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Impact of metabolic syndrome on the risk of atrial fibrillation recurrence after catheter ablation: systematic review and meta-analysis

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Abstract

Purpose—The impact of metabolic syndrome (MetS) on recurrence of atrial fibrillation (AF) after catheter ablation remains uncertain. We conducted a meta-analysis to summarize the relative risks (RR) of AF recurrence after catheter ablation in patients with vs. without MetS and its components.

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Conflict of interest None declared.

Methods—Among 839 articles identified from PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials, we included 23 studies with a total of 12,924 patients (7,594 with paroxysmal AF and 5,330 with nonparoxysmal AF) for analysis. Five of these had complete information on MetS components. Variables assessed comprised study design and population characteristics, AF ablation methods, use of anti-arrhythmic drugs, AF recurrence ascertainment methods, adjustment variables, and other quality indicators.

Results—Our meta-analysis found an elevated risk of AF recurrence after ablation in patients with vs. without MetS (pooled RR, 1.63; 95 % confidence interval (CI), 1.25–2.12). Among components of MetS, hypertension was a predictor of AF post-ablation recurrence in studies without adjustment for other MetS components (RR, 1.62; 95 % CI, 1.23–2.13) but not in those adjusting for two or more additional MetS components (RR, 1.03; 95 % CI, 0.88–1.20). There was a borderline association between overweight/obesity and AF recurrence after ablation (RR, 1.27; 95 % CI, 0.99–1.64).

Conclusions—MetS is associated with an increased risk of AF recurrence after catheter ablation. Further study of the MetS and its components as determinants of AF risk could help refine patient selection and improve procedural outcomes.

Keywords

Pulmonary vein isolation; Syndrome X; Glucose intolerance; Hyperlipidemia; Insulin resistance

1 Introduction

Atrial fibrillation (AF) is among the most common cardiac arrhythmias encountered in clinical practice, with more than 2.3 million prevalent cases in the USA [1, 2]. Catheter ablation has emerged as an effective therapy for patients with symptomatic and drug-refractory AF, but success rates are highly variable, ranging from 22.3 to 91.0 % [3]. To explain the heterogeneity of these success rates, several factors have been identified as potential predictors of recurrence after AF catheter ablation, among them left atrial size, nonparoxysmal AF, sleep apnea, and metabolic syndrome (MetS) [4–6].

MetS is defined as a cluster of central obesity, hypertension, dyslipidemia, and glucose intolerance [7]. Higher recurrence rates after AF ablation were first observed in patients with individual components of MetS, such as obesity, diabetes mellitus (DM), and hypertension [5, 8–10]. More recently, MetS has also been associated with higher recurrence after AF ablation [6, 11, 12]. However, data on this association were inconclusive and estimates varied substantially [6, 11, 13]. We therefore conducted a systematic review and meta-analysis to summarize the relative risks (RR) of AF recurrence after catheter ablation in patients with vs. without MetS or its individual components.

2 Methods

2.1 Study selection

We searched PubMed, EMBASE, and Cochrane Central Register of Controlled Trials for studies published up until June 2012 that investigated recurrence of AF after catheter

ablation in relation to MetS and its components, including obesity, hypertension, dyslipidemia, and DM or glucose intolerance. Table 1 shows the key words used to search eligible articles. All entries retrieved by this strategy were examined to identify studies that satisfied the following predefined inclusion criteria: (1) assessment of recurrence after AF ablation as either primary or secondary outcomes, (2) reporting of an RR and its standard error or 95 % confidence interval (CI), (3) assessment of MetS and/or its components as major exposure(s) included in the final adjusted model. Although our primary objective is to evaluate the association between MetS and AF ablation outcomes, many prior studies only reported individual components of MetS as independent predictors of post-ablation relapse of AF. To achieve a comprehensive summary of the existing literature, we included a study in the general analysis if it assessed any one of the MetS components in relation to the risk of post-ablation AF recurrence. However, we also contrasted the pooled estimates for each individual component based on studies evaluating MetS overall and all of its components (MetS studies) vs. those evaluating only one or more individual components (non-MetS studies).

2.2 Data extraction

Three independent investigators (KJL, NT, and MB) extracted the data from eligible articles, and a fourth investigator (SIC) validated the collected data for accuracy. If available, we extracted RRs, including ratios of cumulative incidence, incidence rates, and odds of developing the outcomes of interest, whichever were reported in the original articles. Table 1 lists the variables evaluated in our analysis. Paroxysmal AF was defined as AF self-terminated within 7 days and nonparoxysmal AF as sustained beyond 7 days, including persistent (≥ 1 year) and long-standing persistent AF (>1 year). Blanking period was defined as a time period since ablation within which the occurrence of AF was not counted as a relapse [14].

