CPAG Summary Report for Clinical Panel – URN 1903: Percutaneous left atrial catheter ablation for the treatment of paroxysmal atrial fibrillation

a) Use of catheter ablation (CA) versus medical therapy (MT) to treat paroxysmal atrial fibrillation (AF)

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Not reported
2.	Progression free survival	Not reported
3.	Mobility	Not reported
4.	Self-care	Not reported
5.	Usual activities	Not reported
6.	Pain	Not reported
7.	Anxiety / Depression	Not reported
8.	Replacement of more toxic treatment	Not reported
9.	Dependency on care giver / supporting independence	Not reported
10.	Safety	Adverse events (AE) or complications were not specifically defined by Skelly et al (2015). However, the WHO defines this as any unfavourable and unintended outcomes temporarily associated with the use of an intervention. Skelly et al (2015) reported on other complications attributable to CA such as cardiac tamponade within 24 months (n=512) [pooled risk from four RCTs of 1.7% (95% CI 0.8 to 3.6)], pericardial effusion within 48 months (n=519) [pooled risk from three RCTs 0.6% (95% CI 0.2 to 1.8)], pulmonary vein stenosis at 12 months [pooled risk based on two studies (n=122) was 1.6% (95% CI 0.4 to 6.3) and pooled risk based on two studies (n=283) with 24-month follow-up was 0.7% (95% CI 0.2 to 2.8). Other ablation-related harms reported in the HTA included perforation at the trans-septal puncture (one RCT n=194, 0.5%), perimyocarditis (two RCTs n=333, 0% to 1.7%) and haematoma at catheter insertion site (2 RCTs n=276, 1.6% to 2.2%). There were no reports of atrio-oesophageal fistula, diaphragmatic paralysis, heart block and pneumothorax. The authors also reported drug intolerance requiring discontinuation based on one RCT (n=99) in 23.2% of patients in the MT arm and 0% in the CA arm.

		This HTA suggests that CA is associated with intervention-related complications and that drug intolerance to antiarrhythmic drugs (AADs) is very common. It is important to patients that treatment of AF represents a favourable balance of successful treatment over complications. These results should be interpreted with caution because of the heterogeneity found among studies comparing CA with MT which may be due to dissimilar patient populations and extent of ablation.
11.	Delivery of intervention	Not reported

No	Outcome measure	Summary from evidence review
1.	Freedom from recurrence of any arrhythmia	Freedom from recurrence was variably defined across trials, with some trials defining it based on the presence of symptoms and others defining it based on duration and frequency of recurrent episodes of arrhythmia (any including AF). The blanking period[1] ranged from 1 to 3 months. Pooled results from 4 RCTs in the health technology appraisal (HTA) by Skelly et al (2015) reported a significant difference in freedom of recurrence of AF between PAF patients treated with CA versus MT. At 12 months 226/286 (79%) of CA patients versus 64/245 (26.1%) of MT patients; risk ratio (RR) 3.06 (95% CI; 2.35 to 3.90) favours CA, $p<0.05$. There was equally a significant difference at 24 to 48 months (3 RCTs) 226/311 (72.6%) of CA patients versus 178/308 (57.8%) in the MT group. RR 1.24 (95% CI 1.11 to 1.47) favours CA, $p<0.05$. The systematic review suggests that CA is better at preventing any arrhythmia than MT. People with AF have higher risks of developing comorbidities such as heart failure and stroke as well as higher all-cause mortality rate. The goal of AF treatment is to establish sinus rhythm and/or achieve rhythm control. Many clinicians believe that achieving either of these goals may lead to a reduction in major cardiovascular events. Following CA, continuation of AADs treatment is sometimes required for some patients to maintain AF freedom. However, avoiding AADs where possible is considered a better outcome especially as it could obviate the ubiquitous undesirable side effects of these drugs. The results should be interpreted with caution because of the limitations of the data included and in the meta-analyses. There was substantial heterogeneity across included studies and a formal assessment of publication bias was not conducted. There was wide variability across studies (in the quality of reporting of study methods, in how outcomes were defined, and in which patients were included). Only one trial was considered to be good quality by the HTA authors; the remaining trials were all considered fair quality. Other important limitations of the evidence base include the small

[1] In the period immediately after AF ablation, early recurrences of atrial arrhythmias (ERAA) are common and may not necessarily imply long-term ablation failure. Therefore, guidelines recommended implementation of a “blanking period” post-ablation during which AF or OAT recurrences need not be counted against long-term ablation success.

