European Society of Cardiology
Europace (2019) **21**, 1509–1518
doi:10.1093/europace/euz179

CLINICAL RESEARCH
Ablation for atrial fibrillation

Sex-related differences in catheter ablation of atrial fibrillation: a systematic review and meta-analysis

Xiaocheng Cheng[1], Qiongwen Hu[2], Lei Gao[1], Jian Liu[1], Shu Qin[1], and Dongying Zhang [1]*

[1]Department of Cardiology, The First Affiliated Hospital of Chongqing Medical University, 1 Youyi Rd, Chongqing 400016, China; and [2]Department of Clinical Laboratory, Chongqing General Hospital, Chongqing 400014, China

Received 29 December 2018; editorial decision 1 June 2019; accepted 5 June 2019; online publish-ahead-of-print 8 July 2019

Aims The sex-related differences in the clinical outcomes of rhythm and safety after catheter ablation remain unclear. The purpose of this study was to compare the clinical outcomes of catheter ablation for atrial fibrillation (AF) in women and men.

Methods and results The Medline and EMBASE databases were searched for published articles up to December 2018. Studies that met our predefined inclusion criteria were included. The primary endpoints were freedom from AF/atrial tachycardia (AT) recurrence, stroke/transient ischaemic attack (TIA), and all-cause mortality. After literature search and detailed assessment, 19 observational studies (151 370 patients; 34% women) were identified. Our analyses showed that the rate of freedom from AF/AT recurrence was lower in women than men at the 2.4-year follow-up [odds ratio (OR): 0.75, 95% confidence interval (CI) 0.69–0.81; $P < 0.0001$]. Moreover, women had an increased risk of stroke/TIA (OR: 1.42, 95% CI 1.21–1.67; $P < 0.0001$) and all-cause mortality (OR: 1.53, 95% CI 1.02–2.28; $P = 0.04$). Nevertheless, for the endpoint of all-cause mortality, there was no significant difference between the two genders in the subgroup of prospective studies (OR: 1.19, 95% CI 0.69–2.05; $P = 0.53$). Additionally, women were more likely to experience major complications compared with men (pericardial effusion/tamponade, major bleeding requiring transfusion, and pacemaker implantation).

Conclusions Women who underwent catheter ablation of AF might experience lower efficacy and a higher risk of stroke/TIA and major complications than men. The reasons for these sex-related differences need to be further studied.

Keywords Atrial fibrillation • Catheter ablation • Sex • Meta-analysis

Introduction

Over the past two decades, catheter ablation has emerged as a safe and effective therapy for the management of atrial fibrillation (AF) and has been associated with a reduction in AF burden and stroke, as well as with improvement in symptoms and quality of life. Catheter ablation is currently recommended as a reasonable alternative first-line therapy for the treatment of drug-resistant AF.[1] Despite the high efficacy of catheter ablation, the number of women who undergo pulmonary vein (PV) isolation is remarkably less than that of men.[2] Additionally, the majority of studies that investigate rhythm and safety outcomes of catheter ablation for AF have consisted predominantly of males.[2,3] Patient stratification and individualized therapy are crucial to optimizing the effectiveness and safety of catheter ablation. However, there is a paucity of data on the effectiveness and safety of catheter ablation in a large cohort study of women. Therefore, we conducted a systematic review and meta-analysis to investigate the clinical outcomes associated with catheter ablation of AF in women vs. men.

* Corresponding author. Tel: +86 150 2531 6809; fax: +86 23 6621 5269. *E-mail address:* cqmezdy@yeah.net

What's new?

- The sex-related differences in the clinical outcomes of rhythm and safety after catheter ablation of atrial fibrillation (AF) remain unclear. Nineteen observational studies with a total of 151 370 patients were identified.
- Our study showed that female sex might be associated with a lower proportion of patients free from AF/atrial tachycardia recurrence after catheter ablation. Moreover, female sex had an increased risk of stroke/transient ischaemic attack and major complications compared with male sex.
- Our data provided physicians and their patients with real-world information about sex-specific outcomes of catheter ablation of AF. The reasons for these sex-related differences need to be further studied.

Methods

Data sources and searches

To identify all the published clinical studies that compared outcomes of catheter ablation of AF in women and men, we performed a comprehensive online search of the literature through the Medline and EMBASE databases (to December 2018), without language restriction. The retrieval strategy used relevant keywords and medical subject heading terms including the following: 'atrial fibrillation', 'gender', 'sex', 'men', 'women', 'male', 'female', 'pulmonary vein isolation', and 'ablation' both separately and in combination. The bibliographies of the reviewed manuscripts were manually retrieved to avoid missing relevant data.

Study selection

Studies were included if they reported primary endpoints of interest in patients undergoing catheter ablation of AF and if they provided detailed information on women vs. men within the main article or subgroup. Catheter ablation was defined as an endocardial ablation procedure (radiofrequency or cryoablation). Inclusion criteria were as follows: (i) studies had to provide reliable data on the assessment of at least one of the primary endpoints; (ii) to minimize the risk of small-study effects, all studies were required to have a minimum of 500 individuals; and (iii) endpoints were reported as numerical events rather than only as hazard ratios, relative risk, or odds rate. If relevant data were not reported in the published articles, we tried to contact the corresponding authors to acquire further information. To ensure that studies were eligible for the prespecified inclusion criteria, retrieval results were reviewed by three authors (C.X., H.Q., and G.L.), who needed to agree on study selection.

Outcomes and definitions

The primary endpoints were the incidence rates of freedom from AF/atrial tachycardia (AT) recurrence, stroke/transient ischaemic attack (TIA), and all-cause mortality. Secondary endpoints were major complications including: pericardial effusion/tamponade, major bleeding requiring transfusion, permanent pacemaker implantation (PMI), PV stenosis, and acute coronary syndrome (ACS). Freedom from AF/AT recurrence was defined as no episode of AF, flutter or tachycardia $\geq$30 s in duration after a 1- or 3-month blanking period off of antiarrhythmic drugs (AADs). Stroke/TIA and all-cause mortality were defined as new onset of stroke/TIA and death from any cause occurring during hospitalization or follow-up. Acute coronary syndrome was defined as acute myocardial infarction (MI) or unstable angina. PV stenosis was defined as moderate to severe stenosis of PV or PV stenosis requiring therapeutic intervention.