2.3 Statistical analysis

All RRs extracted were the most finely adjusted estimates in the original studies. If one study presented estimates for multiple component factors of MetS, all of them were considered. If RRs for the same population were reported more than once but in different articles, only the RRs from the most recent or largest one were included. Random effects models were applied to calculate pooled RRs and their 95 % CIs. Heterogeneity of effect estimates was assessed by the Cochran Q test for heterogeneity and the I^2 statistic, which quantifies the proportion of total variability attributable to between-study variation [15]. Random effects meta-regressions were performed to explore sources of heterogeneity. All the extracted variables listed in Table 1 were examined in meta-regression models and we estimated stratified pooled RRs by the variables with $p < 0.10$ in meta-regression. We explored potential publication bias using both Begg's and Egger's test [16]. Stata 10.1 (Stata Corp., College Station, TX) was used for all analyses. All reported p values are two sided with a significance level of 0.05.

3 Results

Among 839 articles identified from PubMed, EMBASE, and Cochrane Central Register of Controlled Trials, we included 23 studies [4–6, 8–13, 17–30] with a total of 12,924 patients (7,594 with paroxysmal AF and 5,330 with nonparoxysmal AF) for analysis. Figure 1 shows the literature search process. Table 2 summarizes the characteristics of the included studies. Among the selected studies, 5 studies conducted a comprehensive evaluation of MetS overall and its component factors, 17 assessed hypertension, 11 obesity/overweight (six used BMI as a categorical variable and five as a continuous variable), 10 DM, and 9 dyslipidemia in relation to AF recurrence after ablation (Tables 2 and 3). Meta-analysis results are presented below by exposure categories (Fig. 2).

3.1 Metabolic syndrome

Our meta-analysis showed that patients with MetS were at an increased risk of recurrence after AF ablation (RR, 1.63; 95 % CI, 1.25–2.12; Table 3), as compared with those without MetS. Meta-regression revealed that studies with a younger mean age had a significantly higher pooled risk of recurrence (RR, 3.03; 95 % CI, 1.70–5.40) than remaining studies (RR, 1.39; 95 % CI, 1.19–1.62; Table 4). In an exploratory analysis, the studies with a younger mean age were found to have a lower prevalence of hypertension (32.1 vs. 57.1 %; $p < 0.001$) and lower baseline risk of post-ablation AF recurrence among non-MetS controls (21.2 vs. 32.8 %; $p < 0.001$).

Estimates of MetS can potentially vary depending on the diagnostic criteria used. Among the five included studies for MetS, four used National Cholesterol Education Program Adult Treatment Panel III criteria with prevalence of MetS ranging between 18.8 and 49.4 % [8, 11–13] and one used the World Health Organization criteria with a prevalence of 32.4 % [6]. There are no gold standard diagnostic criteria for MetS and its prevalence based on either set of criteria varies without a consistent pattern [31, 32]. In our meta-regression, however, the definition of MetS was not a significant effect modifier ($p = 0.345$).

3.2 Hypertension

The risk of post-ablation AF recurrence was elevated in patients with vs. without hypertension (RR, 1.31; 95 % CI, 1.13–1.51) with significant heterogeneity ($p = 0.016$; Table 3). Contrasting results from MetS studies vs. non-MetS studies, we found pooled estimates were only significant in the latter ($p = 0.077$ for the difference; Fig. 3). In a subgroup analysis, hypertension was not independently associated with higher recurrence after AF ablation in studies adjusting for two or more additional MetS components (RR, 1.08; 95 % CI, 0.94–1.24; $p = 0.042$ for the difference from those without such adjustment). The corresponding RR was 1.30 (95 % CI, 1.00–1.70) in studies adjusting for one additional MetS component and 1.62 (95 % CI, 1.23–2.13) in those without such adjustment. Of note, all the estimates for hypertension from MetS studies ($n=4$) were adjusted for 2 or more MetS components.

