Early risk of mortality, cardiovascular events, and bleeding in patients with newly diagnosed atrial fibrillation

Ilaria Cavallari\textsuperscript{1} and Giuseppe Patti\textsuperscript{2}\textdagger

\textsuperscript{1}Campus Bio-Medico University of Rome, Rome, Italy
\textsuperscript{2}University of Eastern Piedmont, Maggiore della Carità Hospital, Novara, Italy

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is independently associated with a 1.5- to 2.0-fold higher risk of all-cause death and increased morbidity, in particular for heart failure and stroke. Previous studies have shown that the annual rate of death in AF patients is \( \approx 5\% \); however, emerging data indicate that the risk of death, but also of thromboembolic and bleeding complications, is highest early after the diagnosis, especially during the first month. In light of these observations, patients with newly diagnosed AF deserve close monitoring and may benefit from a comprehensive care targeting modifiable risk factors for death, such as heart failure, diabetes, renal impairment, and vascular disease. Aim of this report is to focus on timing and causes of death as well as on temporal trends of cardiovascular and bleeding complications in patients with newly diagnosed AF.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia; incidence and prevalence of AF are predicted to rise steeply in the next future because of longer life expectancy and better detection of silent arrhythmic episodes. According to epidemiological studies, one in four middle-aged adults in Europe and in the USA will develop AF.\textsuperscript{1–3} Despite relevant progresses in the management of AF patients, this arrhythmia is independently associated with a two-fold increased risk of all-cause death in women and a 1.5-fold increase in men. Atrial fibrillation is also associated with higher morbidity, in particular for heart failure and stroke.\textsuperscript{4,5}

In AF patients, oral anticoagulant therapy reduces stroke and improves survival\textsuperscript{6,7} other interventions, such as rhythm and rate control, attenuate arrhythmia-related symptoms and may preserve cardiac function, but did not demonstrate a significant decrease of long-term morbidity or mortality in the overall population of AF patients.\textsuperscript{8,9}

CASTLE-AF was the first study showing that, compared to medical therapy, a strategy of rhythm control with catheter ablation is associated with lower all-cause mortality or hospitalization for recurrent events in a selected population of AF patients with heart failure.\textsuperscript{10} However, optimal public health prioritization, clinical decision-making, and patient counselling require an understanding of the clinical course of the disease including the potential risks and timing of subsequent events.

Aim of this report is to focus on timing and causes of death as well as on temporal trends of cardiovascular and bleeding complications in patients with newly diagnosed AF.

Causes of death and over-time mortality after the diagnosis of atrial fibrillation

A large retrospective, real-world study, including \( \approx 9000 \) patients with AF, reported a yearly rate of death of 5.5\%.\textsuperscript{11} Among all deaths, 54% were cardiovascular and 43% non-cardiovascular; the most frequent causes of death were heart failure (29\%), infection (18\%), and cancer (12\%).
Stroke or bleeding event each accounted for 7% of all deaths. At multivariable analysis, the strongest predictors of all-cause mortality were renal failure (hazard ratio 1.79), heart failure (hazard ratio 1.78), previous bleeding (hazard ratio 1.42), and permanent AF (hazard ratio 1.35). Oral anticoagulant treatment was independently associated with a significantly lower risk of death (hazard ratio 0.62), both cardiovascular (hazard ratio 0.60) and non-cardiovascular (hazard ratio 0.60).

In the same line of evidence, a post hoc analysis of a phase III randomized trial comparing edoxaban, a non-vitamin K antagonist oral anticoagulant (NOAC), with well-managed warfarin, confirmed that the annual rate of death in a contemporary cohort of AF patients is 4.04%. The most common causes of cardiovascular mortality were sudden cardiac death, heart failure, and ischaemic stroke. Fatal bleeding events occurred in 0.21% of patients per year and were significantly less frequent in the edoxaban arms compared to warfarin (0.18% per year with edoxaban 60/30 mg vs. 0.12% with edoxaban 30/15 mg vs. 0.33% with warfarin). As well, the rates of fatal or contributing to death bleeding complications were decreased in the edoxaban arms (0.30% per year with edoxaban 60/30 mg vs. 0.28% with edoxaban 30/15 mg vs. 0.52% with warfarin).

