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par

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TITRE

Analyse nationale de la morbi-mortalité après ablation de la fibrillation atriale ou ablation du nœud atrioventriculaire

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RÉSUMÉ

INTRODUCTION : L'ablation par cathéter de la fibrillation atriale (FA) est devenue la thérapie de choix pour traiter la FA symptomatique malgré les traitements antiarythmiques. Comme alternative, l'ablation du nœud atrio-ventriculaire (NAV) est une technique efficace pour contrôler la fréquence cardiaque.

OBJECTIF : Évaluer la morbi-mortalité de l'ablation de FA et de l'ablation du NAV.

MÉTHODES : Cette étude rétrospective multicentrique française a inclus entre le 1er janvier 2010 et le 31 décembre 2019 tous les patients hospitalisés avec un diagnostic primaire ou secondaire de FA à l'aide de la base de données hospitalière administrative nationale. La morbi-mortalité a été analysée dans la cohorte globale ainsi que dans des échantillons appariés.

RÉSULTATS : Pendant le suivi (moyenne [ET] 2.0 [2.2], médiane [EI] 1.0 [0.1 - 3.3] ans), 2 438 015 patients avec FA ont été inclus (Aucune ablation 2 360 833, ablation de FA 62 490 et ablation du NAV 14 692). En comparaison avec les patients traités sans ablation, l'incidence de la mortalité globale était plus faible chez les patients traités par ablation de FA (hazard ratio ajusté (HR) 0.272, intervalle de confiance à 95% (IC95%) 0.259-0.287, p<0.0001) ou par ablation du NAV (HR ajusté 0.762, IC95% 0.734-0.791, p<0.0001). Après appariement 1/1, chez les patients traités par ablation de FA, les incidences de la mortalité globale (HR 0.662, IC95% 0.557-0.788, p<0.0001), cardiovasculaire (HR 0.617, IC95% 0.471-0.807, p<0.0001) et des hospitalisations pour insuffisance cardiaque (IC) (HR 0.732, IC95% 0.620-0.865, p<0.0001) étaient plus faibles comparées à celles des patients traités par ablation du NAV, contrairement à l'incidence des AVC ischémiques (HR 1.447, IC95% 1.122-1.865, p<0.0001).

CONCLUSION : L'ablation de FA et celle du NAV peuvent être associées à une meilleure survie qu'une stratégie non-invasive. En comparaison à l'ablation du NAV, l'ablation de FA

est associée à des taux plus bas de mortalité globale, cardiovasculaire et d'hospitalisations pour IC mais à une plus grande incidence d'AVC.

Mots clés : Fibrillation atriale, ablation par cathéter, ablation du nœud atrioventriculaire

ABSTRACT

BACKGROUND : Catheter ablation of atrial fibrillation (AF) has become a therapy of choice to treat symptomatic AF in current practice. As an alternative, atrioventricular node (AVN) ablation is an older but efficient procedure to control ventricular rate.

AIM : To assess long-term clinical outcomes of AF ablation and AVN ablation in large cohort of patients with AF and to compare these two procedures.

METHODS : This French multicentric retrospective study enrolled all patients hospitalized with a primary or secondary diagnosis of AF from 1st January 2010 to 31st December 2019, using an administrative hospital-discharge database. Clinical outcomes were analyzed in overall population and in propensity-matched samples.

RESULTS : During follow-up (mean [SD] 2.0 [2.2], median [IQR] 1.0 [0.1-3.3] years), 2,438,015 patients were analysed (No ablation 2,360,833, AF ablation 62,490 and AVN ablation 14,692). Compared to patients treated without ablation, incidence of all-cause death was lower in patients treated with AF ablation (hazard ratio (HR) 0.272, 95% confidence interval (CI) 0.259-0.287, p<0.0001) or AVN ablation (HR 0.762, 95% CI 0.734-0.791, p<0.0001). After propensity-score matching, in patients treated with AF ablation, incidence of all-cause death (HR 0.662, 95% CI 0.557-0.788, p<0.0001), cardiovascular death (HR 0.617, 95% CI 0.471-0.807, p<0.0001) and hospitalization for heart failure (HF) (HR 0.732, 95% CI 0.620-0.865, p<0.0001) were lower compared to patients treated with AVN ablation, unlike incidence of ischemic stroke (HR 1.447, 95% CI 1.122-1.865, p<0.0001).

CONCLUSION : AF ablation and AVN ablation may be associated with better survival compared to non-invasive strategy. Compared to AVN ablation, AF ablation is associated with lower risk of all-cause death, cardiovascular death and hospitalization for HF, but higher incidence of ischemic stroke.

Key words : Atrial fibrillation, catheter ablation, atrioventricular node ablation.

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Table des matières

Abbreviations

AAD: Antiarrhythmic drug

AF: Atrial fibrillation

AVN: Atrio-ventricular node

CABG: Coronary artery bypass graft

COPD: Chronic obstructive pulmonary disease

CRT: Cardiac resynchronization therapy

EF: Ejection fraction

HF: Heart failure

ICD: Implantable cardioverter-defibrillator

LA: Left atrium / Left atrial

LV: Left ventricle / Left ventricular

LVEF: Left ventricular ejection fraction

PCI: Percutaneous coronary intervention

PM: Pacemaker

PMSI: "Programme de Médicalisation des Systèmes d'Information" database

PV: Pulmonary vein

RF: Radiofrequency

Introduction

Arial fibrillation (AF) is the most common arrhythmia with a prevalence between 1 and 2% in France and around 33 million individuals worldwide[1]. AF is associated with increased mortality[2,3] and morbidities as heart failure (HF), stroke and dementia[4,5,6]. Management of AF is complex and multiples approaches have been developed. Rhythm control strategy involves medical therapy with antiarrhythmic drugs (AADs) as well as invasive management with catheter ablation. Currently, AF ablation is recommended in patients with symptomatic paroxysmal or persistent AF refractory to medical therapy (Class I) and it can be chosen as a first-line therapy in paroxysmal AF (Class IIa)[7,8]. Several studies have shown that ablative intervention is more effective than AADs to maintain sinus rhythm, reduce symptoms and improve quality of life in patients with paroxysmal AF[9,10]. However, impact of AF ablation on hard clinical outcomes is more controversial. Several studies exposed that catheter ablation of AF may reduce mortality and morbidity compared to medical therapy[11,12]. In CASTLE-AF trial, AF ablation in patients with left ventricular (LV) dysfunction was associated with reduction of all-cause death or hospitalization for HF compared to AADs[13]. Alternative to rhythm control option is rate control strategy including medical therapy with beta-blockers or calcium channel blockers and invasive management with atrio-ventricular node (AVN) ablation preceded by pacemaker (PM) or implantable cardioverter-defibrillator (ICD) implantation. In 2020 ESC guidelines, AVN ablation is recommended in second-line therapy, in patients unresponsive or intolerant to medical therapy and not eligible for invasive rhythm control strategy (Class IIa)[7]. AVN ablation is associated with less symptoms and better quality of life than medical therapy and complications are relatively rare[14,15]. In literature, few studies have analyzed long-term outcomes of AVN ablation. In absence of history of HF, Ozcan *et al* observed that long-term survival after AVN ablation was similar to that of the general population[16]. In a meta-analysis, AVN ablation with pacing therapy was associated with improvement of left ventricular ejection fraction (LVEF) compared to medical therapy[17].

Catheter ablation has become the therapy of choice to treat symptomatic paroxysmal or persistent AF in current practice when antiarrhythmic agents are not sufficiently efficient. However, high recurrence rate of AF and rare but serious complications of this procedure as cardiac tamponade, pulmonary vein (PV) stenosis, stroke, vascular injury or esophageal fistula are not negligible[18,19]. AVN ablation is a very simple, effective and durable procedure to control ventricular rate, but it does not eradicate AF and implies definitive dependence to an implanted cardiac device.

The aim of the study was to assess long-term clinical outcomes of AF ablation and AVN ablation in a large cohort of patients with AF and to compare outcomes with these two procedures.

