Ablation of atrial fibrillation

de Maat, Gijs Eduard

Chapter 2

Obesity is associated with impaired long-term success of pulmonary vein isolation: a plea for risk factor management before ablation

G.E. de Maat, B.A. Mulder, W.L. Berretty M.I.H. Al-Jazairi, E.S. Tan, A.C.P. Wiesfeld, M.A. Mariani, I.C. Van Gelder, M. Rienstra, Y. Blaauw

Open Heart 2018; In press

ABSTRACT

Aims. Obesity is an increasing health problem and is an important risk factor for the development of atrial fibrillation (AF). We investigated the association of body mass index (BMI) on the safety and long-term efficacy of pulmonary vein isolation (PVI) for drug refractory AF.

Methods. Four hundred-fourteen consecutive patients who underwent transcatheter PVI for AF between 2003 and 2013 were included. Successful PVI was defined as absence of atrial arrhythmia on Holter monitoring or electrocardiogram, without and with anti-arrhythmic drugs during follow-up. Obesity was defined as BMI ≥30 kg/m².

Results. Mean age was 56±10 years, 316 (76%) were male, 311 (75%) had paroxysmal AF and 111 (27%) were obese. After a mean follow-up of 46±32 months (1590 patient years), freedom from atrial arrhythmia and anti-arrhythmic drugs was significantly lower in obese patients compared to non-obese patients (respectively 30% versus 46%, p=0.005, log rank 0.016). With anti-arrhythmic drugs, freedom from atrial arrhythmia was 56% versus 68% (p=0.036). No differences in minor and major adverse events were observed between obese and non-obese patients (major 6% vs. 3%, p=0.105 and minor 5% vs. 5% p=0.512). Sensitivity analyses demonstrated that BMI (as continuous variable) was associated with PVI outcome (hazard ratio 1.08, 95% confidence interval 1.02-1.14, p=0.012).

Conclusion. Obesity is associated with reduced efficacy of PVI for drug-refractory AF. No relation between obesity and adverse events was found.

INTRODUCTION

Trans-catheter pulmonary vein isolation (PVI) using radiofrequency energy is a widespread and well-established technique for treatment of atrial fibrillation (AF)(1-3). Current guidelines indicate that PVI should be considered even before antiarrhythmic drugs (AAD) have failed in patients with paroxysmal AF(2). Catheter ablation is superior to antiarrhythmic drugs for rhythm control in symptomatic paroxysmal AF(4-6) and can also be performed successfully for persistent or long-standing persistent AF(7). However, radiofrequency PVI has only shown moderate success at long-term follow-up(8-10). Several co-morbidities increase the risk for AF(11). Obesity is an independent risk factor for the development and perpetuation of AF(11) and negatively influences success rates of PVI at 1 year follow-up(12). The recent ARREST-AF trial showed that aggressive risk factor management improves long-term outcomes of AF ablation(12). Also, if weight loss is sustained at long-term follow-up, reduction of AF burden and maintenance of sinus rhythm are significantly higher compared to patients with weight fluctuation(13). The aim of the present study was to investigate long-term outcome in consecutive patients undergoing a PVI strategy and to assess procedural safety in obese versus non-obese patients with AF.

METHODS

We retrospectively analyzed all patients scheduled for a first PVI between 2003 and 2013 at the University Medical Center Groningen, The Netherlands. All consecutive patients had highly symptomatic AF and failed at least one AAD. Exclusion criteria for PVI were significant underlying heart diseases and age <18 years or >80 years and less than 12 months follow-up. BMI was determined for all patients at the time of ablation. BMI was calculated by dividing body weight in kilograms by the square of the height in meters. Obesity was defined as BMI ≥ 30kg/m2.