		sample size of the available trials, discrepancies in baseline characteristics, unclear randomisation concealment and lack of assessor blinding. These factors make it difficult to draw strong conclusions regarding the effects and benefits of CA.
2.	Freedom from AF burden	AF burden was defined as the percentage of time in AF (AF episodes longer than 1 minute) according to 7 day Holter recording during follow up. At 5 years, significantly more patients in the radiofrequency ablation (RFA) group (CA) were free from any AF (n=126/146 (86%) versus 105/148 (71%), RR 0.82; 95% CI 0.73 to 0.93) p=0.001 and symptomatic AF (137/146 (94%) versus 126/148 (85%), RR 0.91; 95% CI 0.84 to 0.98) p=0.015. Burden of any AF at 5 years was significantly lower in the CA than in the AADs group. 85% and 95% percentiles for the CA group were 0%, 56% respectively versus 7%, 97% respectively for the AADs group; p=0.003. Corresponding percentiles for symptomatic AF were: 0%, 7% (CA) versus 0%, 11% (AADs), p=0.02. This study suggests that CA is more effective than AADs at reducing AF burden at 5-year follow-up. Freedom from symptomatic paroxysmal AF is of clinical value to patients in terms of reduced risk long-term complications of AF, e.g. stroke and heart failure (HF). AADs, which may be required due to AF recurrence, are often associated with side effects. Long-term AF freedom is also of economic benefit to the health system in terms of reduced requirement for repeat ablation or hospitalisation. These results should be interpreted with caution because of certain limitations to the conduct of the study. Although Holder[2] analysis was blinded, treatments could not be blinded. There was significant loss to follow up although the majority of patients lost to follow-up were included in the analyses. Only AF episodes >1 minute were taken into account, not >30 seconds as currently recommended. AF freedom was based on a single 7-day Holter recording obtained 5 years after the start of the study. No data regarding the occurrence of burden of AF from 2- to 5- years' follow-up were recorded. It cannot be excluded that comparisons between groups would have been different using more intensive monitoring or another cut-off for AF episode length.
3.	Maintenance of sinus rhythm	Sinus rhythm maintenance, which refers to continuation of normal sinus rhythm without appearance of an arrhythmia such as AF, was mainly based on the last ECG recording. Bertaglia et al (2017) reported no significant difference in the long-term maintenance of sinus rhythm between PAF patients treated with CA versus AADs. At 12 years: CA n=22/42 (51.2%) versus AADs n= 22/50 (44%); p=0.402. The goal of AF treatment is to establish sinus rhythm and/or achieve rhythm control. Many clinicians believe that achieving either of these goals may lead to a reduction in major cardiovascular events.

[2] A Holter monitor is a battery-operated portable device that measures and records your heart's activity (ECG) continuously for 24 to 48 hours or longer depending on the type of monitoring used.

		Following CA, continuation of AADs treatment is sometimes required for some patients to remain in sinus rhythm. However, avoiding AADs where possible is considered a better outcome especially as it could obviate the ubiquitous undesirable side effects of these drugs. This result should be interpreted with caution because of certain limitations to the study. Sinus rhythm maintenance was mainly based on the last ECG. Without routine ambulatory monitors and ECGs, long-term arrhythmia recurrence rates and sinus rhythm rates could be overestimated because of the inability to detect subclinical arrhythmias. Although amiodarone was the preferred AADs, the final decision was left to the physician who was not reported to be blinded to the treatment. The physician's belief about the residual risk in each patient could have biased their choice of AADs. Although over 60% of patients had a structural heart disease, most of them had well-preserved systolic function. The data cannot, therefore, be extrapolated to patients with more severe heart disease and impaired systolic function.
4.	Improvement in left ventricular ejection fraction (LVEF)	Improvement in LVEF was defined as the median absolute increase in LVEF from baseline to the 60-month follow-up. At 60 months, Marrouche et al (2018) reported a median LVEF increase in patients with heart failure and AF: CA (n=14) 7% (5 to 16) versus MT (n=11) 8% (-1 to 23); However, the difference was not statistically significant, p=0.81. The study suggests no difference between CA and MT in improving LVEF. A significant increase in LVEF could have a positive impact on clinical outcomes like hospitalisation and quality of life outcomes like walking distance. Therefore this would be beneficial to the patients. This result should be interpreted with caution because of the relatively small number of paroxysmal AF patients assessed for this outcome (14 CA versus 11 medical therapy). Although patients' characteristics were well balanced between the two treatment arms in this study, the relative characteristics were not compared for the subgroup of paroxysmal AF patients reported on in the study. Furthermore, the study was not blinded and a greater number of patients in the ablation group than in the medical therapy group crossed over to the other treatment group. Patients with a worse LVEF at baseline could therefore have been more likely to cross over to the medical therapy group.
5.	Cardiac hospitalisation/re-admission	Hospitalisation or re-hospitalisation for cardiac causes was reported in two of the RCTs included in the HTA by Skelly et al (2015). The studies did not provide further details regarding reasons for hospitalisation. Skelly et al (2015) reported that at 12 to 24 months following CA, patients had fewer cardiac hospitalisations or re-admissions than those on MT based on results from two RCTs. One RCT (n=67) reported, at 12 months, CA 9.4% versus MT 54.3% and the other (n=294), at 24 months, CA 0% versus MT 1.4%. However, results were not pooled and no tests of statistical significance were reported.