3.3 Obesity

There was a borderline association between recurrence after AF ablation and BMI as a categorical variable (RR, 1.27; 95 % CI, 0.99 to 1.64; four studies [6, 8, 11, 13] used 25 kg/m^2 and two studies [12, 24] used 30 kg/m^2 for categorization) but not as a continuous variable (RR per point increase in BMI, 1.00; 95 % CI, 0.94 to 1.07; Table 3). All the MetS studies evaluated BMI as a categorical variable and their results were not significantly different from non-MetS studies (Fig. 3). Significant heterogeneity was found in studies where BMI was assessed as a categorical variable ($p=0.014$; Table 3). In these articles, study populations with lower prevalence of hypertension were associated with a higher pooled estimate for the effect of obesity on AF relapse after ablation ($p=0.048$). The heterogeneity in the estimates for obesity and AF recurrence was not attributable to the cut-off of BMI used ($p=0.52$). Restriction of the analysis to the two studies using BMI 30 kg/m^2 yielded an RR of 1.08 (95 % CI, 0.88–1.32) [12, 24].

3.4 DM and hyperlipidemia

The risk of AF post-ablation recurrence was not elevated in patients with DM (RR, 1.11; 95 % CI, 0.97–1.26), hypertriglyceridemia (RR, 1.07; 95 % CI, 0.89–1.29), or low high-density lipoprotein (HDL; RR, 0.98, 95 % CI, 0.96–1.01; Table 3). Contrasting results from MetS vs. non-MetS studies, there was no significant difference in estimates for either DM or hypertriglyceridemia (Fig. 3; all estimates for HDL were from MetS studies.). While RRs from studies investigating hypertriglyceridemia appeared to be heterogeneous, there was only one study [10] reporting a positive association (RR, 4.01; 95 % CI, 1.84–8.73) for very late recurrence (recurrence >1 year after ablation). The remaining studies reported consistently null findings for any recurrence after a blanking period of 2–3 months (Table 4).

3.5 Quality assessment

For all the exposure categories, out of the eight indicators of Newcastle–Ottawa scale [33], we identified a few associations where the quality of the study could appreciably affect the reported estimates. First, adjustment for additional MetS components could substantially attenuate the positive associations between hypertension and AF recurrence (Table 4). Second, the heterogeneity in estimates for DM was eliminated after excluding the only study without adjustment for additional MetS components (Table 4). Besides, we could not assess the follow-up adequacy for two studies investigating obesity and AF recurrence as they did not report follow-up duration. These two studies yielded a significantly higher pooled RR than that from the remaining studies ($p=0.025$; Table 4). While nondifferential loss to follow-up would have biased the results towards the null, more nonobese patients lost to follow-up remains a plausible explanation of these findings. Variation in AF ablation methods was not shown to be a significant effect modifier in most of the exposure categories. There was a borderline effect modification in one instance, whereby those who did not undergo ablation of sites with complex fractionated atrial electrograms [34] appeared to have somewhat higher hypertension-associated risk of AF recurrence (Table 4).

In the included studies, recurrence of AF was defined as a relapse of “AF alone” or “AF, atrial flutter, or atrial tachycardia” for a duration of at least 30 or 60 s, or without a specified

duration. In our meta-regression, these variations in definition did not influence reported risks of AF recurrence in relation to MetS and its components appreciably, nor did the frequency or length of follow-up, methods of detecting AF recurrence, or length of “blinking period” materially affect our results (data not shown).

3.6 Publication bias

While all the prior studies reported positive associations between MetS and the risk of post-ablation AF recurrence, the tests for small-study effect were significant (p for Begg’s test=0.027; p for Egger’s test=0.002), which indicates small studies tended to find more extreme estimates. Adjustment for possible influence of unpublished articles based on “Trim and Fill” method [35] yielded a conservative pooled RR of 1.43 (95 % CI, 1.05–1.93) for AF recurrence associated with MetS. Moreover, we calculated the fail-safe number for meta-analysis, which estimated the number of unpublished null studies needed to abolish the currently observed association [36]. It was 42 for the association between MetS and post-ablation recurrence of AF, which is greater than the accepted threshold for robustness (>10 plus 5 times the original number of studies) [36]. Alternatively, the small study effect can be an unbiased effect with clinical implications [37]. In our analysis, comparing studies with sample sizes less vs. more than the median, small studies had populations with a younger mean age (53.0 vs. 60.2; $p < 0.001$) and lower prevalence of patients with hypertension (32.1 vs. 57.1 %; $p < 0.001$), both of which variables were associated with higher RRs of AF recurrence associated with MetS. For all the other exposure categories, Begg’s and Egger’s tests revealed no evidence of publication bias (data not shown).

