee-replacement patients. While the two study groups had the same thromboembolic outcomes, there was twice the complication rate in patients treated with warfarin and three times the infection rate, which was anecdotally associated with 'marked swelling'. These authors conclude that any potential advantage of anticoagulation in preventing thromboembolic disease is offset by the danger of the therapy itself.

Anticoagulation induced persisting wound drainage and haematoma following hip and knee surgery is associated with a higher prevalence of wound infection.[30,31] It is a major weakness of studies reporting chemical thromboprophylaxis that bleeding-associated complications such as haematoma and prolonged wound discharge are likely to be underreported. Such studies routinely lack the length of follow-up to determine the eventual joint-related outcomes. The consequences to the patient of a deep periprosthetic infection are potentially dire with potential loss of life, limb function and quality of life.[32] Treatment of a deep infection is enormously costly with over $50 000 on average being expended for each affected patient. Others have found an association between arthrofibrosis in knee arthroplasty patients treated by warfarin.[33]

Guidelines and recommendations

The Arthroplasty Society has debated these issues and uncertainties with some vigour and has developed guidelines to assist surgeons in making these difficult decisions. It is acknowledged that there is a significant morbidity and potential mortality from both the thrombotic complications of surgery and the agents used to minimize this risk. The therapeutic ratio of an antithrombotic regime is a careful balance between the risks of these potentially dangerous agents and the consequences of an uncertain natural history of thrombosis following knee arthroplasty surgery. Surgeons must use caution when accepting guidelines from other craft groups, such as those of the American College of Chest Physicians, who have analysed the data from the thromboembolic perspective alone rather than considering whole of patient outcomes. The issues confronting our patients are more complex than the results of a venogram.

Further assessment and thorough research of these topics is required. It is anticipated that randomized controlled studies assessing mortality risk reduction strategies are beyond the scope of meta-analyses and large prospective studies. The potential to address this question lies with the massive number of patients that can be assessed by population- or registry-based studies. Conversely, the almost-universal observation that patients treated with chemical prophylaxis have a significantly greater morbidity has not been widely reported in the literature, perhaps because of the uncertainty of measurable end points for these problems, which include poorly quantified entities such as limb and joint swelling, haematoma formation, bleeding from the surgical site, wound breakdown, joint stiffness and arthrofibrosis, in addition to increased transfusion requirement, remote bleeding episodes including stroke and prosthetic joint infection.

The Australian Orthopaedic Association thromboembolic guidelines recommend a risk assessment for each patient. The use of widely accepted and relatively safe regimes of multimodal therapy[12] such as compression devices, aspirin and early mobilization may be considered for most patients without thrombophilia risk factors. Patients should be informed of the relative risks of thromboembolic phenomenon, as well as risks of prophylaxis with more hazardous agents such as heparins and warfarin. Patients with an increased risk of thromboembolism are a more contentious issue, as the definition and detection of thrombophilia is poorly defined. Patients with a previous history or a condition known to be associated with thrombophilia are more likely to benefit from a more aggressive regime of thromboprophylaxis and these patients should receive adequate consenting processes before the use of these agents.

The Arthroplasty Guidelines can be accessed from the web based information site at www.aoa.org.

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