The management of anticoagulants in the periendoscopic period for patients with atrial fibrillation: a decision analysis

Gerson L B, Triadafilopoulos G, Gage B F

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Seven strategies for the management of anticoagulants in the periendoscopic period for patients with atrial fibrillation were investigated. The strategies were as follows.

Continue warfarin: a colonoscopy was performed without interrupting warfarin therapy.

Hold warfarin: a colonoscopy was performed after holding warfarin for 5 days.

Repeat colonoscopy: a diagnostic colonoscopy was performed without warfarin interruption, followed by a repeat colonoscopy with warfarin cessation for 5 days if a polyp was detected initially.

Dose reduction: the warfarin dosage was halved on days 4, 3 and 2 pre-procedure, with restoration of the original dose the day before colonoscopy.

Low molecular weight heparin (LMWH): warfarin was ceased for 5 days precolonoscopy with outpatient administration of LMWH 2 days before and 2 days after the procedure.

Unfractionated heparin (UFH): warfarin was ceased for 5 days precolonoscopy with inpatient administration of intravenous heparin 2 days before and 2 days after the procedure.

Vitamin K: warfarin was ceased for 4 days precolonoscopy with an international normalised ratio (INR) drawn 24 hours before the procedure, followed by the administration of 1 mg vitamin K orally if the INR was greater than 2.0 or LMWH if the INR was less than or equal to 1.5.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of 65-year-old patients with non-valvular atrial fibrillation who were taking warfarin and undergoing screening colonoscopy.

Setting
The study setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1978 and 2003. The dates to which the resource
use data related were not reported. The price year was 2003.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies, supplemented by authors' assumptions which were based on the literature.

Modelling
A Markov decision model was used to estimate the cost-effectiveness of the different management strategies. The model was derived from the decision model of Gage et al. (1995; see Other Publications of Related Interest). The time horizon of the model was 10 years.

Outcomes assessed in the review
The outcomes assessed were:

- the estimated stroke rates per 100 patient-years without anti-thrombotic therapy;
- the proportion of strokes and haemorrhagic events that would be fatal;
- the proportion of strokes that would be minor or major;
- the risk of a transient ischaemic attack lasting less than one hour;
- the 30-day probability of haemorrhage with each of the management strategies;
- the probability of procedural-related haemorrhage with screening colonoscopy, colonic biopsy, polypectomy and sphincterotomy;
- the probability of procedural-related complications such as perforation from colonoscopy and from polypectomy;
- the utility of being well while on no therapy, or taking warfarin or aspirin; and
- the utility associated with transient ischaemic attack, minor stroke, moderate-to-severe stroke, recurrent stroke and gastrointestinal haemorrhage.

Study designs and other criteria for inclusion in the review
Not reported.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Approximately 67 studies were included in the review.
Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
The estimated stroke rates per 100 patient-years without anti-thrombotic therapy were:

1.9 for a CHADS2 score of 0,
2.8 for a score of 1,
4.0 for a score of 2,
5.9 for a score of 3,
8.5 for a score of 4,
12.5 for a score of 5, and
18.5 for a score of 6.

The proportion of strokes that would be fatal was 24%.

The proportion of haemorrhagic events that would be fatal was 20%.

Two thirds of strokes were found to be minor and one third was found to be major.

The risk of a transient ischaemic attack lasting less than 24 hours would be one third of that for stroke.

The 30-day probability of haemorrhage per 1,000 patients was 1.6 with the continue warfarin strategy, 1.4 with the hold warfarin and dose reduction strategies, 1.5 with the LMWH and UFH strategies, and 1.3 with the vitamin K strategy.

The probability of procedural-related haemorrhage per 1,000 patients was 0 with screening colonoscopy, 2 with colonic biopsy, 10 with polypectomy and 20 with sphincterotomy.

The probability of perforation per 1,000 patients was 1 from colonoscopy and 3 from polypectomy.

The utility of being well was 1.0 while on no therapy, 0.987 while taking warfarin and 0.998 while taking aspirin.

The utility associated with transient ischaemic attacks was 0.76, minor stroke 0.76, moderate-to-severe stroke 0.39, recurrent stroke 0.12, and gastrointestinal haemorrhage 0.80.

