The cost and benefit of prophylaxis against deep-vein thrombosis in elective hip replacement

DVT/PE Prophylaxis Consensus Forum

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A consensus forum was convened to evaluate the economic considerations associated with prophylaxis against thrombo-embolic disease in patients undergoing hip replacement therapy in South Africa. This forum consists of orthopaedic surgeons, vascular surgeons and a statistician.

Methods. The forum was instructed to evaluate the economic costs of the commonly used forms of prophylaxis of thrombo-embolism in patients undergoing hip replacement surgery in South Africa, looking at short-term events only. The methods used for the prophylaxis of thrombo-embolism in South Africa were determined by a postal survey.

A decision tree was constructed to determine the events that will occur after a clinical decision to use no prophylaxis. The probabilities of these events were then determined. Protocols for and costs of prophylaxis and treatment were established. With the decision tree and these costs, the cost of the various modalities of prophylaxis was then determined.

Results. The probability, determined by the forum, of developing a deep-vein thrombosis (DVT) when no prophylaxis is used was 0.5, with a mortality rate of 2.1%. The cost of this decision was R875. No prophylaxis given, but a venogram performed on day 7, reduced the mortality rate to 0.7%; however, this cost R3 017. The cost of low-molecular-weight heparin was R1 223 (probability 0.26, mortality rate 1.1%), while unfractionated heparin with a graduated compression stocking (GCS) cost R1 351 (probability 0.24, mortality rate 1%). Aspirin with a GCS cost R777 (probability 0.35, mortality rate 1.5%).

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Conclusions. **The use of some form of prophylaxis against DVT formation in patients undergoing elective hip replacement in South Africa is mandatory, as all the methods commonly used reduced the mortality. The use of no prophylaxis but with screening for DVT at day 7 - 10 is not justified as it is very expensive. Aspirin in combination with a stocking is the cheapest form of prophylaxis, but does not reduce the prevalence of DVT and does not reduce mortality sufficiently to be clinically effective. The heparins (possibly in combination with stockings) appear to be most cost-effective but cost between R350 and R500 more per patient than when no prophylaxis is used.**

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The cost of high-quality clinical care is rapidly rising. In order to continue justifying the expense of treatment it is essential to evaluate the benefits of specific interventions, both to the individual in question and to society at large. Such considerations are particularly important in prophylactic measures where the benefits are not measurable in the individual and where many patients are exposed to additional cost and complications without benefit and occasionally even to their detriment.

In order to determine the economic benefits of a prophylactic method, evaluations such as cost-effectiveness and cost-benefit analysis must be performed. Such evaluations are colloquial and must be applied to a very limited set of circumstances. There is currently a need for such a study of the prophylaxis of deep-vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing elective hip replacement in South Africa.

No prospective data are available on the prevalence of DVT and its sequelae in patients undergoing elective hip replacement in South Africa. In order to perform the cost-effectiveness study of thromboprophylaxis in these patients a consensus forum was convened to evaluate the factors that influence the cost of this therapy in South Africa.

The aims of the consensus forum were to: (*i*) establish the forms of prophylaxis commonly used in South Africa in these patients; (*ii*) determine what happens to a patient once one of these forms of prophylaxis has been applied, by constructing a decision tree; (*iii*) determine the probability of each of these events occurring; (*iv*) determine the cost of the events that would influence the overall cost of a prophylactic method; and (*v*) establish the most cost-effective prophylactic method or methods.

Method

A forum was convened consisting of 8 orthopaedic surgeons and 1 physician with an interest in the management of patients requiring hip replacement surgery, 4 vascular surgeons with an interest in thrombo-embolism and a statistician. Prior to the meeting, available information on decision tree analysis, data pertaining to the prophylaxis of DVT and the probabilities of the DVT and its sequelae occurring were circulated to the members of the forum.