Data extraction and quality assessment

Data extraction and presentation for the preparation of this manuscript followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Supplementary material online, *Table S1*).[4] Data abstraction was conducted by three authors (C.X., H.Q., and G.L.), who independently used a predefined, standardized protocol, and data collection instrument. The following study-, patient-, and procedure-related data were extracted from the main paper. Any discrepancies were resolved by discussion among the authors. The Newcastle–Ottawa Quality Assessment Scale (NOS) for observational trials was used to evaluate the quality of the included studies.[5] The NOS scale consists of eight questions with nine possible points. We judged the data based on the selection of populations, the comparability of the groups, and the exposure/outcome of interest by a star system.

Data synthesis and analysis

The odds ratio (OR) with 95% confidence intervals (CIs) was used to analyse dichotomous data, whereas continuous variables were analysed using weighted mean differences. The presence of heterogeneity among studies was evaluated by the Cochran Q test, and the extent of the observed heterogeneity was evaluated by the Higgins I^2 test, which suggests 0–25%, 25–50%, and 50–75% as low, moderate, and high heterogeneity, respectively. In view of the intrinsic differences in study design and demographics, a random-effects model was used to estimate the pooled effects of our meta-analyses.

For the primary endpoints, prespecified sensitivity analyses were performed by iteratively removing one study at a time to confirm that our results were not significantly affected by any single study. Multiple subgroup analyses (according to study design, study quality, and age of patients) were performed to further test the stability of our meta-analysis. To inspect the effect of preselected covariates on the overall effect, we conducted a random-effects meta-regression analysis. The logarithm of OR for the primary endpoints, weighted by the inverse variance of each study, was regressed against age, percentage of hypertension, diabetes mellitus (DM), coronary artery disease (CAD), stroke, smoking history, left ventricular ejection fraction (LVEF), and size of left atrial (LA) diameter in both groups. To detect any publication bias in the primary endpoints, we examined in detail the asymmetry of the funnel plots and further assessed them using the Begg adjusted rank correlation test and the Egger regression asymmetry test. The RevMan software package (Review Manager, Version 5.3) and STATA software 12.0 were used to perform all statistical analyses. *P*-values were two-tailed, and *P*-value $<$0.05 was considered statistically significant.

Results

Characteristics of included studies

Initially, 4461 potentially relevant studies were identified by our search strategy. A total of 4388 of these were excluded according to the evaluation of the title and abstract (*Figure 1*). Fifty-four of the remaining studies were excluded after detailed full-text review as follows: lack of outcomes of interest ($n=23$), duplicates ($n=10$), reviews ($n=7$), sample size <500 ($n=7$), surgical epicardial ablation ($n=5$), and insufficient dates for analysis ($n=2$). After critical appraisal, 19 studies (nine prospective and 10 retrospective

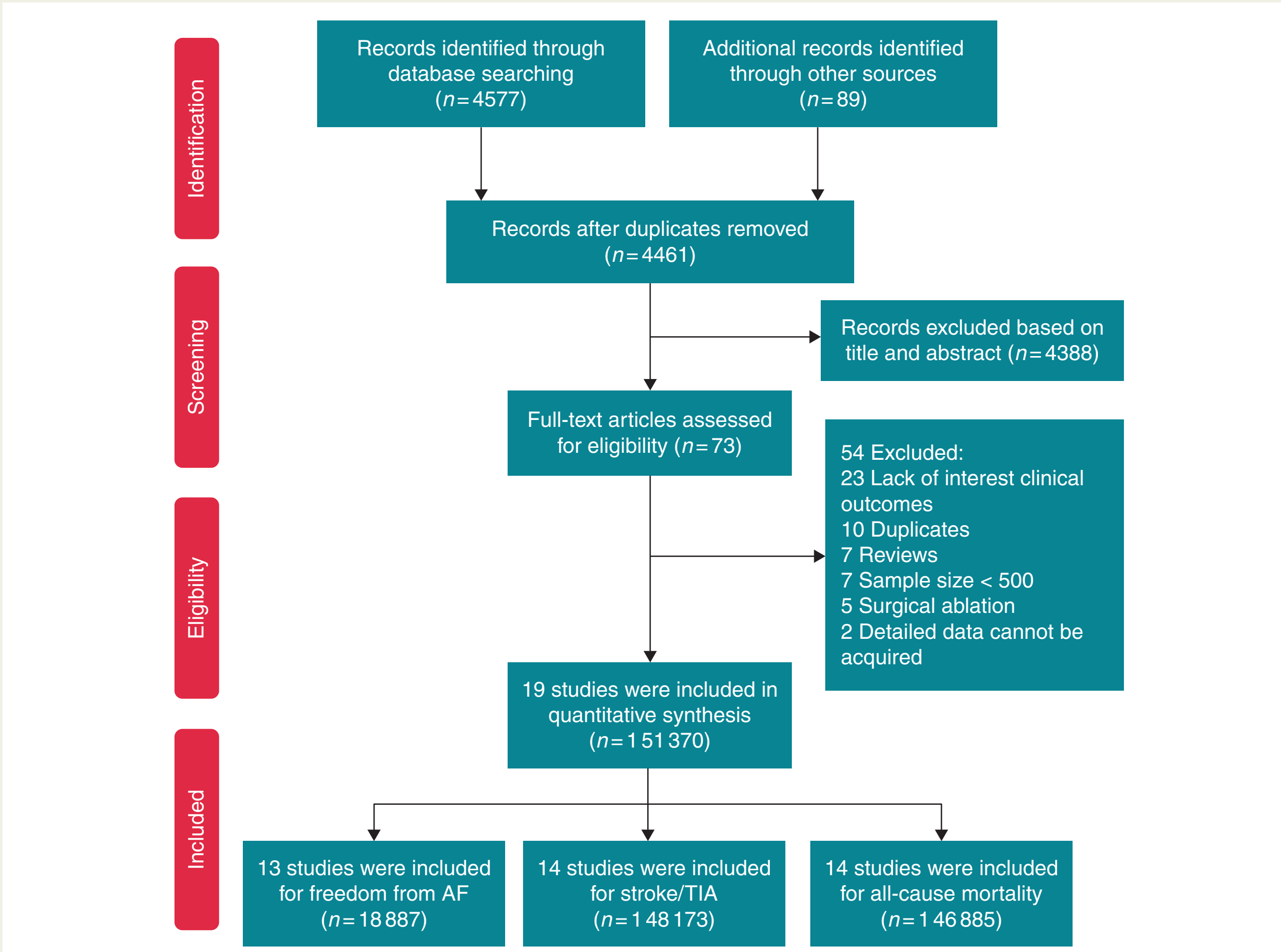

Figure 1 Flow diagram of the study selection process. AF, atrial fibrillation; TIA, transient ischaemic attack.