Methods used to derive estimates of effectiveness
The authors made assumptions to supplement the effectiveness estimates derived from the literature. Their assumptions were based on the literature.

Estimates of effectiveness and key assumptions
In the base-case, the patients were assumed to have a moderate risk of stroke, with an annual stroke rate of 4% without anti-thrombotic therapy.
The authors assumed that when warfarin was held, the INR would reach 1.0 after 5 days, and when warfarin was resumed, the INR would require 5 days to return to the therapeutic range. It was also assumed that 9% of patients in the vitamin K arm would require vitamin K, while 55% would require LMWH.

The authors assumed that the relative risk of nonprocedural rebleeding after an initial haemorrhage was 2.5 and warfarin increased that relative risk by a factor of 2.4. In addition, whenever warfarin was held and the INR was less than 1.5, there would be a rebound hypercoagulability that doubled the probability of stroke. Without this phenomenon, the 30-day probability of stroke would be approximately 0.3% for patients with a moderate risk of stroke.

It was assumed that no rebound hypercoagulability occurred in patients in the continue-warfarin or dose-reduction arms.

The authors assumed that the disutility associated with a colonic perforation would equal that associated with gastrointestinal haemorrhage, and patients would not take warfarin for a mean of 7 days during repair of the perforation. The death rate due to perforation was assumed to be 0.015%.

Finally, it was assumed that patients undergoing a repeat colonoscopy would have a utility of 0.0 during a 1-day preparation and the day of the repeat procedure, while those undergoing screening colonoscopy would have a 35% probability of polypectomy.

**Measure of benefits used in the economic analysis**

The measure of benefits used was the quality-adjusted life-years (QALYs). The utility values were derived from the literature and from the authors’ assumptions, which were based on those reported in the literature. The authors derived utilities for warfarin therapy and stroke from a prior study of 71 patients with atrial fibrillation. The benefits were discounted at an annual rate of 3%.

**Direct costs**

The resource use and costs were not reported separately. The direct costs included in the analysis were those of the third-party payer. These comprised the costs of anti-thrombotic therapy, ischaemic complications, and the costs associated with colonoscopy. The expenditure from a stroke or transient ischaemic attack, and the subsequent annual costs after a neurological event, were derived from diagnosis-related groups plus 20% for professional fees. Facility and professional fees based on Medicare allowable payments were used to derive the costs for endoscopic procedures, gastrointestinal haemorrhages and perforation. The cost of LMWH was derived from wholesale prices. A one-time cost was allocated for nursing time to teach patients how to self-inject. The authors did not include the costs of cardiopulmonary complications arising from conscious sedation, as these complications are rare and treated by prompt drug reversal. Since the costs were incurred during a 10-year period, the future costs were discounted at a rate of 3% per annum. The study reported the average costs. The price year was 2003.

**Statistical analysis of costs**

The costs were treated as point estimates (i.e. the data were deterministic).

**Indirect Costs**

The indirect costs were not included in the analysis.

**Currency**

US dollars ($).

**Sensitivity analysis**

Sensitivity analyses were performed by varying the range of base-case values for the costs, utilities and adverse events related to each strategy. The authors also varied the probability of rebound phenomenon. Scenario analyses were also
performed by including other endoscopic procedures, such as screening colonoscopy without any intervention and for endoscopy with planned biopsy.

**Estimated benefits used in the economic analysis**

The QALYs obtained with the seven strategies were as follows:

- continue warfarin, 7.191 QALYs;
- hold warfarin, 7.197 QALYs;
- repeat colonoscopy, 7.197 QALYs;
- dose reduction, 7.198 QALYs;
- LMWH, 7.196 QALYs;
- UFH, 7.196 QALYs; and
- vitamin K, 7.195 QALYs;

**Cost results**

The costs of the seven strategies were as follows:

- continue warfarin, $12,935;
- hold warfarin, $12,745;
- repeat colonoscopy, $12,930;
- dose reduction, $12,755;
- LMWH, $13,020;
- UFH, $17,800; and
- vitamin K, $12,815;

**Synthesis of costs and benefits**

The costs and benefits were combined using an incremental cost-utility ratio (i.e. the extra cost required to obtain an extra QALY). For the base-case patients undergoing screening colonoscopy, the hold-warfarin and dose-reduction arms had the greatest QALYs and lowest costs, both of them being preferable to continuing warfarin.