Transcatheter radiofreqency PVI strategy

The transcatheter wide circumferential PVI was performed as described previously (14,15). During the 10-year study period, the PVI procedure evolved according to technical modifications. Briefly, point-by-point ablation wide antral lines were created around the pulmonary veins. For the first procedures RF energy was delivered with a non-irrigated ablation catheter, later on this was an irrigated tip. In the initial patients, pulmonary vein isolation was assessed with pacing within the pulmonary veins to conform exit block. From 2011 a circular catheter was used to confirm entrance and exit block. During the first procedure, no additional ablation lines were made. In case the first PVI was unsuccessful, repeat PVI procedures were performed when symptomatic atrial arrhythmias

were present (>3 months after initial PVI), in consultation with the patient and treating physician. Additional (linear) ablation was performed at the discretion of the treating electrophysiologist. Following PVI, oral anticoagulation was immediately restarted after the procedure, and low-molecular-weight-heparin was stopped when INR>2.0 was reached. Oral anticoagulation treatment was given for at least 3 months and thereafter continued based on the CHADS2-score and later on the $CHADS_2VA_2Sc$ (1,2). AADs were discontinued after the first three months blanking period if the patient was free from AF recurrence.

Follow-up

Patients visited our clinic at 3, 6, and 12 months post-PVI. Thereafter, patients were seen annually or on indication. To assess the occurrence of (a)symptomatic atrial arrhythmias, at 6 months 48 to 96-hour Holter monitoring was performed, and at 12 months 24-hour Holter monitoring was performed. At each visit a routine 12-lead ECG was performed, and when atrial arrhythmia was detected, a 12-lead rhythm strip (>30 seconds) was recorded. In case of symptomatic recurrence without documentation, event recording was performed to confirm and classify the atrial arrhythmia. Follow-up data were censored for patients who reached the primary endpoint or had been followed through 1th of December 2015.

Endpoints

Primary endpoint was freedom of atrial arrhythmias i.e. no evidence of AF, atrial flutter, or other atrial arrhythmias with a duration >30 seconds, without use of AADs at the end of follow-up. Procedural safety was investigated by reporting the occurrence of peri- and procedural minor or major adverse events. Major adverse events were defined as those that resulted in death or permanent injury, in temporarily injury that required intervention or specific treatment, (eg. stroke, transient ischemic attack, major bleeding requiring surgery or blood transfusion or >2.0 points hemoglobin decrease, cardiac tamponade and/or perforation, significant or symptomatic pulmonary vein stenosis >70%, pericarditis and/or pericardial effusion, myocardial infarction, phrenic nerve lesion, pneumothorax, pneumonia, and other not pre-defined events). Minor adverse events were defined as bleeding from the femoral artery/vein, femoral aneurysm not requiring intervention, pericardial effusion not requiring intervention and asymptomatic pulmonary vein stenosis(16).

Statistics

Baseline descriptive statistics are presented as mean ± standard deviation or median (range) for continuous variables, if appropriate, and counts with percentages for categorical variables. Differences between subgroups, in terms of patient characteristics at baseline, different follow-up times, and end of study were evaluated by the Student *t* test or the Mann-Whitney U test, depending on normality of the data. Chi-square or Fisher's exact test were used for comparison of categorical variables. By means of Cox-proportional

hazard analyses the association of any increase in BMI with the primary outcome was assessed. Model 1 is adjusted for age and sex, model 2 for age, sex, self-reported obstructive sleep apnoe syndrome, previous class I or III AAD use, LA diameter, AF duration, AF type, chronic heart failure and total number of PVI. Model 3 is adjusted for covariates of Model 2 and also for the other components of the $CHADS_2VA_2Sc$, not included in Model 2: hypertension, diabetes, vascular disease and stroke. No violations of the proportional hazards assumptions were found. All tests of significance were two-tailed, with P values <0.05 assumed to indicate significance.

RESULTS

Patient population

A total of 414 consecutive patients were included in this study. Patient characteristics are shown in **Table 1.** Mean age was 56±10 years. Time since first AF diagnosis was 63 [IQR 29-118] months. AF was paroxysmal in 311 (75%), mean body mass index (BMI) was 27.8±4.1kg/m². Among all patients, 111 (27%) were obese (BMI ≥30kg/m2) and 25 (6%) had a BMI ≥35kg/m2. Distribution of number of patients by BMI is shown in **Figure 1.** Comparing obese (BMI≥30kg/m2) versus non-obese patients (BMI < 30kg/m2), several differences were observed: chronic systolic heart failure (LVEF ≤35%), 10% vs. 4% p=0.034, hypertension 65% vs. 46% p=0.001, self-reported obstructive sleep apnea syndrome 7% vs. 2% p=0.013. Also LA diameter was larger in obese versus non-obese patients (44±5 mm vs. 41±7mm, p <0.001).

