Cost-effectiveness of radiofrequency catheter ablation for 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
The study examined the use of left atrial catheter ablation (LACA) in the treatment of atrial fibrillation (AF).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
Three hypothetical study populations were considered in the analysis. These were 65-year-old patients at low risk of stroke, 65-year-old patients at moderate risk of stroke, and 55-year-old patients at low risk of stroke. Patients at moderate risk of stroke were defined as having one risk factor (hypertension, diabetes mellitus, coronary artery disease, or congestive heart failure), whereas patients at low risk of stroke had no risk factors. Patients with absolute indications or contraindications for anti-thrombotic therapy and with at least two risk factors for stroke were excluded. Similarly, patients who had intractable symptoms or a need for urgent or emergent cardioversion were not included.

Setting
The setting was a hospital and 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 1986 and 2005. No dates for the resource use data were reported. The price year was 2004.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies and authors' opinions.

Modelling
A Markov model was constructed to simulate the treatment of AF in the three hypothetical cohorts using the three strategies under examination. A graphical representation of the model was used. The model had a lifetime horizon with 3-month cycles. Patients entering the model simulation could remain well, die, or move to three alternative health states (disabled from stroke, disabled from intracranial haemorrhage, or disabled from LACA or medication). In all treatment arms, patients received anti-thrombotic or anticoagulant therapy. Patients at moderate risk of stroke received warfarin, whereas patients at low risk of stroke received either warfarin or aspirin. Patients with sinus rhythm restored continued warfarin therapy for an additional 6 months before transitioning to the use of aspirin.
Outcomes assessed in the review
The outcomes derived from the literature were:

the probability and rate estimates for stroke and haemorrhage on aspirin and warfarin therapy for patients with AF and sinus rhythm;

the efficacy and complications associated with LACA, amiodarone and rate control therapies;

the mortality estimates; and

the utilities weights associated with different health states, treatments and complications.

Study designs and other criteria for inclusion in the review
The authors stated that clinical data and utility values were derived from published sources, but did not clearly state whether a systematic review of the literature was undertaken. Limited information on the primary studies was provided. For example, expected survival was derived from US life tables. Meta-analyses and cohort studies were also used. No head-to-head studies were available for the efficacy of LACA in restoring sinus rhythm compared with medical therapy. Complication rates were obtained from large case series.

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
Fifty-one primary studies provided the clinical data.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
The baseline annual stroke risk in sinus rhythm was 0.9% (range: 0.4 to 1.3) in patients at moderate risk and 0.5% (range: 0.2 to 0.7) in patients at low risk.

The annual stroke risk in AF in patients treated with warfarin was 1.3% (range: 1.0 to 2.0) in patients at moderate risk and 0.7% (range: 0.4 to 1.0) in patients at low risk.

The annual stroke risk in AF in patients treated with aspirin was 2.3% (range: 1.6 to 3.6) in patients at moderate risk and 1.1% (range: 1.0 to 1.5) in patients at low risk.

With aspirin, the rate of fatal stroke (within 30 days) was 17.9% (range: 10.1 to 17.9), the rate of moderate to severe
disability was 30.0% (range: 30.0 to 41.7), the rate of mild disability was 41.0% (range: 34.8 to 41.0), and the rate of no
disability after stroke was 11.0% (range: 11.0 to 13.3).

With warfarin, the rate of fatal stroke (within 30 days) was 8.2% (range: 8.2 to 10.1), the rate of moderate to severe
disability was 40.2% (range: 40.2 to 41.7), the rate of mild disability was 42.5% (range: 34.8 to 42.5), and the rate of no
disability after stroke was 9.1% (range: 9.1 to 13.3).

The relative risk for recurrent stroke was 2 (range: 1 to 4). The relative risk for stroke with each decade of age was 1.4
(range: 1.1 to 2.6).

With LACA, the efficacy rate was 80% (range: 50 to 80) and the annual rate of reversion to AF was 2% (range: 1 to 4).

The associated rates of complications were cardiac tamponade 0.7% (range: 0.4 to 1.0), stroke 0.8% (range: 0.0 to 1.5),
atrio-esophageal fistula 0.2% (range: 0.0 to 0.5), other 0.3% (range: 0.0 to 1.0), and death 0.1% (range: 0.0 to 0.3).

With amiodarone therapy, the outcomes associated with cardioversion were overall cardioversion success 85% (range:
80 to 90), mortality 0.01% (range: 0 to 0.1), and stroke risk in first month after procedure 0.27% (range: 0 to 0.8).

The rate of reversion to AF was 30% (range: 20 to 35) in the first 6 months and 5% (range: 2 to 10) yearly after 6
months.

The annual rate of irreversible pulmonary toxicity was 0.5% (range: 0.2 to 1.0) and the annual rate of death from
pulmonary toxicity was 0.1% (range: 0 to 0.3).

