Cost-effectiveness of cardioversion and antiarrhythmic therapy in nonvalvular atrial fibrillation

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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
Cardioversion, with or without antiarrhythmic agents, versus rate control and antithrombotic therapy for treatment of patients with nonvalvular atrial fibrillation.

Type of intervention
Secondary prevention.

Economic study type
Cost-utility analysis.

Study population
Hypothetical patients (50% male) aged 70 years old with persistent nonvalvular atrial fibrillation, without significant left ventricular systolic dysfunction, no arrhythmia-related symptoms or hemodynamic compromise and no absolute indication for or against anticoagulant therapy. Patients were split into 3 distinct groups according to the presence of other risk factors, which indicated their underlying risk of stroke.

Setting
The setting was hospital and community. The economic study was carried out in New Hampshire, USA.

Dates to which data relate
The effectiveness data were taken from studies and models previously published between 1977 and 1998, with the majority published between 1989-98. Resource and cost data were derived from published sources (1992-98), reimbursement rates, hospital cost accounting system, and published schedule from 1997. The price year was 1996.

Source of effectiveness data
The effectiveness data utilised within the model were derived from previously published sources and authors-assumptions for treatment protocols.

Modelling
A Markov model (cycle length = 3 months) was used to estimate a total cost and life expectancy value for each of the various management strategies for each stroke risk group. The model was run until all of the cohort are dead.

Outcomes assessed in the review
All of the parameters used within the model were assessed from the literature. The following parameters were of particular importance: the annual risk of stroke with no therapy for 3 distinct risk groups (low, medium and high); the
annual risk of stroke in patients where sinus rhythm is restored; the reduction in annual stroke risk attributable to use of antithrombotic agents (aspirin and warfarin); the proportion of strokes which were fatal; toxicity associated with antiarrhythmic drugs (quinidine and amiodarone) and the proportion of toxic events which were fatal; probability of successful cardioversion; mortality from cardioversion.

**Study designs and other criteria for inclusion in the review**
No specific design criteria were identified by the authors for inclusion but the date range was 1977-1998. The authors also utilised published reviews of RCTs and other trials for a number of parameters used in the model.

**Sources searched to identify primary studies**
Not stated.

**Criteria used to ensure the validity of primary studies**
Not stated.

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

**Number of primary studies included**
Numerous studies were included.

**Methods of combining primary studies**
Not stated.

**Investigation of differences between primary studies**
Not stated.

**Results of the review**
The annual risk of stroke with no therapy was reported as 1.6% for patients at low risk of stroke, 3.6% for patients at medium risk of stroke and 5.3% for patients at high risk of stroke. The annual risk of stroke in patients where sinus rhythm was restored was reported as 0.5%. The reduction in annual stroke risk attributable to aspirin was reported as 22%, and to warfarin was 68%. 25% of strokes were considered to be fatal. Withdrawal from antiarrhythmic treatment was reported as 1.5% per annum with quinidine and 10% per annum with amiodarone. The excess mortality associated with treatment with quinidine was reported as 1.4% per annum. For amiodarone the excess mortality due to treatment toxicity was reported as 0.1% per annum. The overall probability that cardioversion was successful in restoring sinus rhythm was 85%, and the mortality associated with cardioversion was reported as 0.01%. These formed the principal inputs to the model but a comprehensive list is available in the article at Table 1.

**Methods used to derive estimates of effectiveness**
The authors made a number of assumptions within the model considering treatment protocols.

**Estimates of effectiveness and key assumptions**
The authors assumed that: (1) Patients relapsing into atrial fibrillation (AF) began receiving warfarin (except for cardioversion followed by aspirin on relapse). Patients would spend half of the 3-month model cycle in AF before initiation of warfarin therapy; (2) If antiarrhythmic therapy was discontinued because of adverse effects, it was assumed
that AF would recur at a rate similar to that of the patients undergoing cardioversion without concomitant antiarrhythmic prophylaxis; (3) The initial success rate of cardioversion was not affected by the concomitant use of antiarrhythmic agents; (4) In strategies using quinidine and amiodarone, patients having a nonfatal, nonhemorrhagic stroke who were in sinus rhythm started receiving warfarin, but therapy with the antiarrhythmic drug continued. Patients experiencing the same event who were in atrial fibrillation still received warfarin or changed from aspirin to warfarin therapy; (5) In patients experiencing a major hemorrhage, warfarin therapy was discontinued and, after recovery, aspirin therapy was started. It was assumed that the risk for major hemorrhage from warfarin was independent of the duration of therapy; (6) Warfarin and aspirin therapy altered the likelihood of stroke and hemorrhage but not their severity.

Measure of benefits used in the economic analysis
The measure of benefits used within the analysis was quality adjusted life years gained (incremental QALYs). The model was used to pool information from a variety of sources and to determine the costs and benefits associated with each patient management strategy for a cohort of patients. The utility weights were obtained from the published literature (1992-1996) and authors' estimates.