4 Discussion

Our meta-analysis found that MetS was associated with a 60 % increase in AF recurrence rates after catheter ablation. Among the MetS components, overweight or obesity was a borderline predictor of AF relapse after ablation. Hypertension was associated with AF post-ablation recurrence only in studies without adjustment for other MetS components.

The mechanism underlying the association between MetS and post-ablation recurrence of AF remains unclear. The pathophysiology of AF is believed to involve a trigger (a rapidly firing focus often located inside one or more pulmonary veins) and its interaction with an arrhythmogenic atrial substrate to form a reentrant circuit or circuits [38]. This process is perpetuated by electrical and structural remodeling of the atria. Prior studies have demonstrated that MetS may play an important role in these remodeling processes. For electrical remodeling, MetS has been associated with atrial conduction disturbance and dispersion of refractoriness between the right and left atria [8, 39]; and obesity with a shortened effective refractory period in the pulmonary veins [40]. These electrophysiological abnormalities are thought to stabilize multiple wavelet reentry circuits and maintain AF. MetS is also linked to several features contributing to structural remodeling of the atria. First, MetS, hypertension, obesity, and insulin resistance are associated with left atrial dilation [8, 11, 41], which predisposes to the development of AF substrate characterized by increased nonuniform anisotropy and macroscopic slowing of conduction and promotes reentrant circuits in the atria [42]. Second, myocardial fibrosis,

possibly caused by silent ischemia in DM or by oxidative stress and a proinflammatory state in MetS [43], may serve as an anchor for reentrant circuits, alter the wave-front propagation, and thus sustain AF [39, 44].

In our analysis, the MetS studies reporting higher RRs of AF post-ablation relapse were found to have a younger mean age and lower prevalence of patients with hypertension, which are also associated with a lower baseline recurrence risk in the non-MetS controls. While a possible interpretation of these findings could be that MetS is more predictive of AF recurrence in a younger population with fewer risk factors for AF than in an older population, these observations come from meta-regression with only aggregate (rather than individual-level) data, and should only be viewed as hypothesis generating.

Many prior studies reported individual components of MetS as independent predictors of post-ablation relapse of AF without evaluating all the MetS components [5, 8–11, 17, 18, 25, 29]. We contrasted estimates for each of the MetS components based on studies with comprehensive evaluation of MetS and those without (i.e., MetS and non-MetS studies). We found no significant difference between the two sources except that pooled estimates for hypertension were significant in the non-MetS studies but not in the MetS studies. This difference can be explained by adjustment for other MetS components: hypertension predicted post-ablation recurrence of AF only in studies without adjustment for other MetS components. Among other MetS components, only overweight or obesity had a borderline association after adjusting for other MetS components. The two studies [8, 11] reporting significant associations adjusted their estimates for MetS and thus this association cannot be explained solely by surrogate effect of MetS. The extent to which the MetS as a composite measure exceeds the predictive value for post-ablation AF recurrence contained in its individual components requires further study, but our findings imply MetS may be a more reliable predictor of AF recurrence than any of its components alone.

A prior meta-analysis has reported that obstructive sleep apnea (OSA) diagnosed by polysomnography, but not by Berlin questionnaire, was associated with lower long-term success rates of AF ablation [45]. Among our included studies, there was only one study that adjusted for OSA when estimating the association between obesity and post-ablation AF recurrence and it reported null findings [24]. It is important to note that none of the estimates from the prior meta-analysis for OSA in relation to AF recurrence was adjusted for MetS, nor were the estimates for MetS in the current analysis adjusted for OSA. As both MetS and OSA are associated with obesity, further studies taking into account the correlation between the three factors are needed to confirm these associations.

We need to acknowledge several limitations. First, although our primary objective was to evaluate recurrence after AF ablation in relation to MetS, there were only five studies directly assessing this association. We included studies investigating only individual components of MetS as they have been reported as independent predictors of AF post-ablation recurrence. However, these estimates were subject to confounding by other MetS components and the pooled estimates for the component factors of MetS derived from the 5 MetS studies may not be comparable with those derived by the remaining studies. Second, for meta-analyses to combine and integrate results of independent studies together, the

studies should be similar and comparable. However, we found substantial heterogeneity among estimates for MetS, hypertension, obesity, DM, and hypertriglyceridemia. While stratification of the analysis according to some of the study characteristics provided more homogeneous subgroups, some subgroup analyses were based on relatively few studies and thus the results should be interpreted with caution. In addition, because the studies in question were not randomized controlled trials, but observational studies, the possibility of residual confounding cannot be excluded.

