Australian Government

Medical Services Advisory Committee

Minutes from MSAC 74th Meeting, 22-23 November 2018

Cardiac Ablation for Atrial Fibrillation

MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC advised that catheter ablation for atrial fibrillation (AF) is not cost-effective at the current catheter prices and based on other assumptions in the economic analysis. MSAC suggested there should be further consideration following updated economic modelling using respecified outcomes and inputs (e.g. 10-year time horizon, repeat procedure rates based on MBS data, not including stroke reduction, and better determining the number and mix of catheters used per procedure).

Summary of consideration and rationale for MSAC's advice

AF affects 2–4% of the adult population and is associated with an increased risk of heart failure, stroke and death. Treatment involves rate or rhythm control, anticoagulant therapy and treating underlying risk factors (elevated blood pressure, obesity, alcohol use and sleep apnoea).

For rhythm control, anti-arrhythmic drug (AAD) therapy has been the cornerstone of medical management, but some patients show resistance to AAD or need to discontinue treatment because of side effects. Anticoagulation has been shown to reduce AF-related stroke; however, the use of anticoagulants is sub-optimal.

Cardiac ablation for the treatment of AF is increasingly being performed in symptomatic patients as an alternative to medical management, or when medical management has been ineffective or not tolerated.

MSAC noted that there are currently three Medicare Benefits Schedule (MBS) items for services relating to catheter-based arrhythmia ablation:

- Item 38287 – Ablation of arrhythmia circuit or focus or isolation procedure involving one atrial chamber
- Item 38290 – Ablation of arrhythmia circuit or foci, or isolation procedure involving both atrial chambers and including curative procedures for AF
- Item 38293 – Ventricular arrhythmia with mapping and ablation, including all associated electrophysiological studies performed on the same day.

It is understood that most ablation for AF is performed under item 38290.

These services have been on the MBS since 1998 and have not undergone formal assessment of comparative safety, clinical effectiveness and cost-effectiveness. Although there has been considerable growth in use of these items, the MBS Review Taskforce's Cardiac Services Clinical Committee recently recommended leaving the items unchanged, claiming that growth in services is likely reflective of (i) the increasing number of electrophysiologists, which is improving access to services; and (ii) a change in clinical guidelines, which now identify ablation as a first-line treatment for a number of arrhythmias.

MSAC noted that this application arose because of a claim by consumer groups that cardiac ablation procedures are not readily accessible because the Prostheses List (a list of medical devices for which private health insurers are required to pay benefits) is limited to implantable devices. Ablation catheters are single use non-implantable devices, and therefore are not listed on the Prostheses List (PL). Although cardiac ablation services are funded on the MBS, private health insurers are not obliged to reimburse the cost of catheters. As a result, it is asserted that these procedures are largely provided in public hospitals and hence subject to long waiting times and, where provided in the private sector, there are variable funding arrangements that expose patients to out-of-pocket expenses.

In October 2017, as part of an agreement with the Medical Technology Association of Australia, the government agreed to review the listing criteria for the PL for non-implantable medical devices, including cardiac ablation catheters for AF. In addition, Minister Hunt requested that the Prostheses List Advisory Committee (PLAC) provide advice on options for including cardiac ablation catheters on the PL, including an assessment of comparative clinical and cost-effectiveness. In August 2018, PLAC requested MSAC to undertake a review of the comparative clinical and cost-effectiveness of AF catheter ablation.

The review investigated three research questions:

1. Is there sufficient clinical evidence to demonstrate the superiority of cardiac ablation over treatment with anti-arrhythmic medication? If not, what are the gaps?
2. Are the clinical outcomes different in different age groups?
3. Are there sufficient data to establish that the devices are cost-effective at the prices currently being paid in Australia?

A total of 23 systematic reviews (including two Cochrane reviews) and three health technology assessments met the eligibility criteria for review and were selected based on recency, comprehensiveness and quality.

Is there sufficient clinical evidence to demonstrate the superiority of cardiac ablation over treatment with anti-arrhythmic medication? If not, what are the gaps?

In summary, MSAC accepted that that there is moderate quality evidence that radiofrequency (RF) ablation is superior to medical therapy for enhancing patient freedom from recurrence of atrial arrhythmias (and in particular paroxysmal AF) in both the short and medium term (up to 4 years). However, the need for re-ablation is common, with rates of up to 50% reported. There is low-quality evidence to suggest that cardiac ablation has a beneficial impact on all-cause mortality (however, this benefit appears to be largely driven by the inclusion of patients with heart failure, who are not the subject of the PLAC consideration) and cardiac hospitalisation in patients with AF. Evidence from observational studies suggests that cardiac ablation may decrease the risk of stroke compared with medical therapy, but this benefit is not seen in randomised controlled trials (RCTs), which are likely underpowered for this

outcome. Overall, no definite conclusion could be made about the effect of ablation on the risk of stroke.

