


BMJ Open Long-term mortality of patients ablated for atrial fibrillation: a retrospective, population-based epidemiological study in Apulia, Italy

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ABSTRACT

Objectives Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia associated with substantial morbidity and mortality. Data on long-term risk and mortality after catheter ablation for AF are lacking. The aim of this study was to evaluate all-cause mortality and the long-term risk of death in patients who underwent catheter ablation for AF compared with the general population.

Design Retrospective, population-based epidemiological study.

Setting We analysed data from patients residing in Apulia region who underwent AF ablation between January 2009 and June 2019.

Participants 1260 patients (914 male, mean age 60±11 years).

Outcomes Vital status and dates of death to 31 December 2019 were obtained by using regional Health Information System. The expected number of deaths was derived using mortality rates from the general regional population by considering age-specific and gender-specific death probability provided for each calendar year by the Italian National Institute of Statistics. Standardised mortality ratios (SMRs) were calculated by dividing the observed number of deaths among patients by the expected number of deaths estimated from the general population.

Results During follow-up (6449 person-years), 95 deaths were observed (1.47 deaths per 100 person-years). Although overall long-term mortality after AF ablation was not different to that of the general population (SMR 1.05 (95% CI 0.86 to 1.28; p=0.658)), the number of observed events was significantly increased in patients with heart failure (HF) at baseline or who developed HF during follow-up (SMR 2.40 (1.69 to 3.41; p<0.001) and 1.75 (1.17 to 2.64; p=0.007), respectively) and reduced in those without (SMR 0.63 (0.47 to 0.86; p=0.003)).

Conclusion Long-term mortality of patients undergoing AF ablation is similar to that of the general population. Patients with HF had an increased risk while those without seem to have a better risk profile.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 1%–2% of the general population.¹ AF

Strengths and limitations of this study

- A strength of the study is that it allowed for analysis of long-term mortality among patients who underwent catheter ablation for atrial fibrillation compared with regional and national age-specific and gender-specific rates.
- An important limitation is that our study only involves patients from the Apulia region, which may limit its generalisability to other Italian regions or foreign countries.
- Another limitation is that data are from a single institution that is a reference centre for percutaneous ablation of arrhythmias; the applicability of results to other institutions or populations of patients with a different risk profile may be limited.

is associated with substantial morbidity and mortality, thus portending significant burden to patients, societal health and health economy. Subjects with AF are more likely than subjects without AF to have cardiovascular disease risk factors and pre-existing disease, including heart failure (HF).^{2–4}

Mid-term risk of death in patients with AF varies according to the clinical setting: from 16.4 deaths per 100 person-years of patients hospitalised in a cardiology ward⁵ to a rate of 3.7 fatal events per 100 person-years in patients with AF enrolled in anticoagulation trials having mortality as an outcome.⁶ In real-world patients with AF, the incidence of death is estimated to be, respectively, 1.0 and 3.6 per 100 person-years in those ablated and non-ablated who receive medical therapy (antiarrhythmic drugs or rate control drugs).⁷ Compared with subjects without AF, in a longitudinal population-based cohort, AF has been detected as a multivariate predictor of death that remained associated with mortality also in subjects initially free of clinically relevant

cardiovascular disease.⁴ Among death predictors, HF is included in prognostic scores to evaluate mortality risk of patients with AF.^{5,6}

Catheter ablation has become an important treatment modality for patients with symptomatic drug-refractory paroxysmal and non-paroxysmal AF.⁸ Furthermore, several randomised clinical trials have reported that both AF and HF outcomes can be improved with catheter ablation.^{9–12} In a meta-analysis of randomised clinical trials evaluating patients with AF and coexisting left ventricular systolic dysfunction, catheter ablation has been associated with significant improvements in the clinical, structural and functional capacity compared with AF medical treatment.¹³ Compared with medical therapy, patients ablated for AF have reduced risk of HF and stroke, as well as death.⁷

Although data on long-term risks after catheter ablation for AF with or without HF have been identified,^{17–18} those compared with the general population are not well characterised.

The purpose of this study was to evaluate all-cause mortality and to perform a population-based assessment of the long-term risk of death in patients who underwent catheter ablation for AF compared with the whole general population.