5 Conclusions

Our meta-analysis found that MetS is associated with a 60 % increase in AF recurrence rates after catheter ablation, but did not show hypertension to be independently related to, or overweight/obesity consistently associated with, this outcome. In light of the wide variation in reported studies regarding definition of exposure(s), assessment of covariates, and ascertainment of outcomes, the observed summary association points up the need to better understand MetS and its components as determinants of procedural success. The present findings suggest that presence of the MetS may help clinicians identify patients at higher risk of recurrence after AF ablation who might benefit from close postprocedural follow-up and early management for recurrent AF, which, if not well rate controlled, can be associated with secondary cardiomyopathy and eventually heart failure. While many of the MetS components are modifiable, the impact of treating MetS on AF ablation outcome remains to be investigated.

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Fig. 1.
Flow chart of literature search process

Fig. 2.

Forest plots: risk of AF recurrence after catheter ablation associated with metabolic syndrome and its component factors. [‡], as defined in the original articles: BMI ≥ 25 [6, 8, 11, 13] and BMI ≥ 30 [12, 24]

Fig. 3.

Comparison between studies investigating metabolic syndrome overall vs. only individual component factors. *DM* diabetes mellitus, *HDL* high-density lipoprotein, *MetS* metabolic syndrome. *, all *MetS* studies assessed BMI as a categorical variable and estimates for BMI as a continuous variable are not shown here. †, only estimates for hypertriglyceridemia are listed here for comparison as only *MetS* studies reported estimates for low HDL level (no counterpart for comparison). ‡, *p* values from meta-regression comparing estimates from *MetS* studies vs. those evaluating only individual component factors

Table 1

Literature search strategy and data extraction

Search terms ^a	
“Catheter ablation,” “pulmonary vein isolation,” or “atrial AND fibrillation ablation”	“metabolic syndrome,” “syndrome X,” “insulin resistance,” “hyperglycemia,” “glucose intolerance,” “impaired fasting glucose,” “pre-diabetes,” “dysglycemia,” “obesity,” “body mass index,” “overweight,” “dyslipidemia,” “hyperlipidemia”, “hypertriglyceridemia,” “hypoalphalipoproteinemia,” “hypertension,” or “high blood pressure”
Study characteristics	Year of publication, study period, geographic region, sample size, inclusion and exclusion criteria of the study population, characteristics of enrolled subjects, including mean age, gender distribution, the proportion of patients with DM, obesity, hypertension, structural heart disease, and paroxysmal vs. nonparoxysmal AF, mean BMI, mean LAD, LVEF and AF duration, study design, definitions of MetS and its component factors, AF ablation methods, blanking period [46], use of anti-arrhythmic drugs, definition and ascertainment methods of AF recurrence, and variables adjusted in the original analysis
Quality indicators ^b	Representativeness of the exposed cohort, selection of the nonexposed cohort, reliability of exposure ascertainment, demonstration that outcome of interest was not present at start of the study, comparability of cohorts, validity of outcome ascertainment, adequacy of follow-up, and loss to follow-up

The search was restricted to human studies, excluding estimates published solely in the form of letters, commentaries, abstracts, case reports, or reviews *AF* atrial fibrillation, *BMI* body mass index, *DM* diabetes mellitus, *LVEF* left ventricular ejection fraction, *LAD* left atrial diameter

^aSearch terms were entered as both text words and MeSH terms (if present)

^bEight factors based on Newcastle–Ottawa scale [33]