observational studies) published between 2010 and 2018 met our eligibility criteria and reported desired clinical endpoints of catheter ablation in women compared with men.[6–24]

Table 1 summarizes the baseline characteristics of the included studies. Of the 151 370 patients, 50 846 (34%) women underwent catheter ablation for AF. Because different demographics existed in the endpoints of rhythm and safety outcomes, we summarized baseline demographics for freedom from AF/AT recurrence and complications, respectively (*Table 2*). For the endpoints of freedom from AF/AT recurrence, women undergoing catheter ablation were more likely to be older and to have previous stroke and hypertension. In contrast, men were more likely to have previous DM, CAD, and MI and to have enlarged LA diameter, increased body mass index and less paroxysmal AF (*Table 2* and Supplementary material online, *Table S2*). For the endpoints of safety, women undergoing catheter ablation were more likely to be older and to have previous DM, hypertension, stroke, chronic kidney disease, and valvular heart disease. Men were more likely to have previous CAD, heart failure, and MI (*Table 2* and Supplementary material online, *Table S2*). Fifteen studies were evaluated as good quality (NOS ≥6), indicating a low risk of bias (Supplementary material online, *Table S3*).

Freedom from atrial fibrillation/at recurrence

Thirteen studies with 18 887 patients were included in the quantitative synthesis of freedom from AF/AT recurrence in women vs. men. Low heterogeneity was detected among these studies ($P = 0.30$; I^2 = 14%; Supplementary material online, *Figure S1*). Pooled analysis showed that the rate of freedom from AF/AT recurrence was significantly lower in women than men at the 2.4-year follow-up (61.2% vs. 68.6%; OR 0.75, 95% CI: 0.69–0.81; $P < 0.0001$). The sex-related difference in freedom from AF/AT recurrence was independent of follow-up time (at 1 year, OR: 0.74, 95% CI: 0.65–84; $P < 0.0001$; at 1–3 years, OR: 0.69, 95% CI: 0.59–81; $P < 0.0001$; at ≥3 years, OR: 0.73, 95% CI: 0.61–88; $P = 0.0007$; *Figure 2*). In addition, similar results were found in the subsets of patients without AAD therapy (OR: 0.75, 95% CI: 0.67–83; $P < 0.0001$; Supplementary material online, *Figure S2*), paroxysmal AF (OR: 0.71, 95% CI: 0.61–81; $P < 0.0001$),

Table 1 Baseline characteristics of the included studies

Study/(ref. #)	Year	Study design	Region	Single/ multicentre	PAF (%)	Size (*n*), (female %)	Reported primary outcomes	Follow-up (year)	NOS points
Arshad *et al.*[6]	2010	Retrospective Observational	United States	Single	463 (81.7)	567 (29)	Freedom from AF	1.00	6
Patel *et al.*[7]	2010	Retrospective Observational	United States	Multicentre	1743 (53.4)	3265 (16)	Freedom from AF, stroke/TIA, and mortality	2.81	6
Ammar *et al.*[8]	2011	Retrospective Observational	Germany	Single	503 (100.0)	503 (33)	Freedom from AF and stroke/TIA	3.40	5
Winkle *et al.*[9]	2011	Prospective Observational	United States	Single	270 (32.0)	843 (28)	Freedom from AF and mortality	2.40	6
Yagishita *et al.*[10]	2011	Retrospective Observational	Japan	Single	362 (69.1)	524 (19)	Freedom from AF, stroke/TIA, and mortality	3.67	5
Mohanty *et al.*[11]	2011	Prospective Observational	United States	Single	140 (24.6)	568 (27)	Freedom from AF	1.00	8
Zakeri *et al.*[12]	2012	Retrospective Observational	United States	Single	289 (40.9)	707 (26)	Freedom from AF	1.00	4
Shoemaker *et al.*[13]	2013	Prospective Observational	United States	Single	238 (46.5)	512 (29)	Mortality	In-hospital	6
Takigawa *et al.*[14]	2013	Retrospective Observational	Japan	Single	1124 (100.0)	1124 (23)	Freedom from AF, stroke/TIA, and mortality	3.25	7
Stabile *et al.*[15]	2015	Prospective Observational	Italian	Multicentre	NR	2323 (28)	Stroke/TIA and mortality	30 day	6
Kornej *et al.*[16]	2015	Prospective Observational	German	Single	1292 (62.4)	2069 (34)	Stroke/TIA	1.50	6
Zylla *et al.*[17]	2016	Prospective Observational	German	Multicentre	2350 (64.3)	3652 (33)	Freedom from AF, stroke/TIA, and mortality	1.00	5
Kaiser *et al.*[18]	2016	Retrospective Observational	United States	Multicentre	NR	21 091 (29)	Stroke/TIA and mortality	1.00	6
Ayoub *et al.*[19]	2017	Retrospective Observational	United States	Multicentre	NR	20 360 (50)	Stroke/TIA and mortality	In-hospital	7
Tanaka *et al.*[20]	2017	Prospective Observational	Japan	Multicentre	3229 (64.4)	5013 (27)	Freedom from AF, stroke/TIA, and mortality	2.90	6
Yu *et al.*[21]	2018	Prospective Observational	Korea	Single	557 (70.7)	788 (27)	Freedom from AF, stroke/TIA, and mortality	2.80	8
Kuck *et al.*[22]	2018	Prospective Observational	German	Multicentre	750 (100.0)	750 (39)	Freedom from AF, stroke/TIA, and mortality	1.50	6
Elayi *et al.*[23]	2018	Retrospective Observational	United States	Multicentre	NR	85 977 (32)	Stroke/TIA and mortality	In-hospital	6
Roh *et al.*[24]	2018	Retrospective Observational	Korea	Single	510 (69.5)	734 (50)	Freedom from AF, stroke/TIA, and mortality	4.58	8

AF, atrial fibrillation; NOS, Newcastle–Ottawa quality assessment Scale; NR, no record; PAF, paroxysmal atrial fibrillation; TIA, transient ischaemic attack.