METHODS

Study design and setting

Data were retrospectively derived from the Cardiac Interventional Registry implemented at our hospital (all the interventional procedures carried out at our centre have been recorded in this registry since 2009). AF was defined according to the European Society of Cardiology guidelines.¹ We selected AF ablation procedures performed between January 2009 and June 2019. In particular, all patients had an ECG documentation of AF and the arrhythmia was symptomatic and unresponsive to at least one antiarrhythmic drug.¹ Moreover, HF was defined according to the European Society of Cardiology guidelines⁴ and we included in this analysis all clinical conditions that required hospitalisation. All patients provided written informed consent. The study complied with the principles of the Declaration of Helsinki. Vital status and dates of death to 31 December 2019 were obtained for residents in Apulia by using the regional Health Information System. Follow-up was considered to be administratively censored on 31 December 2019 and was at least 6 months for all patients (maximum: 11 years). Person-years were computed from the date of procedure to death or end of the follow-up. The expected numbers of deaths were derived using mortality rates from the general population of Apulia region and the general Italian population by considering age-specific and gender-specific death probability provided for each calendar year by the Italian National Institute of Statistics (<https://www.istat.it/>).

Statistical analysis

Data were reported as mean±SD, median with IQR or number with percentage. Patients' characteristics at the time of AF ablation procedure were compared according to the presence and occurrence of HF by using the analysis of variance, X^2 or Fisher's exact test as appropriate. Cox proportional-hazards model was used to estimate HRs with 95% CIs. Kaplan-Meier curves were used to describe mortality over time and the log-rank test to compare survival by age groups or presence of HF history. Standardised mortality ratios (SMRs) were calculated by dividing the observed number of deaths among patients by the expected number of deaths estimated from the general population. The 95% CIs of SMRs were estimated using the Poisson distribution considering the expected risk of death as exposure variable. A p value of 0.05 or less was considered statistically significant. All analyses were conducted using STATA software, V.16 (Stata-Corp, College Station, Texas, USA).

Patient and public involvement

No patient involved.

RESULTS

During the study period, a total of 1260 patients residing in the Apulia region underwent AF catheter ablation. More than two-thirds were men with a mean age of 60±11 years. There were 368 (29.2%) patients younger than 55 years, while 453 (36.0%) were in the range 55–65 years and 439 (34.8%) were older than 65 years. At baseline, 141 (11.2%) patients had a history of HF.

From over a total of 6449 person-years follow-up (mean 5.1±3.0 years; median 4.8; IQR 2.6–7.6 years), HF was diagnosed in 87 patients without a history of HF at the time of AF ablation procedure and an overall number of 95 deaths were observed. **Table 1** shows baseline patients' characteristics at the time of AF ablation procedure by HF (1032 without HF at baseline and during follow-up, 141 with a history of HF at baseline and 87 with new onset of HF during follow-up). Compared with patients without HF, those with a history of it at baseline or those developing HF during follow-up were older with a higher prevalence of hypertension, diabetes mellitus, chronic renal disease, chronic obstructive pulmonary disease, vascular and coronary artery disease, and cardiac surgery.

Figure 1A,B shows Kaplan-Meier curves of cumulative mortality over time after catheter ablation for AF in the overall cohort, by age group and in those with or without HF at baseline. Greater age and history of HF were significantly associated with mortality risk (**figure 1B,C**). History of HF had a crude HR of 4.60 (95% CI 3.00 to 7.08; $p<0.001$) with an age-adjusted and sex-adjusted value of 3.06 (1.97 to 4.76; $p<0.001$).