Methods

PMSI database

This study is a French multicentric, longitudinal retrospective study based on data from national hospital-discharge database named "Programme de Médicalisation des Systèmes d'Information" (PMSI). This nationwide database regroups hospitalizations in all French healthcare centers, both public and private, since 2004 and includes around 98% of the French population. Administrative and medical information such as age, gender, date of admission and discharge, primary and related diagnosis, complications, events and procedure during hospitalization are recorded for each hospitalization. All data are standardized and encoded according to the tenth revision of the International Classification of Disease (ICD-10) for pathologies and French national nomenclature (Classification Commune des Actes Médicaux : CCAM) for medical procedures. Information provided by PMSI database are consistent and reliable[20]. An exclusive identifier is assigned to each patient and all data are provided anonymous. Ability to use the PSMI database is controlled and allowed by the French data

protection authority and approved by independent national ethic commission named "Commission Nationale de l'Informatique et des Libertés" (CNIL) warranting that human right, privacy and individual freedoms are respected in accordance with the Declaration of Helsinki of 1964.

Study design and data collection

From 1st January 2010 to 31st December 2019, all patients over 18 years old hospitalized in one of the French healthcare hospitals with a primary or secondary diagnosis of AF were included in the study. Demographics, cardiovascular risk factors and comorbidities were collected based on each hospital medical records. Charlson Comorbidity Index and Frailty Index were assessed to classify patients with multiple comorbidities. CHA_2DS_2-VASc and HAS-BLED scores were calculated to evaluate thrombotic and hemorrhagic risk. After discharge, patients were followed using all rehospitalizations through the study period. For each stay and each patient, clinical outcomes during hospitalization and all diagnosis at discharge were assessed analyzing PMSI codes. All patients were categorized in 3 distinct groups: no ablation, AF ablation and AVN ablation. Index date of each patient was respectively when first episode of AF was diagnosed if no ablation was performed, at first AF ablation or at first AVN ablation.

Clinical outcomes

During the whole follow-up, clinical outcomes as all cause death, cardiovascular death, hospitalization for heart failure and ischemic stroke were identified and analyzed. Heart failure hospitalization was defined as admission for worsening heart failure as the first diagnosis for the hospital stay. A combined endpoint associating cardiovascular death, hospitalization for heart failure and ischemic stroke was also studied. All data on outcomes

were obtained using PMSI database and ICD-10 nomenclature. End of follow-up occurred when patients died or at the end of the study period when last news for the patients were obtained. Events and death happening outside of one of the French healthcare hospitals could not be collected in PMSI database.

Statistical analyses

Continuous data are described as mean ± standard deviation (SD) and as median [interquartile range]. Categorical data are presented as frequencies and percentage. Chi-square test was used to compare qualitative variables and Student's T-test or non-parametric Kruskal-Wallis test when appropriate for quantitative variables.

Propensity score matching was performed to harmonize and reduce significant difference in patient's baseline characteristics between AF ablation group and AVN ablation group and lessen bias due to cofounding variables. Logistic regression analysis was used to calculate propensity score adjusted on all potential cofounding demographic factors and comorbidities listed in **Table 1**. Patients of AF ablation group were matched one to one with patients of AVN ablation group, applying nearest neighbor matching method of propensity score. Standardized differences were calculated between characteristics of AF ablation group and AVN ablation group and a value of 0,10 or less may be considered negligible. Incidence of outcomes in matched cohorts was assessed with Mantel-Haenszel weighing. Incidence of outcomes was analyzed by a proportional hazard regression model to calculate hazard ratio (HR) and two-sided 95% confidence intervals (CI) in unmatched and matched population. All statistical tests were 2 sided. A p value < 0,05 was considered statistically significant. Overall analyses were achieved using STATA software (Stata Corp, College Station, TX).

Results

Baseline characteristics

Between 1st January 2010 and 31st December 2019, a total of 2,438,015 hospitalized patients presented AF and were included in the study (**Figure 1**). 2,360,833 patients (96.8%) had no AF or AVN ablation, 62,490 patients (2.6%) had at least one AF ablation without AVN ablation and 14,692 patients (0.6%) had AVN ablation.

Baseline characteristics of overall cohort are displayed in **Table 1**. In overall population, mean age was 77.2 ± 12.1 years with a slight majority of men (52.8%). In comparison with no ablation group, patients treated with AF ablation were younger, mostly men and Charlson comorbidity index as well as frailty index were significantly lower. Medical history of HF was less often present, but prevalence of dilated cardiomyopathy was higher in patients treated with AF ablation than without ablation. History of ischemic stroke was less frequent and CHA_2DS_2-VASc score was significantly lower in the AF ablation group than in the no ablation group.

In comparison with no ablation group, patients treated with AVN ablation were a little bit younger and had same proportion of men. Charlson comorbidity index was higher in patients treated by AVN ablation but frailty index was lower. History of HF, dilated cardiomyopathy and mitral regurgitation were significantly higher in the AVN ablation group than no ablation group. Prevalence of ischemic stroke was lower but CHA_2DS_2-VASc score was higher in patients treated by AVN ablation than without ablation.

Ablation versus no ablation in overall cohort

Clinical outcomes of overall cohort are presented in **Table 2**. Mean duration of follow-up was 2.0±2.2 years with median of 1.0 [0.1-3.3] year. Compared with patients treated without ablation, incidence of all-cause death was significantly lower in patients treated by AF

ablation (HR 0.272, 95%CI 0.259-0.287, p<0.0001), as same as incidences of cardiovascular death (HR 0.343, 95%CI 0.315-0.374, p<0.0001), rehospitalization for HF (HR 0.659, 95%CI 0.633-0.687), p<0.0001), ischemic stroke (HR 0.907, 95%CI 0.859-0.958, p<0.0001) and combined endpoint (HR 0.603, 95%CI 0.582-0.625, p<0.0001).

Compared with patients treated without ablation, incidence of all-cause death in patients treated by AVN ablation was significantly lower (HR 0.762, 95%CI 0.734-0.791, p<0.0001), as well as incidences of cardiovascular death (HR 0.833, 95%CI 0.788-0.881, p<0.0001) and ischemic stroke (HR 0.813, 95%CI 0.756-0.875, p<0.0001). In patients treated by AVN ablation, incidence of rehospitalization for HF (HR 1.145, 95%CI 1.095-1.197, p<0.0001) and combined endpoint (HR 1.050, 95%CI 1.007-1.094, p=0.02) were significantly higher compared to those in patients treated without ablation.

AF ablation versus AVN ablation in matched cohort

Baseline characteristics of matched AF patients with AF ablation or AVN ablation are displayed in **Table 3**. A total of 5,890 patients were matched one to one in AF ablation and AVN ablation groups. Mean age was 67.2±11.1 years with a majority of men (60.6%). Duration of follow-up was 1.9±2.1 years with median of 1.0 [0.1-3.3] year. Standardized percentage of bias across baseline characteristics in unmatched and matched cohorts are shown in **Supplemental figure 1**.

Clinical outcomes in the matched cohort of patients with AF ablation and AVN ablation are presented in **Table 4**. Incidence rate of all-cause death was 3.98 (3.47-4.58) %/year in AF ablation group and 6.01 (5.42-6.67) %/year in AVN ablation group. In patients treated by AF ablation, risks of all-cause death (HR 0.662, 95%CI 0.557-0.788), p<0.0001) and cardiovascular death (HR 0.617, 95%CI 0.471-0.807, p<0.0001) were lower than in patients treated by AVN ablation (**Figure 2**). In patients treated by AF ablation, incidences of

rehospitalization for HF was lower (HR 0.732, 95%CI 0.620-0.865, p<0.0001) and occurrence of ischemic stroke was higher (HR 1.447, 95%CI 1.122-1.865, p=0.004) than in patients treated by AVN ablation (**Figure 3**). Incidence of the combined endpoint was lower (HR 0.829, 95%CI 0.714-0.962, p=0.01) in patients treated by AF ablation than in those treated with AVN ablation (**Figure 4**).

After second AF ablation: Third procedure versus AVN ablation

Baseline characteristics of these patients are displayed in **Table 5**. A total of 2,215 patients were analyzed with 1,875 patients in third procedure of AF ablation group and 340 patients in two procedures of AF ablation followed by AVN ablation group. Mean age was 62.5±10.4 years with 71.7% of men. Patients treated by a third procedure of AF ablation were younger and had lower Charlson comorbidity index, frailty index and CHA_2DS_2-VASc score. History of HF, dilated cardiomyopathy, coronary artery disease and mitral regurgitation were less frequent in patients treated by a third procedure of AF ablation than in patients treated by two procedures of AF ablation followed by AVN ablation. Previous PM or ICD implantation was 2 times more frequent in patient treated by AVN ablation as a third procedure. No significant difference was found in prevalence of ischemic stroke between the two groups.