Table 2 Baseline demographics in the included studies for the different endpoints

Dichotomous	The demographics of freedom from AF/AT: Total patients	Women, % (*n*)	Men, % (*n*)	*P*-value	The demographics of complications: Total patients	Women, % (*n*)	Men, % (*n*)	*P*-value
PAF	18 514	70.0 (3586)	63.1 (8454)	<0.0001	18 741	71.3 (3795)	64.8 (8698)	<0.0001
DM	12 291	8.6 (293)	10.4 (928)	0.0024	120 293	17.2 (6487)	15.1 (12447)	<0.0001
CAD	12 146	8.4 (283)	14.2 (1247)	<0.0001	120 008	13.8 (5187)	18.3 (15026)	<0.0001
Hypertension	9265	49.0 (1187)	41.2 (2821)	<0.0001	117 267	60.2 (22144)	54.8 (44129/)	<0.0001
Previous stroke	8072	5.8 (119)	4.0 (243)	0.0007	116 641	4.4 (1613)	3.1 (2503)	<0.0001
HF	7891	7.7 (199)	7.1 (377)	0.2862	31 051	23.8 (2237)	25.5 (5522)	0.0014
Prior MI	5526	2.2 (38)	4.7 (176)	<0.0001	112 594	3.9 (1368)	6.3 (4881)	<0.0001
VHD	5510	7.7 (140)	6.2 (230)	0.0463	26 601	1.8 (140)	1.2 (230)	0.0009
CKD	1302	1.5 (8)	1.8 (14)	0.7247	109 871	5.2 (1830)	4.4 (3265)	<0.0001
Continuous	**Total Patients**	**Women (Mean ± SD)**	**Men (Mean ± SD)**	***P*-value**	**Total Patients**	**Women (Mean ± SD)**	**Men (Mean ± SD)**	***P*-value**
Age (years)	18 514	63.2 ± 10.4	59.0 ± 13.6	<0.0001	125 809	64.4 ± 11.0	59.6 ± 11.1	<0.0001
BMI (kg/m^2)	8072	26.6 ± 6.2	27.1 ± 7.1	0.0046	9573	26.1 ± 5.7	26.9 ± 6.7	<0.0001
Duration (AF) (years)	8639	5.6 ± 7.2	5.3 ± 7.9	0.1156	7504	5.5 ± 7.4	5.3 ± 8.2	0.3478
LVEF (%)	7936	60.2 ± 8.6	55.4 ± 9.3	<0.0001	8730	60.4 ± 7.9	56.1 ± 9.3	<0.0001
LAD (mm)	8072	40.7 ± 6.6	43.3 ± 5.6	<0.0001	9573	40.7 ± 6.1	43.0 ± 5.8	<0.0001
Failed AADs (*n*)	5966	2.3 ± 1.7	1.8 ± 2.4	<0.0001	5966	2.3 ± 1.7	1.8 ± 2.4	<0.0001

AAD, antiarrhythmic drug; AF, atrial fibrillation; AT, atrial tachycardia; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; HF, heart failure; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAF, paroxysmal atrial fibrillation; SD, standard deviation; VHD, valvular heart disease.

single ablation procedure (OR: 0.82, 95% CI: 0.74–92; *P* = 0.0005), and studies with comparable baseline characteristics (OR: 0.68, 95% CI: 0.55–83; *P* = 0.0001).

Stroke/transient ischaemic attack

Fourteen studies were included in the analysis of stroke/TIA. There were 654 (0.44%) events among 148 173 participants. Pooled analysis showed that female sex was associated with an increased risk of stroke/TIA compared with male sex (0.51% vs. 0.41%; OR: 1.42, 95% CI: 1.21–1.67; *P* < 0.0001; I^2 = 0, *P* = 0.46; Supplementary material online, *Figure S3*). Similarly, the sex-related difference in the risk of stroke/TIA was independent of follow-up time (in-hospital 0.48% vs. 0.38%; OR: 1.44, 95% CI: 1.22–1.71; *P* < 0.0001; at 1-year follow-up 1.42% vs. 1.08%; OR: 1.32, 95% CI: 1.07–1.63; *P* = 0.009; *Figure 3*).

All-cause mortality

Fourteen studies with 146 885 patients investigated the sex-related difference in all-cause mortality. Moderate heterogeneity was detected in these studies (I^2 = 36%, *P* = 0.11; *Figure 4*), and there were 352 (0.24%) deaths during the in-hospital or follow-up periods. Pooled analysis showed that female sex was associated with a higher risk of all-cause mortality compared with male sex (0.27% vs. 0.22%; OR: 1.53, 95% CI: 1.02–2.28; *P* = 0.04; I^2 = 36%, *P* = 0.11; *Figure 4*). The sex-related difference in the risk of all-cause mortality was still significant during the in-hospital stay (OR: 0.17% vs. 0.12%; 1.57, 95% CI: 1.18–2.09; *P* = 0.002; Supplementary material online, *Figure S4*). There was no significant difference at 1-year follow-up (OR: 1.28 vs. 1.01%; 1.62, 95% CI 0.73–3.59; *P* = 0.24).

Major complications

Our analysis indicated that women undergoing catheter ablation of AF had an increased risk of pericardial effusion/tamponade (OR: 1.57, 95% CI: 1.31–1.88; *P* < 0.0001; *Figure 5A*), major bleeding requiring transfusion (OR: 2.46, 95% CI: 1.89–3.21; *P* < 0.0001; *Figure 5B*), PMI (OR: 2.44, 95% CI: 1.90–3.13; *P* < 0.0001; *Figure 5C*), and a trend towards an increasing risk of PV stenosis (OR: 2.11, 95% CI: 0.93–4.77; *P* = 0.07; *Figure 5D*). However, there was no significant difference in the risk of ACS between the two groups (OR: 0.78, 95% CI: 0.52–1.18; *P* = 0.24; *Figure 5E*).