PVI outcome in the total population

After a mean follow-up of 46±32 months (1590 patient years; median 37, IQR 19-67) a total of 733 procedures were performed, with a median of 2.0 [range 1-5] ablations per patient. Of all patients, 56% underwent multiple ablation procedures. Overall long-term freedom from atrial arrhythmia and AAD was 42% (172/414 patients). With AAD this was 65% (268/414 patients).

PVI outcome according to obesity

After a mean follow-up of 46±32 months (1590 patient years), freedom from atrial arrhythmia and anti-arrhythmic drugs was significantly lower in obese patients compared to non-obese patients (respectively 30% versus 46%, p=0.005, log rank 0.016) (**Table 2 and Figure 2**). With anti-arrhythmic drugs, freedom from atrial arrhythmia was 56% versus 68% (p=0.036) (**Table 2**). There was no difference between both groups in median number of procedures (p=0.500).

Table 1. Baseline characteristics of patients undergoing transcatheter PVI.

	Total group N=414	BMI <30 N=303	BMI ≥30 N=111	p-value
Age, mean±SD years	56 ± 10	56 ± 10	56±10	0.859
Males, n (%)	316 (76%)	236 (78%)	80 (73%)	0.298
Chronic heart failure, n (%)	24 (6%)	13 (4%)	11 (10%)	0.034
Diabetes mellitus, n (%)	21 (5%)	12 (4%)	9 (8%)	0.124
Previous stroke, n (%)	17 (4%)	11 (4%)	6 (5%)	0.407
Hypertension, n (%)	213 (51%)	141 (46%)	72 (65%)	0.001
Vascular disease, n (%)	47 (11%)	36 (12%)	11 (10%)	0.726
$CHADS_2VA_2Sc$ score >1, n (%)	142 (34%)	94 (31%)	48 (43%)	0.019
Hypercholesterolemia, n (%)	79 (19%)	59 (19%)	20 (18%)	0.888
Thyroid dysfunction, n (%)	35 (9%)	21 (7%)	14 (13%)	0.072
Self-reported OSAS, n (%)	13 (4%)	5 (2%)	8 (7%)	0.013
Time since first AF episode, median [IQR] months	63 [29-118]	66 [30-121]	48 [23-108]	0.073
Paroxysmal AF, n (%)	311 (75%)	235 (77%)	76 (68%)	0.095
Non-paroxysmal AF, n (%)	103 (25%)	69 (23%)	34 (32%)	0.095
LA diameter parasternal, mm mean±SD	42 ±6	41±7	44± 5	<0.001
LVEF, mean ± SD	57± 6	58± 5	57± 7	0.234
AAD use				
Class I or III n, (%)	275 (72%)	200 (66%)	75 (68%)	0.921
Amiodarone n, (%)	93 (24%)	58 (19%)	35 (32%)	0.010

AAD= Anti-arrhythmic Drugs, AF= Atrial Fibrillation, IQR = interquartile range, OSAS = obstructive sleep apnea syndrome, LVEF = Left Ventricular Ejection Fraction, SD = standard deviation

Figure 1. BMI distribution of the total patient population.