Clinical outcomes of this cohort are shown in **Table 6.** Mean duration of follow-up was 3.9±2.0 years with median of 3.7 [0.1-3.3] years. In patients treated by a third procedure of AF ablation, rehospitalization for HF (HR 0.529, 95%CI 0.395-0.709, p<0.0001) and combined endpoint (HR 0.557, 95%CI 0.422-0.736, p<0.0001) were lower than in patients treated by two procedures of AF ablation followed by AVN ablation. No significant difference was found in risks of all-cause death (p=0.11), cardiovascular death (p=0.18) and incidence of ischemic stroke (p=0.73) between the two groups.

Discussion

In the present study, we found that AF patients treated by either AF ablation or AVN ablation might have a better survival than patients without ablation. Incidence of the combined endpoint and rehospitalization for HF were higher in patients treated by AVN ablation rather than no ablation, but history of HF and underlying cardiomyopathy were between 2 and 3 times more frequent in AVN ablation group. Our major finding is that AF ablation was associated with significantly lower risks of all-cause death (34% lower), cardiovascular death (38% lower), rehospitalization for HF (27% lower) and of the combined endpoint (17% lower) compared to AVN ablation. However, significant higher risk of ischemic stroke was found in patients treated by AF ablation compared to AVN ablation. In patients who needed a new intervention after two procedure of catheter ablation, we found no significant difference in survival between a third procedure of AF ablation and a procedure of AVN ablation. Combined endpoint and rehospitalization for HF were less frequent in patients treated by a third procedure of AF ablation, and this may be related to higher prevalence of history of HF and underlying cardiomyopathy in patients treated by two procedures of AF ablation followed by AVN ablation.

Outcomes in AF ablation

Catheter ablation of AF is known to be associated with an improvement of symptoms and quality of life compared to AADs, but impact on survival remains uncertain[9,10]. Recently, the CABANA trial randomized in one to one 2,204 patients to assess incidence of death, stroke, bleeding and cardiac arrest in AF ablation versus medical therapy[21]. No significant difference was found in primary combined end point and all-cause death, in intention-to-treat analysis. However, the study suffered from many crossovers and significant results in favor of catheter ablation were obtained in per-protocol analysis. In front of these non-straightforward findings,

some studies intended to assess the generalizability of these results in clinical practice. Using the same inclusion and exclusion criteria than CABANA trial, retrospective studies obtained similar results than the per-protocol analysis with significantly lower rate of primary endpoint and all-cause death in patients treated with AF ablation[22,23]. Noseworthy *et al*, by means of a large US database, exposed that 74% of patients with AF would have been eligible for CABANA trial but almost 50% of patients who undergo catheter ablation would not[23]. Inclusion criteria of CABANA trial involved at least one risk factor of stroke when patients were less than 65 years old, but in real life many young patients who undergo AF ablation do not meet this requirement. CABANA conclusions are relevant, but more evidences are required to warrant significant improvement in survival after AF ablation.

Among patients with HF, AF is frequently co-existing and is associated with worse prognosis[24,25]. From this statement, CASTLE-AF trial randomized 398 patients to evaluate impact of AF ablation on mortality and morbidity in patients with symptomatic AF and HF with reduce ejection fraction (EF)[13]. Significant reduction of 38% of primary endpoint (all-cause death or acute HF hospitalization) has been obtained in patients treated by catheter ablation of AF compared to the medical therapy. However, some studies have criticized findings of CASTLE-AF trial especially the highly selected nature of patients (Biotronik ICD required, HF with preserved EF not included) and high rate of loss to follow-up. As well as CABANA trial, Noseworthy *et al* estimated the generalizability of CASTLE-AF in routine practice using a large US database[26]. They exposed that only 7.8% of patients with AF and HF in real life would be eligible to CASTLE-AF trial. Still, significantly lower all-cause mortality and HF hospitalizations were reported in the overall cohort and trial-eligible cohort but to a lesser extent (18 to 19% reduction of primary endpoint). In front of these data, new 2020 ESC guidelines recommended catheter ablation as first-line therapy in AF patients with LV dysfunction due to tachycardia-induced cardiomyopathy (Class I) or with HF and reduced LVEF (Class IIa)[7].

Outcomes in AVN ablation

AVN ablation preceded by PM or ICD implantation is often considered as a former and palliative therapy and is actually recommended in second intention after medical therapy for rate control in AF. However, many studies have shown significant functional benefits in patients treated by AVN ablation compared to medical therapy[14,15]. In the literature, data on long-term survival after AVN ablation is lacking and heterogeneous. In a meta-analysis, Chatterjee *et al* observed no difference in term of mortality between AVN ablation and medical therapy in general population with AF[27]. More recently, Garcia *et al* exposed in a retrospective study that AVN ablation was associated with a better survival compared to medical therapy in patient with multiples comorbidities[28]. Findings of this study are concordant with those obtained in the present analysis. In the overall cohort, we found a significantly lower rate of all cause death and cardiovascular death in patients treated by AVN ablation compared to the no ablation group. Despite the lack of randomization to compare these two groups and slightly younger patients in AVN ablation group, Charlson comorbidity index was higher and HF or underlying cardiomyopathy were more frequent in patients treated by AVN ablation than without ablation, who makes these results clinically relevant.

Among patients with native narrow QRS who undergo AVN ablation preceded by PM, permanent right ventricular pacing is associated with LV dyssynchony who can lead to LV remodeling, decline LVEF and HF symptoms[29,30]. These findings could explain the difficulty to find significant improvement in clinical outcomes with this procedure. In this context, APAF-CRT trial randomized 102 patients with symptomatic permanent AF, narrow QRS and history of HF to assess outcomes of AVN ablation associated with cardiac resynchronization therapy (CRT) compared to medical therapy[31]. The primary composite endpoint of death due to HF, hospitalization for HF and worsening HF was significantly lower in patients treated by AVN ablation + CRT compared to medical therapy (HR 0.38, 95%CI 0.18–0.81), especially among patients with initial LVEF < 35% (HR 0.18, 95%CI 0.05–0.66).

AF ablation versus AVN ablation

Clinical reports comparing AF ablation and AVN ablation are very limited. In 2005, Hsieh *et al* showed in a prospective study that in elderly AF patients, AVN ablation was associated with higher incidence of HF compared to AF ablation[32]. No significant difference was found in term of survival or incidence of ischemic stroke. In 2008, the PABA-CHF trial analyzed functional outcomes of AVN ablation + CRT versus AF ablation in patients with symptomatic AF and HF with reduced EF[33]. It reported significant improvements of symptoms, quality of life and LVEF in patient treated by AF ablation rather than AVN ablation + CRT, although the lack of improvement with CRT during follow-up was an unexpected and relatively surprising finding.

Results of our study are globally consistent with these findings. In addition to the lower incidence of heart failure hospitalization, we found that AF ablation may be independently associated with a better survival compared to AVN ablation. Further studies are warranted to confirm these data. We reported higher incidence of ischemic stroke in patients treated by AF ablation. This could be explained by peri-procedural risk of catheter ablation or an inappropriate discontinuation of anticoagulation therapy in patient with pauci-symptomatic paroxysmal AF since these findings were observed on a longer-term follow-up than the peri-procedural period.

AF ablation and recurrences

After catheter ablation, early recurrence of AF defined by recurrence during the first 3 months, occur in more than 50% of patients[34]. Impact of early recurrence of AF on long-term success of ablation procedure is uncertain. In the acute phase, myocardial inflammation due to ablation and delayed effect of radiofrequency (RF) may contribute to premature recurrence of AF[35,36]. Almost one third of patients with early recurrence have no further episode of AF

during long term follow-up[37]. Currently, a period of blanking lasting 1 to 3 months after AF ablation is recommended for evaluating clinical results of the procedure, during which new intervention should be eluded. Late recurrence of AF described as recurrence during the first year excluding the blanking period, happen in 25% of patients[18]. After a third AF ablation, late recurrence rate is up to 40%[38]. Unlike early recurrence, late recurrence of AF is strongly associated with PV reconnection[39].

