ARE RECOMMENDATIONS FOR THE ROUTINE USE OF PHARMACOLOGICAL THROMBOPROPHYLAXIS IN TOTAL HIP ARTHROPLASTY JUSTIFIED?

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At the 1998 meeting of the International Hip Society, a survey of the participants revealed that there was widespread disagreement concerning the issue of what type of prophylaxis, if any, should be considered for the prevention of thromboembolism in patients receiving total hip replacement (THR). The presentations ranged from a randomised study, indicating the effectiveness of prophylaxis in reducing the incidence of deep-vein thrombosis (DVT), to a reiteration of an earlier suggestion, by Murray, Britton and Bulstrode, that “guidelines which recommend their routine use to prevent death after hip replacement are not justified”. We believe that the existing published evidence, including the estimated low death rate pointed out by Murray et al, justifies the use of some type of prophylaxis for patients undergoing THR.

The reasoning for the recommendation by Murray et al that prophylaxis is not necessary can be summarised as follows:

1) The present use of pharmacological treatment is based on an earlier assumption that death due to pulmonary embolism (PE) is fairly common (1% to 2%), while in reality the death rate is probably no more than 1 to 3 per 1000. Thus, any possible benefit from pharmacological prophylactic treatment is very small.

2) The results from earlier randomised studies which show a significant reduction in the surrogate variable, venographic-positive DVT, do not necessarily imply that there would be a subsequent reduction in the overall death rate.

3) If prophylactic treatment results in an increased death rate from complications, other than PE, of 0.05% or more, the use of prophylactic treatment may actually be harmful.

4) Since there is no firm statistical conclusion as to the type of prophylaxis which should be used, or even whether any such treatment is necessary, any guidelines as to its routine use are not justified.

After reviewing the results reported by Murray et al, along with some additional publications not included in the Murray statistics, we find that we agree with some of their conclusions but take issue with their basic view that there is no good evidence for the use of prophylaxis for the prevention of death due to PE. We do not believe that the existing data justify their conclusions and the personal experiences of the senior author (HCA) bear this out. We base our view on an examination of the points indicated above by Murray et al.

Does a low death rate for untreated patients obviate the need for prophylactic treatment? Murray et al are correct in stating that a presumed death rate of 1% to 2% due to PE after THR is too high and that the actual rate for untreated patients today is certainly less than 1%. Their estimate of 0.12% was based on 3432 patients. This analysis did not include the work by Warwick et al in which only the high-risk patients received prophylactic treatment. The death rate due to PE for those 1162 patients was 0.34%, including three deaths in hospital. Murray et al did not include the study by Warwick et al in their meta-analysis because some of the high-risk patients did receive prophylaxis. In our view, the approach used by Warwick et al is the one which most surgeons would consider as an alternative to treating all patients prophylactically, and consequently should be included in any meta-analysis. In an additional study by Fender et al, not included in the review of Murray et al, the death rate, within 42 days of surgery, was 0.19% among 2111 treated and untreated patients. In that study there was one death due to PE among the 667 patients (0.15%) who were not treated. Based on the combined reports by Murray et al, Warwick et al and Fender et al, a reasonable estimate of the death rate in mostly untreated patients would be between 0.15% and 0.2% or about two deaths out of every 1000 operations. Today there are over 600 000 THRs carried out annually worldwide. Consequently, a possible reduction of 50% or more in the presumed death rate from PE of 0.2% would result in a worldwide saving of over 600 lives each year.

Is there any good statistical evidence to support the view that an overall reduction in the death rate from PE of 50% or more is possible with chemical prophylaxis? In early 1970, a protocol using warfarin was instituted at UCLA. Although some of the details have changed with time, it has remained as an inpatient treatment with low-dose warfarin designed to affect the prothrombin time. Over 4200 operations have been carried out with only one death, presumed but not confirmed to be due to PE (0.024%). This successful experience with warfarin is not unique to UCLA as Balderston et al encountered no deaths from PE in 1372 consecutive operations using this drug. An
additional 600 patients have subsequently been operated on by the senior author (HCA) with no deaths from PE.

The rate for fatal PE in patients treated with warfarin estimated by Murray et al\textsuperscript{1} based on 5162 operations was 0.05\% (2 of 5162). This included 3000 of the patients treated at UCLA. If the 2972 patients treated with warfarin but not included in the report by Murray et al\textsuperscript{1} are combined with the 5162 patients, and if the 1162 patients with four deaths from the study by Warwick et al\textsuperscript{2} as well as the one death out of 667 from the study of Fender et al\textsuperscript{3} are included in the non-treated group, there is a significant difference of 0.13\% (Fisher’s exact test, p = 0.016) between the non-treated (8 of 5261; 0.17\%) and warfarin groups (3 of 8134; 0.04\%). Fender et al\textsuperscript{3} reported three deaths in treated patients, but none of these had received warfarin. There are currently no randomised studies of adequate sample size comparing a warfarin-treated with a non-treated group.

**Do earlier studies demonstrating a reduction in the rates of DVT prove that a reduction in death rate also follows?** Clearly, the answer to the above question is ‘no’. Treatment which affects surrogate variables may not necessarily lead to an equivalent effect on the outcome of interest. These randomised studies do lend weight to the results of the treatment discussed above, and help to provide statistical evidence of a substantial reduction in death from PE when chemical prophylaxis is used.

**Does prophylactic treatment with warfarin result in an increased risk of death due to other causes?** Murray et al\textsuperscript{1} suggest that any possible benefit of prophylactic treatment would easily be offset by an increased risk of death due to other causes. This suggestion is not borne out in the study by Fender et al\textsuperscript{3} in which the overall death rate for untreated patients was 1.05\% compared with 0.82\% for those receiving various prophylactic measures. The estimated death rates for patients treated with warfarin at UCLA v untreated patients for causes other than PE based on the analysis by Murray et al,\textsuperscript{1} are very similar (0.24\% v 0.21\%). This suggested increased possible death rate of 0.03\% for causes other than PE does not offset the suggested benefit of the prophylaxis of 0.14\% discussed earlier. Thus, even if we presume a small increased death rate due to other causes, we still have a net reduction in the death rate of 0.11\%.

**Is treating all patients cost-effective?** The cost of the low-dose warfarin protocol is only about $US300.00 (£195.00) per operation. Given an estimated average cost of about $US20 000 (£13 000.00) for a THR, this represents a trivial additional amount when considering the possibility of saving one to two lives per 1000 operations. Thus, a reasonable decision concerning cost benefit may be based on an estimated cost of about $US300 000 (£194 800.00) medical dollars per one to two lives saved ($US300 (£195.00) times 1000 operations).

**Conclusion.** Unlike Murray et al,\textsuperscript{1} we find the statistical evidence that the use of a low-dose warfarin protocol results in a substantial reduction in the death rate as a result of PE, to be convincing. In addition, since the overall death rate due to other causes appears to be very similar to that for untreated patients, and since the number of THRs carried out worldwide is large, the small benefit from the use of chemical prophylaxis does result in a potential worldwide saving of over 600 lives, annually. In view of the small additional cost of providing this benefit, we conclude that guidelines which recommend the routine use of chemical prophylaxis to prevent death after hip replacement are justified.

Patients should have the option of management with prophylaxis. While the issue of what type of treatment works best is still open to question, based on our review of the statistical evidence to date we cannot consider discontinuing the regime with warfarin which we currently use.

**References**