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UNIVERSITÀ DEGLI STUDI DI TORINO

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Introduction

The risk of atrial fibrillation (AF) in patients affected by diabetes mellitus (DM) is increased and likely multifactorial (1,2). DM, both type 1 and type 2, impact coronary micro- and macrovasculature and as such results in left ventricular diastolic dysfunction and, consequently, atrial structural remodeling (3). In addition, patients with DM have higher levels of systemic inflammatory markers, particularly in the setting of poor glycemic control (4). Chronic systemic inflammation can result locally in higher levels of atrial myocyte breakdown and fibrosis (5), and as a consequence provides sources of AF initiation and maintenance. Finally, diabetic autonomic neuropathy can increase the risk of AF occurrence (6), in particular incidence of asymptomatic AF, and potentially raises the risk of thromboembolic events (7).

Catheter ablation of AF (AFCA) is a well-established treatment option for patients with symptomatic AF refractory to antiarrhythmic drugs (AADs) (8,9). Despite a relatively high incidence of late recurrences, long-term efficacy in maintaining sinus rhythm (SR) is encouragingly high, especially if compared to the long-term efficacy and tolerance of pharmacologic approaches (10). DM patients are often included among patients undergoing AFCA, and although this procedure has been reported more effective in achieving rhythm control compared to AADs in general (11), data concerning this subset population are limited to small, short-term studies and may not be specifically generalized. Therefore, the present systematic review and meta-analysis aims to investigate the long-term outcome of AFCA in patients with DM, focusing on procedural safety, long-term efficacy in achieving rhythm control, and predictors of recurrence, to improve knowledge in search of predictors of recurrence that could improve candidatesô choice, or direct towards treatment of patientsô reversible factors that may negatively impact the outcome of the procedure.

Methods

The present study was conducted in accordance to current guidelines, including the recent Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement, as well as recommendations from The Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) (12,13).

Search strategy and study selection

MEDLINE/PubMed and Cochrane database were searched for pertinent articles published in English from 2002 until October 2013, according to published recommendations (14). The following terms: ñatrial fibrillationò AND ñcatheter ablationò AND (ñdiabetes mellitusò OR ñdiabetic patientsò) were used to identify all the published articles referring to this specific population. A second search was then performed using the following terms: ñatrial fibrillationò AND ñcatheter ablationò AND (ñlong-term outcomeò OR ñlong-term resultsò), to retrieve published articles referring to long-term results of this procedure among the general population; among them, all the studies presenting a mean follow-up of at least 2 years were selected, and the corresponding Author was contacted for quantitative details on DM patients (established diagnosis or use of glucose lowering drugs and/or insulin), offering coauthorship in this work. Each included study was approved by an institutional review committee and all subjects gave informed consent.

Data extraction

Retrieved citations were first screened independently by 2 unblinded reviewers (authors: M.A. and M.M.) with divergences resolved after consensus. If the citations were deemed potentially pertinent, they were then appraised as complete reports according to the following explicit selection criteria:

(i) human studies, (ii) published between 2002 and October 2013, (iii) investigating patients affected by type 1 or type 2 DM, or (iv) studies with unselected patients undergoing AFCA with a mean follow-up of at least 2 years. Exclusion criteria were (one enough for exclusion): (i) non-human setting, (ii) duplicate reporting (in which case the manuscript reporting the largest sample of patients was selected), (iii) studies including patients undergoing surgical or hybrid AF ablation, or (iv) studies without comprehensive follow-up description, including duration and AF recurrence rates. DM was defined as current treatment with glucose-lowering drugs or previous diagnosis of DM according to current recommendations (15).

Statistical analysis

Continuous variables were reported as mean (standard deviation) or median (range), and categorical variables as n (%), weighted for sample size of each study and according to standard error by logarithmic transformation. Funnel plot analysis was used to evaluate potential publication bias, and Cochran Q2 tests and I2 to investigate heterogeneity. Using rates of event as dependent variables, a meta-regression analysis was performed to test whether an interaction between baseline clinical features (age, body mass index [BMI], paroxysmal AF and basal glycated hemoglobin level), and incidence of AF recurrences was present. Due to the observational design of most of the included studies, random effect was performed for all analysis. Statistical analyses were performed with Comprehensive Metanalysis (Trial Version) and Review Manager.