A meta-analysis investigating long term success of catheter ablation showed that recurrence of AF after 5 years follow-up was around 47% after single ablation procedure and 21% after multiples procedure[40]. Obesity, left atrial (LA) volume and non-paroxysmal AF are strong predictors of long-term AF recurrence[41,42,43]. Recurrence of AF after one year is associated with PV reconnection but also with development of non-PV triggers[44]. Takigawa *et al* exposed that in patients who underwent second procedure of AF ablation, non-PV AF foci were present in nearly half of patients and were associated with higher rate of AF recurrence on follow-up[45]. Successful ablation of these non-PV triggers may decrease AF recurrence rate but the overall risk remain higher than in patients with only PV triggers[45]. Non-PV AF foci are usually localized in LA posterior wall, mitral peri-annular area or LA appendage[46]. Isolation of these regions implies extensive ablation lines causing micro- and macro-reentrant circuit by scarring the LA who can lead to provoked arrhythmias as LA flutter[47]. Incidence of LA flutter after catheter ablation is estimated around 10%[47]. LA flutter is most of the time highly symptomatic, resistant to AADs and more challenging to ablate than right atrial flutter[48,49]. We were not able to evaluate these mechanistic aspects in our nationwide analysis. In our study, there was no difference in term of survival between catheter ablation and AVN ablation in patients who needed a new intervention after second AF ablation. In the recent literature, Szegedi *et al* found that repeated procedure of AF ablation was a strong and independent predictor of complications as pericardial tamponade, PV stenosis or thromboembolic cerebrovascular events[50]. These findings associated with the high rate of AF

recurrence after successive ablations should be integrated to determine the best therapeutic option when AF reappears after multiples ablations.

Limits of the study

This study is subject to limitations inherent of the retrospective and non-randomized design. First, several hidden cofounders could remain but with meticulous adjustment on the several main variables, it is unlikely that residual cofounding factors had significant impact on the results reported for outcomes. Second, all data collected were based on PMSI administrative database and misclassification could exist. However, reliability of this process has been proved and encoded data are regularly inspected by health care insurance due to their bond with reimbursement[20]. Third, data on medical therapy were lacking. Fourth, out-of-hospital mortality could not be recorded with PMSI database and therefore was not included in analysis.

Conclusion

In AF patients, AF ablation and AVN ablation may be associated with better survival compared to non-invasive strategy. Compared to AVN ablation, AF ablation is associated with lower risk of all cause death, cardiovascular death and hospitalization for HF, but higher incidence of ischemic stroke. After two procedures of AF ablation, there was no significant difference in terms of survival between a third procedure of AF ablation and a procedure of AVN ablation.

TABLES AND FIGURES

Table 1. Baseline characteristics of AF patients.

	No ablation (n=2360833)	AF ablation (n=62490)	AV node ablation (n=14692)	Total (n=2438015)
Age, years	77.7±11.8	60.5±10.6	74.1±10.4	77.2±12.1
Gender (male)	1235836 (52.3)	44341 (71.0)	7677 (52.3)	1287854 (52.8)
CHA2DS2-VASc score	3.5±1.6	1.7±1.4	4.1±1.5	3.4±1.6
HASBLED score	2.6±0.8	1.9±0.9	2.8±0.9	2.6±0.8
Charlson comorbidity index	3.5±2.8	1.3±1.9	3.9±2.8	3.5±2.8
Frailty index	9.5±9.2	2.2±3.8	8.2±8.2	9.3±9.2
Hypertension	1431555 (60.6)	26738 (42.8)	10642 (72.4)	1468935 (60.3)
Diabetes mellitus	501535 (21.2)	6647 (10.6)	3848 (26.2)	512030 (21.0)
Heart failure	715576 (30.3)	11942 (19.1)	11172 (76.0)	738690 (30.3)
History of pulmonary edema	59481 (2.5)	952 (1.5)	1423 (9.7)	61856 (2.5)
Aortic stenosis	148642 (6.3)	907 (1.5)	1260 (8.6)	150809 (6.2)
Aortic regurgitation	58610 (2.5)	1331 (2.1)	945 (6.4)	60886 (2.5)
Mitral regurgitation	138813 (5.9)	4898 (7.8)	3580 (24.4)	147291 (6.0)
Previous endocarditis	10657 (0.5)	85 (0.1)	97 (0.7)	10839 (0.4)
Dilated cardiomyopathy	161203 (6.8)	7785 (12.5)	6610 (45.0)	175598 (7.2)
Coronary artery disease	584264 (24.7)	11420 (18.3)	6497 (44.2)	602181 (24.7)
Previous myocardial infarction	117429 (5.0)	1756 (2.8)	872 (5.9)	120057 (4.9)
Previous PCI	94756 (4.0)	3439 (5.5)	1641 (11.2)	99836 (4.1)
Previous CABG	11569 (0.5)	448 (0.7)	218 (1.5)	12235 (0.5)
Vascular disease	422196 (17.9)	5980 (9.6)	3713 (25.3)	431889 (17.7)
Previous pacemaker or Defibrillator	155099 (6.6)	3367 (5.4)	12563 (85.5)	171029 (7.0)
Ischemic stroke	171757 (7.3)	1892 (3.0)	714 (4.9)	174363 (7.2)
Intracranial bleeding	52178 (2.2)	359 (0.6)	196 (1.3)	52733 (2.2)
Smoker	157586 (6.7)	6508 (10.4)	1490 (10.1)	165584 (6.8)
Dyslipidemia	511851 (21.7)	13855 (22.2)	5500 (37.4)	531206 (21.8)
Obesity	337631 (14.3)	11344 (18.2)	3504 (23.8)	352479 (14.5)
Denutrition	214522 (9.1)	730 (1.2)	1315 (9.0)	216567 (8.9)
Alcohol related diagnoses	120124 (5.1)	2276 (3.6)	808 (5.5)	123208 (5.1)
Abnormal renal function	165576 (7.0)	1248 (2.0)	2361 (16.1)	169185 (6.9)
Lung disease	398344 (16.9)	5018 (8.0)	3145 (21.4)	406507 (16.7)
Sleep apnea syndrome	122619 (5.2)	6477 (10.4)	1692 (11.5)	130788 (5.4)
COPD	226250 (9.6)	2704 (4.3)	2052 (14.0)	231006 (9.5)
Liver disease	87600 (3.7)	1206 (1.9)	926 (6.3)	89732 (3.7)
Gastroesophageal reflux	53021 (2.2)	2429 (3.9)	462 (3.1)	55912 (2.3)
Thyroid diseases	228026 (9.7)	6449 (10.3)	3386 (23.0)	237861 (9.8)
Inflammatory disease	143311 (6.1)	2278 (3.6)	1323 (9.0)	146912 (6.0)
Anaemia	352996 (15.0)	2472 (4.0)	2347 (16.0)	357815 (14.7)
Previous cancer	395054 (16.7)	4181 (6.7)	1826 (12.4)	401061 (16.5)
Cognitive impairment	236677 (10.0)	193 (0.3)	496 (3.4)	237366 (9.7)

Values are n (%) or mean±SD. CABG=coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; PCI=percutaneous coronary intervention; SD=standard deviation.

Table 2. Clinical outcomes during the whole follow-up (mean [SD] 2.0 [2.2], median [IQR] 1.0 [0.1-3.3] years) in the unmatched cohort of patients with AF treated with no ablation, AF ablation or AV node ablation.

	No ablation (n=2360833)	**AF ablation (n=62490)**	**AV node ablation (n=14692)**				
	Incidence rate, %/year (95%CI)	**Incidence rate, %/year (95%CI)**	**Incidence rate, %/year (95%CI)**	**Adjusted HR (95% CI) for AF ablation**	p	**Adjusted HR (95% CI) for AV node ablation**	p
All-cause death	13.23 (13.20-13.26)	1.35 (1.29-1.43)	10.80 (10.41-11.21)	0.272 (0.259-0.287)	<0.0001	0.762 (0.734-0.791)	<0.0001
Cardiovascular death	4.00 (3.98-4.02)	0.48 (0.44-0.52)	4.81 (4.55-5.08)	0.343 (0.315-0.374)	<0.0001	0.833 (0.788-0.881)	<0.0001
Rehospitalization for HF	9.36 (9.33-9.39)	2.17 (2.08-2.26)	14.64 (14.02-15.30)	0.659 (0.633-0.687)	<0.0001	1.145 (1.095-1.197)	<0.0001
Ischemic stroke	2.43 (2.41-2.44)	0.74 (0.70-0.78)	1.44 (1.34-1.54)	0.907 (0.859-0.958)	<0.0001	0.813 (0.756-0.875)	<0.0001
Combined endpoint	14.01 (13.97-14.05)	2.98 (2.87-3.09)	17.28 (16.59-18.00)	0.603 (0.582-0.625)	<0.0001	1.050 (1.007-1.094)	0.02

Values are n (incidence rate, %/year). Combined endpoint = cardiovascular death, hospitalization for heart failure or ischemic stroke; CI=confidence interval; HF=heart failure; HR=hazard ratio; PY = patient-year

Table 3. Baseline characteristics of matched AF patients with AF ablation or AV node ablation.