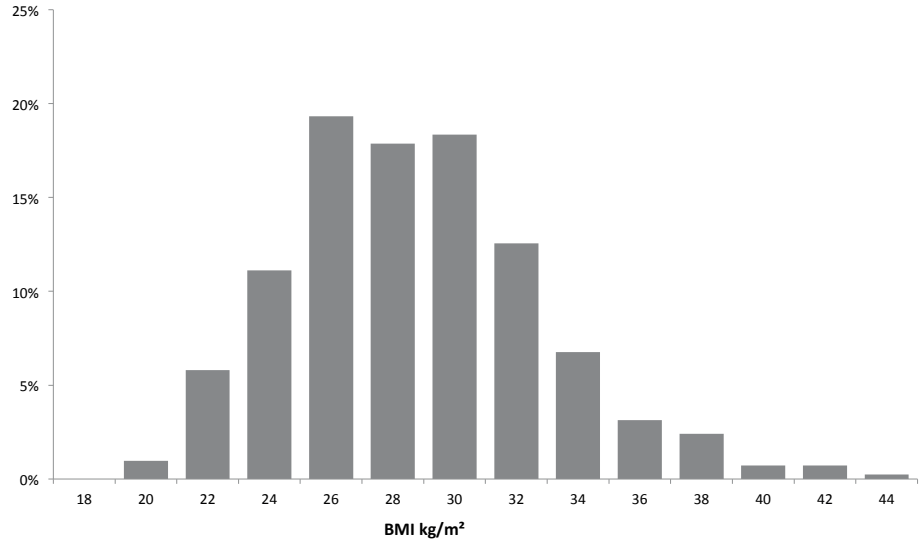


Table 2. Efficacy and safety outcomes of multiple procedure follow-up.

	Total	BMI <30	BMI ≥30	p-value
Total n PVI median [range]	2.0 [1-5]	2.0 [1-4]	2.0 [1-5]	0.505
Multiple procedure success				
12 months FU no AAD, n (%)	119 (29%)	93 (31%)	26 (23%)	0.178
12 months with and without AAD, n (%)	221 (53%)	163 (54%)	58 (52%)	0.911
long-term FU no AAD, n (%)	172 (42%)	139 (46%)	33 (30%)	0.005
long-term FU with and without AAD, n (%)	268 (65%)	206 (68%)	62 (56%)	0.036
Major adverse events				
Procedure related death	0	0	0	
Cardiac tamponade/perforation	9	5	4	
Thrombo-embolic event	4	2	2	
Air-embolic event	2	2	1	
Total (multiple procedures)	16 (4%)	9 (3%)	7 (6%)	0.105
Minor adverse events				
Femoral bleeding/aneurysm/AVF	14	9	5	
Pericardial effusion no intervention	4	3	1	
Phrenic nerve lesion	1	1	0	
Pulmonary vein stenosis (asymptomatic)	1	1	0	
Pericarditis	1	1	0	
Total (multiple procedures)	21 (5%)	15 (5%)	6 (5%)	0.512
Major or minor adverse events (multiple procedures)	37 (9%)	24 (8%)	13 (12%)	0.158

AAD= Anti-arrhythmic Drugs, AVF= arterial-venous fistula, BMI= Body Mass Index, FU = Follow-Up, PVI= Pulmonary Vein Isolation.