MSAC noted that the benefit of ablation is similar whether it is used as first or second line treatment.

In relation to the safety of cardiac ablation. MSAC noted that the rate for major complications was 3-4% and these included device complications (damage to adjacent structures) and procedure-related complications (e.g., vascular access). MSAC accepted that cardiac ablation is probably less safe than medical therapy but overall it is acceptably safe when performed by experienced proceduralists.

The key findings from the evidence review are summarised in Table 1.

Table 1 Key findings and strength of evidence: cardiac ablation (CA) vs. medical therapy (MT)

Outcome	Population	No. of studies *[source]*[a]	Strength of evidence[b]	Conclusion
All-cause mortality	Any AF	10 RCT (NR) FU 6-53 months *[Barra 2018]*	Low	**Favours CA** 4.2% for CA vs. 8.9% for MT; P=0.001. Similar results when 8 OBS are included in analysis. Benefit is attributed to inclusion of HF patients.
	Paroxysmal AF	2 RCT (N=408) FU to 24 months *[AHRQ 2015]*	Low	**No difference** 0.97% for RFA vs. 2.0% for MT; P=NS. Similar results for RFA with FU to 12 months.
	Persistent AF	3 RCT (N=559) FU 6-24 months *[Chen 2018]*	Low	**No difference** 2.7% for CA vs. 8.1% for MT; P=0.05.
Stroke	Any AF	7 RCT, 10 OBS (NR) FU 6-53 months *[Barra 2018]*	Low	**Favours CA** 2.3% for CA vs. 5.5% for MT; P<0.001. No significant difference when OBS are excluded. Benefit is attributed to inclusion of HF patients.
	Paroxysmal AF	2 RCT (N=194) FU 12-24 months *[AHRQ 2015]*	Insufficient	**No difference** 0% for RFA vs. 0% for MT; P=NS. Definitive conclusions are not possible.
	Persistent AF	1 RCT (N=146) FU 12 months *[AHRQ 2015]*	Insufficient	**No difference** 0% for RFA vs. 0% for MT; P=NS. Definitive conclusions are not possible.
Arrythmia recurrence	Any AF	11 RCT (N=1481) FU mean 19 months *[Khan 2018]*	Moderate	**Favours CA** 27.0% for CA vs. 63.8% for MT; P<0.001. Similar results for 6 RCTs of HF patients.
Freedom from arrythmia recurrence	Paroxysmal AF	3 RCT (N=619) FU 24-48 months *[AHRQ 2015]*	Moderate	**Favours CA** 72.6% for RFA vs. 57.8% for MT; P<0.05. Similar results for 4 RCTs with FU to 12 months.
	Persistent AF	3 RCT (N=559) FU 6-24 months *[Chen 2018]*	Moderate	**Favours CA** 61.2% for CA vs. 30.3% for MT; P<0.00001. Similar results for patients without AADs after CA.
Repeat ablation	Any AF	8 RCT (N=430) FU 6-12 months *[AHRQ 2015]*	Insufficient	Ranges from 0 – 53% after RFA. Definitive conclusions are not possible.