Framework

The forum was instructed to evaluate the economic costs of the commonly used forms of prophylaxis of thrombo-embolism in patients undergoing elective hip replacement surgery in South Africa, looking at short-term events only. The methods used for prophylaxis against thrombo-embolism by South African orthopaedic surgeons were determined by a postal survey (unpublished data).

Decision tree

A decision tree was constructed using the following steps:

1. Each participant was asked to consider the possible events, in respect of the development of a DVT, and the likelihood that such events would occur after a clinical decision to use no prophylaxis had been made. Once this had been performed, the participant was asked to construct a decision tree.
2. Thereafter, a published decision tree was evaluated by the members of the forum.[1]
3. This decision tree was then modified to include the suggestions made by the forum.
4. The resultant decision tree was then re-evaluated and was finally accepted unanimously by the forum.

The forum agreed that this decision tree would be applied to all physical and pharmacological forms of prophylaxis but not if a venogram or duplex Doppler were performed routinely during the postoperative stage. As a result, a similar process to that outlined above was performed to establish a decision tree for the clinical option of giving no prophylaxis but performing a venogram between postoperative days 7 and 10.

Probability of events

The expected outcomes depend on the probability of various events occurring. These include the probability that the patient has a DVT or PE, the probability that clinical signs are present, and the probability that the DVT is correctly diagnosed.

The probability of an event occurring was derived using techniques similar to those described above. The odds of a patient developing a DVT with the various forms of prophylaxis were initially independently estimated by each member of the forum. These values were then summarised by the geometric mean odds and subsequently converted to probabilities.[2] Once these probabilities were available the forum compared them to those used by other authors in their decision tree analysis. The probabilities ultimately used were derived from the above values and with information available from the literature.

Cost of events

Protocols for and costs of prophylaxis and treatment were established. These are summarised in Table I. It was agreed that only directly identifiable costs should be considered and that the death of a patient did not result in any additional costs.

Table I. Protocols and retail or Scale of Benefits costs (R) for prophylaxis and treatment, December 1996

	Dose	Cost/ dose	Cost/ 10 days
Cost of prophylaxis			
Enoxaparine	40 mg/day	60.19	601.90
Calciparine	5 000 units three times daily	16.41	492.30
Warfarin	5 mg/day	0.50	5.00
Aspirin	300 mg/day	0.25	2.50
Pair of above-knee stockings (grade 2)			162.00
Intermittent pneumatic compression (suitable for 300 patients/device)			45.00
Cost of diagnosing a DVT			Cost
Unilateral venogram			650.78
Duplex Doppler (10% of limbs require a venogram)			356.78
Cost of diagnosing a PE			Cost
Chest radiograph			79.40
Perfusion scan			414.90
Ventilation scan (required in 75% of patients)			311.18
ECG			34.50
Blood gas			50.50
Physician consultation			132.00
Pulmonary angiogram (required in 1% of patients)			17.00
		Cost of event	1 039.48

Cost of treating a DVT (50% of patients only develop a proximal DVT)

	Unit price	No.	Cost
Proximal DVT			
Hospitalisation	425.10	5 days	2 125.50
Heparin (30 000 units/day)	35.85/ 5 000 U	5 days	1 075.50
Heparin administration costs	100.00	5 days	500.00
Physician consult	40.00	5 days	200.00
Physiotherapy	129.90	5 days	666.80*
Full blood count	39.30	2.5	98.25
Partial thromboplastin time	21.90	5	109.50
Prothrombin index	19.40	12	232.80
Warfarin	0.50	180 days	90.00
Post-discharge consultations	72.00	7	504.00
Elastic stockings (grade 3)	262.00	1	262.00
		Cost of proximal DVT	5 864.35
Distal DVT			
Hospitalisation	425.10	5 days	2 125.50
Physician consult	40.00	5 days	200.00
Physiotherapy	129.90	5 days	666.80*
Full blood count	39.30	1	39.30
Partial thromboplastin time	21.90	1	21.90
Prothrombin index	19.40	9	174.60
Warfarin	0.50	90 days	45.00
Post-discharge consultations	72.00	3	216.00
Elastic stockings (grade 3)	262.00	1	262.00
		Cost of distal DVT	3 751.10
		Cost of all DVTs	4 807.73
		(i.e. the mean of treating a proximal and a distal DVT)	

* Includes an assessment charge of R17.30 charged once only.