Results

Search results

As highlighted in Figure 1 and Representative Figure, the first search identified 85 abstracts referring to AFCA in DM patients; among this group, 74 were excluded following application of the inclusion and exclusion criteria; 11 of them were selected and full text was read by two Authors; 7 were excluded because of incomplete baseline or follow-up characteristics. Four trials were finally included (11,16-18) meeting all the pre-specified inclusion criteria.

The second search identified 681 abstracts referring to long-term results of AFCA; among them, 646 were excluded following application of the inclusion and the exclusion criteria. Thirty-five of them were selected and full text was read by two Authors; 11 were excluded because of incomplete baseline or follow-up characteristics, 4 because reporting duplicate data and one because DM patients were not included. Following this selection approach, 19 trials were identified, and the corresponding Author contacted, offering co-Authorship in return for data concerning DM patients. Besides 8 Authors which could not participate, due to the fact that the required data were not easily or promptly available from their dataset, 11 provided requested data regarding DM patients (19-29).

First Author, study design, publication date and main characteristics of each included study are reported in Table 1.

Baseline patients characteristics

A total of 1,464 patients with DM were finally included from 15 studies. Based on the X studies reporting this detail X% were type I and X% type 2 DM patients. Baseline characteristics are shown in Table 2. Mean age from each study ranged from 55 to 65 years, and 33% were women. Paroxysmal AF accounted for 65% of the population. Concerning pharmacological therapy, 55% of

the patients were treated with AADs at the time of ablation, and 85% were on oral anticoagulants. The majority of patients received oral glucose-lowering drugs, and 15% were on insulin treatment.

Catheter ablation protocol and complications

AFCA procedural features are reported in Table 3. Major procedural complication rates ranged from 1.5 to 5.0% (mean 3.5%). The most frequent complications were related to the access site and to cerebral thromboembolic events. Redo procedures were performed in 37 (27-43)% of the cases.

Follow-up and recurrences

Mean follow-up was 27 months, ranging from 20 to 33 months. Recurrences were defined, consistently within all the studies, as episodes of AF or atrial tachycardia or atypical atrial flutter lasting at least 30 seconds detected during follow-up, with a blanking period of 3 months after ablation (Table 1). Overall long-term efficacy in SR maintenance after AFCA was 66 (58-73)% (Figure 2). Freedom from AF after a single procedure ranged, instead, from 41 to 56%. As illustrated in Figure 3, the number of patients receiving AADs significantly decreased during follow-up from 55 (46-74)% to 29 (17-41)% ($p<0.001$).

A meta-regression analysis (Figure 4) was performed to assess whether an interaction between relevant baseline clinical features and incidence of AF recurrence was present: advanced age (Beta 0.12 [0.09 - 0.15], $p<0.001$), higher basal glycated hemoglobin levels (Beta 0.5 [0.1 - 0.9], $p<0.001$) and higher BMI (Beta 0.08 [0.01-0.15], $p<0.001$) related to a higher AF recurrence rate. Paroxysmal vs. persistent AF (Beta 0.001 [-0.002 - 0.13], $p=0.81$), instead, did not relate to AF recurrences.

Discussion

Current evidences regarding the safety and efficacy of AFCA in DM patients are based on small trials or observational studies enrolling up to 150 patients. The real world safety and efficacy of AFCA in subset populations requires multicenter experiences. By not including available literature only but directly contacting each Corresponding Author of published long-term AFCA experiences, the present collaborative multicenter meta-analysis is the first study, to the best of our knowledge, to include a relevant number of patients with DM. These data are clinically significant because, as previously discussed, DM patients are prone to develop AF, often present more comorbid disease states, and are at higher risk for AF complications such as stroke (8) and heart failure (5). Effective treatment by AFCA may therefore warrant significant benefits not only in terms of symptoms control but also in reducing the risk of complications related to AF and/or to its pharmacological treatment in patients with DM.