Outcome	Population	No. of studies *[source]*[a]	Strength of evidence[b]	Conclusion
	Paroxysmal AF	4 RCT (N=337) FU 12-48 months *[AHRQ 2015]*	Insufficient	Ranges from 12.5 – 49.2% after RFA. Definitive conclusions are not possible.
	Persistent AF	5 RCT (N=246) FU 6-12 months *[AHRQ 2015]*	Insufficient	Ranges from 8.1 – 53.8% after RFA. Definitive conclusions are not possible.
Cardiac hospitalisation/ re-admission	Any AF	4 RCT (N=629) FU mean 19 months *[Khan 2018]*	Low	**Favours CA** 9.6% for CA vs. 31.5% for MT; P=0.001. Similar results (P=0.01) for 3 RCTs of HF patients.
	Paroxysmal AF	2 RCT (N=361) FU 12-24 months *[AHRQ 2015]*	Insufficient	**Favours CA** 17.0% for CA vs. 40.9% for MT; P=NR. Definitive conclusions are not possible.
	Persistent AF	2 RCT (N=349) FU 6-24 months *[Chen 2018]*	Insufficient	**Favours CA** 1.7% for RFA vs. 11.5% for MT; P=0.0002. Definitive conclusions are not possible.
Pulmonary vein stenosis	Any AF	6 RCT (N=1109) FU mean 19 months *[Khan 2018]*	Low	**No difference** 1.2% for RFA vs. 0% for MT; P=0.09. Events are uncommon.
	Paroxysmal AF	5 RCT (N=544) FU 1-24 months *[AHRQ 2015]*	Insufficient	0.7% for RFA. Definitive conclusions are not possible. Events are uncommon.
	Persistent AF	2 RCT, 1 OBS (N=295) FU 1-12 months *[AHRQ 2015]*	Insufficient	0.3% for RFA. Definitive conclusions are not possible. Events are uncommon.
Pericardial effusion	Any AF	5 RCT, 1 OBS (N=930) FU 1 month *[AHRQ 2015]*	Insufficient	0.8% for RFA. Definitive conclusions are not possible. Events are uncommon.
	Paroxysmal AF	3 RCT (N=519) FU 1 month *[AHRQ 2015]*	Insufficient	0.6% for RFA. Definitive conclusions are not possible. Events are uncommon.
	Persistent AF	1 RCT, 1 OBS (N=274) FU 1 month *[AHRQ 2015]*	Insufficient	1.5% for RFA. Definitive conclusions are not possible. Events are uncommon.
Cardiac tamponade	Any AF	8 RCT, 2 OBS (N=1056) FU 1-24 months *[AHRQ 2015]*	Insufficient	1.4% for CA. Definitive conclusions are not possible. Events are uncommon.
	Paroxysmal AF	4 RCT, 1 OBS (N=597) FU 1-24 months *[AHRQ 2015]*	Insufficient	1.5% for RFA. Definitive conclusions are not possible. Events are uncommon.
	Persistent AF	3 RCT, 1 OBS (N=231) FU 1 months *[AHRQ 2015]*	Insufficient	1.7% for RFA. Definitive conclusions are not possible. Events are uncommon.

Outcome	Population	No. of studies *[source]*[a]	Strength of evidence[b]	Conclusion
Major bleeding	Any AF	7 RCT (N=811) FU mean 19 months *[Khan 2018]*	Low	**Favours MT** 3.7% for CA vs. 0.2% for MT; P=0.02
	Paroxysmal AF	1 RCT (N=67) FU 1 month *[AHRQ 2015]*	Insufficient	6.3% for RFA vs. 1.9% for MT; P=NR. Definitive conclusions are not possible. Events are uncommon.
	Persistent AF	1 OBS (N=412) FU 1 month *[AHRQ 2015]*	Insufficient	1.3% for RFA vs. 0.8% for MT; P=NR. Definitive conclusions are not possible. Events are uncommon.

Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; CA, cardiac ablation; CBA, cryoballoon ablation; FU, follow up; HF, heart failure; MT, medical therapy; NR, not reported; NS, not statistically significant; OBS, observational study; RCT, randomised controlled trial; RFA, radiofrequency ablation.

a Refers to the published review that provides the best evidence.

b Strength of evidence has been judged informally by the authors of the Rapid Review.

Is there sufficient clinical evidence to demonstrate the superiority of one cardiac ablation technique over another?

MSAC noted that evidence comparing cryoballoon ablation with medical therapy is insufficient to draw firm conclusions regarding efficacy or safety. However, there is moderate quality comparative evidence that there is no difference between cryoablation and radiofrequency ablation in achieving freedom from AF.

The key findings from studies comparing the two techniques is summarised in Table 2.

Table 2 Key findings and strength of evidence: RF ablation vs. cryoablation

Outcome	Population	No. of studies *[source]*[a]	Strength of evidence[b]	Conclusion
All-cause mortality	Any AF	0 studies	-	-
	Paroxysmal AF	1 OBS (N=396) FU mean 23 months *[AHRQ 2015]*	Insufficient	**No difference** 1.2% for CBA vs. 0% for RFA. Definitive conclusions are not possible.
	Persistent AF	0 studies	-	-
Stroke	Any AF	NR (N= 4058) FU ≥12 months *[Cardoso 2016]*	Low	**No difference** 0.2% for CBA vs. 0.3% for RFA; P=0.63.
	Paroxysmal AF	0 studies	-	-
	Persistent AF	0 studies	-	-
Arrythmia recurrence	Any AF	5 RCT (N=1306) FU 12-40 months *[Cardoso 2016]*	Moderate	**No difference** 62.4% for CBA vs. 61.1% for RFA; P=0.99. Similar results when 14 OBS are included in analysis.
	Paroxysmal AF	NR (N=6055) FU 12-40 months *[Cardoso 2016]*	Moderate	**No difference** 66.3% for CBA vs. 62.1% for RFA; P=0.28.
	Persistent AF	0 studies	-	-