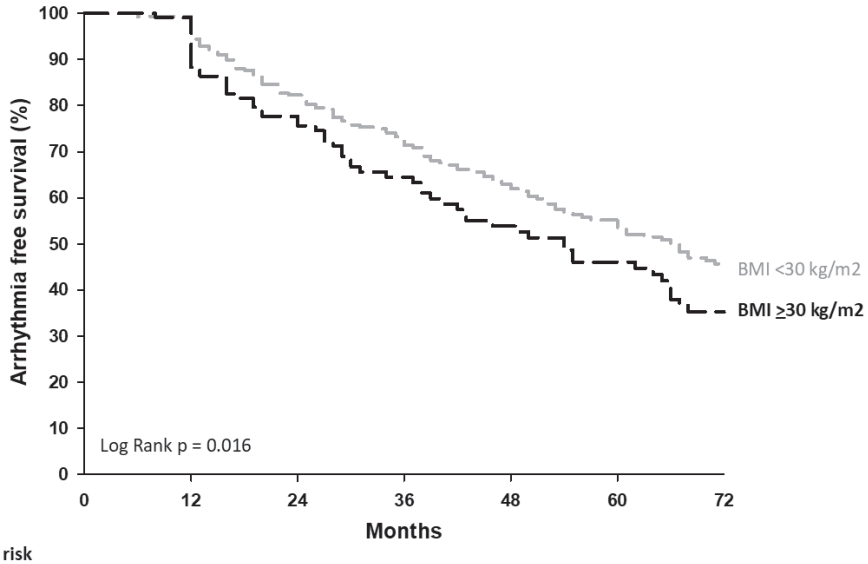
Adverse event according to obesity

Table 2 shows the peri- and procedural minor or major adverse events. In 37 (9%) patients, adverse events occurred, being major in 16 (4%) patients and minor in 21 (5%) patients. There was no in-hospital mortality. No differences in minor and major adverse events were observed between obese and non-obese patients (major 6% vs. 3%, p=0.105 and minor 5% vs. 5% p=0.512, **Figure 3**).

Association of BMI and PVI outcome

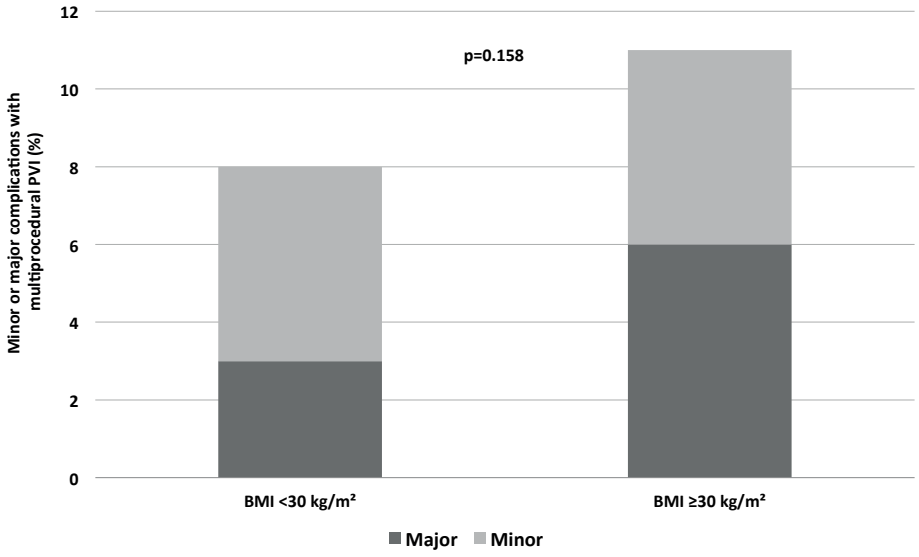
As sensitivity analyses, we performed multivariate Cox-proportional hazard analyses and assessed whether an increase in BMI (modeled as continuous covariate) was associated with an increased risk atrial arrhythmia recurrence. No violations of the proportional hazards assumptions were found. **Table 3** shows the outcome of different models. When

Figure 2. long-term freedom from atrial arrhythmia and anti-arrhythmic drugs for obese versus non-obese patients following multiple procedures.



No. At risk							
BMI <30	303	300	208	162	117	90	68
BMI >30	111	109	77	56	43	34	26

Figure 3. Major and minor adverse events.



BMI = Body Mass Index PVI = Pulmonary Vein Isolation

adjusting for the covariates included in Model 2, any increase in BMI was associated with failure of PVI with a hazard ratio of 1.07 (95% confidence interval 1.00-1.15), p=0.039. Model 3 showed that any increase of BMI was associated with failure of PVI with a hazard ratio of 1.09 (95% confidence interval 1.01-1.16), p=0.017.

Table 3. Sensitivity analyses of the association of BMI and long-term outcome after multivariable adjusted analyses.

	HR (95% CI)	p-value
Model 1	HR 1.08 (1.02-1.14)	p=0.012
Model 2	HR 1.09 (1.02-1.16)	p=0.039
Model 3	HR 1.09 (1.01-1.16)	p=0.017

Model 1 is adjusted for age and sex. Model 2 is adjusted for age, sex, obstructive sleep apnoe syndrome, previous class I or III AAD use, LA diameter, AF duration, AF type, chronic heart failure and total number of PVI procedures. Model 3 adjusted for all factors mentioned previously and also hypertension, diabetes, vascular disease and stroke.