The sensitivity analysis showed that the results were sensitive to the procedural-associated risk of haemorrhage and the risk of stroke. Sensitivity analyses of the utilities did not change the results. When the risk of rebound hypercoagulability was varied from no rebound to a six-fold increase in the probability of stroke, the hold-warfarin strategy would be preferred when there was no risk of rebound, while the dose-reduction strategy would be preferred when the rebound effect exceeded a two-fold increase in stroke risk. The strategies were equivalent when the rebound effect was a 1.5 to two-fold increase in the risk of stroke.

In the scenario analysis, the continue-warfarin strategy was preferred if the probability of polypectomy was 1% or less. The hold-warfarin strategy was most cost-effective if the likelihood of polypectomy exceeded 60%, or if there was a low risk of stroke despite atrial fibrillation.
Authors' conclusions
Temporary warfarin cessation and halving the warfarin dose for several days before endoscopy were the preferred strategies for most patients. Periendoscopic heparin therapy was not cost-effective for patients with non-valvular atrial fibrillation.

CRD COMMENTARY - Selection of comparators
The authors compared different management strategies of anticoagulants for patients with atrial fibrillation, all of which appear to have been relevant. You should decide if the seven strategies compared in this study represent current practice in your own setting.

Validity of estimate of measure of effectiveness
The authors did not report that a systematic review of the literature was undertaken to identify relevant research and minimise biases. The authors also failed to report how the sources were searched for relevant studies, and the methodology of their review, extraction and synthesis of the data. However, the authors did include a wide range of studies (over 65 studies were included in the review). Apart from a few exceptions, the studies were generally published after 1990 and, hence, were more likely to represent current practice. The authors supplemented the effectiveness data derived from the literature with their own assumptions, also based on the literature. However, it was sometimes difficult to distinguish their assumptions from actual estimates derived from the literature. The authors performed appropriate sensitivity analyses and scenario analyses, using ranges that appear to have been appropriate.

Validity of estimate of measure of benefit
The measure of benefits was modelled. The Markov model used to derive these measures was appropriate. As the benefits could be incurred during a 10-year period, future QALYs were appropriately discounted at a rate of 3% per annum.

Validity of estimate of costs
All the categories of cost relevant to the perspective adopted were included in the analysis. In addition, all the relevant costs for each category appear to have been included, although the authors reported that the costs of cardiopulmonary complications from conscious sedation were not included since they were rated and treated by prompt drug reversal. The costs and the quantities were not reported separately, which will limit the generalisability of the authors' results. The costs were derived from published sources, and appropriate sensitivity analyses of the costs were performed. As the costs could be incurred during a 10-year period, discounting was relevant and was appropriately performed. Medicare charges were used to proxy prices, hence the costs reported in the study might not be the actual costs to the hospital. The price year was reported, which will enhance any future inflation exercises.

Other issues
The authors reported that the results of their study were in line with the American Society of Gastrointestinal Endoscopy Guidelines, which also favour continuing warfarin therapy before a screening endoscopy without biopsy (as shown in the sensitivity analysis). However, the authors' results favoured dose reduction or temporary warfarin cessation in the typical patient undergoing screening colonoscopy. The issue of generalisability to other settings was addressed in the sensitivity and scenario analyses. The authors do not appear to have presented their results selectively. However, even though they reported that incremental cost-utility ratios were performed, none were reported. These would have been desirable to determine the relative cost-effectiveness of the hold-warfarin and dose-reduction strategies. The authors reported a further limitation to their study in that their estimates of risk of haemorrhage were based on cohort studies with few adverse events. Likewise, they reported that their estimates for the short-term risks of stroke while holding warfarin, or reducing the dose, were based on interpolations from chronic therapy and could be inaccurate.

Implications of the study
The authors reported that large prospective trials could validate their conclusions by comparing different strategies of anticoagulation management.

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