Evaluation of the effect of oral anticoagulants on all-cause mortality within 3 months of the diagnosis of atrial fibrillation: results from the GARFIELD-AF registry

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BACKGROUND

- Real-world clinical evidence, generated from high-quality prospective observation studies, has an important role in establishing the value of new therapies, compared with standard of care, in every day clinical practice.
- The largest multinational prospective registry, the Global Anticoagulant Registry in the FIELD–Atrial Fibrillation (GARFIELD-AF), captures the diversity of treatment and outcomes in populations beyond the constraints of randomised clinical trials.
- When comparing the benefits and harms of treatments delivered in everyday practice, we need to account for differences in the distribution of baseline characteristics between treatment groups.[1] Statistical methods must be used to minimise the effects of confounding in order to obtain an unbiased estimate of the treatment effect.

PURPOSE

- Using data from the largest multinational prospective registry in atrial fibrillation (GARFIELD-AF), we examined whether treatment effects of oral anticoagulant (OAC) on all-cause mortality, stroke/systemic embolism and major bleeding are manifest within 3 months of diagnosis of AF in patients with a CHA_2DS_2-VASc score ≥2 (including gender).
- Safety and effectiveness analyses were conducted for the following comparisons:
  - OACs vs. no OAC
  - Non-vitamin K antagonist oral anticoagulants (NOACs) vs. Vitamin K antagonists (VKAs).

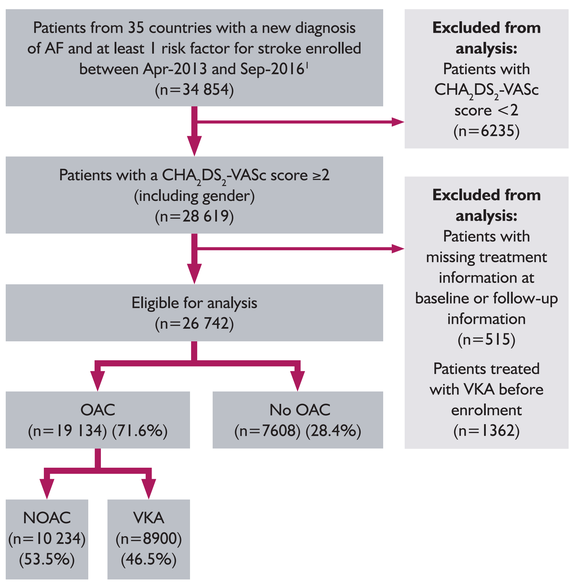
METHODS

- Patients, who were enrolled into GARFIELD-AF between Apr-2013 and Aug-2016 (cohorts 3-5), with a new diagnosis of AF, a CHA_2DS_2-VASc score ≥2 (including gender) and no missing outcome variables were included in this analysis (Figure 1). Over this time period, NOACs were available in most countries.
- We used a propensity weighting scheme, recently proposed by Li and colleagues,[2] to evaluate the adjusted associations between drug use (at baseline) and all-cause mortality within 3 months from the start of treatment.
- This new method overlaps weights and optimises the efficiency of comparisons by defining the population with the most overlap in the covariates between treatment groups.
- Covariates considered for the model included: cohort, care setting location and specialty at diagnosis, demographics (age, sex, race, country), medical history (type of AF, diabetes, stroke, transient ischaemic attack, bleeding, hypertension, cirrhosis, CABG, smoking, alcohol consumption, systemic embolism, vascular disease, chronic kidney disease, acute coronary syndromes, carotid occlusive disease, dementia, heart failure, hypothyroidism, hyperthyroidism, baseline antiplatelet use), and presentation features (heart rate, systolic blood pressure, diastolic blood pressure, body mass index).
- Weights were then applied to Cox proportional hazards models to estimate the effects of each comparison on the endpoint.