Outcome	Population	No. of studies *[source]*[a]	Strength of evidence[b]	Conclusion
Repeat ablation	Any AF	5 RCT (N=1306) FU 12-40 months *[Cardoso 2016]*	Moderate	**No difference** 10.2% for CBA vs. 9.0% for RFA; P=0.61. Similar results when OBS are included in analysis.
	Paroxysmal AF	1 RCT (N=50) FU 12 months *[AHRQ 2015]*	Insufficient	**Favours RFA** 24.0% for CBA vs. 0% for RFA; P=0.01. Definitive conclusions are not possible.
	Persistent AF	0 studies	-	-
Cardiac hospitalisation/ re-admission	Any AF	0 studies	-	-
	Paroxysmal AF	0 studies	-	-
	Persistent AF	0 studies	-	-
Pericardial effusion	Any AF	3 RCT, 10 OBS (N=7117) *[Cardoso 2016]*	Low	**Favours CBA** 0.8% for CBA vs. 2.1% for RFA; P<0.001. No significant difference when OBS are excluded from analysis.
	Paroxysmal AF	11 studies (N=5821) *[Cardoso 2016]*	Low	**Favours CBA** 0.8% for CBA vs. 2.1% for RFA; P<0.01.
	Persistent AF	0 studies	-	-
Pericardial tamponade	Any AF	2 RCT, 6 OBS (N=5120) *[Cardoso 2016]*	Low	**Favours CBA** 0.4% for CBA vs. 1.4% for RFA; P=0.002.
	Paroxysmal AF	7 studies (N=5020) *[Cardoso 2016]*	Low	**Favours CBA** 0.3% for CBA vs. 1.3% for RFA; P<0.01.
	Persistent AF	0 studies	-	-
Pulmonary vein stenosis	Any AF	3 OBS (N=4295) *[AHRQ 2015]*	Low	**No difference** 0% for CBA vs. 0% for RFA.
	Paroxysmal AF	2 OBS (N=4171) *[AHRQ 2015]*	Low	**No difference** 0% for CBA vs. 0% for RFA.
	Persistent AF	0 studies	-	-
Major vascular complications	Any AF	7 studies (NR) *[Cardoso 2016]*	Low	**No difference** 1.1% for CBA vs. 1.3% for RFA; P=0.52.
	Paroxysmal AF	0 studies	-	-
	Persistent AF	0 studies	-	-

Abbreviations: AF, atrial fibrillation; CBA, cryoballoon ablation; FU, follow up; NR, not reported; OBS, observational study; RCT, randomised controlled trial; RF, radiofrequency; RFA, radiofrequency ablation.

a Refers to the published review that provides the best evidence.

b Strength of evidence has been judged informally by the authors of the Rapid Review.

Recent findings from the CABANA trial

The findings from the high-level clinical evidence review are consistent with findings from the landmark Catheter ABlation vs ANtiarrhythmic Drug Therapy in Atrial Fibrillation (CABANA) trial, which is yet to be formally published but has recently been reported in a conference presentation. This large RCT (*N*=2204) found that cardiac ablation was associated with a significant reduction in recurrence of AF compared with 'current state-of-the-art pharmacologic therapy' at a median follow-up of approximately 4 years. However, there was no statistically significant difference between arms in the primary endpoint of the trial (the

composite of all-cause mortality, disabling stroke, serious bleeding, or cardiac arrest) or the individual components of the primary endpoint using an intention-to-treat (ITT) approach.

Despite CABANA being the largest randomised trial of cardiac ablation, and the most comprehensive and inclusive study evaluating outcomes such as mortality, stroke and cardiac hospitalisation, interpretation of the findings from this trial are confounded by incomplete blinding and high rates of crossover between arms. Nevertheless, the results from this trial, when published in full, may provide valuable additional evidence to inform the clinical effectiveness and cost-effectiveness of cardiac ablation compared with medical therapy.