Summary of included studies

Table 2

First author	Publish year	Sample size	AF recurrence rate (%)	Follow-up (months)	Paroxysmal AF (%)	Mean age	Female (%)	Structural heart disease (%)	HTN (%)	DM (%)
Chang [8]	2009	282	29.8	N/A	76.6	51.6	24.5	7.3	30.6	8.1
Cai [11]	2011	186	25.3	N/A	86.6	55.1	33.9	16.7 (CAD: 9.7)	34.4	10.2
Wokhlu [17]	2010	774	35.8	36.0	55.3	54.0	19.0	11.0 ^b	36.0	6.0
Tang [13]	2009	654	37.0	15.7	79.8	57.0	28.9	11.9	55.0	11.9
Arya [5]	2010	674	24.4	N/A	84.6	57.3	31.0	6.0 ^b	49.7	N/A
Berrueto [18]	2007	148	26.4	13.1	60.8	52.0	17.6	19.6	33.8	N/A
Bhargava [19]	2009	1404	27.4	56.1	51.9	55.8	24.0	56.3	N/A	N/A
Chao [20]	2010	132	26.5	23.0	100.0	50.7	30.3	10.5 ^b	32.6	9.1
Chao [9]	2010	228	11.0	18.8	100.0	52.3	26.8	20.4 ^b	29.7	28.5
Chao [21]	2011	232	15.9	25.4	100.0	53.4	27.6	15.5 ^b	35.4	6.5
Chilukuri	2009	210	21.4	25.0	56.7	58.0	20.0	N/A	50.0	9.0
Hwang [23]	2010	81	37.0	9.0	71.6	51.7	14.8	N/A	34.6	7.4
Jongnarangsin [24]	2008	324	39.2	7.0	72.2	57.0	24.1	11.0 ^b	46.0	N/A
Khaykin [25]	2011	385	42.0	33.6	63.1	58.0	23.0	24.0	45.0	28.0
Letsas [26]	2009	72	38.9	12.5	63.9	54.9	19.0	14.0 (CAD: 3)	19.0	22.0
Letsas [27]	2011	226	42.0	14.4	59.3	55.9	18.6	25.7	45.6	N/A
Okumura [28]	2011	50	42.0	14.0	56.0	61.3	24.0	8.0	42.0	10.0
Patel [4]	2010	3000	23.1	32.0	53.4	55.7	22.8	11.1 ^b	42.9	13.3
Shah [10]	2008	264	8.7	35.0	87.1	56.0	35.0	15.0 ^b	41.0	N/A
Themistoclakis [29]	2008	1298	22.5	41.0	53.9	56.1	22.0	32.0 (CAD: 11)	33.0	N/A
Wong [30]	2011	102	57.8	16.7	37.3	58.0	28.0	17.6 ^b	56.9	5.9
Berkowitsch [12]	2012	702	47.3	15.6	59.3	58.0	29.1	8.8 ^b	69.3	6.6
Mohanty [6]	2012	1496	34.0	21.0	29.3	62.6	26.4	12.3 ^b	52.4	4.9

First author	Mean BMI (kg/m ²)	Mean LAD (mm)	Mean LVEF (%)	Mean AF duration (years)	Blanking period ^a	AF ablation strategy	MetS or its component assessed	Variables adjusted
Chang [8]	24.6	38.6	59.2	4.4	2	PVI, linear, and then CFAE sequentially if AF persists for patients with PAF (NPAF gets PVI and linear ablation regardless)	MetS, BMI 25, HTN, DM, TG, and HDL levels	type of AF, CAD, LAD, LVEF, BMI, HTN, DM, TG, and HDL levels
Cai [11]	N/A	35.0	68.7	5.4	3	PVI, linear, and then CFAE	MetS, BMI 25, and DM	Obesity, DM, MetS, AF duration, NPAF, duration of AF, LAD, ablation strategy(segmental pulmonary vein isolation vs. circumferential pulmonary vein ablation), ERAF, and procedural failure
Wokhlu [17]	30.3	N/A	57.7	6.4	2	PVI±linear ablation	DM	Age, DM, HTN, NPAF, family history of AF, LAD, and circumferential PVI
Tang [13]	25.4	38.4	63.0	6.5	3	PVI±linear ablation and CFAE until AF is terminated or all identified CFAE were eliminated	MetS, BMI 25, HTN, DM, TG, and HDL levels	HTN, BMI, fasting blood glucose, TG and HDL levels, MetS, type/duration of AF, LAD, LVEDD, and ablation strategies
Arya [5]	N/A	N/A	N/A	4.0	3	PVI±linear ablation if AF persists	HTN	LAD, age, gender, HTN, termination of AF during ablation, LV dysfunction, and type of AF, ablation time, and early recurrence(<7 days)
Bernuez [18]	N/A	41.4	60.0	6.2	1	PVI±linear ablation	HTN	Age, long-standing persistent AF, HTN, LAD, and LVEDD
Bhargava [19]	N/A	43.4	54.5	6.4	2	PVI±SVC isolation+ablation of non-PV triggers+linear ablation (for NPAF)	HTN	age, gender, LVEF, LAD, duration of AF, hypertension, structural heart disease, and type of AF
Chao [20]	24.5	37.3	N/A		2	PVI±SVC isolation or ablation of non-PV ectopy if any	BMI ^d	BMI, LAD, PA-PDI interval, Left atrial activation time, and left atrial voltage
Chao [9]	24.9	38.5	58.9	4.2	2	PVI±SVC isolation or ablation of non-PV ectopy if any	DM	Age, LAD, LVEF, and the use of AAD
Chao [21]	24.9	38.2	59.9	4.2	2	PVI±SVC isolation or ablation of non-PV ectopy if any	HTN	Age, HTN, LAD, LVEF, LA total activation time and renal function
Chilukuri	29	N/A	58.0	6.4	3	PVI	HTN, BMI ^d , DM	Age, gender, AF duration, BMI, LAD, LVEF, persistent AF, HTN, DM, and OSA
Hwang [23]	24.9	N/A	62.6	5.1	2	PVI±linear ablation	HTN	age, HTN, persistent AF, PVI method, early recurrence of AF, LVEF, and LA volume index
Jongnarangsin [24]	29.6	44.0	56.0		2	PVI±CFAE	HTN, BMI 30	age, sex, BMI, type/duration of AF, OSA, LAD, LVEF, and HTN
Khaykin [25]	29	42.4	N/A	7.5	3	PVI±CFAE if AF persists	HTN	Early recurrence of AF, NPAF, HTN, LAD,