Direct costs
Costs associated with initial treatment, hospitalisation, diagnosis and treatment of side effects, death and annual care under each regime were included within the model. The costs were given per event and the resource use was determined by the model, although not specifically detailed within the paper. The costs of initial cardioversion and treatment of side effects were determined from the literature (1992-1998). Drug costs were taken from published schedules. The costs of initial treatment and annual care for each regime and the costs of hospitalisation were generated using hospital cost-accounting systems. All costs were discounted at an annual rate of 3%. The quantity/cost boundary adopted was that of the third party provider. The price year was 1996, and published costs were inflated/deflated to this price year.

Statistical analysis of costs
Not stated.

Indirect Costs
Not assessed.

Currency
US dollars ($).

Sensitivity analysis
One way sensitivity analysis was undertaken for various key variables to identify the impact of uncertainty upon the results. In addition, a scenario analysis was undertaken to provide estimates of cost-effectiveness for patients aged 65 and 75 years old.

Estimated benefits used in the economic analysis
For the high risk group: cardioversion followed by aspirin on relapse generated 8.41 QALYs; cardioversion followed by warfarin on relapse and cardioversion followed by cardioversion and quinidine on relapse both generated 8.68 QALYs; whilst cardioversion followed by cardioversion and amiodarone on relapse generated 8.98 QALYs. For the medium risk group: cardioversion followed by aspirin on relapse generated 8.76 QALYs; cardioversion followed by warfarin on relapse generated 8.86 QALYs; cardioversion followed by cardioversion and quinidine on relapse generated 8.79 QALYs; whilst cardioversion followed by cardioversion and amiodarone on relapse generated 9.05 QALYs. For the low risk group: cardioversion followed by aspirin on relapse generated 9.21 QALYs; cardioversion followed by warfarin on relapse generated 9.07 QALYs; cardioversion followed by cardioversion and quinidine on relapse generated 8.92 QALYs.
QALYs; whilst cardioversion followed by cardioversion and amiodarone on relapse generated 9.15 QALYs. It was not stated whether the benefits were discounted, but given the time horizon over which the benefits accrue, discounting should have been undertaken.

**Cost results**

The total costs of the strategies for the different risk groups were: Cardioversion followed by aspirin on relapse cost $21,300 (high), $18,300 (medium) and $14,000 (low). Cardioversion followed by warfarin on relapse cost $18,400 (high), $16,900 (medium) and $14,800 (low). Cardioversion followed by cardioversion and quinidine on relapse cost $19,900 (high), $18,900 (medium), $17,700 (low). Cardioversion followed by cardioversion and amiodarone on relapse cost $21,200 (high), $20,500 (medium) and $19,600 (low). All costs were discounted at an annual rate of 3%.

**Synthesis of costs and benefits**

The strategies which did not involve cardioversion were dominated by the strategies including cardioversion (in some form) for every risk group and therefore results were not reported for these strategies. For the high and medium risk groups cardioversion with warfarin on relapse was the least costly strategy, whilst cardioversion followed by cardioversion and amiodarone on relapse was associated with a cost of $9,300 per QALY (high) and $18,900 (medium); other strategies were dominated. For the low risk group cardioversion followed by aspirin on relapse was the least-cost strategy; all other strategies were dominated. The results were sensitive to: changes in the risk of stroke for those in whom sinus rhythm was restored; the utility associated with amiodarone therapy; the annual care cost of amiodarone therapy; the efficacy of warfarin in reducing the stroke rate and the utility associated with warfarin treatment. The scenario analysis found results to be robust to patient age for all risk groups.

**Authors’ conclusions**

The authors concluded that cardioversion should be the initial stage in the management of patients with nonvalvular atrial fibrillation, with the second stage of treatment dependent upon the patients’ underlying risk of stroke, as represented by the presence of other risk factors. For patients at medium or high risk of stroke the second stage of treatment should involve repeated cardioversion plus amiodarone on relapse. For patients at a low risk of stroke relapse should be treated with aspirin therapy.

**CRD COMMENTARY - Selection of comparators**

The reason for the choice of comparison strategies is clear. You, as a user of this database, should consider whether these health technologies apply to your setting.

**Validity of estimate of measure of benefit**

The authors have identified a wide range of studies from which they have determined parameter values for the model. There was no apparent selective use of data, but few details were provided concerning how the studies were identified and the selection process undertaken. Therefore it is difficult to determine the internal validity of the model. Sensitivity analysis has been undertaken to illustrate the impact of variation within the parameters upon the results of the analysis, although the results were not fully reported. It was not stated within the paper whether health benefits were discounted. However, given the time horizon over which the benefits accrue, discounting could have been undertaken.

**Validity of estimate of costs**

The costs used originate from the USA, and therefore may be inappropriate for use within the NHS. The analysis focused upon the costs of the procedures from the perspective of the health care provider and ignored any patient or societal costs. Resource quantities were derived from the model but were not reported separately from prices.

**Other issues**

The authors relied on published data from the literature which has inherent biases. The data are often from specialised

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medical settings and are not externally valid which, a fact which should have been acknowledged by the authors. The issue of generalisability to other settings or countries was not addressed. Appropriate comparisons were made with the results of other studies within the area and to the cost-effectiveness of other programmes. There was appropriate use of modelling to evaluate the cost-effectiveness of the various patient management strategies.

Implications of the study
The reader is referred to the authors' conclusions.

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None stated

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