		The systematic review suggests that CA is better at hospitalisation or re-hospitalisation than MT. This can have a positive impact on complications and morbidity, for example due to infection. In general, acute hospital beds are a limited resource and increased hospital admissions are an important burden to health resources as well as for the patients. This result should be interpreted with caution because of the small size of the studies included. In addition, the studies did not provide further details regarding reasons for hospitalisation and the extent to which hospitalisation for re-ablation procedures or crossover from medical therapy to ablation was included.
6.	Reablation	Repeat ablations (i.e. reablation for arrhythmia recurrence) were reported only if they occurred after the blanking period, which was typically three months. Skelly et al (2015) reported that, based on data from three RCTs (n=184), the frequency of reablation following CA ranged from 0% to 43% within 12 months of CA. The results were not pooled. Over follow-up periods ranging from longer than 12 months to 48 months, frequency of reablation varied across four trials including 619 patients, this ranged from 12.5% to 49.2% with a pooled risk of 24.2% (95% CI 12.6 to 41.5). The HTA suggests that reablation is very common in patients who have undergone CA. These results are important because they reflect whether or not the primary or secondary treatment of AF with CA has been successful. These results should be interpreted with caution because the criteria for deciding which patients required reablation was not specified and could have varied between the different trials and clinical centres.
7.	Composite of death or hospitalisation for worsening heart failure (HF)	This refers to a composite of death from any cause or worsening of heart failure that led to an unplanned overnight hospitalisation. Patients requiring intravenous medication for HF or substantial increase and/or addition of thiazide to a loop were deemed to have worsening HF. Reasons for worsening of HR may include AF, acute coronary syndrome and hypertension. At a median follow-up of 37.6 month, Marrouche et al (2018) reported composite of death or hospitalisation for worsening HF in: CA n=17/54 (31.5%) versus MT n=34/64 (53.1%); HR 0.60 (95% CI 0.34 to 1.08), in favour of CA, p value was not reported. This study suggests no difference between CA and MT at reducing composite of death or hospitalisation for worsening HF than MT. AF and HR are common co-existing conditions, with AF increasing the risk of stroke, hospitalisation for HF and death. Successful treatment of AF can therefore substantially alter long-term outcomes in patients with HF. These results should be interpreted with caution because there was a lack of blinding with regard to randomisation and treatment. It would have been quite difficult to perform a truly blinded trial with a sham ablation procedure, but the lack of blinding could have led to bias in such decisions as whether to admit a patient for worsening

		HF. A greater number of patients in the CA group than in the MT group crossed over to the other treatment group, but the results of per-protocol and as-treated analyses were similar to those of the primary analysis. Finally, although MT (for both AF and HF) was managed systematically, we cannot exclude the possibility that a different or more aggressive approach to medical management might have influenced the trial results. Furthermore, side effects and unwillingness to take AADs were listed as recruitment criteria, and it was not clear whether this could have affected the outcome in the MT arm.
8.	Stroke occurrence	None of the trials included in this study provided criteria or definitions for stroke diagnosis although they distinguished stroke from transient ischaemic attack (TIA). Skelly et al (2015) reported no difference in stroke occurrence within 30 days based on pooled results from three RCTs (n=481) [CA 0% to 0.7% versus medical therapy 0%; no test of statistical significance reported] and beyond 30 days based on two RCTs [CA n=0/98 (0%) versus MT n=0/96 (0%), p=NS]. No transient ischaemic attacks (TIAs) were reported at 12 or 48 months; however, one RCT (n=294) reported 0.7% in both the CA (1/146) and MT (1/148) groups. No p values were reported. The systematic review suggests no difference between CA and MT in the occurrence of stroke. AF is associated with an increased risk of stroke, which affects nearly 7% of AF patients with heart failure each year. Furthermore, ischaemic stroke that occurs in the setting of AF tends to be either fatal or of moderate to high severity in most patients. Therefore avoiding this would be beneficial to patients. This result should be interpreted with caution because none of the studies included in this systematic review provided criteria or definitions for stroke diagnosis. Anticoagulation was used in all patients receiving CA but anticoagulant used was variable reported for the medical group. The follow up period was too short to give any conclusive insight into the risk of strokes in the longer term.
9.	Major bleeding	Major bleeding complications were defined as the occurrence of cardiac tamponade or haemopericardium that required intervention or caused symptoms, the need for transfusion, haematoma requiring intervention, massive haemoptysis, haemothorax, and retroperitoneal bleeding. There was no difference in the risk of 30-day major bleeding, haemorrhage, or transfusion between treatment groups. Major bleeding occurred in 2/32 (6.3%) CA patients versus 1/35 (1.9%) in the MT group. No tests of statistical significance were reported. The systematic review suggests no difference in bleeding between CA and MT. Bleeding, including requirement for hospitalisation and transfusion, is a known risk in the management of AF. The requirement for effectiveness anticoagulation in the pre, peri and post procedure stages further contribute to this risk. Major bleeding could lead to complications like subarachnoid haemorrhage, intestinal bleeding and subdural bleeding.