First author	Mean BMI (kg/m ²)	Mean LAD (mm)	Mean LVEF (%)	Mean AF duration (years)	Blanking period ^a	AF ablation strategy	MetS or its component assessed	Variables adjusted
Letsas [26]	26.1	40.6	54.8	5.5	1	PVI	HTN, BMI ^d , DM, dyslipidemia	ACEI/ARB use, number of failed AAD, CFAE ablation, and BMI, termination of AF during ablation
Letsas [27]	26.6	40.9	57.4		3	PVI	HTN	Age, gender, LVEF, LAD, LVEDD, type/duration of AF, HTN, DM, dyslipidemia, BMI, structural heart disease, AAD use after ablation, use of statins, ACEI, WBC, CRP, and fibrinogen level
Okumura [28]	25.1	N/A	N/A	5.9	2	PVI+CFAE if AF persists	HTN and BMI ^d	Fibrinogen level, uric acid level, HTN, and CRP
Patel [4]	27.1	42.6	52.9	N/A	N/A	PVI+linear ablation+SVC isolation	HTN and DM	NPAF, BMI, HTN, MMP-2, carboxyl-terminal telopeptide of collagen type I, and BNP level
Shah [10]	31	54.0	56.0	6.5	12 ^c	PVI	HTN and dyslipidemia	Age, LVEF, LAD, HTN, DM, CAD, non-PV triggers, and type of AF
Themistoclakis [29]	N/A	44.0	55.0	6.6	3	PVI+SVC isolation	Dyslipidemia	Duration of AF, dyslipidemia, HTN
Wong [30]	28	N/A	N/A	N/A	3	PVI+linear ablation	BMI ^d	Age, type/duration of AF, LAD, HTN, and SVC isolation
Berkowitsch [12]	27.0	N/A	60.0	5.0	3	PVI+CFAE/linear ablation if AF persists	MetS, BMI, 30, HTN, DM, TG, and HDL levels	LA volume and OSA, LVEF, sex, valvulopathy, BMI, and AF chronicity
Mohanty [6]	28.3	43.2	56.0	4.9	3	PVI+linear ablation+SVC isolation if PV-like potentials were recorded+CFAE if identified	MetS, obesity ^{d,e} , HTN, DM, and dyslipidemia	MetS factors, type of AF, LA area/body surface area, eGFR, LVEF, creatinine, age, ablation technique, intraprocedural cardioversion, DCM/HOCM, and uric acid level

AAD antiarrhythmic drugs, ACEI angiotensin converting enzyme inhibitor, AF atrial fibrillation, ARB angiotensin receptor blocker, BMI body mass index, BNP brain natriuretic peptide level, CAD coronary artery disease, CFAE (ablation of) sites with complex fractionated atrial electrograms, DM diabetes mellitus, GFR glomerular filtration rate, HDL low high-density lipoprotein levels, HTN hypertension, LAD left atrial diameter, LVEF left ventricular ejection fraction, LVEDD Left ventricular end-diastolic dimension, LVEDS Left ventricular end-systolic dimension, MetS metabolic syndrome, MMP metalloproteinase, N/A not available, NPAF nonparoxysmal atrial fibrillation, OSA obstructive sleep apnea, PA-PDI interval the time interval from the initiation of the P-wave deflection to the peak of the mitral inflow A-wave on pulse-wave Doppler imaging, PVI pulmonary vein isolation, SVC superior vena cava, TG hypertriglyceridemia