Cost of treating pulmonary embolism (25% require admission to ICU)

	Unit price	No.	Proportion requiring ICU	Cost
Ward costs				
Hospitalisation	425.10	10 days	1.00	4 251.00
Heparin (30 000 units/day)	35.85/ 5 000 U	7 days	1.00	1 505.70
Heparin administration costs	100.00	7 days	1.00	700.00
Physician consult	40.00	10 days	1.00	400.00
Physiotherapy	129.90	10 days	1.00	1 333.60
Blood gas	50.50	2	1.00	101.00
Full blood count	39.30	1	1.00	39.30
Urea and electrolytes	59.20	1	1.00	59.20
Liver function tests	114.30	1	1.00	114.30
Partial thromboplastin time	21.90	7	1.00	153.30
Prothrombin index	19.40	12	1.00	232.80
Chest radiograph	79.40	3	1.00	238.20
ECG	34.50	1	1.00	34.50
Ventilation/perfusion scan	829.80	1	0.01	8.30
Warfarin	0.50	180 days	1.00	90.00
Post-discharge consults	72.00	7	1.00	504.00
Elastic stockings (grade 3)	262.00	1	1.00	262.00
Insertion of caval filter	12 000.00	1	0.001	12.00
Intensive care				
Hospitalisation	1 688.50	3 days	0.25	1 266.38
Physician consult	191.50	3 days	0.25	143.63
Intensivist	478.80 (day 1) 191.50 (day 2)	3 days	0.25	215.45
Physiotherapy	129.90	3 days	0.25	97.43
Heparin administration costs	300.00	3 days	0.25	225.00
Blood gas	50.50	7	0.25	88.38
Full blood count	39.30	5	0.25	49.13
Urea and electrolytes	59.20	4	0.25	59.20
Liver function tests	114.30	2	0.25	57.15
Partial thromboplastin time	21.90	3	0.25	16.43
Prothrombin index	19.40	3	0.25	14.55
			Cost of event	12 271.93

Cost of treating a serious haemorrhagic complication (10% require admission to ICU)

	Unit price	No.	Proportion requiring ICU	Cost
Ward costs				
Hospitalisation	425.10	5 days	1.00	2 125.50
Physiotherapy	129.90	5 days	1.00	527.30
Full blood count	39.30	1	1.00	39.30
Blood products	240.00	2	1.00	480.00
Re-operation	5 000.00	1	0.25	1 250.00
Intensive care				
Hospitalisation	1 688.50	3 days	0.10	506.55
Intensivist	478.80 (day 1) 191.50 (day 2)	3 days	0.10	258.54
Physiotherapy	129.90	3 days	0.10	38.97
Blood gas	50.50	7	0.10	35.35
Full blood count	39.30	5	0.10	19.65
			Cost of event	5 281.16

Cost-effectiveness

The benefit of each of the modalities of prophylaxis and its cost-effectiveness were determined by applying the agreed probabilities of developing a DVT and the costs derived for each event to the decision tree (e.g. cost of no prophylaxis = 0.5(0.2[Confirm DVT + Treat DVT] + 0.8[0.2*0.9*0.28{Confirm PE + Treat PE} + 0.8*0.08{Confirm no PE}]) + 0.5(0.16[Confirm no DVT] + 0.84*0.08 [Confirm no PE]) = 874.89).