Table 2 shows follow-up data and reports mortality in comparison with expected risk in the general population, and **figure 2** displays graphically the estimated SMR with 95% CI of observed in the regional population. In

Table 1 Patients' characteristics at the time of procedure of atrial fibrillation ablation and the number of deaths according to the presence and occurrence of heart failure

	Overall n=1260	Without heart failure* n=1032	History of heart failure at baseline n=141	New onset of heart failure during follow-up n=87	P for difference†
Male	914 (72.5%)	751 (72.8%)	110 (78.0%)	53 (60.9%)	0.018
Age (years)	60±11	59±11	64±11	66±12	<0.001
Hypertension	615 (48.8%)	469 (45.4%)	85 (60.3%)	61 (70.1%)	0.001
Diabetes mellitus	115 (9.1%)	64 (6.2%)	27 (19.1%)	24 (27.6%)	<0.001
Chronic renal disease	48 (3.8%)	26 (2.5%)	17 (12.1%)	5 (5.7%)	0.004
COPD	86 (6.8%)	47 (4.6%)	30 (21.3%)	9 (10.3%)	<0.001
Vascular disease	61 (4.8%)	41 (4.0%)	16 (11.3%)	4 (4.6%)	0.002
Coronary artery disease	86 (6.8%)	54 (5.2%)	21 (14.9%)	11 (12.6%)	0.009
Cardiac surgery	30 (2.4%)	17 (1.6%)	6 (4.3%)	7 (8.0%)	0.001
Previous stroke or TIA	32 (2.5%)	27 (2.6%)	3 (2.1%)	2 (2.3%)	1.000
History of cancer	68 (5.4%)	52 (5.0%)	10 (7.1%)	6 (6.9%)	0.418
Deaths during follow-up	95	41	31	23	

Mean±SD, number and percentage of patients.

*No heart failure at baseline and during follow-up.

†P for difference was calculated by analysis of variance, X² or Fisher's exact test as appropriate.

COPD, chronic obstructive pulmonary disease; TIA, transient ischaemic attack.

the overall cohort, the 10-year mortality rate was 14.2% without a significant excess of mortality expected in the general population of the same age and gender (SMR 1.05, 95% CI 0.86 to 1.28; $p=0.658$). Although the 10-year mortality rate increased across age groups (1.7% in <55 years, 7.3% in 55–65 years and 32.3% in those >65 years), the comparison with the expected risk was not statistically significant: SMR 0.96 (95% CI 0.40 to 2.31; $p=0.929$), 1.02 (95% CI 0.65 to 1.60; $p=0.933$) and 1.06 (95% CI 0.84 to 1.34; $p=0.620$), respectively, for patients in the group of <55, 55–65 and >65 years. Patients with HF at baseline or those with a new onset during follow-up had a higher mortality rate (41.5% and 35.1%, respectively) than those without (table 2). Compared with the general population, an excess of mortality was observed in patients with HF at baseline (SMR 2.40, 95% CI 1.69 to 3.41 $p=0.001$) and in those with a new onset during follow-up (SMR 1.75, 95% CI 1.17 to 2.64; $p=0.007$). In patients without HF, a lower risk than expected was observed especially among those remaining free from HF during follow-up (table 2). An SMR of 0.82 (95% CI 0.64 to 1.05; $p=0.117$) in patients without a history of HF at baseline was more significant than those free from HF during follow-up (0.63, 95% CI 0.47 to 0.86; $p=0.003$).

When observed mortality was compared with the general Italian population, all results were similar to the results in Apulia (table 2).

DISCUSSION

In the current study, we provide a long-term analysis of mortality among patients with symptomatic AF who

underwent catheter ablation with respect to age and HF coexistence, and we assessed the risk of death compared with that in the general regional population over the same period. Aside from the association of the absolute risk with patients' age and presence of HF, the main finding of this study was that the overall long-term mortality of patients ablated for AF was not different from the general population. Second, mortality after AF ablation was higher in subjects with a pre-existing history of HF and in those with a diagnosis made during follow-up. In patients with AF without HF, observed deaths were lower than expected according to regional mortality rates. The analyses of long-term outcome were based on a cohort from an Italian centre with a high procedural volume and on expected risk over a follow-up of 11 years considering age-specific and gender-specific annual mortality rates of the general regional population.