	AF ablation (n=2945)	AV node ablation (n=2945)	Standardized difference *	Total (n=5890)
Age, years	66.8±9.5	67.4±12.5	-5.9	67.2±11.1
Gender (male)	1794 (60.9)	1772 (60.2)	1.6	3566 (60.6)
CHA2DS2-VASc score	3.0±1.6	3.0±1.5	-3.4	3.0±1.5
HASBLED score	2.5±0.9	2.4±0.9	4.2	2.4±0.9
Charlson comorbidity index	2.8±2.6	2.7±2.5	3.7	2.7±2.5
Frailty index	4.8±5.9	4.6±6.1	2.6	4.7±6.0
Hypertension	1806 (61.3)	1808 (61.4)	-0.1	3614 (61.4)
Diabetes mellitus	590 (20.0)	593 (20.1)	-0.3	1183 (20.1)
Heart failure	1547 (52.5)	1452 (49.3)	8.0	2999 (50.9)
History of pulmonary edema	150 (5.1)	165 (5.6)	-2.2	315 (5.3)
Aortic stenosis	131 (4.4)	115 (3.9)	2.5	246 (4.2)
Aortic regurgitation	131 (4.4)	119 (4.0)	2.0	250 (4.2)
Mitral regurgitation	472 (16.0)	494 (16.8)	-2.1	966 (16.4)
Previous endocarditis	11 (0.4)	10 (0.3)	0.5	21 (0.4)
Dilated cardiomyopathy	917 (31.1)	911 (30.9)	0.5	1828 (31.0)
Coronary artery disease	999 (33.9)	974 (33.1)	1.9	1973 (33.5)
Previous myocardial infarction	125 (4.2)	134 (4.6)	-1.5	259 (4.4)
Previous PCI	276 (9.4)	270 (9.2)	0.7	546 (9.3)
Previous CABG	41 (1.4)	50 (1.7)	-2.9	91 (1.5)
Vascular disease	524 (17.8)	521 (17.7)	0.3	1045 (17.7)
Ischemic stroke	128 (4.3)	122 (4.1)	1.0	250 (4.2)
Intracranial bleeding	38 (1.3)	26 (0.9)	4.1	64 (1.1)
Smoker	368 (12.5)	373 (12.7)	-0.6	741 (12.6)
Dyslipidemia	964 (32.7)	973 (33.0)	-0.7	1937 (32.9)
Obesity	680 (23.1)	723 (24.6)	-3.6	1403 (23.8)
Denutrition	90 (3.1)	127 (4.3)	-5.7	217 (3.7)
Alcohol related diagnoses	160 (5.4)	185 (6.3)	-4.1	345 (5.9)
Abnormal renal function	200 (6.8)	172 (5.8)	3.4	372 (6.3)
Lung disease	458 (15.6)	429 (14.6)	2.8	887 (15.1)
Sleep apnea syndrome	405 (13.8)	330 (11.2)	8.1	735 (12.5)
COPD	271 (9.2)	293 (9.9)	-2.6	564 (9.6)
Liver disease	113 (3.8)	129 (4.4)	-2.7	242 (4.1)
Gastroesophageal reflux	133 (4.5)	80 (2.7)	9.8	213 (3.6)
Thyroid diseases	526 (17.9)	521 (17.7)	0.5	1047 (17.8)
Inflammatory disease	179 (6.1)	152 (5.2)	3.7	331 (5.6)
Anaemia	268 (9.1)	258 (8.8)	1.1	526 (8.9)
Previous cancer	334 (11.3)	311 (10.6)	2.6	645 (11.0)
Cognitive impairment	25 (0.8)	36 (1.2)	-2.7	61 (1.0)

***** Standardized difference for AF vs AV node ablation

Table 4. Clinical outcomes during the whole follow-up (mean [SD] 1.9 [2.1], median [IQR] 1.0 [0.1-3.1] years) in the matched cohort of patients with AF treated with AF ablation or AV node ablation.

	AF ablation (n=2945)			**AV node ablation (n=2945)**				
	Person-time, PY	**Failures**	**Incidence rate, %/year (95%CI)**	**Person-time, PY**	**Failures**	**Incidence rate, %/year (95%CI)**	**HR (95% CI) for AF ablation vs AV node ablation**	p
All-cause death	5044.7	201	3.98 (3.47-4.58)	5904.5	355	6.01 (5.42-6.67)	0.662 (0.557-0.788)	<0.0001
Cardiovascular death	5044.7	82	1.63 (1.31-2.02)	5904.5	153	2.59 (2.21-3.04)	0.617 (0.471-0.807)	<0.0001
Rehospitalization for HF	3963.4	242	6.11 (5.38-6.93)	4117.1	331	8.04 (7.22-8.95)	0.732 (0.620-0.865)	<0.0001
Ischemic stroke	9886.3	140	1.42 (1.20-1.67)	10572.8	105	0.99 (0.82-1.20)	1.447 (1.122-1.865)	0.004
Combined endpoint	3829.7	316	8.25 (7.39-9.21)	4051.5	390	9.63 (8.72-10.63)	0.829 (0.714-0.962)	0.01

Values are n (incidence rate, %/year). Combined endpoint = cardiovascular death, hospitalization for heart failure or ischemic stroke; CI=confidence interval; HF=heart failure; HR=hazard ratio; PY = patient-year

Table 5. Baseline characteristics in the unmatched cohort of patients with AF treated with 3 procedures of AF ablation or with 2 procedures of AF ablation followed by AV node ablation.

	3 procedures of AF ablation (n=1875)	2 procedures of AF ablation followed by AV node ablation (n=340)	p	Total (n=2215)
Age, years	61.5±10.3	68.0±9.2	<0.0001	62.5±10.4
Gender (male)	1410 (75.2)	176 (51.8)	<0.0001	1586 (71.7)
CHA2DS2-VASc score	1.6±1.4	2.8±1.4	<0.0001	1.8±1.5
HASBLED score	1.9±0.8	2.4±0.8	<0.0001	2.0±0.8
Charlson comorbidity index	1.5±1.9	2.6±2.3	<0.0001	1.7±2.0
Frailty index	2.5±3.6	4.7±5.8	<0.0001	2.8±4.1
Hypertension	773 (41.2)	202 (59.4)	<0.0001	975 (44.1)
Diabetes mellitus	169 (9.0)	53 (15.6)	0.0002	222 (10.0)
Heart failure	335 (17.9)	137 (40.3)	<0.0001	472 (21.3)
History of pulmonary edema	21 (1.1)	10 (2.9)	0.01	31 (1.4)
Aortic stenosis	22 (1.2)	9 (2.6)	0.03	31 (1.4)
Aortic regurgitation	27 (1.4)	9 (2.6)	0.11	36 (1.6)
Mitral regurgitation	167 (8.9)	45 (13.2)	0.01	212 (9.6)
Previous endocarditis	0 (0.0)	0 (0.0)	-	0 (0.0)
Dilated cardiomyopathy	260 (13.9)	98 (28.8)	<0.0001	358 (16.2)
Coronary artery disease	287 (15.3)	91 (26.8)	<0.0001	378 (17.1)
Previous myocardial infarction	34 (1.8)	16 (4.7)	0.001	50 (2.3)
Previous PCI	73 (3.9)	16 (4.7)	0.48	89 (4.0)
Previous CABG	5 (0.3)	3 (0.9)	0.08	8 (0.4)
Vascular disease	124 (6.6)	47 (13.8)	<0.0001	171 (7.7)
Previous pacemaker or Defibrillator	75 (4.0)	36 (10.6)	<0.0001	111 (5.0)
Ischemic stroke	53 (2.8)	10 (2.9)	0.91	63 (2.8)
Intracranial bleeding	4 (0.2)	2 (0.6)	0.22	6 (0.3)
Smoker	190 (10.1)	29 (8.5)	0.36	219 (9.9)
Dyslipidemia	373 (19.9)	90 (26.5)	0.01	463 (20.9)
Obesity	348 (18.6)	81 (23.8)	0.02	429 (19.4)
Denutrition	14 (0.7)	4 (1.2)	0.42	18 (0.8)
Alcohol related diagnoses	53 (2.8)	14 (4.1)	0.2	67 (3.0)
Abnormal renal function	17 (0.9)	14 (4.1)	<0.0001	31 (1.4)
Lung disease	128 (6.8)	33 (9.7)	0.06	161 (7.3)
Sleep apnea syndrome	158 (8.4)	32 (9.4)	0.55	190 (8.6)
COPD	71 (3.8)	18 (5.3)	0.19	89 (4.0)
Liver disease	28 (1.5)	6 (1.8)	0.71	34 (1.5)
Gastroesophageal reflux	60 (3.2)	14 (4.1)	0.39	74 (3.3)
Thyroid diseases	207 (11.0)	69 (20.3)	<0.0001	276 (12.5)
Inflammatory disease	52 (2.8)	14 (4.1)	0.18	66 (3.0)
Anaemia	45 (2.4)	19 (5.6)	0.001	64 (2.9)
Previous cancer	86 (4.6)	16 (4.7)	0.92	102 (4.6)
Cognitive impairment	3 (0.2)	0 (0.0)	0.46	3 (0.1)