Based on the present analysis, AFCA in patients with DM reports an overall complication rate of 3.5 (1.5-5.0)%. This incidence is similar to that reported amongst the general AFCA populations (10) and, although a direct comparison between DM and non-DM patients was not performed, these results provide indirect evidence that the procedure does not relate to disproportionate procedural risks.

Similar to safety, the long-term SR maintenance rates were favorable, compared to available data concerning efficacy of AADs therapy in the general population. In this multi-center analysis approximately half of the patients were free from AF following the first procedure. With the inclusion of redo procedures the long-term SR maintenance rate improved to 66%: this result is comparable to long-term outcomes reported in general AFCA populations, that typically include patients with both their first and redo ablations (10,30). The relatively large proportion (37%) of patients requiring more than one procedure to achieve effective long-term SR maintenance may be

explained by the aforementioned complexity of the electrical and anatomical atrial substrate and metabolic alterations of DM patients (4,5). Furthermore, the frequent need for redo procedures in this large population did not result in a linear increase in procedural complications. The included studies cover a wide temporal interval, however this did not influence: baseline characteristics and AF ablation outcome did not differ among patients included in the earliest (e.g. Pappone, 2003) compared to youngest (e.g. Hunter, 2012, Neumann 2013) studies. Of note, follow-up monitoring included periodic Holter ECG assessments in almost all studies, except Bunch et al. that were driven by clinical symptoms and ECG only, while Vogt et al. and Neumann et al. required 7-days Holter recordings. Despite these discrepancies study design also did not significantly influence incidence of recurrences. The only notable difference that emerges, instead, relates to follow-up durations: longer follow-up studies (e.g. Bunch, 2011) report higher recurrence rates compared to shorter follow-up studies.

DM patients with AF carry a worse prognosis than those in SR (31). Therefore, safe and effective rhythm control treatments that prove to be able to maintain SR long-term may reduce or negate the long-term negative impact of AF in DM patients, turning into prognostic positive effects. Other AF treatment options present, in fact, several limitations. Previous studies have reported higher recurrence rates after AF electrical cardioversion for patients with compared to those without DM (32), and lower efficacy of AADs in animal studies (33). In addition, DM patients may be more exposed to the frequent and potentially harmful adverse effects of AADs treatment, due to the large prevalence of silent ischemic heart disease and heart failure (31). For these reasons the finding that AFCA may, at least, reduce the proportion of patients requiring pharmacological treatment with AADs during follow-up is, indeed, clinically relevant.

Based on the present meta-regression analysis, advanced age, high BMI and higher basal glycated hemoglobin levels relate to higher AF recurrence rates, suggesting a role for DM-related metabolic alterations in promoting arrhythmic recurrences. The role of the electroanatomical atrial myocites

alterations described in patients with DM, magnified by the concomitant presence of obesity (one of the markers of the metabolic syndrome) (4,5) emerges, in fact, more evidently than AF duration (paroxysmal or persistent AF) and other ñclassicalò recurrence predictors (34). This finding, deviant from what is documented in the general population, is also sustained by the need, despite inclusion of a majority of paroxysmal AF patients (65%), for frequent redo procedures and wide substrate modification (linear lesions and/or CFAE ablation in the left atrium) to achieve effective long-term rhythm control. Optimal glyco-metabolic control and weight reduction may, therefore, be crucial to optimize AF management (35,36,37) and enhance ablation outcomes (38). In fact, a one point increase in basal glycated hemoglobin raised by 0.5 the odds ratio of AF relapse during the long-term follow-up, suggesting that even small changes in DM control can impact outcomes. Finally, an interaction between left atrial enlargement and AFCA outcome was not identified: this surprising finding may most probably be explained by the very large prevalence of patients with enlarged left atrium (over 80%) included in the analysis.