Sensitivity analysis

A sensitivity analysis was performed to evaluate the influence of some variables on the cost-effectiveness of prophylaxis. The variables studied were: (*i*) the use of duplex Doppler in the screening for and diagnosis of DVT; (*ii*) changing the probabilities of whether a DVT would develop to reflect those published in a recent meta-analysis;[3] (*iii*) evaluation of prophylactic modalities not commonly used in South Africa (e.g. low-dose peri-operative heparin, adjusted dose-fractionated heparin, and intermittent pneumatic compression); and (*iv*) changing the proportion of proximal (popliteal vein and more proximal) to distal DVTs according to published rates[3] (evaluating the hypothesis that the sequelae and costs are mostly due to proximal DVTs).

Results

The methods of prophylaxis used in South Africa by orthopaedic surgeons include: no prophylaxis, no prophylaxis but venography or duplex Doppler at day 7 - 10, low-molecular-weight heparin, low-molecular-weight heparin and stockings, unfractionated heparin and stockings, and aspirin and stockings.

The decision trees and the probabilities used for the economic evaluation are presented in Figs 1 and 2. The probabilities, determined by the forum, of developing a DVT, of dying from that DVT and the risk of bleeding for each of the above prophylactic options are presented in Table II. The results of the cost-effectiveness are also summarised in this table. The cost-effectiveness data are presented in terms of the retail cost (Scale of Benefits) of each form of prophylaxis per patient during December 1996, as well as the money spent to prevent a DVT from occurring and the cost of each life saved.

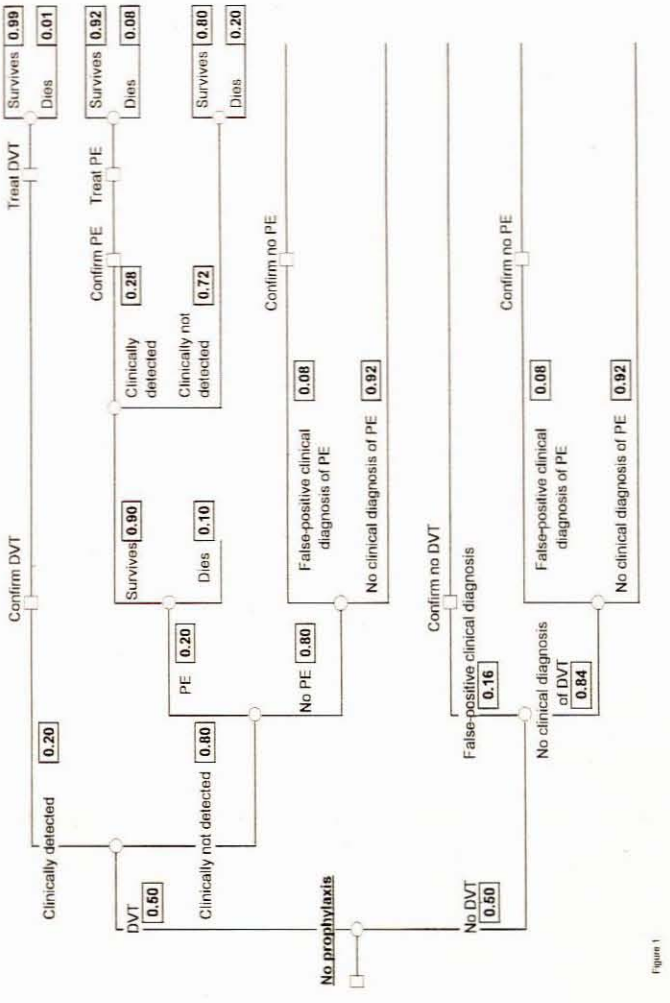

Fig. 1. Decision tree analysis for the clinical option of giving no prophylaxis against thrombo-embolism. Similar decision trees were used to determine the outcome for the other physical and pharmacological forms of prophylaxis. The only changes made were the probabilities of a DVT occurring or not. (Squares represent clinical decisions or actions. Circles represent chance events. Numbers in bold squares represent the probability of such an event happening.)