Table 6. Clinical outcomes during the whole follow-up (mean [SD] 3.9 [2.0], median [IQR] 3.7[2.3-5.5] years) in the unmatched cohort of patients with AF treated with 3 procedures of AF ablation or with 2 procedures of AF ablation followed by AV node ablation.

	3 procedures of AF ablation (n=1875)			**2 procedures of AF ablation followed by AV node ablation (n=340)**				
	Person-time, PY	**Failures**	**Incidence rate, %/year (95%CI)**	**Person-time, PY**	**Failures**	**Incidence rate, %/year (95%CI)**	**Adjusted HR (95% CI) for AF ablation vs AV node ablation**	p
All-cause death	6954.5	24	0.35 (0.23-0.51)	1723.4	25	1.45 (0.98-2.15)	0.558 (0.271-1.148)	0.11
Cardiovascular death	6954.5	9	0.13 (0.07-0.25)	1723.4	12	0.70 (0.40-1.23)	0.459 (0.149-1.414)	0.18
Rehospitalization for HF	6388.4	144	2.25 (1.91-2.65)	1313.9	112	8.52 (7.08-10.26)	0.529 (0.395-0.709)	<0.0001
Ischemic stroke	8645.3	52	0.60 (0.46-0.79)	2231.9	21	0.94 (0.61-1.44)	0.897 (0.481-1.675)	0.73
Combined endpoint	6305.3	174	2.76 (2.38-3.20)	1293.1	119	9.20 (7.69-11.01)	0.557 (0.422-0.736)	<0.0001

Values are n (incidence rate, %/year). Combined endpoint = cardiovascular death, hospitalization for heart failure or ischemic stroke; CI=confidence interval; HF=heart failure; HR=hazard ratio; PY = patient-year

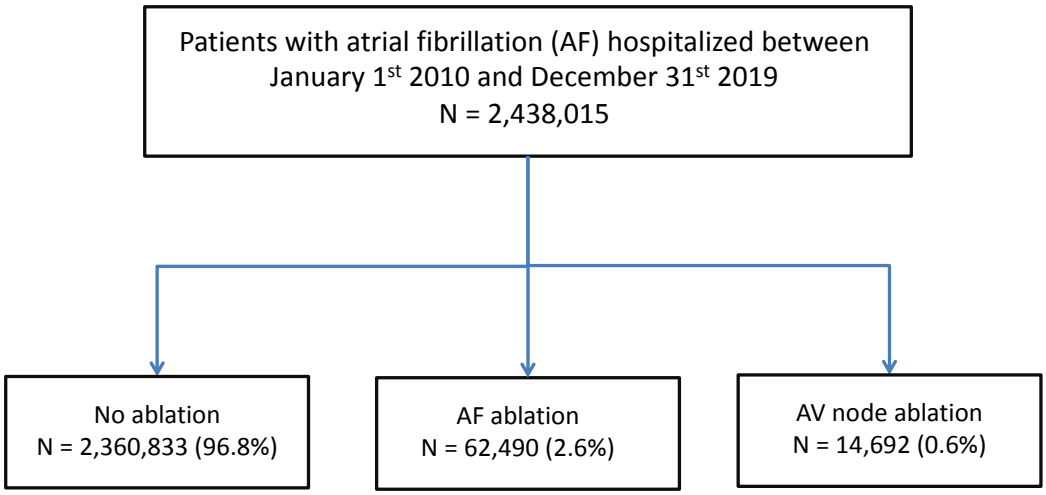
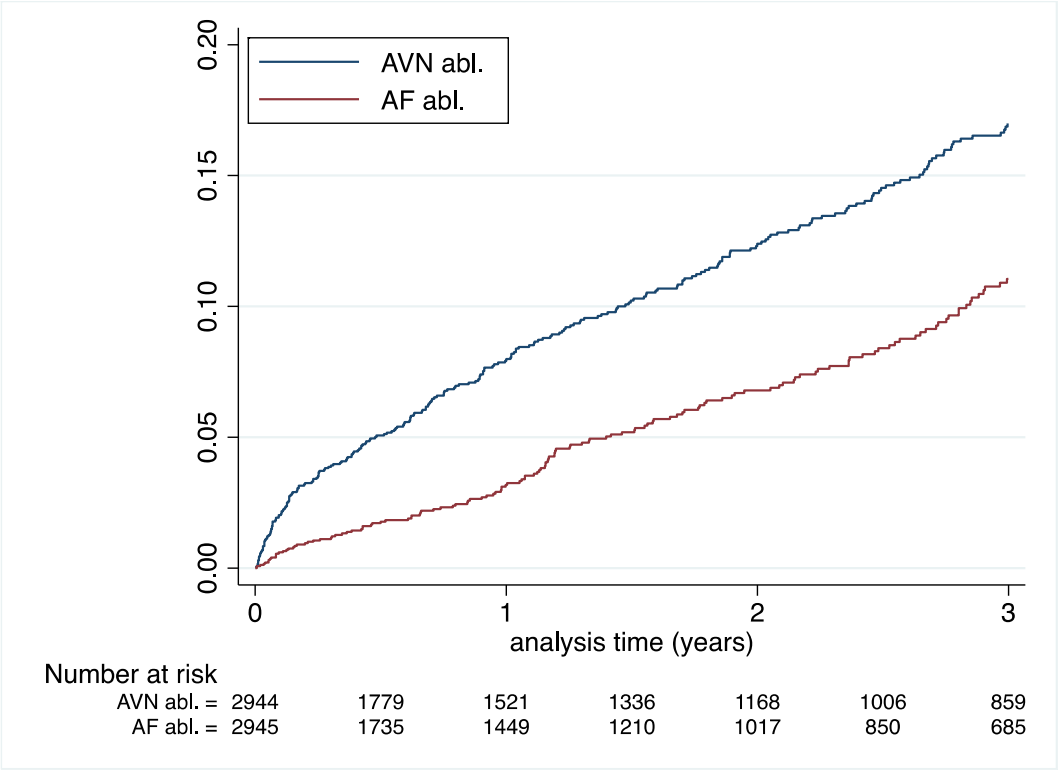