Limitations

This study presents the following limitations. First, AFCA is a relatively recent and developing procedure, with different centers using different protocols and tools. AFCA procedural characteristics may grow heterogeneity; however, in this study safety and efficacy outcomes did not present time-related trends. This limitation therefore serves also as strength, as these data provide a real world understanding of AFCA outcomes and as such are more likely to replicate individual practices. Second, DM is a progressive disease, even in case of optimal glycemic control, and the heterogeneity among DM patients, with its variable progression over follow-up, may affect atrial substrate properties and consequently AFCA outcome. Additionally, being type I DM patients scarcely represented (<X%), results cannot be generalized specifically to this subset of patients.

Third, the low prevalence of patients with obstructive sleep apnea syndrome, impaired renal function, and on insulin treatment (compared to oral glucose-lowering drugs) may reflect a selection, in each individual study, of patients with less severe DM and lower comorbidities/complications, limiting generalization of the results to this setting of patients. Fourth, although heterogeneity was appraised by random effect, this meta-analysis, in order to include the largest amount of data available from current literature, combines randomized controlled trials with observational studies. The enrolled population may therefore be affected by selection bias of single centersô experience and preference in referring patients to AFCA. Finally, meta-regression analysis does not allow clinicians to drive causative inferences, but only speculative. The absence of a control population, although data are indirectly compared to previously published meta-analyses performed on the general population, may limit the strength of the results. The focus of the present work, however, is to detect predictors of outcome intrinsic to DM patients, useful to improve candidatesô choice, or direct towards treatment of patientsô reversible factors that may negatively impact outcome. Large prospective multicenter clinical trials are however warranted to precisely define AFCA safety and efficacy in this group of patients.

Conclusion

AFCA complications rate and long-term SR maintenance in patients with DM are comparable to those reported amongst the general population, although with a relatively frequent need of redo procedures. Performing the procedure among younger patients with an optimal glycol-metabolic control may be crucial to improve outcome. Eventually, AFCA is related to a subsequent reduced need of AADs, limiting the risk of their frequent adverse effects.

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M.A. conceived the design of this work. M.A. and M.M. reviewed the literature, performed the selection of the studies and wrote the manuscript. F.D.A. performed the statistical analyses and contributed to write the manuscript. C.P., V.S., T.J.B, T.N., R.J.S, R.J.H, G.N., M.F., A.F., G.T., D.K., P.J., R.W. and J.M.K. retrieved the required data from their centersô population and revised the manuscript. F.G. revised and approved the final version of the manuscript.

Conflicts of interest: none.

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Table 1. First Author, publication date, population and main characteristics of the included studies.

First Author, Country, Year of Publication	Study design	N. patients	Follow-up (months)	AF recurrence monitoring	Paroxysmal AF (%)	Age (years)	Baseline AADs use (%)	SR at follow-up end (%)
Forleo, Italy, 2009 (11)	Randomized, multi center	35	12	ECG and 24-hours Holter ECG at 1, 3 and every 3 months	46	63	-	80
Tang, China, 2006 (16)	Prospective, single center	31	13	ECG and 24-hours Holter ECG at 1, 3, 6 and 12 months	81	62	-	68
Chao, Taiwan, 2010 (17)	Retrospective , single center	65	19	ECG and 24-hours Holter ECG at 2 weeks and every 1 to 3 months	-	56	35	81
Gu, China, 2011 (18)	Prospective, single center	150	23	ECG and 24-hours Holter ECG at 2 weeks, 1, 3, 6, 9, 12 and every 6 months	-	59	55	76
Pappone, Italy, 2003 (19)	Prospective controlled trial, single center	589	46	ECG and 24-hours Holter ECG at 1, 3, 6, 12 and every 6 months	69	61	67	69
Gaita, Italy, 2008 (20)	Randomized controlled trial, single	43	21	ECG and 24-hours Holter ECG at 1, 3, 6, 12, 18 and 24	49	62	76	61