Table II. Results (R), December 1996

Method of prophylaxis	Proportion developing a DVT	Proportion dying	Proportion developing a serious haemorrhage	Cost of prophylaxis per patient	Additional cost per DVT prevented*	Additional cost per life saved*
No prophylaxis	0.50	0.021	0	875		
No prophylaxis (venogram on day 7)	0.50	0.007	0	3 017	No DVT prevented	135 610
LMWH	0.26	0.011	0.02	1 223	1 452	34 606
LMWH plus stockings	0.21	0.009	0.02	1 311	1 502	35 806
UFH	0.29	0.012	0.04	1 264	1 854	44 191
UFH plus stocking	0.24	0.010	0.04	1 351	1 833	43 686
Aspirin plus stocking	0.35	0.015	0.007	777	-488	-11 644

LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.
Costs have been rounded off to the nearest rand.
* Compared with the cost of no prophylaxis.

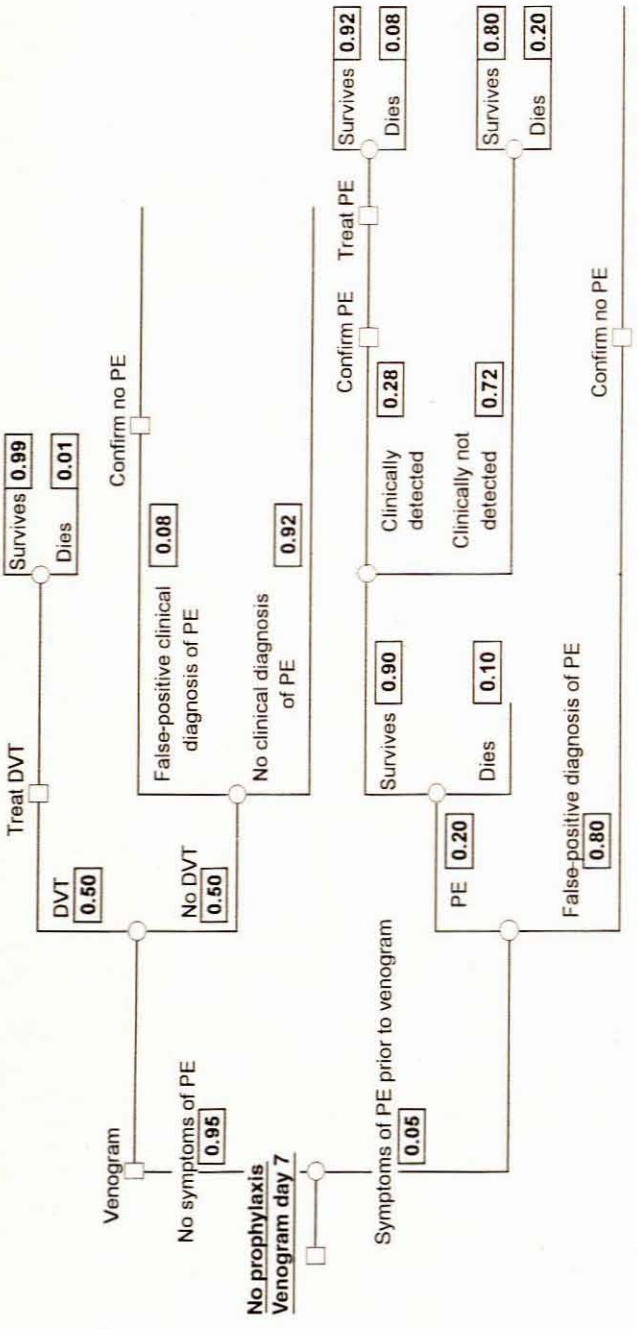

Fig. 2. Decision tree analysis for the clinical option of giving no prophylaxis against thrombo-embolism but performing a venogram at day 7 to 10. (Squares represent clinical decisions or actions. Circles represent chance events. Numbers in bold squares represent the probability of such an event happening.)