Sensitivity, subgroup, and meta-regression analysis

Sensitivity analysis (using the single-study-removed method) showed good stability in the clinical endpoints of freedom from AF/AT recurrence, stroke/TIA, and all-cause mortality (Supplementary material online, *Figure S5*). Moreover, after excluding the largest sample size study by Elayi *et al.*,[23] female sex was still associated with a higher risk of stroke/TIA (OR: 1.30, 95% CI: 1.02–1.65; *P* = 0.03) and a trend for increasing risk of mortality (OR: 1.73, 95% CI: 0.96–3.12; *P* = 0.07) compared with male sex. If the excluded studies with more than 200 patients (six studies involving 1598 patients) were included in the quantitative synthesis, we found that the result of each primary endpoint was still similar to previous findings (Supplementary material online, *Figure S6*). For endpoints of freedom from AF/AT recurrence and stroke/TIA, the results were similar to previous findings in the subgroup of prospective studies, older patients, and high-quality studies (Supplementary material online, *Table S4*). In the subgroup of

Study or Subgroup	Women Events	Women Total	Men Events	Men Total	Weight	Odds Ratio M-H, Random, 95% CI
Freedom from AF/AT at 1 year follow-up						
Arshad *et al.* 2010	110	164	274	403	9.4%	0.96 [0.65, 1.41]
Winkle *et al.* 2011	121	169	368	465	8.7%	0.66 [0.44, 0.99]
Mohanty *et al.* 2011	98	154	304	414	9.1%	0.63 [0.43, 0.94]
Zakeri *et al.* 2012	134	184	424	523	9.2%	0.63 [0.42, 0.93]
Takigawa *et al.* 2013	222	260	784	864	8.3%	0.60 [0.39, 0.90]
Zylla *et al.* 2016	575	1155	1280	2346	44.0%	0.83 [0.72, 0.95]
Kuck *et al.* 2018	215	293	369	457	11.3%	0.66 [0.46, 0.93]
Total (95% CI)		2379		5472	100.0%	0.74 [0.65, 0.84]
Total events	1475		3803			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.90$, df = 6 ($P = 0.33$); $I^2 = 13\%$						
Test for overall effect: Z = 4.71 ($P < 0.00001$)						
Freedom from AF/AT at 1 to 3 years follow-up						
Patel *et al.* 2010	355	518	2129	2747	26.4%	0.63 [0.51, 0.78]
Winkle *et al.* 2011	74	110	238	312	9.0%	0.64 [0.40, 1.03]
Takigawa *et al.* 2013	216	260	768	864	12.5%	0.61 [0.42, 0.90]
Tanaka *et al.* 2017	764	1370	2204	3643	36.6%	0.82 [0.73, 0.93]
Yu *et al.* 2018	134	215	417	573	15.5%	0.62 [0.44, 0.86]
Total (95% CI)		2473		8139	100.0%	0.69 [0.59, 0.81]
Total events	1543		4756			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 7.38$, df = 4 ($P = 0.12$); $I^2 = 46\%$						
Test for overall effect: Z = 4.53 ($P < 0.00001$)						
Freedom from AF/AT at ≥3 years follow-up						
Ammar *et al.* 2011	86	168	184	335	24.2%	0.86 [0.59, 1.25]
Winkle *et al.* 2011	38	59	121	163	8.2%	0.63 [0.33, 1.19]
Yagishita *et al.* 2011	77	97	352	427	11.0%	0.82 [0.47, 1.42]
Takigawa *et al.* 2013	206	260	750	864	26.0%	0.58 [0.41, 0.83]
Roh *et al.* 2018	262	367	280	367	30.6%	0.78 [0.56, 1.08]
Total (95% CI)		951		2156	100.0%	0.73 [0.61, 0.88]
Total events	669		1687			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.86$, df = 4 ($P = 0.58$); $I^2 = 0\%$						
Test for overall effect: Z = 3.39 ($P = 0.0007$)						

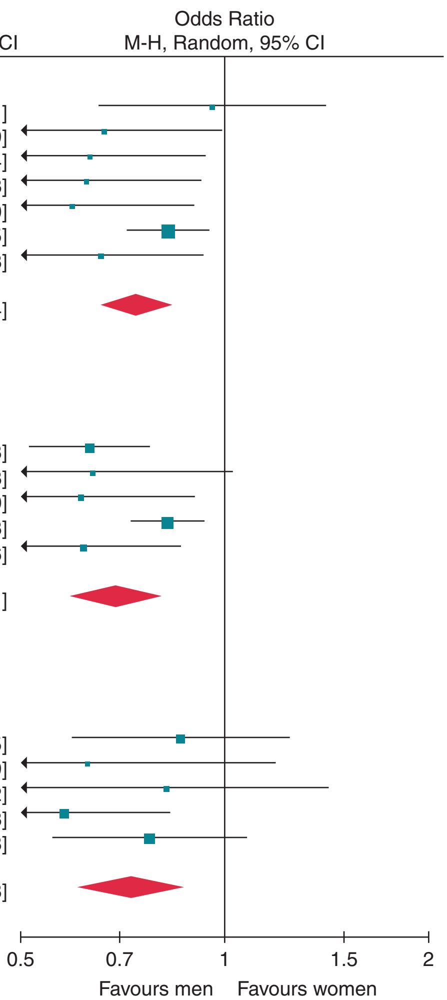

Figure 2 Forest plot of freedom from AF/AT in women vs. men at 1-, 1 to 3-, and ≥3-year follow-up after catheter ablation. AF, atrial fibrillation; AT, atrial tachycardia; CI, confidence interval.

retrospective studies, the risk of all-cause mortality was higher in women than in men (OR: 2.22, 95% CI 1.06–4.63; $P = 0.034$). However, there was no significant difference between the two genders in the subgroup of prospective studies (OR: 1.19, 95% CI: 0.69–2.05; $P = 0.53$). For the primary endpoints, meta-regression indicated that no significant correlation between the preselected covariates and the overall treatment effect of catheter ablation was observed (Supplementary material online, *Table S5*).

Publication bias

For the primary endpoints, visual inspection of the funnel plot including all studies showed symmetry, indicating a low risk of publication bias (Supplementary material online, *Figure S7*). Moreover, Egger and Begg tests showed that no significant potential publication bias existed in each primary endpoint ($P_{begg} = 0.669$ and $P_{egger} = 0.138$ for freedom from AF/AT recurrence; $P_{begg} = 0.827$ and $P_{egger} = 0.660$ for stroke/TIA; $P_{begg} = 0.533$ and $P_{egger} = 0.171$ for all-cause mortality).