	center			months				
Katritsis, Greece, 2008 (21)	Prospective, single center	5	43	ECG and 24-hours Holter ECG at 6 weeks and every 3 months	100	65	-	60
Pappone, Italy, 2011 (22)	Randomized controlled trial, single center	5	48	ECG and 48-hours Holter ECG at 3, 6, 12 months	100	60	-	60
Medi, Australia, 2011 (23)	Retrospective, single center	2	31	ECG and 24-hours Holter ECG at 3, 6, 12 and every 6 months	100	59	50	0
Weerasooriya, France, 2011 (24)	Prospective, single center	3	56	ECG and 24-hours Holter ECG at 1, 3, 6, 12 and every 12 months	100	58	100	33
Bunch, USA, 2011 (25)	Retrospective, single center	342	58	ECG and visit at 3, 6, 12 and every 12 months	48	68	54	47
Hunter, UK, 2012 (26)	Retrospective, multi center	60	42	ECG and 24-hours Holter ECG at 3, 6, 12 and every 12	42	62	-	72

				months				
Neumann, Germany, 2013 (27)	Prospective, single center	63	33	ECG and 7-days Holter ECG at 3, 6, 9, 12 and every 12 months	52	61	63	60
Vogt, Germany, 2013 (28)	Prospective, single center	44	18	ECG and 7-days Holter ECG at 3, 6, 9, 12 months; ECG every 6 months later	95	63	74	61
Fiala, Czech Republic, 2014 (29)	Prospective, single center	27	37	ECG and 24-hours Holter ECG at 3, 6, 12 and every 6 months; tele-ECG for 3 weeks	0	63	26	63

AF: atrial fibrillation. AADs: antiarrhythmic drugs. SR: sinus rhythm. ECG: electrocardiogram.

Table 2. Baseline characteristics of the study population (1,464 patients).

	Mean Value (Lower-Upper 95% CI)
Age, years	62 (55-65)
Female gender, %	33 (24-48)
BMI, kg/m^2	30 (27-32)
Mean follow-up, months	27 (20-33)
Basal glycated hemoglobin, %	6.8 (5.5-8.1)
Type of AF - Paroxysmal, % - Persistent, % - Long standing persistent, %	 65 (54-67) 21 (19-26) 14 (10-19)
Duration of AF, months	42 (34-49)
EHRA class - *I, %* - *II, %* - *III or IV, %*	 *18 (17-27)* *21 (16-29)* *41 (35-48)*
Hypertension, %	80 (75-91)
Prior stroke or TIA, %	6.0 (4.0-11.5)
Cardiomiopathy - Ischemic, % - Hypertensive, % - Valvular heart disease, % - Idiopathic, %	 17 (14-31) 12 (8-19) 1.5 (0.5-5.0) 5.0 (3.0-7.0)
QRS duration, msec	94 (85-100)
Previous electrical cardioversion, %	67 (56-71)

Impaired renal function (eGFR < 60) ml/min), %	9.0 (4.0-13.0)
Thyroid disease	
- Hyperthyroidism, %	4.5 (3.2-9.5)
- Hypothyroidism, %	14 (6-21)
Dyslipidemia, %	41 (35-56)
- LDL levels, mg/dl	117 (90-125)
- HDL levels, mg/dl	50 (43-63)
- Triglycerides levels, mg/dl	180 (145-210)
Chronic lung disease, %	7.5 (6.0-9.0)
Obstructive sleep apnea, %	7.0 (5.0-12.0)
Baseline medical therapy, %	
- Anti-arrhythmic drugs, %	55 (46-74)
- Beta blockers, %	78 (67-81)
- Oral anticoagulants, %	85 (80-89)
- Aspirin, %	15 (11-15)
Oral glucose lowering drugs use, %	85 (77-91)
- Biguanides, %	61 (50-65)
- Thiazolidinediones, %	5.0 (3.0-8.0)
- Dipeptidyl Peptidase-4 inhibitors, %	5.0 (2.0-8.5)
- Sulfonylureas, %	44 (27-51)
Insulin use, %	15 (12-21)
LV ejection fraction, %	56 (50-61)
LV diastolic dysfunction, %	67 (61-74)
Left atrium area, cm^2	27 (22-29)

CI: confidence interval. BMI: body mass index. AF: atrial fibrillation. TIA: transient ischemic attack. LV: left ventricular.