The cost of not giving prophylaxis to a patient is R875 while the cost of using no prophylaxis but performing routine venography at day 7 - 10 is R3 017. However, by performing a venogram, 14 lives per 1 000 patients treated will potentially be saved. Using low-molecular-weight heparin, or unfractionated heparin plus a stocking, is cheaper than this option, yet saves a similar number of lives (10 and 11 per 1 000 patients treated, respectively). Aspirin and a stocking are the cheapest form of prophylaxis but do not prevent as many DVTs and deaths. Use of this technique, however, results in cost-saving in respect of preventing a DVT or saving a life, compared with using no prophylaxis.

Sensitivity analysis

The factors modified for the sensitivity analysis revealed that (Table III):

1. The use of duplex Doppler to make the diagnosis of a DVT reduces the cost to the patient receiving prophylaxis by approximately R50. In the group of patients in whom a duplex Doppler is performed routinely between days 7 and 10 the saving would be R280 per patient. Despite this saving, this particular option still remains the most expensive, costing the patient R2 737 compared with R875 for no prophylaxis at all. Furthermore, recent evidence suggests that duplex Doppler may not be as accurate in the diagnosis of DVT in patients who have undergone joint replacement surgery.[4]
2. The probabilities of developing a DVT and a proximal DVT, published in the modified meta-analysis performed by Planes *et al.*,[3] are shown in Table III. These authors only evaluated prospective studies that included patients undergoing venographic control of both lower limbs after elective hip replacement surgery. This includes information on the modalities not commonly used in South Africa, such as intermittent pneumatic compression. This analysis claims that warfarin (sufficient to double the INR) and intermittent pneumatic compression have similar mortality rates to low-molecular-weight heparin but cost less and, as a result, are very cost-effective.
3. Low-molecular-weight heparin and warfarin have a lower proportion of proximal DVT formation than the other modalities evaluated by the meta-analysis of Planes *et al.*[3] As a result (and assuming that it is the proximal DVTs that cause the significant sequelae) low-molecular-weight heparin and particularly warfarin become more cost-effective.

Discussion

The decision tree used by the consensus forum in the evaluation of the benefits and cost-effectiveness of prophylaxis against DVT and PE in patients undergoing elective hip replacement surgery is similar to one that has been previously validated.[1] The probabilities used in the decision tree analysis are those that were considered by the forum to reflect South African conditions most closely. This information is likely to contain inaccuracies as no local study of these conditions has been performed. In addition, much of the information required for such an analysis is not available because sufficiently large studies do not exist. For example, a large meta-analysis was required to determine the difference in mortality between general surgical patients dying from PE compared with patients receiving no prophylaxis.[5] Further inaccuracies may be caused by applying the same decision tree and probabilities to all types of prophylaxis.

This study has only evaluated the immediately apparent costs of the prophylaxis against DVT and the subsequent management of a DVT and its short-term sequelae. No long-term costs, such as the cost of venous ulceration and chronic pulmonary hypertension, have been taken into consideration. Similarly, neither have the costs to society of

Table III. Sensitivity analysis (R), December 1996

Method of prophylaxis	Proportion developing a DVT	Proportion dying	Proportion developing a serious haemorrhage	Cost of prophylaxis per patient	Additional cost per DVT prevented*	Additional cost per life saved*
Analysis using published data on all DVTs						
LMWH	0.145	0.006	0.02	1 051	497	11 847
UFH	0.26	0.011	0.04	1 114	1 436	34 211
Aspirin	0.427	0.018	0.007	874	-955	-22 765
Warfarin	0.187	0.008	0.04	711	-185	-4 414
Adjusted-dose heparin	0.17	0.007	0.08	1 362	2 437	58 079
Intermittent pneumatic compression	0.233	0.010	0	626	1 327	-31 633
Analysis using published data of proximal DVTs†						
LMWH	0.05	0.004	0.02	1 009	377	7 889
UFH	0.183	0.015	0.04	1 179	1 265	50 780
Warfarin	0.048	0.004	0.04	744	-420	-7 737
Adjusted-dose heparin	0.132	0.011	0.08	1 661	2 383	78 796
Intermittent pneumatic compression	0.148	0.012	0	478	-1 487	-44 215

Costs have been rounded off to the nearest rand.
* Compared with the cost of no prophylaxis.
† Assuming that PE only arise from proximal DVTs.

a death or long-term disability from pulmonary hypertension or venous ulceration been considered. The inclusion of these variables would substantially complicate the issue and would require, e.g. considerations of the value (in monetary terms) of life, all of which were beyond the scope of the forum.