Discussion

Incorporating the available published evidence, we found that the rate of freedom from AF/AT recurrence was lower in women than men after catheter ablation of AF. Moreover, women might have an increased risk of stroke/TIA and all-cause mortality compared with men. Additionally, women were more likely than men to experience pericardial effusion/tamponade, major bleeding, and pacemaker implantation.

In agreement with a prior study,[25] our data showed that 66.5% of patients were free from AF/AT at the 2.4-year follow-up. Despite a higher prevalence of paroxysmal AF and less enlargement of LA diameter, long-term success rates were lower in females than males. Patel *et al.*[7] found that females experienced more AF recurrence than males after PV isolation. It was noted that females scheduled to undergo ablation in this study were older and had less paroxysmal AF and more comorbidities, which were attributed to more advanced structural remodelling and led to lower success rates. However, two

Study or Subgroup	Women Events	Women Total	Men Events	Men Total	Weight	Odds Ratio M-H, Random, 95% CI
In-hospital stroke/TIA						
Patel *et al.* 2010	4	518	17	2747	2.3%	1.25 [0.42, 3.73]
Ammar *et al.* 2011	3	168	3	335	1.1%	2.01 [0.40, 10.08]
Takigawa *et al.* 2013	1	260	6	864	0.6%	0.55 [0.07, 4.61]
Stabile *et al.* 2015	7	643	4	1680	1.8%	4.61 [1.35, 15.81]
Kornej *et al.* 2015	7	696	8	1373	2.7%	1.73 [0.63, 4.80]
Zylla *et al.* 2016	3	1197	10	2452	1.7%	0.61 [0.17, 2.23]
Kaiser *et al.* 2016	52	6137	95	14954	24.3%	1.34 [0.95, 1.88]
Ayoub *et al.* 2017	6	10180	10	10180	2.7%	0.60 [0.22, 1.65]
Yu *et al.* 2018	0	215	2	573	0.3%	0.53 [0.03, 11.09]
Kuck *et al.* 2018	2	293	2	457	0.7%	1.56 [0.22, 11.16]
Elayi *et al.* 2018	146	27821	199	58156	61.2%	1.54 [1.24, 1.90]
Roh *et al.* 2018	2	367	1	367	0.5%	2.01 [0.18, 22.21]
Total (95% CI)		48495		94138	100.0%	1.44 [1.22, 1.71]
Total events	233		357			
Heterogeneity: Tau² = 0.00; Chi² = 10.16, df = 11 (*P* = 0.52); I² = 0%						
Test for overall effect: Z = 4.31 (*P* < 0.0001)						
Stroke/TIA at ≥1 year follow-up						
Ammar *et al.* 2011	7	168	15	335	5.2%	0.93 [0.37, 2.32]
Yagishita *et al.* 2011	2	97	1	427	0.7%	8.97 [0.80, 99.93]
Kornej *et al.* 2015	14	696	17	1373	8.6%	1.64 [0.80, 3.34]
Zylla *et al.* 2016	11	1115	21	2258	8.1%	1.06 [0.51, 2.21]
Kaiser *et al.* 2016	91	6137	165	14954	65.6%	1.35 [1.04, 1.75]
Tanaka *et al.* 2017	14	1370	33	3643	11.0%	1.13 [0.60, 2.12]
Roh *et al.* 2018	3	367	1	367	0.8%	3.02 [0.31, 29.13]
Total (95% CI)		9950		23357	100.0%	1.32 [1.07, 1.63]
Total events	142		253			
Heterogeneity: Tau² = 0.00; Chi² = 4.46, df = 6 (*P* = 0.61); I² = 0%						
Test for overall effect: Z = 2.62 (*P* = 0.009)						

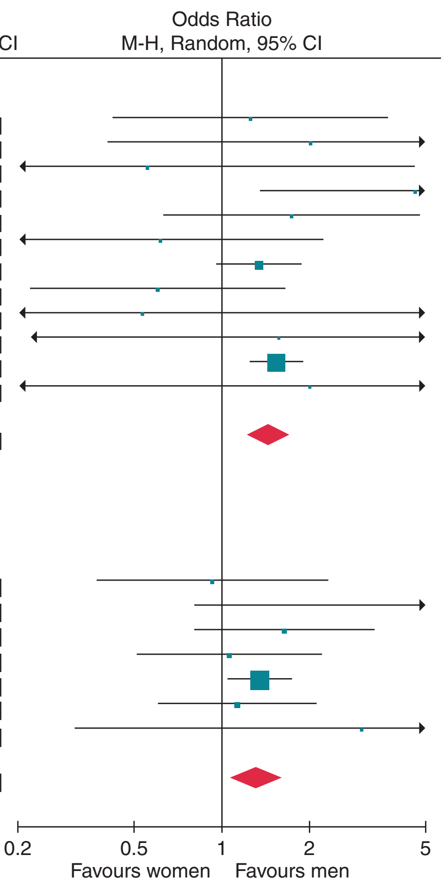

Figure 3 Forest plot of stroke/TIA in women vs. men in-hospital and ≥1-year follow-up after catheter ablation. CI, confidence interval; TIA, transient ischaemic attack.

Study or subgroup	Women Events	Women Total	Men Events	Men Total	Weight	Odds ratio M-H, random, 95% CI
Patel *et al.* 2010	5	518	0	2747	1.8%	58.86 [3.25, 1066.02]
Winkle *et al.* 2011	7	235	7	608	10.2%	2.64 [0.91, 7.60]
Yagishita *et al.* 2011	3	97	7	427	6.9%	1.91 [0.49, 7.54]
Shoemaker *et al.* 2013	1	146	0	366	1.5%	7.56 [0.31, 186.57]
Takigawa *et al.*2013	0	260	2	864	1.7%	0.66 [0.03, 13.84]
Stabile *et al.* 2015	0	643	0	1680		Not estimable
Zylla *et al.* 2016	6	1180	19	2391	12.3%	0.64 [0.25, 1.60]
Kaiser *et al.* 2016	4	6137	3	14954	6.0%	3.25 [0.73, 14.53]
Ayoub *et al.* 2017	3	10180	1	10180	2.9%	3.00 [0.31, 28.85]
Tanaka *et al.* 2017	30	1380	76	3643	25.2%	1.04 [0.68, 1.60]
Yu *et al.* 2018	0	215	0	573		Not estimable
Kuck *et al.* 2018	1	293	1	457	2.0%	1.56 [0.10, 25.06]
Elayi *et al.* 2018	73	27821	103	58156	29.5%	1.48 [1.10, 2.00]
Roh *et al.* 2018	0	367	0	367		Not estimable
Total (95% CI)		49472		97413	100.0%	1.53 [1.02, 2.28]
Total events	133		219			
Heterogeneity: Tau² = 0.12; Chi² = 15.71, df = 10 (*P* = 0.11); I² = 36%						
Test for overall effect: Z = 2.07 (*P* = 0.04)						