		These results are limited as they are based on only one study. The risk could also be heterogeneous depending on the method of ablation and experience of the centre. Further larger multicentre trials are required to establish the risk of bleeding in this population.
10.	Quality of life (QoL)	QoL was assessed using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) physical (PCS) and mental component scores (MCS) (range 0 to 100, higher scores indicating better well-being). Skelly et al (2015) reported no statistical differences between treatment groups for the SF-36 MCS at 12 months based on two RCTs (n=406); this held true whether the analysis was done using the difference in mean scores at follow-up 2.26 (95% CI -2.12 to 7.40) or using the difference in change from baseline scores 1.88 (95% CI -0.47 to 4.50). For PCS, CA was favoured over MT when the pooled estimate was calculated using differences in mean follow-up scores (overall effect 2.85; 95% CI 0.93 to 4.82), however when the analysis was based on the change from baseline the effect was no longer statistically meaningful (overall effect 2.88; 95% CI 0.18 to 5.25). No p values were reported. The authors also reported no difference in both QoL measures at 24 months, MCS scores [one RCT (n=294) CA: 51.1 ± standard deviation(SD) 9.2 versus MT 50.9 ± SD 8.0] and PCS scores [one RCT (n=294) CA: 50.0 ± SD 8.8 versus MT 47.9 ± SD 8.9] and 48 months for MCS scores [one RCT (n=198) CA: 52.9 ± SD 9 versus MT 51.9 ± SD 9] and PCS scores [one RCT (n=198) CA: 52.3 ± SD 9 versus MT 52.6 ± SD 8]. No other details were reported. The study suggests no difference in QoL between CA and MT at 24-month follow-up. Quality of life is likely to be valuable to patients. These results should be interpreted with caution because of the heterogeneity found among studies comparing CA with MT which may be due to dissimilar patient populations and extent of ablation.
11.	All-cause mortality	All-cause mortality was defined as any death past the 30-day peri-procedural time up to 12 (or 13) months or for which timing of mortality was not reported. All-cause mortality included all causes of mortality whether or not it was felt to be due to atrial fibrillation (AF) or complications of AF treatment. Skelly et al (2015) reported no difference in all-cause mortality between the intervention groups within 30 days based on pooled results from three randomised controlled trials (RCTs) (n=570) [catheter ablation (CA) 0% to 0.7% versus medical therapy (MT) 0%]; however, no test of statistical significance was reported. There was also no difference between the two study arms at up to 12 months [three RCTs (n=333) CA 0% to 1% versus MT 0% to 3.6%)] and at 24 months [two RCTs (n=408) CA 1.4% versus MT 2.8%] p value not reported for both. The systematic review suggests no difference in all-cause mortality between CA and MT. This result should be interpreted with caution because the study