Table 3. Catheter ablation procedural features and long-term rates of SR maintenance of the study population (1,464 patients)

	Mean Value (Lower-Upper 95% CI)
First ablation procedure	
PV isolation, %	100 (100-100)
PV isolation alone, %	72 (56-81)
Left isthmus line, %	21 (16-34)
Roof line, %	17 (11-20)
CFAE, %	7.0 (3.0-11.0)
Fluroscopy time, minutes	26 (15-34)
Procedural time, hours	3.1 (1.5-3.3)
Post procedural cardioversion, %	21 (17-34)
Overall complications, %	3.5 (1.5-5.0)
Access site complications, %	1.5 (0.5-3.0)
Stroke/TIA, %	1.0 (0.5-2.0)
Cardiac tamponade, %	1.0 (0.5-1.5)
Others, %	0.5 (0.5-1.0)
Redo procedure, performed in 37 (27-43)% of the patients	
Time after first procedure, months	12 (7-21)
PV isolation, %	97 (90-100)
PV isolation alone, %	44 (29-55)
Left isthmus line, %	50 (45-53)
Roof line, %	30 (20-37)
CFAE, %	15 (11-19)
Overall complications, %	3.0 (0-6.0)

Access site complications, %	1.5 (0-3.0)
Stroke/TIA, %	1.5 (0-3.0)
Cardiac tamponade, %	0
First procedure efficacy, % Final efficacy, %	50 (41-56) 66 (58-73)

CI: confidence interval. PV: pulmonary veins. CFAE: complex fractionated atrial electrograms. TIA: transient ischemic attack.

Figure legends

Figure 1. Search criteria and flow chart of the studies screened and included in the systematic review. AF: atrial fibrillation. DM: diabetes mellitus.

Figure 2. Forest plot of the included studies concerning atrial fibrillation recurrence rate at follow-up end, highlighting the statistic relevance of the results from each single study. CI: confidence interval.

Figure 3. Medical therapy at baseline and follow-up end (1,464 patients), showing significant reduction in AADs ($p<0.001$) and oral anticoagulants ($p<0.001$) use during follow-up. AADs: antiarrhythmic drugs.

Figure 4. Meta regression analysis assessing the impact of age (A, Beta 0.12 [0.09 - 0.15], $p<0.001$), BMI (B, Beta 0.08 [0.01-0.15], $p<0.001$), paroxysmal AF (C, Beta 0.001 [-0.002 - 0.13], $p=0.81$), and basal glycated hemoglobin level (D, Beta 0.5 [0.1 - 0.9], $p<0.001$) on long-term incidence of AF recurrences. AF: atrial fibrillation. BMI: body mass index.

Figure 1.

