Supplementary material

Cost-effectiveness of left atrial appendage closure for stroke prevention in atrial fibrillation: a systematic review appraising the methodological quality.

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Quality assessment of primary studies using ECOBIAS checklist

Part A: General bias in economic evaluations

(i) Narrow perspective bias

None of the original studies included in this review considered a societal perspective, which is recommended by most economic evaluation guidelines (1-4), nor discussed in detail the potential implications of broadening the perspective (5). Six studies reported a healthcare provider perspective (6-11) while the rest reported a healthcare payer perspective.

(ii) Inefficient comparator bias

All the economic evaluations considered in this review had specifically mentioned the comparator at the outset, and the chosen comparator was appropriate for the research question.

(iii) Cost-measurement omission bias

All groups of authors except one (11) presented the items/ events they costed with relevant references in a table. However, the list was not exhaustive for some studies. For example, four studies (8, 12-14) did not listed how peri-procedural complications of the LAAC procedure were costed, although these complications were included in the model structure.

(iv) Intermitten data collection bias

Only two studies (10, 15) listed follow-up cost for patients who underwent LAAC procedure, which is an important source of cost in chronic disease care such as AF. Although earlier studies suggested estimation of total cost based on intermittently collected data, for example three months during a one-year period (16, 17), now it is known to lead to bias (18).

(v) Invalid valuation bias

All studies considered unit costs, costs of individual facilities or combined estimates of different reference settings or tariffs for cost prices, as recommended (19).

(vi) Ordinal ICER bias

All authors used QALY, which uses a cardinal scale, to measure the health outcomes in AF, thus leaving out the ordinal ICER bias.

(vii) Double counting bias

None of the studies incorporated a treatment consequence in cost as well as QALY estimations.

(viii) Inappropriate discounting bias

Most authors of primary analyses referenced local guidelines for the rate of discounting used in their models (7-11, 13, 14, 20). Studies were considered as having high risk bias when they either have not provided the discount rate, or when a proper reference was not provided for the chosen discount rate. None of the studies analysed the effect of different rates on the ICER value.

(ix) Limited sensitivity analysis bias

Most primary studies reported sensitivity analyses, but these were limited to parameter uncertainty. Only a few studies performed scenario analysis to discuss how the cost-effectiveness of interventions change in different possible scenarios (6, 15, 20).

(x) Sponsor bias

Profit-making companies funded three studies included in this review, and a majority (80%) of author groups declared having conflicts of interest. None of the studies reported rigorous independent assessment prior to results dissemination as recommended for sponsored studies (21, 22).

(xi) Structural assumption bias

None of the studies specified sources of data used to develop the model structure. Also, justifications for model assumptions were not described by any study. The structure of a model was consistent with the condition being investigated in majority of studies. Two studies (6, 20) excluded the state of myocardial infarction, which is a very common complication in AF. One study (6) attributed this non-inclusion to data unavailability, but the good practice guidelines recommend conceptual structure is driven by the decision problem, not by data availability (23). Health states of another study (20) contained only ischaemic stroke, categorised according to the modified Rankin scale.

Another important aspect in data identification is adherence to treatment. Compliance has shown to influence ICER substantially (24), therefore is recommended that accurate information about adherence is incorporated into the model (19). Poor compliance is a

significant problem among AF patients (25), but only four studies (41,42,44,48) incorporated treatment adherence rates into the model. This may have an impact in the final reported ICER.

Part B: Model specific bias

(xii) No treatment comparator bias

All included studies considered appropriate comparisons in accordance with their research questions, hence were at low risk of no treatment comparator bias.

(xiii) Wrong model bias

All primary studies used Markov models for their economic evaluation, which is the appropriate for AF which is continuous over time and where important events like stroke and bleeding may happen more than once.

(xiv) Limited time horizon bias

Considering a lifetime time horizon seems important in AF as the risk of disease recurrence and complications increase with age. Half of the models considered 20 years horizon irrespective of labelling it as lifetime or not, and only one study (6) considered 10 years with the base case cohort starting at the age of 65 years, which may not be long enough to capture all relevant cost and outcomes.

(xv) Bias related to data identification

All economic evaluations included in this review used randomised controlled trials (RCT) as the body of evidence for input parameters. Although all studies clearly stated which RCTs were used to derive inputs for the economic model, none explicitly reported what methodology was used to identify these trials. Moreover, none of the papers discussed the quality or relevance of data from pivotal trials.

(xvi) Bias related to baseline data and treatment effects

LAAC-related clinical parameters were exhaustively retrieved from PROETCT-AF and/or PREVAIL trials that compared LAAC with warfarin by all studies except Labori and colleagues (20) who decided it was inappropriate to use data from these trials due to differences in the study populations. Similar to the study by Labori et al, many other studies had disparities

between the model population and trial population like contraindications to OAC, mean stroke risk and bleeding risk, yet used trial for model inputs.

Studies comparing LAAC with novel OAC used indirect comparison techniques to convert treatment effects for LAAC and warfarin from mentioned pivotal trials to derive treatment effects for LAAC and novel OAC, but none presented how this was done except one study (15). In addition, some studies (8, 11, 26) did not meta-analyse data from PROTECT-AF and PREVAIL trails to derive clinical inputs for LAAC but used only PROTECT-AF data which proved non-inferiority of LAAC against warfarin. Excluding PREVAIL trial may have produced biased results as its data failed to prove non-inferiority of LAAC against warfarin for ischaemic stroke prevention (27).

(xvii) Bias related to quality-of-life weights (utilities)

Some studies only presented the mean utility score used for model input parameters (6, 7), while others very briefly described the methods adhered to in estimating this mean score (8, 12-14). Several studies described using quality-of-life short form-12 collected during Watchman ASAP trial (8) and PROTECT-AF trial (13, 14) to retrieve QALY estimates for LAAC. On the other hand, three studies (9-11) reported that no quality-of-life estimates were available for LAAC and used relevant data in percutaneous coronary interventions instead.

(xviii) No transparent data incorporation bias

All studies comparing LAAC with a novel OAC used indirect comparison techniques to derive clinical inputs for LAAC as available pivotal trials compared LAAC only with warfarin, but only one study (15) presented how this was done. In addition, three out of ten studies (8, 10, 11) reported that they used patient-level Markov microsimulation models, but transition probabilities for events listed in their tables were not specified by any patient-level data.

(xix) Limited scope bias

All included studies presented and discussed probabilistic sensitivity analyses which evaluate parameter uncertainty. None of the studies assessed the economic model for methodological or structural uncertainty, thus making the studies high risk for limited scope bias.

(xx) Bias related to internal consistency

None of the primary studies reported analysis for the internal consistency of the model in terms of its mathematical logic as recommended by best practice guidelines (19).

List of abbreviations

AF – atrial fibrillation
ECOBIAS - modified Economic Evaluations Bias checklist
ICER – incremental cost-effectiveness ratio
LAAC – left atrial appendage occlusion
NOAC – novel oral anticoagulants
OAC – oral anticoagulants
PROTECT-AF – WATCHMAN left atrial appendage system for embolic protection in patients with atrial fibrillation trial
QALY – quality adjusted life years
RCT – randomised clinical trial
REVEAL - Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy trial

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