DISCUSSION

This retrospective and observational study demonstrates that obesity is associated with lower >1year success of PVI. Procedural safety was comparable between obese and non-obese patients.

Obesity as cause of atrial fibrillation

Obesity is an important health problem with an increasing prevalence. There is abundant evidence for the involvement of obesity in the development of AF. Obese individuals have up to 2.4-fold increased risk for new-onset AF(17). Several mechanisms may underlie the relation between obesity and new-onset of AF. This might be related to structural and electrophysiological remodeling caused by elevated end-diastolic pressure, inflammation, and increased plasma volume(18). Animal models of obesity demonstrated increased levels of atrial fibrosis and higher susceptibility and sustainability of AF. In humans, electro-anatomical mapping in obese patients showed areas of low voltages indicative of increased atrial fibrosis(18). Weight loss has been associated with a decrease of the AF burden in patients(19). Following weight reduction lower levels of inflammatory markers were measured and electro-anatomical mapping demonstrated recovery of atrial voltages(13). In our study, hypertension, chronic heart failure and an enlarged atrial size, all parameters associated with a lower success rate of rhythm control, were more frequently present in obese patients(3).

Influence of obesity on PVI outcome

More and more data become available on obesity and atrial arrhythmia recurrences following PVI. A report of 226 patients with symptomatic, drug-refractory paroxysmal and persistent AF (mean BMI 26.6 ± 3.5 kg/m²) showed that BMI was not predictive for AF recurrence at a mean follow-up of just over 1 year, although a trend to a higher AF recurrence was found in patients with higher BMI(20). Cha et al. showed similar results in their study of 523 symptomatic, medication-refractory AF patients (58% paroxysmal, 42% persistent or permanent AF) undergoing PVI. The study showed no difference in success of catheter ablation between the groups of BMI >25 (18%), BMI 25 to 29.9 kg/m² (44%) and BMI ≥30 (38%) at 12-24 months follow-up(21). However, the main finding of our study is that we observed a lower success rate of PVI in obese vs. non-obese patients during >1year follow-up, Differences between these studies may be explained by differences in clinical characteristics of the patients and follow-up duration. Of note, we also observed no difference in efficacy during the first year of follow-up, but only after long-term follow-up. The results of present study seem in accordance with the recently published data by Sanders et al. who demonstrated that aggressive risk factor reduction including weight loss improves the outcome of PVI in obese patients(12). The >1year freedom from atrial arrhythmias in our study is comparable to long-term efficacy rates reported by others (7-9,22). Also, the reported adverse events rates are comparable(16).

Clinical relevance

Since both obesity and AF pose an epidemic threat, it is important to recognize that AF is not only more frequent in obese patients but also that long-term efficacy of PVI seem reduced compared to non-obese patients. In order to improve long-term results of PVI, patient selection is pivotal(23). Therefore, as stated in the new AF guidelines, in obese patients weight loss together with management of other risk factors should be considered to reduce AF burden and symptoms, before invasive treatment modalities are deployed(3).

Strengths and limitations

Our study was retrospective, precluding definite conclusions about cause-effect relations of obesity and PVI outcome. However, strengths of our study was that we had a >1500 patient years follow-up in most patients with extensive Holter recordings, which increased the probability of observing any atrial arrhythmia recurrence. Firstly, short and asymptomatic episodes of AF might be undetected. Secondly, obesity is often accompanied by more comorbidities, so obesity may reflect a clustering of cardiovascular risk factors that may impact PVI outcome, though even after multivariable adjustment the association of BMI with PVI outcome remained. Thirdly, the incidence of OSAS was low and may been caused by the fact we only collected self-reported OSAS, and no structural polysomnography was

performed in our cohort. Fourthly, the present analysis did not offer the opportunity to look into temporal associations between weight gain of loss and success of PVI.

CONCLUSIONS

Obesity is associated with reduced efficacy of PVI for drug-refractory AF. No relation between obesity and procedural adverse events was found. This emphasize that risk factor reduction before ablation including weight loss should be implemented in the work up of symptomatic AF patients referred for AF ablation.

REFERENCES

(1) European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, et al. ESC Guidelines for the management of atrial fibrillation. Europace 2010 Oct;12(10):1360-1420.