RESULTS

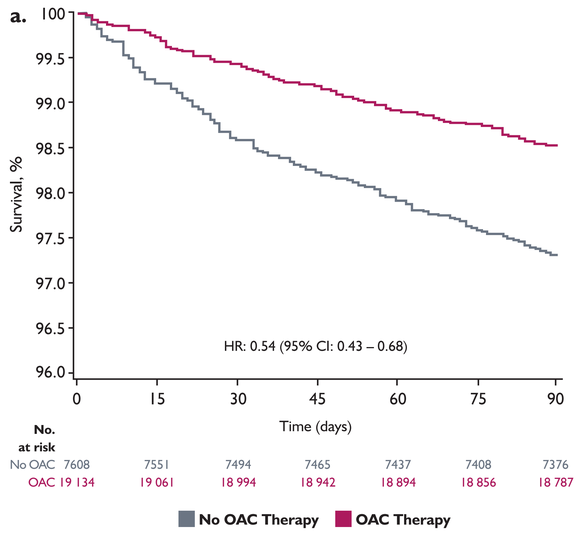
- The study population comprised 19,134 anticoagulated patients (10,234 [NOACs]; 8,900 [VKAs]) and 7,608 patients without OAC (of the latter, 63.3% received anti-platelets).
- In total, 423 patients died within 3 months of diagnosis of AF (Kaplan-Meier survival rate of 98.4% at 3 months).
- The causes of death were: cardiovascular (in 40.4% of cases), non-cardiovascular (36.4%) and unknown (21.7%).
- Congestive heart failure (15.8%), cancer (8.3%), respiratory failure (5.7%), and infection (5.7%) were the most common known causes of death. These were followed by: sepsis (5.4%), myocardial infarction (5.0%), non-haemorrhagic stroke (5.0%), and sudden death (5.0%).
- After weighting, standardised differences showed a balance between the 31 baseline variables and drug use.
- Weighted hazard ratios (HR) for all-cause mortality were:
  - 0.54 (95% CI, 0.43−0.68); P <0.001 for the comparison of OAC vs non OAC; and
  - 0.68 (95% CI, 0.50−0.92); P=0.014 for NOACS vs VKAs (Figure 2).
- OAC (vs no OAC) was associated with a trend towards a decreased risk of stroke/systemic embolism without a significant increased risk in major bleeding at 3 months. Neither reached statistical significance for the assessment of NOAC versus VKA (Table 1).

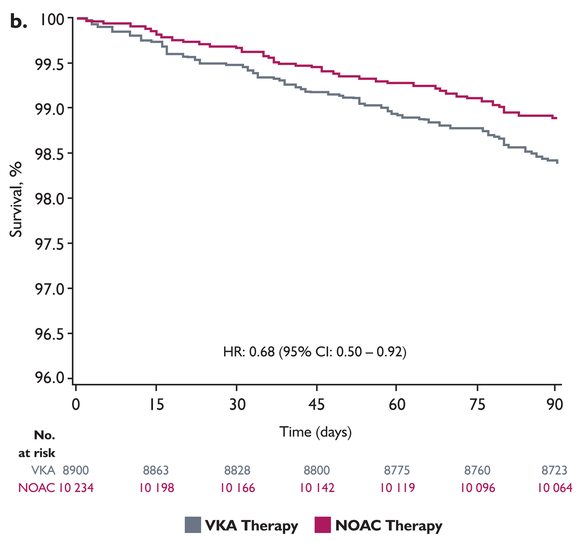
Figure 1. *Selection of population for analysis*



NOAC=non-vitamin K antagonist oral anticoagulation, OAC=oral anticoagulation, VKA=vitamin K antagonist.

Figure 2. *Survival curves for the comparison of a. OAC vs. no OAC and b. NOAC vs. VKA in patients with a CHA_2DS_2-VASc score ≥2 (including gender)*





CI=confidence interval, HR=hazard ratio, NOAC=non-vitamin K antagonist oral anticoagulation, OAC=oral anticoagulation, VKA=vitamin K antagonist.

Table 1. *Adjusted hazard ratios (HRs) for clinical outcomes at 3 months*

Treatment	Outcome	Adjusted HR (95% CI)
OAC vs No OAC	All-cause Mortality	0.54 (0.43 – 0.68)
	Stroke / SE	0.60 (0.40 – 0.90)
	Major Bleeding	1.41 (0.80 – 2.48)
NOAC vs VKA	All-cause Mortality	0.68 (0.50 – 0.92)
	Stroke / SE	0.63 (0.35 – 1.11)
	Major Bleeding	0.69 (0.37 – 1.27)

CI=confidence interval, HR=hazard ratio, NOAC=non-vitamin K antagonist oral anticoagulation, OAC=oral anticoagulation, SE=systemic embolism, VKA=vitamin K antagonist

CONCLUSIONS

- We have previously described the higher rates of mortality over the first few months after the diagnosis of AF compared with rates of mortality over 2 years follow-up.[3]
- In these analyses, we show that there are significant mortality differences in favour of OACs, even after adjustment for 31 baseline variables. These differences are manifest within 3 months from diagnosis (number needed to treat, NNT=76 [95% CI: 59-107]).
- The benefit of NOACs (relative to VKAs) on mortality was also observed by 3 months (NNT=167 [95% CI: 109-352]).
- These findings extend the evidence from randomised trials with data from a prospective multinational registry population with newly diagnosed AF.
- They also raise questions about the impact of anticoagulation, beyond stroke prevention.
- Additional investigations into impact of OAC and NOACs on other outcomes are warranted.

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REFERENCES

1. Rosenbaum PR and Rubin DB. The Central Role of the Propensity Score in Observational Studies for Causal Effects. *Biometrika* 1983; 70,41: C55
2. Li F, et al. Balancing Covariates via Propensity Score Weighting. *J Am Stat Assoc* 2018; 113(521): 390-400. doi: 10.1080/01621459.2016.1260466
3. Bassand JP, et al. Two-year outcomes of patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. *Eur Heart J* 2016; 37: 2882-9

DECLARATION OF INTEREST

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