Recent Australian guidance on management of AF

MSAC noted that the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand have recently published *Australian clinical guidelines for the diagnosis and management of atrial fibrillation* (2018). The recommendations in relation to percutaneous catheter AF ablation are as follows:

- Catheter ablation should be considered for symptomatic paroxysmal or persistent AF refractory or intolerant to at least one Class I or III anti-arrhythmic medication [GRADE quality of evidence: High; GRADE strength of recommendation: Strong].
- Catheter ablation can be considered for symptomatic paroxysmal or persistent AF before initiation of anti-arrhythmic therapy [GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong].
- Catheter ablation can be considered for symptomatic paroxysmal or persistent AF in selected patients with heart failure with reduced ejection fraction [GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong].

The guidelines advise that AF ablation is an effective procedure for appropriately selected patients with symptomatic AF. The procedure is considered applicable to patients who have failed or are intolerant to anti-arrhythmic drugs, or for some patients who decline medical therapy. It also notes that outcomes are better when experienced operators are performing the procedure in high-volume centres.

The Australian guidelines acknowledge that patients frequently report a 'dramatic improvement' in quality of life with AF ablation, and that the procedure may have a mortality benefit in patients with heart failure. The CABANA trial is noted as an ongoing study awaiting publication.

Are the clinical outcomes different in different age groups?

No systematic reviews were identified that focus on the effect of age on clinical outcomes for cardiac ablation. The AHRQ 2015 health technology assessment concluded that there were no studies that provide evidence as to how age modifies the effects of the interventions. However, the authors noted two poor-quality observational studies that provide data specifically in populations over the age of 65 years. One found no statistical difference in mortality risk between cardiac ablation and medical therapy, whereas the other found a lower mortality risk in the ablation group.

One systematic review (Barra 2018) performed a meta-regression to assess the individual impact of moderator variables on the effectiveness of cardiac ablation. The analysis showed that, for studies with a higher mean patient age, cardiac ablation had a more pronounced benefit in reducing all-cause mortality and stroke. In contrast, all other systematic reviews that analysed potential sources of heterogeneity by meta-regression found that age was not a contributory confounder. Given that many of these reviews included studies with participants in a narrow age range, it is unlikely that a significant effect would be found.

Are there sufficient data to establish that the devices are cost-effective at the prices currently being paid in Australia?

Based on the data included in the high-level review, it appears that cardiac ablation using either RF ablation catheters or cryoablation catheters is not cost-effective at the device prices

currently being paid in Australia (average prices of $2300 for mapping catheters, $6000 for RF ablation catheters, and $4065 for cryoablation catheters). The incremental cost-effectiveness ratio (ICER) of the different types of ablation compared with medical therapy at 12 months was found to be $110,321 per QALY for RF ablation and $95,481 per QALY for cryoablation. The ICER over a longer duration was not calculated.

Sensitivity analyses showed that the model is relatively insensitive to all changes in variables (despite the use of a wide range of values for the assumptions), except for the cost of the catheters. When the costs of mapping and ablation catheters are assumed to be $500 each (i.e. the total cost of all catheters for each ablation procedure is $1000), the indicative ICER for catheter ablation versus medical therapy is approximately $54,031 per QALY.

MSAC noted that the potential cost of ongoing oral anticoagulants and anti-arrhythmic therapy will affect the economic model because of the long timeframe that patients need to use these medical therapies. However, this cost is not a major driver of the ICER.

Although some published economic evaluations report that cardiac ablation is cost-effective, these evaluations appear to be driven by the inclusion of outcomes in heart failure patients (who are out of scope for the current consideration) or the assumption that cardiac ablation reduces the rate of subsequent stroke and/or mortality (claims that are not supported by the available clinical evidence).

MSAC noted that a number of simplifying assumptions were required to develop the focused economic evaluation and that a more comprehensive economic evaluation with a longer time horizon and more specific inputs would generate more reliable estimates of cost-effectiveness. MSAC suggests that any further economic modelling should include a longer timeframe for benefit over medical therapy of 10 years, use a MBS-derived repeat procedure rate (about 20%) and include more robust assumptions about the type and number of catheters used per procedure.

What is the likely financial impact of listing the devices on the Prostheses List?

MSAC noted that the total cost of cardiac catheters (mapping catheters, RF ablation catheters and cryoablation catheters) is currently $44 million to $50 million per year to private health insurers (PHIs), and $24 to $27 million per year to the MBS. The current estimate of costs to PHIs is similar to an estimate from the Department of Health of total PHI outlays for cardiac ablation devices (roughly $43 million), based on data and market share assumptions from a medium size health insurer. If it is assumed that the listing of the devices on the PL generates a 10% increased uptake in the private sector use of these services the net increase in cost to PHIs is estimated to be $4 million to $5 million per year, and the net increase in cost to the MBS is estimated to be approximately $2 million per year. However, these estimates are highly uncertain.