Figure 1. Flow chart of the study patients



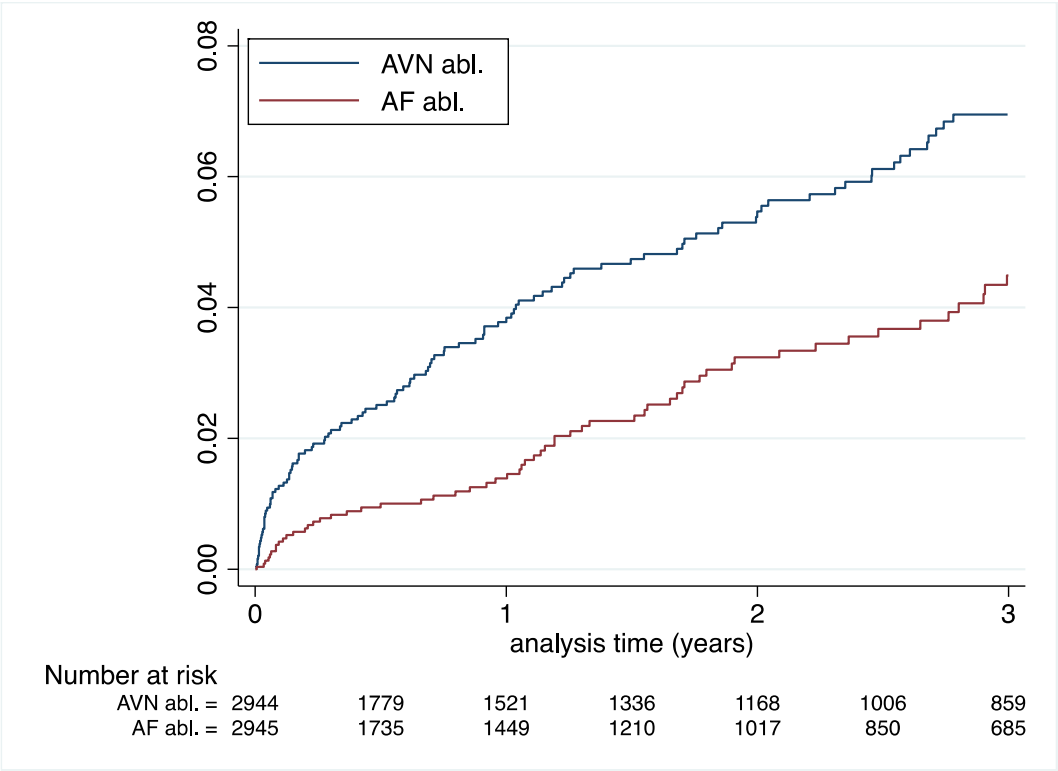
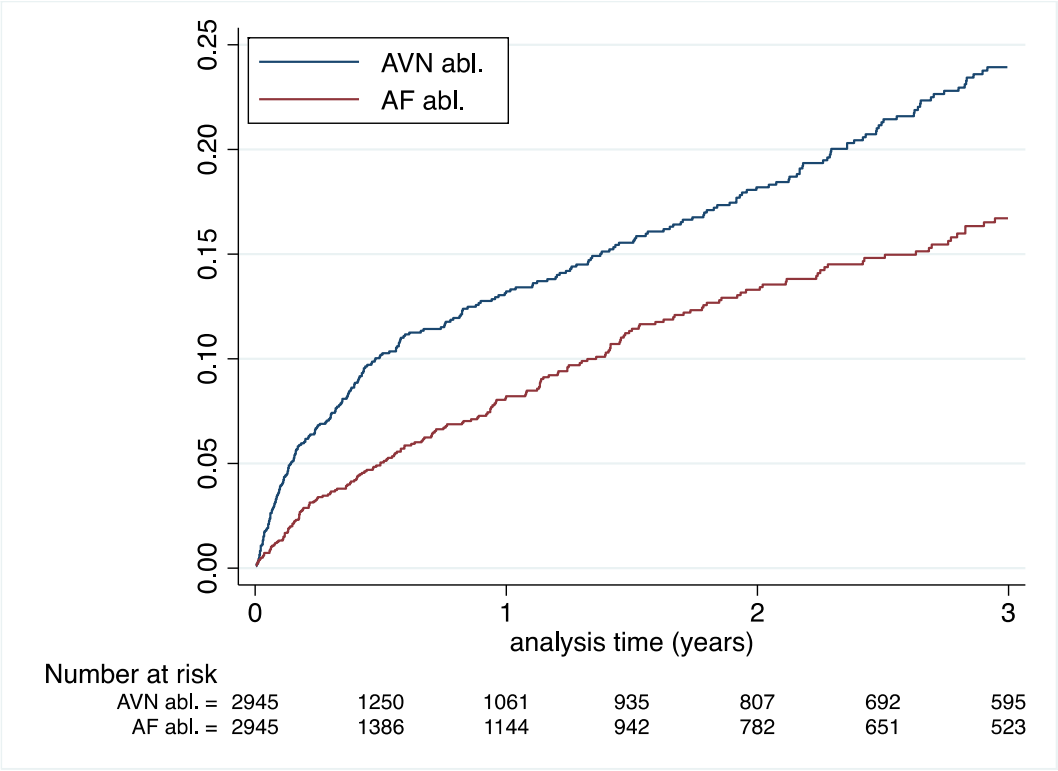


Figure 2. Incidences for all-cause death (top panel) and cardiovascular death (lower panel) in the matched patients with AF treated with AF ablation or AV node ablation.



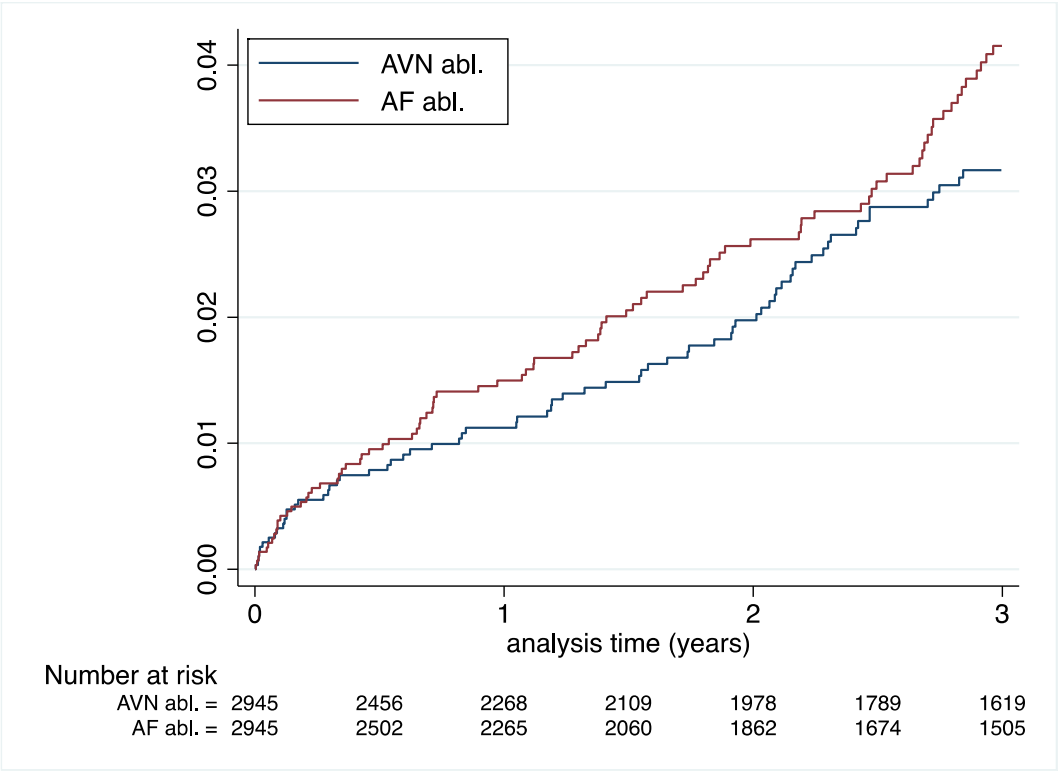


Figure 3. Incidences for rehospitalization for heart failure (top panel) and ischemic stroke (lower panel) in the matched patients with AF treated with AF ablation or AV node ablation.