Mortality in patients undergoing ablation for AF appears to be associated with a reduced mortality compared with drug therapy.^{1 8} No previous studies reported mortality data comparing patients undergoing AF ablation with the general population. Our analysis showed that the long-term mortality after AF ablation was not higher than the risk of subjects from the general population of the same age and gender, suggesting that after catheter ablation, the clinical outcome of patients may be good enough to observe a number of deaths not different from the one expected in the general population. However, a mortality gap between patients with and without HF was observed. The coexistence of AF with HF was associated with an excess mortality after the ablation procedure, while

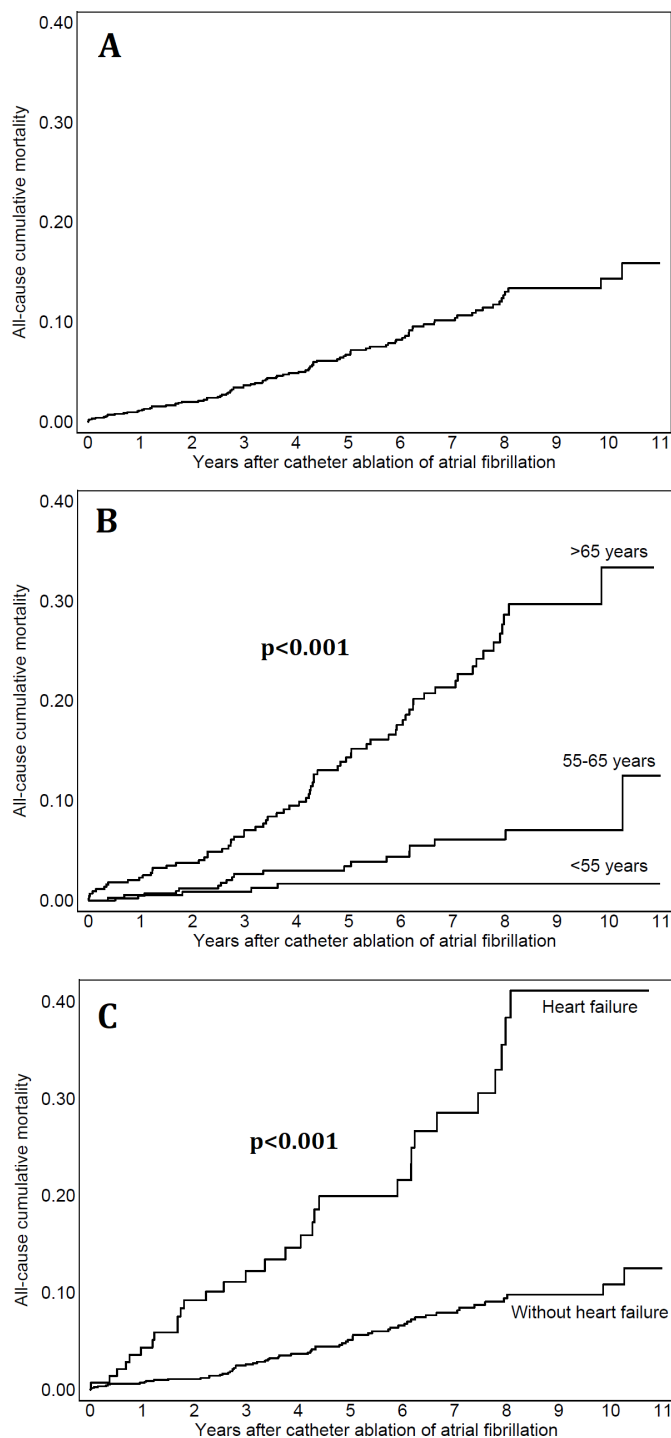


Figure 1 Kaplan-Meier mortality estimate curve in overall patients (A), in those stratified by age at the time of catheter ablation of atrial fibrillation (B), and by the presence of heart failure (C).

patients without HF had a mortality rate better than the general population.

Although AF leads to increased death rates, a better management of this condition may have reduced the net impact of AF on mortality over time.^{14 15} The growing availability and use of catheter ablation for AF may partially explain the mortality reduction. Most patients who are treated with medical therapy, compared with the

ablated one, are older with more frequent comorbidities, and at higher risk of death, heart failure admission and stroke.⁷ Evidence of the beneficial effects of AF ablation on minimising death rates is lacking. The CABANA trial did not show superiority of ablation versus drug therapy for a combined primary outcome including death, stroke, severe bleeding or cardiac arrest,¹⁶ while the CASTLE-AF trial reported lower mortality associated with ablation in patients with AF and HF with reduced ejection fraction.¹⁰ Recent data including patients with HF with preserved ejection fraction and AF showed that, compared with medical therapy, catheter ablation decreases HF hospitalisation and symptoms.^{17–19}

Compared with randomised trials, often based on combined endpoints to increase statistical power and epidemiological evaluations of mortality after catheter ablation for AF, this study was focused on a long-term evaluation of death rate compared with the general population over the same period. Findings of our study provide important insight regarding health risks after catheter ablation compared with the general population, which would be useful in counselling of patients symptomatic of AF.