		sizes were likely insufficient to effectively determine the effect of AF ablation on mortality or detect statistical differences between treatment groups.
12.	Cost effectiveness	The incremental cost-effectiveness ratio (ICER), usually measured as cost/quality-adjusted life year (QALY), and is a summary measure representing the economic value of an intervention, compared with an alternative. An ICER is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect) to provide a ratio of 'extra cost per extra unit of health effect'. In a cost effectiveness analysis from a UK NHS perspective, Reynolds et al (2014) reported an ICER of £21,957 per QALY gained, with the use of cryoballoon ablation versus AADs. The authors concluded that, beyond a threshold of £22 000 per QALY gained, ablation becomes the more cost effective intervention, with probabilities of 86% and 97.2% of being cost effective at thresholds of £30,000 and £40,000 per QALY gained, respectively. In the UK the QALY is most frequently used as the measure of health effect, enabling ICERs to be compared across disease areas. In decision-making ICERs are most useful when the new intervention is more costly but generates improved health effect. ICERs reported by economic evaluations are compared with a pre-determined threshold in order to decide whether choosing the new intervention is an efficient use of resources. There is no published official ratio that defines what is cost effective, but in the UK, a threshold of £20,000 to £30,000 is generally assumed to reflect cost effectiveness. These results should be treated with caution because, although the analysis took a UK NHS perspective, there were limitations to the methodology and other factors that could have biased the results. The efficacy assessment was based on one single RCT CA versus AADs, which showed a beneficial effect of CA over AADs; however this effect size is considerably greater than that observed in other CA versus AADs studies, mostly due to a higher recurrence rate in the AADs group. The results of this study might have exaggerated the contribution of CA to the base case analysis. The study was supported by Medtronics International, and all the authors of the study had either received honoraria from or worked for Medtronics (manufacturers of balloon dilation catheters).

b) Use of catheter ablation (CA) versus surgical ablation (SA) to treat paroxysmal atrial fibrillation (AF)

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Not reported
2.	Progression free survival	Not reported
3.	Mobility	Not reported

4.	Self-care	Not reported
5.	Usual activities	Not reported
6.	Pain	Not reported
7.	Anxiety / Depression	Not reported
8.	Replacement of more toxic treatment	Not reported
9.	Dependency on care giver / supporting independence	Not reported
10.	Safety	Major peri-procedural complications were defined as events within 30 days from the ablation procedure resulting in prolonged or repeat hospitalization, bleeding requiring transfusion or intervention, and long-term disability. Jan et al (2018) reported a trend of major peri-procedural complication rates higher in SA treated 3/24 patients (12.5%) versus 0/26 (0%) who underwent CA. No test of statistical significance was reported. The RCT suggests a higher incidence of major peri-operational complications associated with SA compared to CA however, it is uncertain whether this is significant. In general, minimally invasive surgical approaches to AF ablation carry a higher risk of peri-procedural complications compared to CA. The result of this study has shown a similar pattern. This result is limited in its generalisability because it is a small single-centre study and the statistical significance of the difference is not reported.
11.	Delivery of intervention	Not reported

No	Outcome measure	Summary from evidence review
1.	Incidence of AF/atrial tachycardia (AT)/atrial flutter (AFL) recurrence	Freedom from AF is normally defined as freedom from atrial arrhythmia lasting at least 30 seconds at follow-up. However recurrence was defined as any episode lasting 6 minutes or more. Jan et al (2018) reported a significant reduction in recurrence of AF/AT/AFL with surgical ablation (SA) compared with CA. At a mean follow-up of 30.5 months, recurrence was observed in 8/24 (33.4%) of SA versus 17/26 (65.4%) CA patients; odds ratio (OR) 3.78 (95% CI 1.17 to 12.19), p=0.048.

		The study suggests that SA is better at reducing recurrence of AF/AT/AFL compared with CA. People with AF have higher risks of developing comorbidities such as heart failure and stroke as well as higher all-cause mortality rate. The goal of AF treatment is to establish and maintain sinus rhythm and/or achieve rhythm control. Many clinicians believe that achieving either of these goals may lead to a reduction in major cardiovascular events. This result should be interpreted with caution because of limitations to the study. Firstly, the small number of patients included limits the strength of its findings. Secondly, all patients received an Implantable Loop Recorder (ILR); recurrence of AF/AT/AFL was defined as any episode lasting 6 minutes or more. This remarkably longer than the usual definition for AF recurrence. It is still not clear whether this threshold for recurrence represent significant reduction in the risk of AF complications, or what the impact of this level of reduced recurrence is on the patients' quality of life. Finally, only point-by-point method of CA was used, therefore the results may not be easily extrapolated to continuous cryoballoon technique of CA.
2.	Re-intervention	Re-intervention refers to cardioversion or re-ablation after a 3-month blanking period. In the RCT by Jan et al (2018), through the entire follow-up period (30.5±SD 6.9 months), 9/26 (34.6%) patients after CA and 4/24 (16.7%) after SA required re-intervention. No test of statistical significance was reported. It is unclear from the RCT whether there is a significant difference in the re-intervention rates between SA and CA. The requirement for re-intervention, which signifies failure of the initial intervention, exposes the patients to further risks of complications and is a significant burden on healthcare resources. This result is inconclusive because it is based on very small numbers and no statistical analysis of significance was recorded.