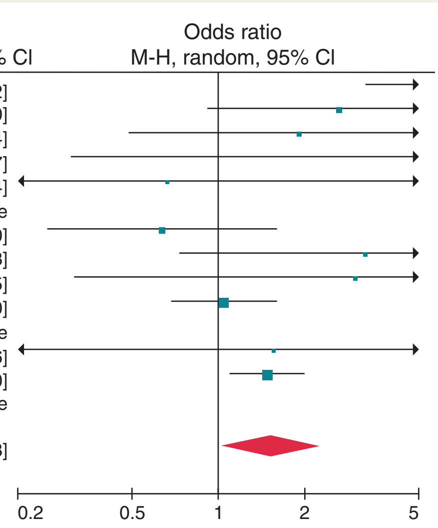

Figure 4 Forest plot of all-cause mortality in women vs. men after catheter ablation.

Study or subgroup	Women Events	Women Total	Men Events	Men Total	Weight	Odds ratio M-H, random, 95% CI	
Pericardial effusion/tamponade (A)							
Patel *et al.* 2010	2	518	8	2747	1.3%	1.33 [0.28, 6.27]	
Ammar *et al.*2011	6	168	5	335	2.1%	2.44 [0.74, 8.13]	
Takigawa *et al.* 2013	6	260	15	864	3.2%	1.34 [0.51, 3.48]	
Zylla *et al.* 2016	18	1198	18	2454	6.3%	2.06 [1.07, 3.98]	
Kaiser *et al.* 2016	234	6137	427	14954	31.4%	1.35 [1.15, 1.59]	
Ayoub *et al.* 2017	54	10180	18	10180	8.9%	3.01 [1.76, 5.14]	
Yu *et al.* 2018	1	215	8	573	0.7%	0.33 [0.04, 2.65]	
Kuck *et al.* 2018	4	293	2	457	1.1%	3.15 [0.57, 17.30]	
Elayi *et al.* 2018	1577	27821	2414	58156	40.0%	1.39 [1.30, 1.48]	
Roh *et al.* 2018	24	367	10	367	5.0%	2.50 [1.18, 5.30]	
Total (95% CI)		47157		91087	100.0%	1.57 [1.31’ 1.88]	
Total events	1926		2925			(I^2 = 41%, P = 0.08)	P < 0.00001
Major bleeding requiring transfusion (B)							
Yagishita *et al.* 2011	2	97	0	427	0.8%	22.38 [1.07, 469.99]	
Zylla *et al.* 2016	36	1115	30	2259	18.7%	2.48 [1.52, 4.05]	
Ayoub *et al.* 2017	47	10180	18	10180	16.3%	2.62 [1.52, 4.51]	
Tanaka *et al.* 2017	34	1370	55	3643	21.7%	1.66 [1.08, 2.56]	
Elayi *et al.* 2018	325	27821	243	58156	42.5%	2.82 [2.38, 3.33]	
Total (95% CI)		40583		74665	100.0%	2.46 [1.89, 3.21]	
Total events	444		346			(I^2 = 42%, P = 0.14)	P < 0.00001
Permanent pacemaker implantation (C)							
Zylla *et al.* 2016	50	1198	34	2454	31.9%	3.10 [1.99, 4.82]	
Kaiser *et al.* 2016	1	6137	1	14954	0.8%	2.44 [0.15’ 38.97]	
Tanaka *et al.* 2017	77	1370	75	3643	65.7%	2.22 [1.64, 3.02]	
Roh *et al.* 2018	2	367	2	367	16%	1.00 [0.14, 7.14]	
Total (95% CI)		9072		21418	100.0%	2.44 [1.90, 3.13]	
Total events	130		132			(I^2 = 0%, P = 0.52)	P < 0.00001
Pulmonary vein stenosis (D)							
Patel *et al.* 2010	6	518	12	2747	68.8%	2.67 [1.00, 7.15]	
Ammar *et al.* 2011	1	168	1	335	8.6%	2.00 [0.12, 32.17]	
Takigawa *et al.* 2013	1	260	1	864	8.7%	3.33 [0.21, 53.46]	
Zylla *et al.* 2016	1	1115	4	2251	13.9%	0.50 [0.06, 4.52]	
Total (95% CI)		2061		6197	100.0%	2.11 [0.93, 4.77]	
Total events	9		18			(I^2 = 0%, P = 0.57)	P = 0.07
Acute coronary syndrome (E)							
Takigawa *et al.* 2013	0	260	1	864	1.6%	1.10 [0.04, 27.20]	
Zylla *et al.* 2016	2	115	5	2257	6.0%	0.81 [0.16, 4.18]	
Kaiser *et al.*2016	44	6137	172	14954	63.9%	0.62 [0.45, 0.87]	
Elayi *et al.* 2018	14	27821	23	58156	28.5%	1.27 [0.65, 2.47]	
Total (95% CI)		35333		76231	100.0%	0.78 [0.52, 1.18]	
Total events	60		201			(I^2 = 19%, P = 0.30)	P = 0.24