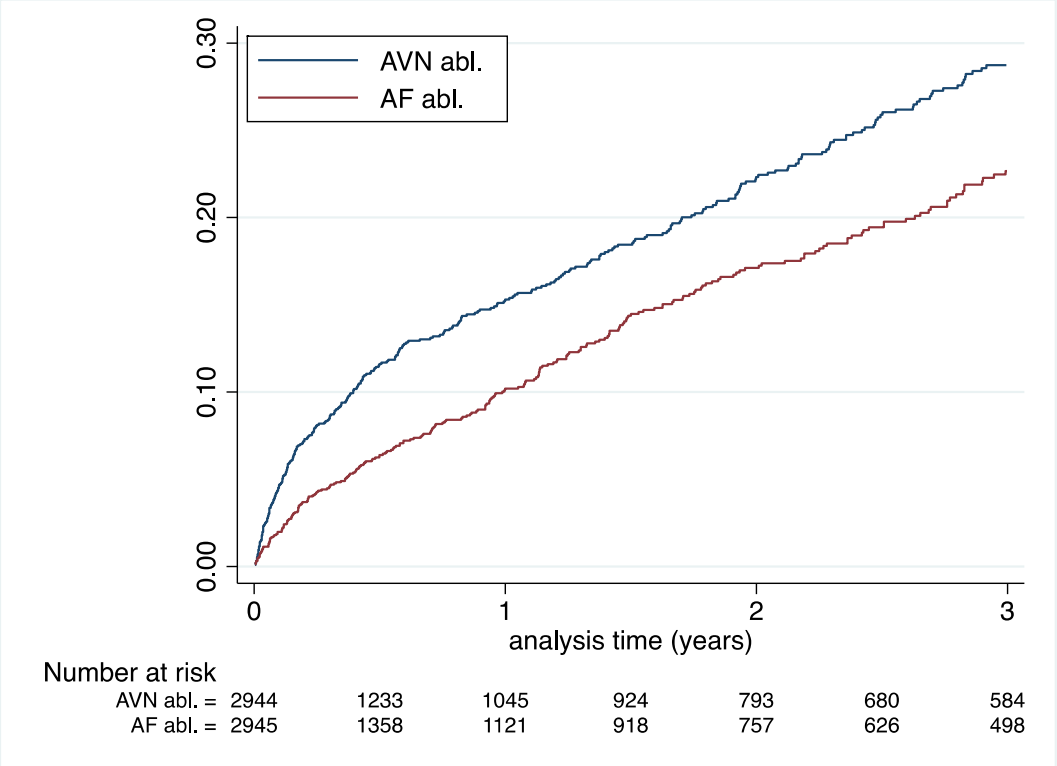
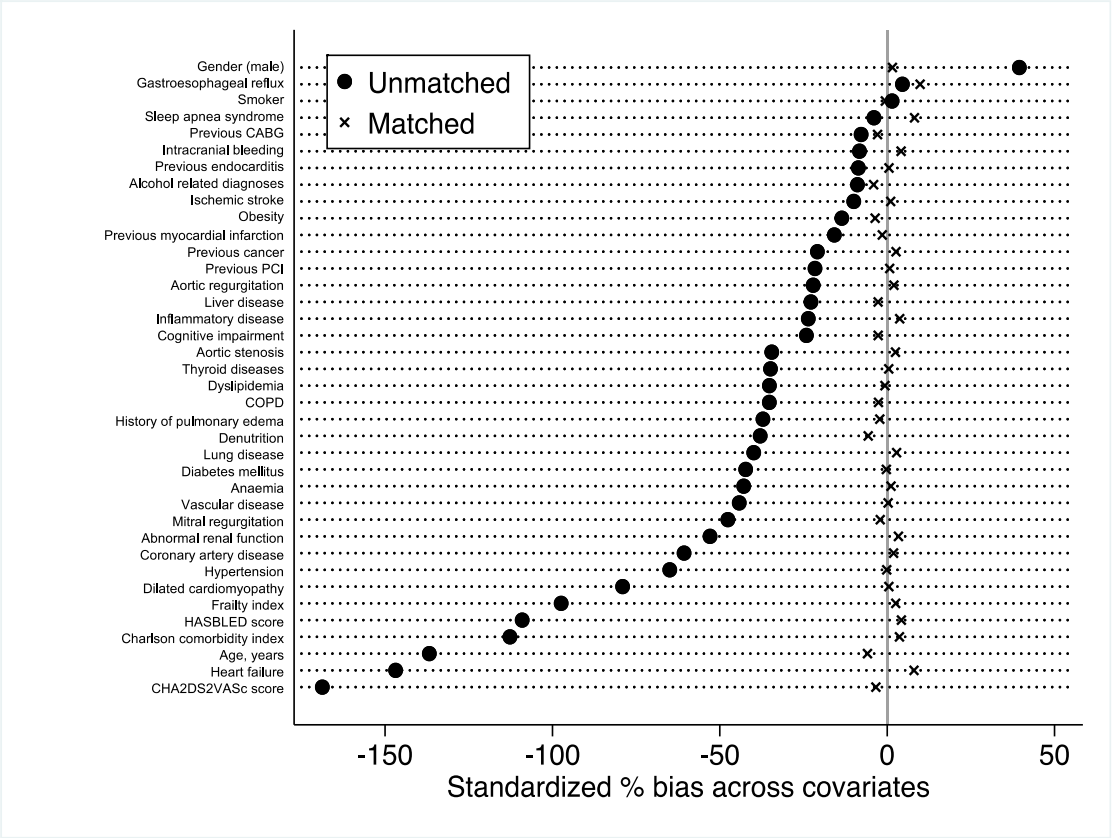


Figure 4. Incidences for the combined endpoint of cardiovascular death, rehospitalization for heart failure or ischemic stroke in the matched patients with AF treated with AF ablation or AV node ablation.



CABG=coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; PCI=percutaneous coronary intervention.

Supplemental figure 1. Standardized percentages of bias across main baseline characteristics in unmatched and matched AF patients treated with AF ablation and AV node ablation.

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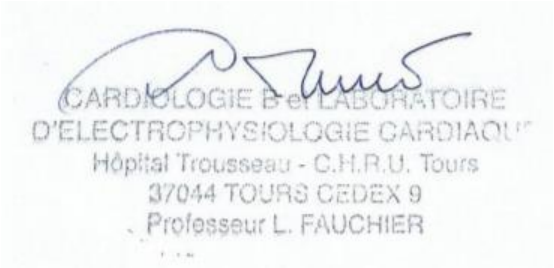

Vu, le Doyen
De la Faculté de Médecine de Tours
Tours, le

SPIESSER Pascal
46 pages – 6 tableaux – 5 figures

Résumé :

Introduction : L'ablation par cathéter de la fibrillation atriale (FA) est devenue la thérapie de choix pour traiter la FA symptomatique malgré les traitements antiarythmiques. Comme alternative, l'ablation du nœud atrio-ventriculaire (NAV) est une technique efficace pour contrôler la fréquence cardiaque.

Objectif : Évaluer la morbi-mortalité de l'ablation de FA et de l'ablation du NAV.

Méthodes : Cette étude rétrospective multicentrique française a inclus entre le 1er janvier 2010 et le 31 décembre 2019 tous les patients hospitalisés avec un diagnostic primaire ou secondaire de FA à l'aide de la base de données hospitalières administrative nationale. La morbi-mortalité a été analysée dans la cohorte globale ainsi que dans des échantillons appariés.

Résultats : Pendant le suivi (moyenne [ET] 2.0 [2.2], médiane [EI] 1.0 [0.1 - 3.3] ans), 2 438 015 patients avec FA ont été inclus (Aucune ablation 2 360 833, ablation de FA 62 490 et ablation du NAV 14 692). En comparaison avec les patients traités sans ablation, l'incidence de la mortalité globale était plus faible chez les patients traités par ablation de FA (hazard ratio ajusté (HR) 0.272, intervalle de confiance à 95% (IC95%) 0.259-0.287, p<0.0001) ou par ablation du NAV (HR ajusté 0.762, IC95% 0.734-0.791, p<0.0001). Après appariement 1/1, chez les patients traités par ablation de FA, les incidences de la mortalité globale (HR 0.662, IC95% 0.557-0.788, p<0.0001), cardiovasculaire (HR 0.617, IC95% 0.471-0.807, p<0.0001) et des hospitalisations pour insuffisance cardiaque (IC) (HR 0.732, IC95% 0.620-0.865, p<0.0001) étaient plus faibles comparées à celles des patients traités par ablation du NAV, contrairement à l'incidence des AVC ischémiques (HR 1.447, IC95% 1.122-1.865, p<0.0001).

Conclusion : L'ablation de FA et celle du NAV peuvent être associées à une meilleure survie qu'une stratégie non-invasive. En comparaison à l'ablation du NAV, l'ablation de FA est associée à des taux plus bas de mortalité globale, cardiovasculaire et d'hospitalisations pour IC mais à une plus grande incidence d'AVC.

Mots clés : Fibrillation atriale, ablation par cathéter, ablation du nœud atrioventriculaire.

Jury :

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