(2) Authors/Task Force Members, Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation. Europace 2012 Aug 24.

(3) Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016 Oct 7; 37(38):2893-2962.

(4) Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design. Europace 2012 Apr;14(4):528-606.

(5) Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. JAMA 2010 Jan 27;303(4):333-340.

(6) Morillo CA, Verma A, Connolly SJ, Kuck KH, Nair GM, Champagne J, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. JAMA 2014 Feb 19;311(7):692-700.

(7) Mont L, Bisbal F, Hernandez-Madrid A, Perez-Castellano N, Vinolas X, Arenal A, et al. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). Eur Heart J 2014 Feb;35(8):501-507.

(8) Ouyang F, Tilz R, Chun J, Schmidt B, Wissner E, Zerm T, et al. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. Circulation 2010 Dec 7;122(23): 2368-2377.

(9) Tilz RR, Rillig A, Thum AM, Arya A, Wohlmuth P, Metzner A, et al. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy. J Am Coll Cardiol 2012 Nov 6;60(19):1921-1929.

(10) Weerasooriya R, Khairy P, Litalien J, Macle L, Hocini M, Sacher F, et al. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? J Am Coll Cardiol 2011 Jan 11;57(2): 160-166.

(11) Vermond RA, Geelhoed B, Verweij N, Tieleman RG, Van der Harst P, Hillege HL, et al. Incidence of Atrial Fibrillation and Relationship With Cardiovascular Events, Heart Failure, and Mortality: A Community-Based Study From the Netherlands. J Am Coll Cardiol 2015 Sep 1;66(9):1000-1007.

(12) Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. J Am Coll Cardiol 2014 Dec 2;64(21):2222-2231.

(13) Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, et al. Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY). J Am Coll Cardiol 2015 May 26;65(20):2159-2169.

(14) De Maat GE, Van Gelder IC, Rienstra M, Quast AF, Tan ES, Wiesfeld AC, et al. Surgical vs. transcatheter pulmonary vein isolation as first invasive treatment in patients with atrial fibrillation: a matched group comparison. Europace 2014 Jan;16(1):33-39.

(15) Tan ES, Mulder BA, Rienstra M, Wiesfeld AC, Ahmed S, Zijlstra F, et al. Pulmonary vein isolation of symptomatic refractory paroxysmal and persistent atrial fibrillation: A single centre and single operator experience in the Netherlands. Neth Heart J 2009 Oct;17(10):366-372.

(16) Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circ Arrhythm Electrophysiol 2010 Feb;3(1):32-38.

(17) Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. Am J Med 2005 May;118(5):489-495.

(18) Nalliah CJ, Sanders P, Kottkamp H, Kalman JM. The role of obesity in atrial fibrillation. Eur Heart J 2015 Sep 14.

(19) Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, et al. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation: The CARDIO-FIT Study. J Am Coll Cardiol 2015 Sep 1;66(9):985-996.

(20) Letsas KP, Siklody CH, Korantzopoulos P, Weber R, Burkle G, Mihas CC, et al. The impact of body mass index on the efficacy and safety of catheter ablation of atrial fibrillation. Int J Cardiol 2013 Mar 20;164(1):94-98.

(21) Cha YM, Friedman PA, Asirvatham SJ, Shen WK, Munger TM, Rea RF, et al. Catheter ablation for atrial fibrillation in patients with obesity. Circulation 2008 May 20;117(20):2583-2590.

(22) Teunissen C, Kassenberg W, van der Heijden JF, Hassink RJ, van Driel VJ, Zuithoff NP, et al. Five-year efficacy of pulmonary vein antrum isolation as a primary ablation strategy for atrial fibrillation: a single-centre cohort study. Europace 2016 Feb 2.

(23) EHRA Scientific Committee Task Force:, Gorenek B, Pelliccia A, Benjamin EJ, Boriani G, Crijns HJ, et al. European Heart Rhythm Association (EHRA)/European Association of Cardiovascular Prevention and Rehabilitation (EACPR) position paper on how to prevent atrial fibrillation. Europace 2016 Nov 4.