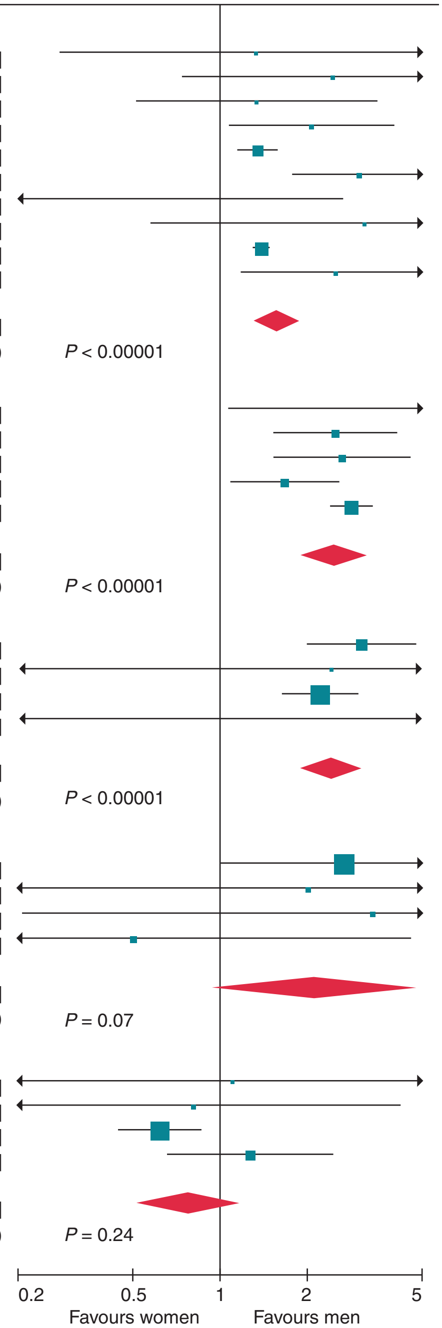

Figure 5 Forest plot of pericardial effusion/tamponade (*A*), major bleeding requiring transfusion (*B*), permanent pacemaker implantation (*C*), pulmonary vein stenosis (*D*), and acute coronary syndrome (*E*) in women vs. men after catheter ablation. CI, confidence interval.

studies with comparable baselines also found that women experience higher recurrence than men.[11,21] Moreover, in the subset of patients with a single ablation procedure and patients off AAD, the results were also similar to our findings. Sex-specific differences in physiological, electrical, and structural characteristics of the atria, which might result in higher AF recurrence in the female than male sex, include lower repolarizing ion currents, prolonged action potential duration in female atria, greater frequency of non-pulmonary triggered activity, and more pronounced AF-associated fibrotic remodelling.[7,26,27]

It is well established that females with AF have an increased risk for stroke in comparison with males even after adjustment for risk factors.[28] In accordance with previous findings,[29] 0.44% in-hospital stroke/TIA was reported in our study. The risk of stroke/TIA was 1.4-fold higher in-hospital stay and was 1.3-fold higher at the 1-year follow-up in women than in men. The increased risk of stroke/TIA may be explained by three factors. First, women undergoing PV isolation were older with increased comorbidities. Second, the long-term success rate was lower in women. Third, genetic factors, vascular biology, hormonal, or thromboembolic factors that differ between women and men might lead to a higher risk of stroke.[27] It is important for physicians to discuss the ongoing risks and benefits of anticoagulant therapy, particularly when coupled with a high CHA_2DS_2-VASc score and the high likelihood of recurrence of AF.

In the present study, the risk of in-hospital mortality was extremely low (~0.14%). These findings were in line with the 0.06–0.60% estimated death risk for catheter ablation of AF.[30,31] Several studies have attempted to address potential sex-specific differences in the risk of death,[17,18] and showed no obvious difference between women and men. It was notable that the findings of these studies were limited by small sample sizes. Our data analysed over 140 000 patients and found that female sex might be associated with an increased risk of all-cause mortality, especially for in-hospital mortality. The increased risk of death may be partially explained by the fact that women undergoing catheter ablation were older and had increased comorbidities and major complications. Nevertheless, there was no significant difference between the two genders in the subgroup of prospective studies. Thus, considering the discrepancy of baseline characteristics and the inconsistent findings between retrospective and prospective studies, our findings on all-cause mortality still need to be confirmed in the future.

Our data showed that female sex was associated with a significantly increased risk of major complications after catheter ablation, which agreed with previous findings.[18,19] Michowitz *et al.*[32] found that women have a 1.83-fold higher risk for developing cardiac tamponade, slightly higher than our results (1.57-fold). The increased risk of major bleeding might be due to the higher prevalence of chronic kidney disease in women than men. The increased risk of PMI in women may be explained by the fact that women were more often prescribed AAD therapy than invasive catheter ablation,[33] and excessive use of AAD may potentially trigger symptomatic bradycardia. A possible explanation for sex-related differences in major complications in women was that females were more likely to be older and to have increased comorbidities. Nevertheless, Ayoub *et al.*[19] conducted a propensity score-matched study and confirmed that females were at higher risk of developing post-operative major complications than males. A higher complication risk in women suggested that incremental caution and preoperative discussion of anticipated risk in women are completely necessary.

Strengths and limitations

Our analysis included 19 studies (available in the literature to date) from multiple centres and countries. It is the largest study aiming to provide physicians and their patients with real-world information about sex-specific outcomes of catheter ablation. However, this meta-analysis has several limitations. First, 10 of these included studies are retrospective in nature, subjecting our results to possible bias. Although we tried to conquer this limitation by the fulfilment of multiple sensitivity and subgroup analyses and meta-regression analyses, selection bias could still not be ruled out. Second, for clinical endpoints of safety, female sex undergoing catheter ablation had increased preoperative cardiovascular risk. Whether the poorer in-hospital and long-term outcomes after catheter ablation in women can be counterbalanced by these increased risks of intervention are unclear. Third, detailed information regarding AF type, strategy of ablation, and perioperative medication use (AAD, β-blocker, platelet inhibitors, and anticoagulant) in most studies was not available. Therefore, unmeasured confounders may exist in our findings. Lastly, the available data in studies did not allow for a separate analysis for cardiac and non-cardiac death, haemorrhagic, and non-haemorrhagic stroke.

Conclusions

In summary, data from our meta-analysis suggested that female sex might be associated with a lower proportion of patients free from AF/AT recurrence after catheter ablation of AF. Moreover, female sex was associated with an increased risk of stroke/TIA. In addition, major complications were more often in the female sex. The reasons for these sex-related differences in catheter ablation of AF need to be further studied.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: none declared.

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Corrigendum

doi:10.1093/europace/euz242
Online publish-ahead-of-print 29 August 2019

Corrigendum to: Gorenek B, et al. Cardiac arrhythmias in acute coronary syndromes: position paper from the joint EHRA, ACCA, and EAPCI task force [*Europace* 2014;**16**:1655–1673]

In the original version of the above article, Steen B. Kristiansen was omitted from the author list in error. This has now been corrected online.