National Institute for Health and Clinical Excellence

VENOUS THROMBOEMBOLISM (VTE) GUIDELINE

Stakeholder Comments

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Document. Indicate if you are referring to the **Full version**, or the **NICE version**.	**Page Number** Indicate **Page number** or **'general'** if your comment relates to the whole document	**Line Number** Indicate **Line number**	**Comments** **Please insert each new comment in a new row.**
Full	General		It is gratifying that NICE is attempting to produce an evidence base for two of the clinical problems that have bedevilled orthopaedic surgeons for many years. As you may have found there is considerable orthopaedic literature on the subject. You are to be congratulated on your extensive literature search.
Full	26	16	As with figures quoted throughout the report the number of Joint replacements quoted is 50% too low. According to the 2006 NJR report approximately 161,765 hip and knee arthroplasty procedures are performed annually in England and Wales (with a further 10% in Scotland). We suggest using the more accurate and up to date population based data from the relevant NJR's.
Full	26	21-2	The overall risk of death (from all causes) following joint replacement at three months following arthroplasty (using the NJR registered cases and HES linked dataset reported in the 2006 NJR report) is 0.5% in 147,578 cases following hip arthroplasty and 0.4% following148,321 knee arthroplasties. Similar data from the Scottish Arthroplasty Project reported in detail (Howie et al JBJS 87B 2005 1675-80) suggests that, of those who died, venous thromboembolism was the cause of death in approximately 30% therefore the risk of fatality being caused by clot in the three months following arthroplasty surgery is at worst 0.22%. We suggest that this is an absolute figure, which are population based and not an estimate as used in your economic models. The figure used for your economic model should at least be less than the overall death rate at three months and be based on registry data from very large real numbers not estimates from industry or historical data.

Full	27	2	As you correctly note in this section the endpoint in many trials is surrogate. There are many arguments over this however the best arguments are made later in your own document. Most embolic events take place after discharge and the discontinuation of most of the studies quoted. The endpoint measure in these studies has been taken before the main event (DVT or PE) is known to occur, this is a serious methodological flaw. Indeed early work suggests that the event is delayed but not prevented by active chemical prophylaxis (Sikorski JM et al JBJS 63B 171-7 1981). Furthermore rebound thrombophilia is known to occur following most chemical prophylaxis regimens so a case can be made for these episodes being caused by chemical prophylaxis (Dahl OE et al Thromb Haem 1998 77 26-31). We suggest that only trials that continue for a minimum four weeks following discontinuation of an active treatment are used in meta analysis studies and that all further research uses this as a basic standard. Efficacy Vs effect.
Full	32	6-21	We support and concur with the identification of high risk categories as outlined in this section but wish to point out that there are no studies on the use of prophylaxis in any of these groups of unfortunate patients, indeed all patients in these groups have been specifically excluded in most studies using drugs. We submit that any advice on the use of prophylaxis for these groups should be noted as expert opinion rather than evidence based. These issues question the heterogeneity and applicability of the highly selected populations used for randomised studies into prophylaxis when applied to the general population (again efficacy Vs effect). We suggest that urgent research is required on the role of prophylaxis in high-risk groups and that the key role of thrombophilia and lifetime risk is further explored. The drug you recommend is specifically advised for use with caution in elderly patients (BNF 2006), this should be noted, clarified and included in consent.
Full	32	23-4	Informed consent involves the explanation of benefit and risk, with and without treatment. It is especially important when discussing prevention to discuss the risks of prophylaxis. Specific to the risks in joint replacement is the increase in bleeding, which the guidelines rightly recognise, and consequential increased infection risk. It should also be noted that higher doses of heparin are recommended for orthopaedic patients therefore the bleeding estimates should be based on the bleeding rates for the higher dose (as the benefits are based on this). Later in your document you note that the risk of drug prophylaxis (CVA, MI) is of the same order of magnitude (but half) the benefit of PE prophylaxis based on your estimates (disputed earlier) Primum non nocere.
Full	32	25-8	Compression stockings have been looked at extensively in