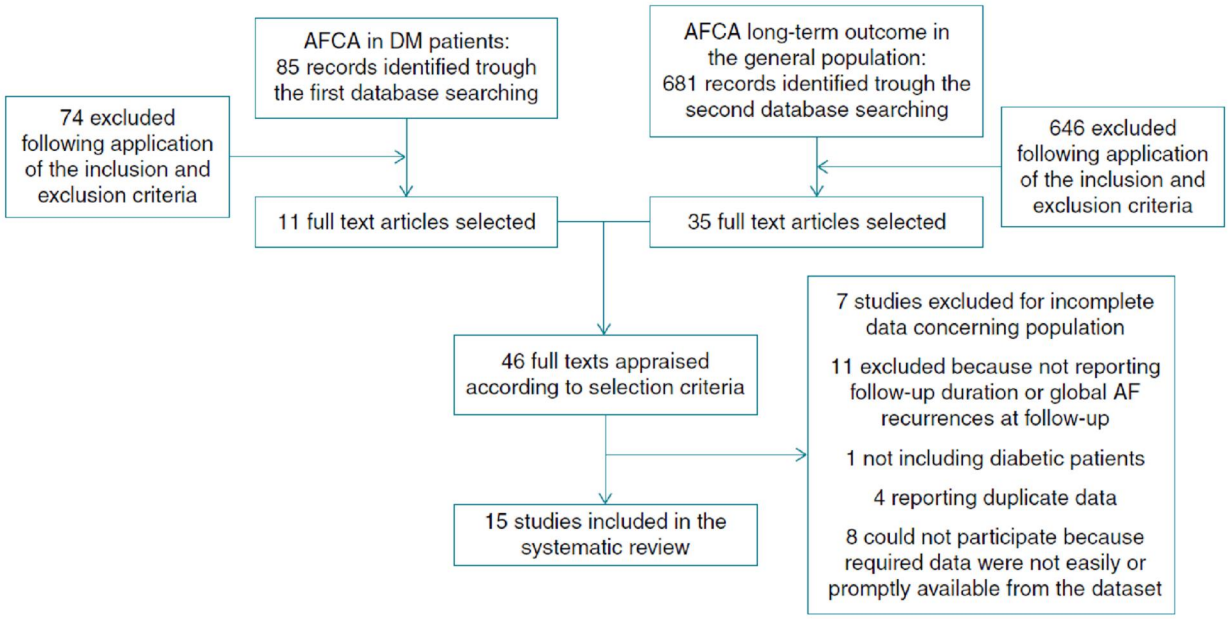
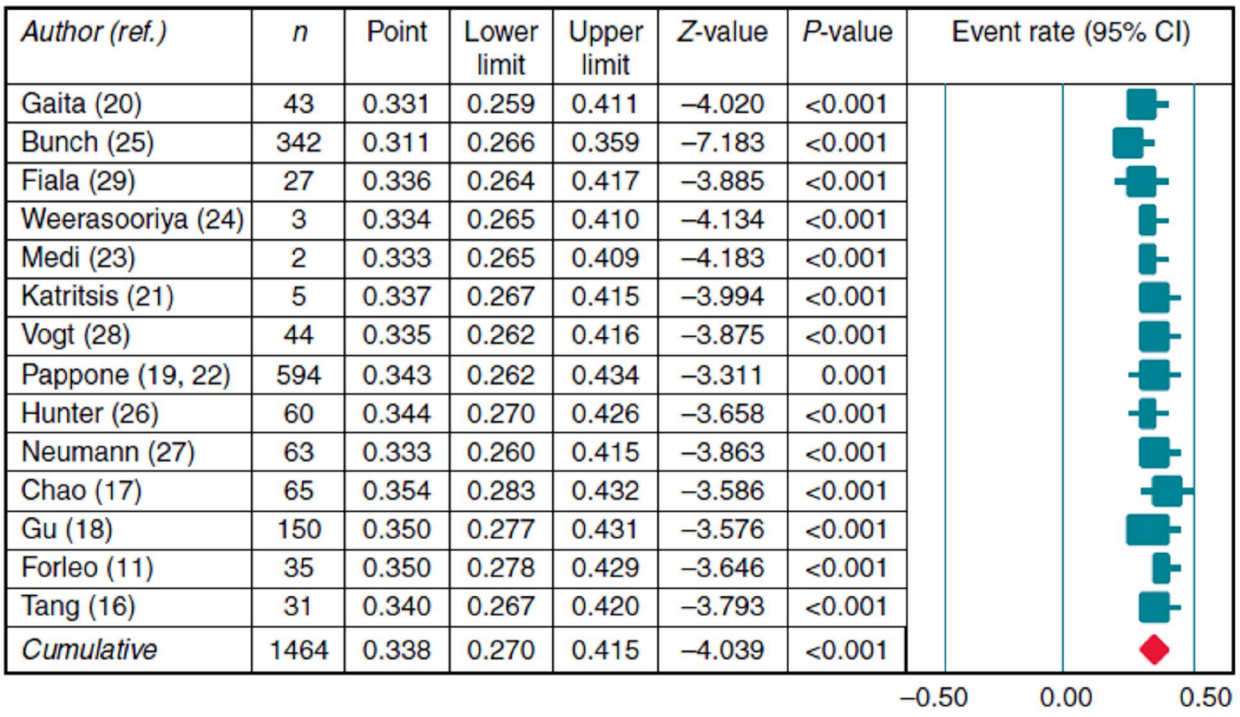