In cohorts of patients with newly diagnosed AF, mortality trends appear higher during the first year, and especially, in the first month after the diagnosis. In the GARFIELD-AF registry indicated a mortality rate of 4.3 per 100 person-years during the first 12-month observation period after the diagnosis of AF. Of note, 13.5% of patients died within 1 month [6.8; 95% confidence interval (CI) 6.1–7.6 per 100 patient-years], 29.1% died during the 2- to 4-month time interval (4.9; 95% CI 4.5–5.3 per 100 person-years), 29.0% during the 5- to 8-month time interval (3.8; 95% CI 3.5–4.1 per 100 person-years), and 28.4% died during the 9- to 12-month time interval (3.8; 95% CI 3.5–4.1 per 100 person-years) (Figure 1). Patients who died in the first 12 months after the diagnosis tended to be older and had a higher prevalence of comorbidities than those who survived the first 12 months; however, there were no major differences in the baseline characteristics of patients who died within the first month in comparison with those who died subsequently, but within 12 months, although reduced left ventricular ejection fraction, heart failure and no antithrombotic or antiplatelet-only treatment were more prevalent in the early-death subgroup.

Despite the abovementioned evidence, a definitive causality link between newly diagnosed AF and higher risk of death during the first month cannot be established; in fact, the observation that in AF patients without multiple additional comorbidities (e.g. those with CHA2DS2-VASc scores between 0 and 2) there was no increase in the risk of early death suggests that AF may not be in itself a causal factor for early mortality.

**Temporal trends in the risk of cardiovascular events in atrial fibrillation patients**

In the GARFIELD-AF registry, the incidence of the composite outcome measure including non-fatal stroke and systemic embolism during the first 12-month observation period after the diagnosis of AF was 1.3 per 100 patient-years (95% CI 1.2–1.4). Notably, during the first 4 months the rates of stroke or systemic embolism were significantly higher compared with the overall event rates (+35%), whereas beyond 4 months the event rates were lower and modestly declined over the course of follow-up. In detail, of the total 657 strokes and systemic embolisms, 14.9% occurred during the first month (2.3, 95% CI 1.9–2.8, per 100 person-years), 28.0% occurred during the 2- to 4-month observation period (1.5, 95% CI 1.3–1.7, per 100 person-years—average of 9.3% per month), 31.9% occurred during the 5- to 8-month observation period (1.3, 95% CI 1.1–1.5, per 100 person-years—average of 8.0% per month), and the remaining 25.1% occurred during the 9- to 12-month observation period (1.0, 95% CI 0.9–1.2, per 100 person-years—average of 6.2% per month) (Figure 2). However, regarding the increased risk of thromboembolic events observed early after the AF diagnosis, this may be due to inadequate values of international normalized ratio after the initiation of warfarin therapy (which was the anti-coagulant of choice in ~40% of patients included in the registry), but the transient hypercoagulability reported at the onset of AF episodes may be also involved. Differences between NOACs and warfarin in terms of early risk-benefit may exist, as suggested by a 69% relative reduction of 1-month mortality with NOACs.

**Temporal trends in the risk of bleeding in atrial fibrillation patients**

In the GARFIELD-AF registry, the rate of non-fatal major bleeding during the first 12-month observation period following the diagnosis of AF was 0.8 per 100 patient-years (95% CI 0.8–0.9). Similarly to the temporal trends of thromboembolic complications, the risk of non-fatal bleeding was significantly increased during the first 4 months after the diagnosis compared with the overall event rates (+56%); beyond 4 months, the major bleeding rates tended to decline. In detail, of the total 411 major bleeding events, 15.3% occurred during the first month (1.5, 95% CI 1.2–1.9, per 100 person-years), 30.6% occurred during the 2- to 4-month observation period (1.0, 95% CI 0.8–1.2, per 100 person-years—average of 10.2% per month), 28.2%
during the 5- to 8-month observation period (0.7, 95% CI 0.6–0.8, per 100 person-years—average of 7.0% per month), and the remaining 25.7% during the 9- to 12-month observation period (0.7, 95% CI 0.6–0.8, per 100 person-years—average of 6.4% per month) (Figure 2). This course could be related to the fact that subjects at higher risk of bleeding tend to bleed early after the initiation of anticoagulation and bleeding is often the reason for anticoagulation temporary interruption or permanent discontinuation; therefore, a natural selection of subjects remaining on long-term anticoagulation due to good tolerability may be hypothesized.

**Conclusions**

Newly diagnosed AF could represent a marker of early death as a consequence of worsening concomitant comorbidities. An early increase in the risk of stroke and major bleeding has been observed after the diagnosis (especially within 1 month). Anticoagulation, especially the use of NOACs, decreases the risk of death, although major bleeding events tend to occur early after the diagnosis and are highest during the first month. In light of these observations, patients with newly diagnosed AF deserve close monitoring and may benefit from a comprehensive care targeting modifiable risk factors for death, such as heart failure, diabetes, renal impairment, and vascular disease.