Although previous data reported that ablation improves outcome in patients with AF and HF,^{9–12} our analysis reported that mortality of patients with HF who underwent AF catheter ablation persists more than the general population. The mortality data were similar in patients with HF documented at admission compared with patients who had the onset of HF during follow-up. These data suggest that an early treatment of AF to avoid persistent forms and an optimal HF treatment are crucial to improve outcome in these patients. The increased mortality found in our cohort of patients with HF may be explained by the differences in survival of patients with AF with and without HF. The incidence rate after new AF is higher in patients with HF with reduced than preserved ejection fraction (30.2 vs 25.7 deaths per 100 person-years), while those without HF are at much more lower risk (12 deaths per 100 person-years).²⁰ Moreover, in patients with HF, the association of AF with worse cardiovascular outcomes is significant in patients with reduced and mid-range ejection fraction but not in those with preserved systolic function.²¹ Data from the Framingham Heart Study show that AF occurs in more than half of individuals with HF and that HF occurs in more than one-third of individuals with AF.²⁰ The onset of AF precedes and follows both HF (both preserved and reduced ejection fraction). However, AF and HF conjointly lead to a poor prognosis, with a higher risk among those with reduced ejection fraction.²⁰ In the absence of HF, according to our data, mortality after cardiac ablation of AF was lower than the general population. A significant risk of mortality has been reported for AF at older age (70 years or more) in adjusted analyses based on a large cohort of adult and elderly European men and women.²² At younger age, from 40 to 69 years, the risk of mortality over a follow-up time of up to 10 years was not significantly related to new-onset AF.²² Patients with

Table 2 Mortality and expected risk during follow-up with standardised mortality ratios (SMRs) in relation to age categories, history of heart failure and development of heart failure

	Patients n	Deaths (n)	10-year mortality rate (%)	Follow-up (person-years)	Event rate (100 person-years)	Expected deaths in Apulia (n)	SMR (95% CI) vs Apulia	Expected deaths in Italy (n)	SMR (95% CI) vs Italy
Overall	1260	95	14.2	6449	1.47	90.8	1.05 (0.86 to 1.28) p=0.658	92.9	1.02 (0.84 to 1.25) p=0.829
Age (years)									
<55	368	5	1.7	1992	0.25	5.2	0.96 (0.40 to 2.31) p=0.929	5.4	0.93 (0.39 to 2.23) p=0.00871
55–65	453	19	7.3	2333	0.81	18.6	1.02 (0.65 to 1.60) p=0.933	19.6	0.97 (0.62 to 1.52) p=0.888
>65	439	71	32.2	2124	3.34	66.9	1.06 (0.84 to 1.34) p=0.620	67.9	1.05 (0.83 to 1.32) p=0.708
History of heart failure at baseline									
No	1119	64	10.8	5825	1.10	77.8	0.82 (0.64 to 1.05) p=0.117	79.7	0.80 (0.63 to 1.03) p=0.079
Yes	141	31	41.5	623	4.98	12.9	2.40 (1.69 to 3.41) p<0.001	13.2	2.34 (1.65 to 3.33) p<0.001
New onset of heart failure during follow-up*									
No	1032	41	7.0	5259	0.78	64.7	0.63 (0.47 to 0.86) p=0.003	66.3	0.62 (0.46 to 0.84) p=0.002
Yes	87	23	35.1	567	4.06	13.1	1.75 (1.17 to 2.64) p=0.007	13.4	1.72 (1.14 to 2.59) p=0.009

The p values were calculated according to Poisson model.

*New onset of heart failure refers to 1119 patients without a history of heart failure at the time of the atrial fibrillation ablation procedure.

