Executive Summary

1. Background

Atrial Fibrillation (AF) is the most common arrhythmia associated with a variety of cardiovascular conditions and increased rates of stroke, death. Its treatment is still widely debated due to the large variety of therapeutic options and there remains uncertainty about the health impact of using ablation and its place in therapy. In this study, only the ablation strategies aimed to control cardiac rhythm in patients with AF are evaluated.

2. Objectives

We aim to provide scientific and objective evidence to healthcare providers and patients to help their decision about rhythm control treatment of atrial fibrillation (AF) by detail following objectives. The specific objectives of this study were (1) to evaluate comparative clinical effectiveness and safety of catheter ablation (CA) and other treatment strategies(AADs therapy, surgical procedures, cardioversion) for controlling rhythm of patients with atrial fibrillation through systematic review, (2) to describe basic information about burden of disease and rhythm control treatment pattern for patients with AF in Korea and (3) to compare healthcare outcomes of catheter ablation and surgical procedures in patients with AF using national health insurance claims data in Korea.

3. Systematic reviews

Sixty-seven studies were included in our systematic review(CA vs AADs 13 studies, CA vs surgical strategies 3 studies, CA vs Cardioversion 2 studies, CA-any other CA 50 studies). Primary outcomes of this review were all-cause mortality, CVD mortality,

stroke/transient ischemic attack(TIA), major complications, congestive heart failure (CHF), CVD-related hospitalizations and free from AF/AT(atrial tachyarrhythmia). Secondary outcomes were quality of life(QOL), symptom frequency/severity, complications. Data synthesis basically were conducted by study design (RCT, NRS) and if there were no heterogeneity exploratory analysis were performed to explore the trend of estimates through combining RCT and cohort studies. Data were evaluated separately for each comparison.

[CA vs AADs]

A total of 11 studies (8 RCTs, 3 Cohort studies) representing 2,785 patients were included. Four RCTs reported on all-cause mortality, and RR was 0.76 (95% CI 0.18-3.19, $I^2=0\%$). According to the exploratory integrated analysis of 4 RCTs and 2 NRS, there was significant difference (RR 0.37, 95%CI 0.18-0.77). One prospective cohort study reported on cardiovascular-related mortality 3.1% (18/589) of patients in the CA group and 10.1% (59/582) in the drug therapy group died (RR 0.30, 95% C I0.18-0.50). The rates of stroke/transient ischemic attack (TIA) between both groups was insignificant (RR 1.95, 95% CI 0.34-11.04, I²=0%) in 5 RCTs. Two studies (RCT & NRS) reported on the rate of heart failure, and RR was 0.57 (95% CI 0.37-0.86, P=0.007, I²=0%). CA, in comparison with AAD therapy, significantly increased freedom from AT/AF (RR 3.06, 95% CI 2.34-3.99, P<0.00001, I^2 =55%) in 8 RCTs at one year follow-up. As the results of subgroup-analysis in accordance with the percentage of paroxysmal AF that causes heterogeneity, there was significant difference (paroxysmal >65%, RR 3.66, 95% CI 2.80-4.78; paroxysmal ≤65%, RR 2.23, 95% CI 1.66-3.01). In a RCT with four year follow up, there was a significant trend towards increased freedom from AT/AF in CA group (RR 1.29, 95% CI 1.04-1.59). Fewer major complications were reported in the CA group compared with AAD group (3 RCTs, 1 NRS; RR 0.60, 95% CI 0.26-1.35,

$P=0.21, I^2=41\%$).

Critical appraisal of this systematic review showed a trend of favor of catheter ablation in the management of AF. However, there is limited evidence to suggest that catheter ablation may be a better rhythm control treatment option compared to AAD therapy.

[CA vs Surgical procedures]

In CA versus surgical procedures, three studies (1 RCT, 2 cohort studies) representing 584 patients were included. In a retrospective cohort study, RFCA showed higher all-cause mortality than surgical ablation but there was no significant difference (RR 2.00, 95% CI 0.18-21.63). there is no study reported CVD mortality. There were no statistical differences in the rate of stroke/TIA (RR 0.72, 95% CI 0.23-2.24, I^2 =3%), the rate of heart failure (RR 4.84, 95% CI 0.24-98.88, 1 RCT). RFCA, in comparison with surgical ablations, significantly decreased freedom from AF/AT recurrence (RR 0.67, 95% CI 0.56-0.81, I^2 =44%). In the combined results of freedom from AF/AT recurrence, trend by study design was consistent both direction and significance. More complications were reported in the RFCA group compared with the surgical treatment group (RR 2.07,95% CI 1.31-3.27, I^2 =0%).

In this review to evaluate effectiveness and safety comparing CA and surgical procedures, we found that surgical ablations are promising treatment option compared with CA but need to be confirmed.

[CA vs Cardioversion]

In CA versus elective electrical cardioversion, two studies (1 RCT, 1 cohort study) representing 227 patients were included. No studies reported all-cause mortality, CVD mortality, the rate of CHF or CVD-related hospitalization. In the rate of stroke/TIA, the results of two studies showed different direction and reported that there were

no statistically significant difference (RR 2.22, 95% CI 0.21-23.15 in RCT, RR 0.20, 95% CI 0.02-1.68 in cohort study). In a RCT (Gupta et al, 2006), a reduction was reported from the cardioversion group in terms of the recurrence of AT/AF but not significant (RR 0.56, 95% CI 0.05-5.79). On the other hand, in a cohort study (Rossillo et al, 2006) a significant increase of freedom from AT/AF recurrence was reported from PVI group compared with cardioversion group (RR 2.06, 95% CI 1.56-2.72).

In CA versus elective cardioversion, we are unable to confirm the comparative clinical effectiveness and safety due to insufficient evidence.