The relative risk for non-cardiovascular mortality was 1.08 (range: 1.03 to 1.14).

Clinical probabilities associated with haemorrhage and rate control therapy as well as mortality adjustments were also
reported.

Health utilities for the well state were 0.998 when receiving aspirin and 0.987 when receiving warfarin or amiodarone.

In terms of stroke, the utility weights were 0.76 for mild residual defect and 0.39 for moderate to severe residual
defect. A utility weight of 0.6 was assigned to persistent pulmonary toxicity.

Short-term quality of life adjustments due to complications, hospitalisations and procedures were also reported.

Methods used to derive estimates of effectiveness
The authors made some assumptions that were used in the decision model.

Estimates of effectiveness and key assumptions
The ablation re-do rate associated with LACA was 30% (range: 15 to 40). Other assumptions associated with the
clinical patterns of patients receiving the different treatments were reported.

Measure of benefits used in the economic analysis
The summary benefit measure used was the expected quality-adjusted life-years (QALYs). These were estimated by
combining quality of life data and life expectancy. Expected survival was also estimated although it was not combined
with the costs. Both the QALYs and life-years (LYs) were discounted at an annual rate of 3%.

Direct costs
The perspective of the third-party payer appears to have been used, although the authors stated that the perspective was
societal. The health services included in the cost analysis were ablation and its potential complications, atrioesophageal
fistula, cardioversion, telemetry unit admission, amiodarone pulmonary toxicity, intracranial bleed or stroke,
extracranial haemorrhage, death, aspirin, warfarin (including monitoring), amiodarone, digoxin (including monitoring) and atenolol. The unit costs were presented separately from the quantities of resources used for only a few items. The costs were derived from multiple sources, including Medicare reimbursement rates (professional and facility costs), hospital accounting information, published literature, and the Red Book for wholesale drug costs. The sources of resource use were unclear. Discounting was relevant, as the long-term costs were evaluated, and an annual discount rate of 3% was used. The price year was 2004.

Statistical analysis of costs
The costs were treated deterministically in the base-case.

Indirect Costs
The indirect costs were not included in the economic analysis.

Currency
US dollars ($).

Sensitivity analysis
Univariate sensitivity analyses were carried out for all model parameters. Alternative values were mainly derived from published sources. A threshold analysis was also performed for 1-year LACA efficacy of 80% and annual stroke risk in patients with restored sinus rhythm, in order to assess the minimum level of LACA efficacy and stroke risk reduction needed to make LACA cost-effective. Finally, a second-order Monte Carlo simulation was used to carry out a multivariate sensitivity analysis. Specific probability distributions were assigned to model inputs (normal for non-skewed parameters, log-normal for skewed variables).

Estimated benefits used in the economic analysis
In the cohort of 65-year-old patients at moderate risk of stroke, the expected QALYs were 10.81 with rate control plus warfarin, 10.75 with amiodarone plus warfarin, and 11.06 with LACA plus warfarin. The corresponding expected LYs were 11.47 (rate control + warfarin), 11.45 (amiodarone + warfarin) and 11.55 (LACA + warfarin), respectively.

In the cohort of 55-year-old patients at moderate risk of stroke, the expected QALYs were 13.95 with rate control plus warfarin, 13.81 with amiodarone plus warfarin, and 14.26 with LACA plus warfarin. The corresponding expected LYs were 14.80 (rate control + warfarin), 14.75 (amiodarone + warfarin) and 14.88 (LACA + warfarin), respectively.

In the cohort of 65-year-old patients at low risk of stroke, the expected QALYs were 11.21 with rate control plus aspirin, 11.02 with amiodarone plus aspirin, and 11.40 with LACA plus aspirin. The corresponding expected LYs were 11.65 (rate control + aspirin), 11.60 (amiodarone + aspirin) and 11.70 (LACA + aspirin), respectively.

Cost results
The total lifetime costs in the 65-year-old cohort at moderate risk were $39,391 with rate control, $43,358 with amiodarone and $52,369 with LACA.

In the 55-year-old cohort at moderate risk, the total lifetime costs were $50,509 with rate control, $55,795 with amiodarone and $59,380 with LACA.

In the 65-year-old cohort at low risk, the total lifetime costs were $24,540 with rate control, $38,425 with amiodarone and $43,036 with LACA.

All patients at moderate risk received warfarin, while patients at low risk received aspirin in addition to LACA, amiodarone or medical rate control.
Synthesis of costs and benefits
Incremental cost-utility ratios were calculated to combine the costs and QALYs of the alternative strategies.

In all three cohorts, amiodarone therapy was dominated by rate control therapy. The incremental cost per QALY gained with LACA over rate control therapy was $51,800 in the 65-year-old cohort at moderate risk, $28,700 in the 55-year-old cohort at moderate risk, and $98,900 in the 65-year-old cohort at low risk.