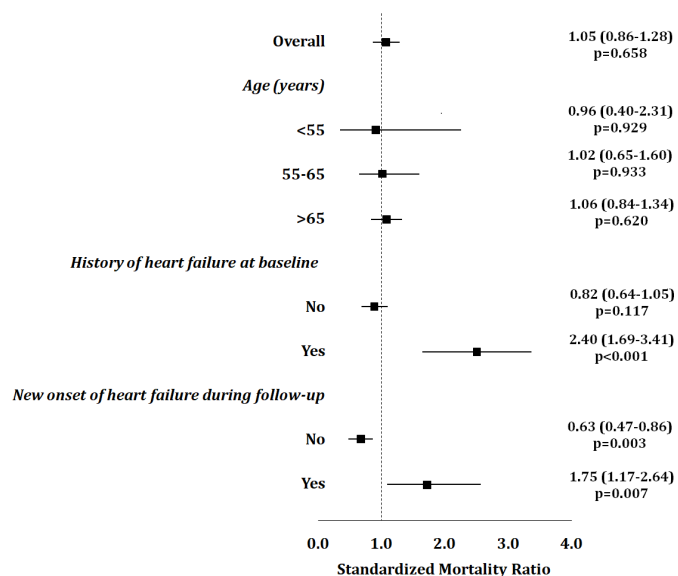


Figure 2 Standardised mortality ratios with 95% CIs relative to the comparison between observed mortality and expected from the general population of Apulia region.

HF were older than those without. In the general population, morbidities other than cardiovascular diseases affect overall survival. Neoplasms are the first leading cause of years of life lost and deaths.²³ It is possible that patients who underwent catheter ablation for AF without a history of HF and remain free from it after the procedure are at lower risk than the unselected general population also because the risk of AF diagnosis is influenced by socio-economic factors, and patients' demographic differences exist in the use of catheter ablation.^{24 25}

The present study has several limitations. Data are from a single institution that is a reference centre for percutaneous ablation of arrhythmias. We compared all-cause mortality in the study cohort with the general population and we performed subgroup analyses only according to HF presence at baseline or by its occurrence during follow-up. For a complete analysis of the effect of comorbidities on different causes of death, comorbidity information for both patients and reference population is necessary. On the other hand, the main purpose of the present epidemiological study was to analyse overall long-term mortality in patients, selecting those at lower risk and comparing it with the general population without identifying prognostic factors.

CONCLUSIONS

Long-term mortality of patients undergoing AF ablation is similar to that of the general population, suggesting that after this therapeutic procedure, there is no excess of mortality compared with the overall expected. Compared with the general population, patients with HF have a significantly higher probability of death, while those without HF seem to have a better risk profile.

Contributors ADM contributed to the study conception and design, wrote the manuscript and approved the final version, NV contributed to the study conception and design, provided critical feedback on subsequent drafts of the manuscript and approved the final version. FT provided critical feedback on subsequent drafts of the manuscript and approved the final version. FQ provided critical feedback on subsequent drafts of the manuscript and approved the final version. PG contributed to the statistical analysis and approved the final version. MG provided critical feedback on subsequent drafts of the manuscript and approved the final version. ADM is the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval Ethical approval (number 5690) was granted by the Azienda Universitaria Ospedaliera Consorziale-Policlinico Bari.

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Data availability statement Data are available upon reasonable request.