^aBlanking period: time to recurrence assessment, before which AF recurrence was not counted as a relapse [46]

^bProportion of coronary artery disease

^cVery late recurrence

^dAs a continuous variable

Defined as BMI $\geq$ 25 or waist circumference $\geq$ 102 cm in men and $\geq$ 88 cm in women

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Table 3

Meta-analysis of the risk of atrial fibrillation recurrence after catheter ablation associated with metabolic syndrome and its component factors

Exposures	No. of studies	Pooled estimates	<i>p</i> values for association	<i>I</i> -squared ^a (%) (95%CI)	<i>p</i> values for heterogeneity ^b
Metabolic syndrome	5	1.63 (1.25–2.12)	0.000	54 (0–83)	0.068
Hypertension	17	1.31 (1.13–1.51)	0.000	47 (8–70)	0.016
Obesity/overweight ^c	6	1.27 (0.99–1.64)	0.051	65 (16–85)	0.014
BMI ^d	5	1.00 (0.94–1.07)	0.961	11 (0–81)	0.343
DM	10	1.11 (0.97–1.26)	0.129	44 (0–73)	0.064
Hypertriglyceridemia	6	1.07 (0.89–1.29)	0.484	69 (27–87)	0.007
Low HDL level	3	0.98 (0.96–1.01)	0.120	(0–90)	0.985

BMI body mass index, *DM* diabetes mellitus, *HDL* low high-density lipoprotein, *MetS* metabolic syndrome

^a*I*² statistic described by Higgins et al. to assess heterogeneity

^bCochrane Q test for heterogeneity

^cAs defined in the original articles: BMI 25 [6, 8, 11, 13] and BMI 30 [12, 24]

^dAs a continuous variable

Table 4

Subgroup analyses and meta-regression for the risk of atrial fibrillation recurrence after catheter ablation associated with metabolic syndrome and its component factors

Exposures	Variables	Subgroup	No. of studies	Pooled estimates	p values for association	p values for heterogeneity ^b	p values from meta-regression
Metabolic syndrome	Mean age	Low (<median)	2	3.03 (1.70–5.40)	<0.001	0.394	0.083
		High (median)	3	1.39 (1.19–1.62)	<0.001	0.482	
HTN	Adjustment for other MetS components	No adjustment	7	1.62 (1.23–2.13)	0.001	0.085	Ref
		Adjusted for 1 additional component	5	1.30 (1.00–1.70)	0.05	0.118	0.286
		Adjusted for 2 additional components	5	1.08 (0.94–1.24)	0.295	0.454	0.042
	CFAE	No	10	1.54 (1.24–1.92)	<0.001	0.053	0.043
		Yes	7	1.12 (0.96–1.30)	0.15	0.272	
	Linear ablation	No	6	1.40 (1.09–1.78)	0.007	0.282	0.511
		Yes	11	1.29 (1.08–1.54)	0.005	0.015	
Obesity/overweight ^a	Proportion of HTN	Low (< median)	3	2.32 (1.20–4.50)	0.013	0.138	0.048
		High (median)	3	1.09 (0.97–1.23)	0.15	0.666	
	Adjustment for OSA	No	5	1.29 (0.98–1.70)	0.071	0.006	0.852
		Yes	1	1.24 (0.53–2.90)	0.62	–	
	Report of follow-up length	No	2	2.97 (1.61–5.50)	0.001	0.267	0.025
		Yes	4	1.10 (0.97–1.23)	0.135	0.826	
DM	Adjustment for other MetS components	No adjustment	1	3.25 (1.21–8.72)	0.019	–	Ref
		Adjusted for 1 additional component	3	1.20 (0.87–1.64)	0.263	0.011	0.102
		Adjusted for 2 additional components	6	1.07 (0.95–1.20)	0.29	0.897	0.074
Dyslipidemia	Timing of recurrence assessment	Investigated very late recurrence (>12 months)	1	4.01 (1.84–8.73)	<0.001	–	0.026
		Investigated recurrence after 2–3 months	5	1.00 (1.00–1.00)	0.994	0.429	

BMI body mass index, *HTN* hypertension, *CFAE* (ablation of) sites with complex fractionated atrial electrograms, *DM* diabetes mellitus, *Ref* reference group, *OSA* obstructive sleep apnea

^a As defined in the original articles: *BMI* 25 [6, 8, 11, 13] and *BMI* 30 [12, 24]

^b Cochrane Q test for heterogeneity