NON-INTERVENTIONAL STUDY REPORT ABSTRACT

Title:

Major bleeding in patients with atrial fibrillation treated with apixaban versus warfarin in combination with amiodarone: the APIXAMIO study.

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Name and Affiliation of The Main Author:

Angelo Modica, MD, PhD
Internal medicine lead, Internal Medicine
Medical affairs Pfizer AB

Keywords:

apixaban, warfarin, amiodarone, safety, effectiveness

Rationale and Background:

This non-interventional study was designated as a PASS and was conducted voluntarily by Pfizer.

In a sub-analysis of the ARISTOTLE trial, amiodarone use was associated with increased risk of stroke and systemic embolism and lower TTR when used with warfarin. Furthermore, apixaban consistently reduced the rate of stroke and systemic embolism, death and major bleeding compared with warfarin in patients treated with amiodarone. However, randomized controlled trials (RCTs), are in general considered to involve a more selected patient population than is usually seen in real life, meaning that frail patients are frequently excluded in RCTs. We decided therefore to investigate whether we could replicate the relative safety-relations in terms of major bleeding, between apixaban and warfarin in combination with amiodarone, in real life reflecting a broader unselected AF patient population.

This real-world study describes the patient characteristics in patients treated with amiodarone in combination with either apixaban or warfarin and compared safety outcomes in these two patient cohorts if possible after feasibility assessment.

Research Question and Objectives:

The main scope of this study was to compare safety outcomes in patients treated with apixaban versus warfarin in combination with amiodarone.

Study Design:

Retrospective observational cohort study.

Primary Objective:

To compare the occurrence of major bleeding (including fatal bleeding, intracranial bleeding, gastrointestinal bleeding, and other bleeding) in patients treated with amiodarone in combination with apixaban versus warfarin.

Secondary Objectives:

To compare patients treated with amiodarone in combination with apixaban versus warfarin regarding occurrence of:

- *Intracranial bleeding:*
- *Intracranial bleeding.*
- *Gastrointestinal bleeding*
- *Other bleeding*

Exploratory objectives: To compare patients treated with amiodarone in combination with apixaban versus warfarin regarding occurrence of:

- *All-cause mortality*
- *Cardiovascular mortality*
- *Ischemic stroke or systemic embolism.*

Setting:

This retrospective observational cohort study was based on data from various Swedish health registries: the National Patient Register, the National Dispensed Drug Register and the National Cause of Death Register. The National Patient Register is a mandatory registry containing primary and secondary diagnoses based on International Classification of Diseases (ICD) codes for all hospitalizations and outpatient visits in Sweden since 1987.

Subjects and Study Size:

All patients with non-valvular atrial fibrillation (AF) in the National Patient Register and the National Dispensed Drug Register, in Sweden, with concomitant use of amiodarone and warfarin or apixaban between 2013-06-01 – 2018-12-31 were included in the study. A total of 12,103 patients met the inclusion/exclusion criteria and 8,686 patients were included after propensity score matching.

Inclusion Criteria:

To be eligible for inclusion in the study, patients must have met all the following inclusion criteria:

1. *Patients that have one or more AF (ICD-10 I48) diagnosis registered in the National Patient Register*

2. *Patients ≥18 years*

3. *Patients who had a filled prescription for amiodarone and apixaban or warfarin during the identification period.*

Exclusion Criteria

Patients meeting any of the following criteria were not included in the study:

1. *Patients with valvular AF (defined as patients with mechanical heart valves (Z952) implanted before index, or with a diagnosis of mitral stenosis before and including index date (I342, I050, I052, Q232).*

2. *Patients with an acute venous thromboembolism 6 months period before and including the index date (I26, I801, I802, I803, I808, I809, I822, I823, I828, I829, O223, O871, O882).*

3. *Patients with diagnosis or procedure-code for hip/knee replacement surgery within 6 weeks before and including index date (NFB, NFC, NGB, NGC, NFG, NGG).*

4. *Diagnosis codes indicating pregnancy 9 months before and including index date (A34, O00-O99, Z33, Z34, Z35, Z36, Z37, Z39, Z640, Z641).*