			orthopaedic practice and their use is sometimes questioned though they may reduce swelling. The above knee versions often roll down and are difficult to apply following arthroplasty surgery. They may actually produce a reverse gradient (Best et al JBJS B 2000 82 116-8) and randomised studies have shown no benefit (Hui et al JBJSB 1996 78 550-4) The combination with boots has also been questioned (Warwick et al J Arth 2002 17 446-48)
Full	33	1-5	We disagree with this bald statement for arthroplasty patients because of the multiple problems outlined elsewhere.
Full	34	6-8	We agree with these sentiments but would suggest a more helpful if pragmatic guide is given which includes the word “uninterrupted” and suggests breaking the journey up. Where necessary thrombo-prophylaxis may be advised.
Full	34	15-17	Because of our concerns about the figures used for the incidence of death and the period of time used to cost prophylaxis (see later) we feel that after recalculation and comparing the results with aspirin in your economic model your conclusions may change.
Full	34	31-2	Approximately half the patients undergoing arthroplasty are on medication for hypertension and prophylaxis to prevent arterial emboli. Clear guidance on the concomitant administration of ACE inhibitors and Calcium channel blockers (both increasing post op potassium when used with heparin) and drugs such as aspirin and clopidrogel is necessary. Again these patients were excluded from the carefully controlled randomised studies you quote in your meta analysis therefore the potential side effects and risk of complication (MI and CVA) are greater if active cardiovascular treatment is altered. (Efficacy Vs effect). It should be noted that the overall mortality in those patients on heparins is greater at three months (though not due to PE!) and that MI is as common following THR as PE. Most patients are on some form of NSAID many have multi joint aches from generalised OA; again consent will have to include the analgesia Vs prophylaxis debate.
Full	35	15-17	We agree that if chemical prophylaxis is used at all it should be for a minimum period of 4 weeks, indeed most studies would suggest that the increased risk extends much beyond this (Thomas DP BMJ 2001 322 686-7, Howie et al JBJS B 87B 1675-1680). Unfortunately the complications of Fondaparinux increase after this period and it does not have an extended licence. However your economic model should extend the use of active prophylaxis to at least 4 weeks to be valid given the advice in your own report with which we concur. Perhaps given this the risk and benefits of prolonged aspirin prophylaxis should be included in your (now extended and corrected) economic model.
Full	45	6	Secondary outcomes should include overall death rates at 3 months
Full	45	15	The incidence of DVT that has been used for the modelling is the rate detected in studies by either

			venography or special scans (and includes many calf vein thrombosis of uncertain import). Whilst a useful research tool, what is relevant is the incidence of readmission with DVT/PE or death – these being that which generate cost for the health service (patients with “investigation evident” or asymptomatic DVT do not entail cost, only those who become symptomatic do, therefore no saving can be generated through prophylaxis) An economic model should be based on the actual readmission rate where that is known (otherwise unachievable cost reduction is assumed). The Scottish arthroplasty project gives accurate record of the readmission rates with DVT/PE (2.27% of readmission with DVT/PE and 0.22% death at three months) and should be used in preference to estimated and assumed figures that may be wildly inaccurate and unachievable.
Full	65	16	Surely this should be “higher”; you have not defined “very” which is emotive rather than accurate.
Full	136	14	In your document you note both that the risk remains for at least 4 weeks and that most episodes take place after discharge for THR at least. It is illogical (and biased) to use this cost assumption, Active prophylaxis for 4 weeks must be assumed and you must assume complication rates will double. Fondaparinux own data shows this reduces the incidence of DVT.
Full	137	2	This table includes some wildly elevated incidence and assumptions. For THR the baseline DVT risk can be nowhere near 45% even if the estimates in your own HES data are out by a factor of ten! (In reality cost savings can only be generated if an admission occurs). Symptomatic PE is much less and the death rate for all causes following THR at 3 months is 0.5% (a very exact figure) not the 6% shown on your chart.
	General		Whatever strategy is adopted it should reduce the overall mortality at 3 months, which is what the patients and their carers want. This should be an endpoint, whatever the cause, if we kill more with treatment than we prevent emboli the strategy must be a failure. We have been unable to find any data on post phlebitic syndrome and THR but would point out that if it were a common occurrence then the large number of joint replacements per year (161000) would have created an epidemic, which has not materialised. If, as you appear to recommend, prophylaxis is to be continued for 4 weeks with Fondaparinux or LMWH this will have significant cost implications. Currently (from the NJR data) just over 50% of patients undergoing hip and knee replacement receive LMWH, 1% receive fondaparinux, mostly for 7 – 10 days. If all patients were to receive one of these the approximate annual cost increase for hips and knees alone would be many million pounds for LMWH, three times that for fondaparinux. Alternately you could use the actual death and readmission rates in your cost estimates as savings on these may be achievable. It should be noted that there is now a considerable and

			growing literature to show that during lower limb arthroplasty there are substantial intraoperative embolic episodes which are not thrombotic (but may be thrombogenic) in nature and can be detected in the cerebral circulation. Existing and suggested prophylaxis schedules will not alter these episodes. Certainly much more research needs to be focussed on these (often cerebral) emboli. We believe that independent evidenced based guidance for DVT prophylaxis is long overdue. We agree that patients should be assessed for risk and treated appropriately. There should be a policy in place for early mobilisation mechanical prophylaxis and regional anaesthesia. Each unit should have readmission rates monitored. Any drug prophylaxis should be continued for a minimum period of 4 weeks. We question the cost benefit of active prophylaxis using heparins for 4 weeks. Research should be focussed on identifying patients with intrinsic high risk factors and that any prophylactic treatment for these patients should be assessed after at least two weeks discontinuation of active prophylaxis.

Please add extra rows as needed