The mortality rate from PE after elective hip replacement surgery (calculated from the decision tree) in individuals not receiving any form of prophylaxis is 2.1%. This lies in the middle of the range of 1.4 - 3.4% which is commonly published in the literature.[3] The most dramatic drop, to a mortality rate of 0.7%, can be expected if all DVTs are prospectively identified by venography or duplex Doppler in the postoperative phase and then appropriately treated. This option is, however, very expensive and costs R3 017 per patient treated (compared with R875 for no prophylaxis) and R135 610 for every life saved.

Prophylaxis with a low dose of subcutaneous heparin (low-molecular or unfractionated) reduces the mortality rate to a level similar to that associated with routine postoperative venography (1.1% and 1.2% respectively), but is cheaper. Local opinion is strongly opposed to the use of unfractionated heparin, as it is felt that this agent is associated with an unacceptably high incidence of septic complications, based on the unpublished results of a study performed during the 1980s. This benefit for low-molecular-weight heparin is further enhanced by the results of the sensitivity analysis, which indicate that the incidence of DVT formation while using low-molecular-weight heparin is roughly 50% of that when unfractionated heparin is used. Furthermore, low-molecular-weight heparin appears to reduce substantially the chance of proximal DVT formation.

The use of the heparins (low-molecular-weight and unfractionated) in combination with graduated compression stockings is thought to reduce the mortality rate further and thereby improve on the cost-effectiveness. The information on the basis of which this decision was made is more tenuous although, as a generalisation, stockings appear to reduce the chances of developing a DVT by a further 5% when combined with a pharmacological agent.

Aspirin combined with graduated compression stockings was found to be the cheapest form of prophylaxis. This conclusion is, however, based on poor data and is most likely an underestimation of the true incidence of DVT in patients given this form of prophylaxis. In addition, the mortality rate is appreciably higher than in a group receiving a heparin in combination with stockings. As a result this form of prophylaxis is less effective from a clinical perspective.

The sensitivity analysis, using the data published by Planes *et al.*,[3] indicates that the use of a heparin need not necessarily be the most cost-effective form of prophylaxis. Warfarin and intermittent pneumatic compression are very effective forms of prophylaxis and may reduce the mortality rate to levels that approximate that found with the heparins. Similar results have been shown by others.[1] The possible benefit of intermittent pneumatic compression is, however, reduced, when the probability of developing a proximal DVT (and discounting complications caused by distal DVTs) is considered.

Conclusion

The use of some form of prophylaxis against DVT formation in patients undergoing elective hip replacement in South Africa is mandatory, as all the methods used locally reduce the mortality rate of this condition by approximately 50% or more. Use of no prophylaxis but with screening for DVT at day 7 to 10 is not justified, as it is very expensive and does not reduce the mortality substantially. Similarly, although aspirin in combination with a graduated compression stocking is the cheapest form of prophylaxis, it does not reduce the prevalence of DVT efficiently and subsequently does not reduce mortality sufficiently to be clinically effective. The heparins and particularly low-molecular-weight

heparin (possibly in combination with stockings) appear to be most cost-effective but do still cost between R300 and R500 more than no prophylaxis at all. Ideally duplex Doppler should be used primarily for screening and diagnosing DVTs as this would save in the region of R50 per patient, but duplex Doppler is not available to all surgeons performing total hip replacement surgery.

Intermittent pneumatic compression and, particularly, low-dose warfarin may be more cost-effective than the heparin and must therefore be investigated in a future prospective cost-effectiveness study.

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