The univariate sensitivity analysis showed that the most influential variables were the risk of stroke in AF with warfarin, the discount rate, LACA cost, the utility and haemorrhage risk with warfarin therapy, the rate of recurrence of AF after LACA, and the conversion rate to sinus rhythm with rate control therapy. LACA was substantially less cost-effective when short-term time horizons (5 or 10 years) were used.

The threshold analysis suggested that, in the 65-year-old moderate-risk cohort, at the base-case estimate of 80% for 1-year LACA efficacy, an annual stroke risk in sinus rhythm of <= 0.76% and <=0.15% would result in a cost-utility ratio of less than $50,000 and $100,000 per QALY, respectively. Thus, the relative risk of stroke with long-term sinus rhythm should decrease by 42% and 11%, respectively, compared with patients in AF on warfarin (1.3% per year), to yield cost-utility ratios below these thresholds. Consistently, as LACA efficacy decreased, the stroke risk reduction with long-term sinus rhythm should increase for the same corresponding cost-utility ratio threshold. In the 55-year-old moderate stroke risk cohort, lower LACA efficacy rates were needed to satisfy the $50,000 and $100,000 per QALY thresholds, since younger patients live longer and are exposed to higher lifetime risk for stroke and haemorrhage from anticoagulant therapy.

The probabilistic sensitivity analysis showed that, in the 55-year-old moderate-risk cohort, LACA had a 4% probability of having a cost per QALY gained of greater than $100,000, and an 82% probability of having a cost per QALY gained of less than $50,000 in comparison with rate control therapy. More uncertainty was observed in the 65-year-old moderate-risk cohort, with 22% of simulations being greater than $100,000 per QALY gained and only 40% of simulations being less than $50,000 per QALY gained.

Authors’ conclusions
The use of left atrial catheter ablation (LACA) in patients with atrial fibrillation (AF) was not cost-effective in patients at low risk for stroke. However, in moderate-risk patients, LACA could be cost-effective if sufficiently high LACA efficacy rates in restoring sinus rhythm translated into lower morbidity.

CRD COMMENTARY - Selection of comparators
The choice of the comparators was appropriate as they represented both the conventional approaches and the new intervention for AF. The authors noted that, in the current study, LACA consisted of encircling lesions around the pulmonary veins, but AF could be eliminated using a variety of other approaches. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were derived from the literature, although the details and conduct of a systematic review were not reported. Therefore, it was unclear whether the primary studies were identified selectively. Limited information on the primary sources of data was provided, which made it difficult to assess the validity of the clinical estimates. Further, the authors made some assumptions to derive specific probability values used in the model. However, an extensive sensitivity analysis was carried out to deal with the uncertainty surrounding some model inputs. The authors did not address the issue of homogeneity amongst the primary studies and did not report the approach used to combine the clinical estimates.

Validity of estimate of measure of benefit
QALYs are a validated and appropriate measure of benefit since they incorporate two dimensions of health (survival and quality of life) that are relevant for patients with AF. The utility values were reported for all health states, but
details of the sources of such data were not reported. A further advantage of QALYs is that they are comparable with the benefits of other healthcare interventions. The LYs were also estimated. The benefits were discounted, as in accordance with US recommendations for economic evaluations.

**Validity of estimate of costs**
The analysis of the costs was restricted to direct medical costs. This means that, although the authors explicitly stated that a societal perspective was adopted, the perspective could be more appropriately described as that of a third-party payer. However, the inclusion of indirect costs associated with productivity losses would have been interesting, especially for the younger cohort of patients. Detailed information on the unit costs was provided in an appendix to the paper, but only few details of resource consumption were provided. Therefore, it may be difficult to replicate the complete analysis in other settings. The sources of the costs were reported for all items and were consistent with the viewpoint of the third-party payer. Discounting was performed and was appropriate given the long-term time horizon of the model. The impact of using different discount rates was investigated in the sensitivity analysis. The authors reported the price year, which will assist when performing reflation exercises in other time periods.

**Other issues**
The authors stated that prior studies had not assessed the cost-effectiveness of LACA in AF. Therefore, comparisons with the results from other economic evaluations were not possible. The issue of the generalisability of the analysis to other settings was not explicitly addressed, although the sensitivity analysis attempted to consider a number of alternative scenarios. Further, the use of a threshold analysis might provide interesting results from the perspective of the decision-makers. The authors noted some strengths and disadvantages of their analysis. The authors stated that LACA is likely to be more cost-effective if younger patients are considered, but is not cost-effective for patients older than 65 years.

**Implications of the study**
The study results suggest that LACA might be cost-effective in AF patients at moderate risk of stroke. The authors stated that the current analysis could help in designing future clinical trials and economic evaluations of LACA.

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None stated.

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**Other publications of related interest**
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