Figure 2.



Author (ref.)	*n*	Point	Lower limit	Upper limit	*Z*-value	*P*-value	Event rate (95% CI)
Gaita (20)	43	0.331	0.259	0.411	–4.020	<0.001	
Bunch (25)	342	0.311	0.266	0.359	–7.183	<0.001	
Fiala (29)	27	0.336	0.264	0.417	–3.885	<0.001	
Weerasooriya (24)	3	0.334	0.265	0.410	–4.134	<0.001	
Medi (23)	2	0.333	0.265	0.409	–4.183	<0.001	
Katritsis (21)	5	0.337	0.267	0.415	–3.994	<0.001	
Vogt (28)	44	0.335	0.262	0.416	–3.875	<0.001	
Pappone (19, 22)	594	0.343	0.262	0.434	–3.311	0.001	
Hunter (26)	60	0.344	0.270	0.426	–3.658	<0.001	
Neumann (27)	63	0.333	0.260	0.415	–3.863	<0.001	
Chao (17)	65	0.354	0.283	0.432	–3.586	<0.001	
Gu (18)	150	0.350	0.277	0.431	–3.576	<0.001	
Forleo (11)	35	0.350	0.278	0.429	–3.646	<0.001	
Tang (16)	31	0.340	0.267	0.420	–3.793	<0.001	
Cumulative	1464	0.338	0.270	0.415	–4.039	<0.001	

Figure 3.

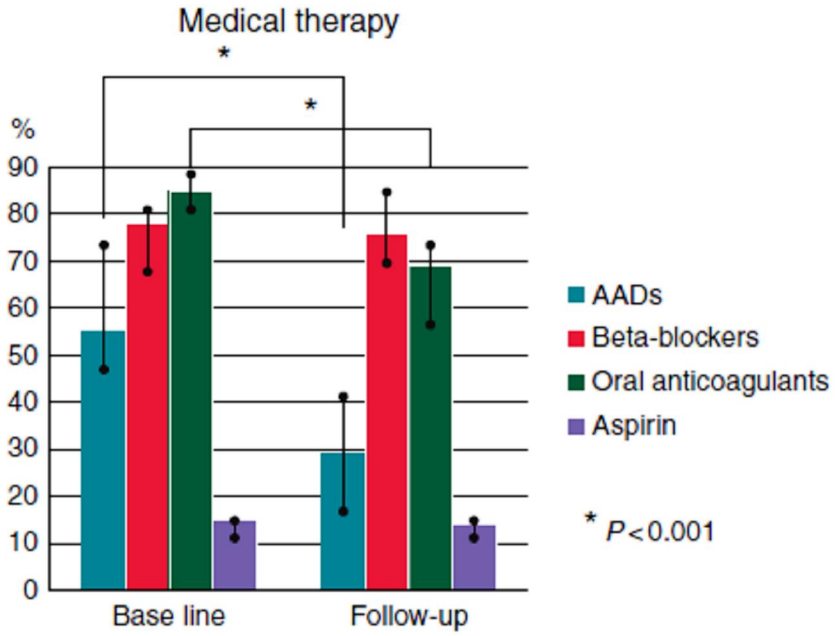


Figure 4.