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REFERENCES

- Hindricks G, Potpara T, Dagres N, *et al*. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European association for Cardio-Thoracic surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of cardiology (ESC) developed with the special contribution of the European heart rhythm association (EHRA) of the ESC. *Eur Heart J* 2021;42:373-498.
- Carlisle MA, Fudim M, DeVore AD, *et al*. Heart Failure and Atrial Fibrillation, Like Fire and Fury. *JACC Heart Fail* 2019;7:447-56.
- Wang TJ, Larson MG, Levy D, *et al*. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham heart study. *Circulation* 2003;107:2920-5.
- Ponikowski P, Voors AA, Anker SD, *et al*. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of cardiology (ESC). developed with the special contribution of the heart failure association (HFA) of the ESC. *Eur J Heart Fail* 2016;18:891-975.
- Samaras A, Kartas A, Akrivos E, *et al*. A novel prognostic tool to predict mortality in patients with atrial fibrillation: the BASIC-AF risk score. *Hellenic J Cardiol* 2021;62:339-48.
- Hijazi Z, Oldgren J, Lindbäck J, *et al*. A biomarker-based risk score to predict death in patients with atrial fibrillation: the ABC (age, biomarkers, clinical history) death risk score. *Eur Heart J* 2018;39:477-85.
- Yang P-S, Sung J-H, Jang E, *et al*. Catheter ablation improves mortality and other outcomes in real-world patients with atrial fibrillation. *J Am Heart Assoc* 2020;9:e015740.
- Calkins H, Hindricks G, Cappato R, *et al*. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace* 2018;20:e1-160.
- Hunter RJ, Berriman TJ, Diab I, *et al*. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol* 2014;7:31-8.
- Marrouche NF, Brachmann J, Andresen D, *et al*. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018;378:417-27.
- Di Biase L, Mohanty P, Mohanty S, *et al*. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. *Circulation* 2016;133:1637-44.
- Kuck K-H, Merkely B, Zahn R, *et al*. Catheter ablation versus best medical therapy in patients with persistent atrial fibrillation and

- congestive heart failure: the randomized AMICA trial. *Circ Arrhythm Electrophysiol* 2019;12:e007731.
- 13 Kheiri B, Osman M, Abdalla A, *et al.* Catheter ablation of atrial fibrillation with heart failure: an updated meta-analysis of randomized trials. *Int J Cardiol* 2018;269:170–3.
 - 14 Schmidt M, Ulrichsen SP, Pedersen L, *et al.* 30-Year nationwide trends in incidence of atrial fibrillation in Denmark and associated 5-year risk of heart failure, stroke, and death. *Int J Cardiol* 2016;225:30–6.
 - 15 López-López JA, Sterne JAC, Thom HHZ, *et al.* Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. *BMJ* 2017;359:j5058.
 - 16 Packer DL, Mark DB, Robb RA, *et al.* Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA* 2019;321:1261–74.
 - 17 Rattka M, Kühberger A, Pott A, *et al.* Catheter ablation for atrial fibrillation in HFpEF patients-A propensity-score-matched analysis. *J Cardiovasc Electrophysiol* 2021;32:2357–67.
 - 18 Black-Maier E, Ren X, Steinberg BA, *et al.* Catheter ablation of atrial fibrillation in patients with heart failure and preserved ejection fraction. *Heart Rhythm* 2018;15:651–7.
 - 19 Di Monaco A, Guida P, Vitulano N, *et al.* Catheter ablation of atrial fibrillation with uninterrupted anticoagulation: a meta-analysis of six randomized controlled trials. *J Cardiovasc Med* 2020;21:483–90.
 - 20 Santhanakrishnan R, Wang N, Larson MG, *et al.* Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation* 2016;133:484–92.
 - 21 Zafrir B, Lund LH, Laroche C, *et al.* Prognostic implications of atrial fibrillation in heart failure with reduced, mid-range, and preserved ejection fraction: a report from 14 964 patients in the European Society of Cardiology Heart Failure Long-Term Registry. *Eur Heart J* 2018;39:4277–84.
 - 22 Morseth B, Geelhoed B, Linneberg A, *et al.* Age-Specific atrial fibrillation incidence, attributable risk factors and risk of stroke and mortality: results from the MORGAM Consortium. *Open Heart* 2021;8:e001624.
 - 23 GBD 2017 Italy Collaborators. Italy's health performance, 1990-2017: findings from the global burden of disease study 2017. *Lancet Public Health* 2019;4:e645–57.
 - 24 Lunde ED, Joensen AM, Lundbye-Christensen S, *et al.* Socioeconomic position and risk of atrial fibrillation: a nationwide Danish cohort study. *J Epidemiol Community Health* 2020;74:7–13.
 - 25 Kummer BR, Bhave PD, Merkler AE, *et al.* Demographic differences in catheter ablation after hospital presentation with symptomatic atrial fibrillation. *J Am Heart Assoc* 2015;4:e002097.