[CA vs other CA]

Fifty studies (41 RCTs, 9 Cohort studies) with 6,081 patients were included which compared different CA methods. Overall, the studies had 'poor' methodological quality. The CA methods were various. Comparisons were performed between 16 criteria.

1) CPVA/PVI/LA+additional linear vs. CPVA/PVI/LA

Sixteen studies compared the effects of inhibiting recurrence of AT/AF in CPVA/PVI/LA plus linear ablation and CPVA/PVI/LA (12 RCTs, RR 1.10, 95% CI 0.97-1.25, P=0.14, I²=64%; 4 Cohort, RR 1.18, $I^2 = 47\%$). 95% 1.02-1.36, P=0.03, The CI rates of stroke/TIA/thrombo-embolic between events both groups was insignificant (RR 0.75, 95% CI 0.20-2.81, P=0.67, I²=0%) in 5 RCTs.

2) CPVA/PVI vs. SPVA

Six RCTs reported on the freedom from AT/AF, but there was no significant difference (RR 0.97, 95% CI 0.89-1.06, P=0.53, I^2 =62%). Four RCTs reported on the rate of stroke/TIA/thrombo-embolic events, however, as the outcomes differed we were able to combine the data for meta-analysis. In a RCT with long-term follow up, RR was 3.0(95% CI 0.32-27.87, P=0.33).

3) PVI+CFAE vs. PVI

7 RCTs compared the freedom from AT/AF in PVI plus CFAE and PVI, but the difference was no significant (RR 1.10, 95% CI 0.91-1.33, I^2 =52%).

4) CPVA/PVI vs. selective PVI

Three RCTs compared the freedom from AT/AF in CPVA/PVI and selective PVI (RR 1.04, 95% CI 0.92-1.17, P=0.54, I²=0%). Integrated analysis of the data from 3 cohort (2 prospective, 1 retrospective) showed same direction, but heterogeneity was significant (RR 1.31, 95% CI 0.92-1.86, $I^2 = 73\%$). The rates of stroke/TIA/thrombo-embolic events between both groups was insignificant (RR 1.08, 95% CI 0.11-10.19, P=0.95, I²=0%) in 2 RCTs.

5) CFAE vs. PVI

Three RCTs compared the freedom from AT/AF in CFAE and PVI. RR was 0.45 (95% CI 0.17-1.14), but there was significant heterogeneity (I^2 =85%). This was resolved by subgroup analysis according to the follow up period (f/u≤12 months, RR 0.76, 95% CI 0.59-0.98, I^2 =0%; f/u>12 months, RR 0.16, 95% CI 0.06-0.41, I^2 =NA).

6) The rest of criteria groups included only one or two studies. The results showed statistically significant differences in the freedom from AT/AF were as follows:

Intervention CA	Control CA	Included studies	Random, M-H pooled RR [95%Cl]	l ²
PVI + CFAE	CFAE	2	4.16 [2.03-8.52]	40%
Biatrial ablation	LA ablation	2	1.37 [1.05-1.79]	0%
Anatomic GP	Selective GP	2	1.98 [1.37-2.85]	0%
PVI + GP	PVI	1	1.62 [1.06-2.47]	NA
PVI + CTI + MI	PVI+CTI	1	1.33 [1.05-1.69]	NA
CPVA+segmental PV ostia	CPVA	1	0.71 [0.54-0.93]	NA

Few studies reported on all-cause mortality and the rates of stroke/TIA/thrombo-embolic events, and the data could not be combined in meta-analysis. Adverse events, such as pericardial effusion, cardiac tamponade, PV stenosis etc., occurred in fewer than 5% in most of studies.

4. Data analysis of national health insurance claims data

The analysis for current status of patients who diagnosed AF was studied by the Health Insurance Review & Assessment Service's health insurance claims data. The age-standardized patients with diagnosed AF during 2007~2011 was increased from 403.4 patients per 100,000 populations in 2007 to 435.6 patients in 2010 but thereafter, it showed decreasing tendency to 424.8 patients in 2011. By sex, men had shown higher rate of AF than women. The patients who treated with non-pharmacologically such as, CA or surgery, in AF were being likely low and the ratio of CA had shown increasing trend by year. It was similar to patients with newly diagnosed AF. With increasing age, prediction score, such as CHADS₂, CHA₂DS₂-VASc, HATCH and CCI, were increased.

The average health care utilization per patients with newly diagnosed AF within 1 year were estimated to be 2,800,000 KRW(cost) and 15.1 days(length of stay). By the year 2010 compared to 2008, the average health care costs were increase 18% for patients with lone AF and 15% for AF.

5. Conclusions

In this systematic review from sixty-seven studies including RCT and observational studies, it should not yet be concluded that catheter ablation is better than other treatments for rhythm control in patients with AF. (1) In CA versus AADs, there is insufficient

evidence to suggest that CA can be a better treatment compared with AADs therapy in AF patients. (2) In CA versus surgical procedures, through exploratory meta-analysis combining RCT and NRS we found that surgical ablations are promising treatment option compared with CA. (3) In CA versus electrical cardioversion, 2 studies(RCT 1, NRS 1) evaluated the safety and effectiveness of using catheter ablation compared with elective electrical cardioversion for the treatment of AF so were qualitatively reviewed. (4) In comparisons with different CAs, there is limited evidence to suggest which ablation technique was the best. Just, this results needed to interpret cautiously, because the evidence level of most outcomes was evaluated from 'moderate' to 'very low' quality.

More trials and further long-term studies using clinical data of patients with AF are needed to confirm these findings. Also, we need to evaluate cost-effectiveness in an aspect of recurrence demonstrated significant reduction compared CA with AADs for providing more helpful information to patients, clinicians and healthcare providers.