**Conflict of interest:** none declared.

**References**

1. Heeringa J, van der Kuip DAM, Hofman A, Kors JA, van Herpen G, Stricker BHC, Stijnen T, Lip GYH, Wittens JCM. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006; 27:949–953.
2. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D’Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004;110:1042–1046.
3. Go AS, Hylek EM, Phillips KA, Chang Y, Hart MG, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001; 285:2370–2375.
4. Stewart S, Hart CL, Hole DJ, McMurtry JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002; 113:359–364.
5. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991; 22:983–988.
6. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007; 146:857–867.
7. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deedwany A, Ezekowitz MD, Camm AJ, Diez JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomized trials. *Lancet* 2014; 383:955–962.
8. Kirchhof P, Breithardt G, Camm AJ, Crijns HJ, Kuck KH, Vardas P, Wegscheider K. Improving outcomes in patients with atrial fibrillation rationale and design of the Early treatment of Atrial fibrillation for Stroke prevention Trial. *Am Heart J* 2013; 166:442–448.
9. Al-Khatib SM, Allen LA Poiteau NM, Chatterjee R, Crowley MJ, Dupre ME, Kong DF, Lopes RD, Povsic TJ, Raju SS, Shah B, Kosienski AS, McBroom AJ, Sanders GD. Rate- and rhythm-control therapies in patients with atrial fibrillation: a systematic review. *Ann Intern Med* 2014; 160:760–773.
10. Marrouche NF, Brachmann M, Andreassen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Poff J, Schunkert H, Christ H, Vogt J, Bunsch D; CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018; 378:417–427.
11. Fauchier L, Villejoubert O, Clementy N, Bernard A, Pierre B, Angoulvant D, Ivenes F, Babuty D, Lip GYH. Causes of death and influencing factors in patients with atrial fibrillation. *Am J Med* 2016; 129:1278–1287.
12. Giugliano RP, Ruff CT, Witvliet SD, Nordio F, Murphy SA, Kappelhof JAN, Shi M, Mercuri MF, Antman EM, Braunwald E. Mortality in patients with atrial fibrillation randomized to edoxaban or warfarin: insights from the ENGAGE AF-TIMI 48 trial. *Am J Med* 2016; 129:850–857.e2.
13. Benjamin EJ, Wolf PA, D’Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998; 98:946–952.
14. Piccini JP, Hammill BG, Sinner MF, Hernandez AF, Walkey AJ, Benjamin EJ, Curtis LH, Heckbert SR. Clinical course of atrial fibrillation in older adults: the importance of cardiovascular events beyond stroke. Eur Heart J 2014;35:250–256.
15. Bassand J-P, Accetta G, Camm AJ, Cools F, Fitzmaurice DA, Fox KAA, Goldhaber SZ, Goto S, Haas S, Hacke W, Kayani G, Mantovani LG, Misselwitz F, ten Cate H, Turpie AGG, Verheugt FWA, Kakkar AK; GARFIELD-AF Investigators. Two-year outcomes of patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. Eur Heart J 2016;37:2882–2889.
16. Miyasaka Y, Barnes ME, Bailey KR, Cha SS, Gersh BJ, Seward JB, Tsang TSM. Mortality trends in patients diagnosed with first atrial fibrillation: a 21-year community-based study. J Am Coll Cardiol 2007;49:986–992.
17. Bassand J-P, Accetta G, Al Mahmeed W, Corbalan R, Eikelboom J, Fitzmaurice DA, Fox KAA, Gao H, Goldhaber SZ, Goto S, Haas S, Kayani G, Pieper K, Turpie AGG, van Eckels M, Verheugt FWA, Kakkar AK; for the GARFIELD-AF investigators. Risk factors for death, stroke, and bleeding in 28,628 patients from the GARFIELD-AF registry: rationale for comprehensive management of atrial fibrillation. PLoS One 2018;13:e0191592.
18. Bassand J-P, Virdone S, Goldhaber SZ, Camm AJ, Fitzmaurice DA, Fox KAA, Goto S, Haas S, Hacke W, Kayani G, Mantovani LG, Misselwitz F, Pieper KS, Turpie AGG, van Eckels M, Verheugt FWA, Kakkar AK; for the GARFIELD-AF Investigators. Early risks of Death, stroke/systemic embolism, and major bleeding in patients with newly diagnosed atrial fibrillation. Circulation 2019;139:787–798.