5. *Patients dispensing simultaneously more than one OAC (ATC code B01AA03, B01AE07, B01AF01, B01AF02, B01AF03) during the identification period.*

Variables and data sources:

This retrospective observational cohort study was based on data from various Swedish health registries: the National Patient Register, the National Dispensed Drug Register and the National Cause of Death Register. The National Patient Register is a mandatory registry containing primary and secondary diagnoses based on International Classification of

Diseases (ICD) codes for all hospitalizations and outpatient visits in Sweden since 1987. The National Dispensed Drug Register contains data on all prescribed medications dispensed at pharmacies in Sweden since 2005. The National Cause of Death Register was established in 1961 and is a mandatory registry that contains mortality data including date and cause of death. The Swedish health registries provide complete national coverage and each of the registries has been highly validated. Data linkage between registries was performed by the National Board of Health and Welfare in Sweden using the 10-digit person registration number available to all Swedish citizens.

Individual propensity scores for the likelihood of receiving apixaban + amiodarone rather than warfarin + amiodarone were obtained by logistic regression performed using the following covariates: age, sex, hypertension, diabetes mellitus, prior major bleeding, stroke/transient ischemic attack (TIA)/systemic embolism, myocardial infarction, percutaneous coronary intervention (PCI)/coronary artery bypass graft surgery (CABG), heart failure, peripheral arterial disease, chronic kidney disease, liver disease, asthma, chronic obstructive pulmonary disease, cancer within 3 years, other antithrombotic drugs within preceding 6 months (aspirin, clopidogrel, ticagrelor, prasugrel, low-molecular-weight heparin) as well as oral anticoagulant within 1 year.

Results:

Patient characteristics and comorbidities

After applying inclusion and exclusion criteria, 12,103 patients treated with amiodarone and concomitant warfarin or apixaban were included (4,343 [35.9%] patients treated with apixaban and 7,760 [64.1%] patients treated with warfarin). Patients receiving warfarin tended to be older, more often male and with higher occurrence of heart failure, myocardial infarction and ischemic stroke than those treated with apixaban. Patients treated with apixaban had more often a history of cancer and prior intracerebral hemorrhages. After propensity score matching, 8,686 patients remained in the study (4,343 [50.0%] treated with apixaban and 4,343 [50.0%] treated with warfarin). Balance in baseline characteristics in relation to oral anticoagulant treatment after propensity score matched cohort was achieved for most variables.

Major Bleeding

The median follow-up was 4.4 months and with a total of 172 events for the primary endpoint of major bleeding. The incidence rate of major bleeding events was 4.3/100 patient-years for patients treated with apixaban + amiodarone and 4.5/100 patient-years for patients treated with warfarin + amiodarone. No statistical difference was observed for major bleeding when comparing apixaban + amiodarone versus warfarin + amiodarone
(HR 1.03; 95% CI 0.76 – 1.39). Neither were there any significant differences for the secondary separate bleeding outcomes including gastrointestinal bleeding (HR 1.28; 95% CI 0.71 – 2.29), intracranial bleeding (HR 0.42; 95% CI 0.17 – 1.03) and other bleeding events (HR 1.07; 95% CI 0.74 – 1.56).

Stroke and Systemic Embolism

The exploratory outcome of stroke and systemic embolism occurred at an incidence rate of 1.3 and 1.5/100 patient-years in the apixaban + amiodarone and the warfarin + amiodarone group, respectively. No significant difference was observed when comparing the treatment strategies (HR 0.98; 95% CI 0.58-1.68).

All-cause Mortality and CV Mortality

The incidence rate of the exploratory outcome all-cause mortality was 7.2 and 6.9/100 patient-years for patients treated with apixaban + amiodarone versus warfarin + amiodarone, respectively. There was no significant difference in rates of all-cause mortality associated with apixaban + amiodarone compared to warfarin + amiodarone (HR 1.23; 95% CI 0.96 – 1.57). The exploratory outcome CV mortality occurred at an incidence rate of 6.2 and 5.6/100 patient-years in the apixaban + amiodarone and the warfarin + amiodarone group, respectively. No significant difference in CV mortality was observed when comparing apixaban + amiodarone versus warfarin + amiodarone (HR 1.15; 95% CI 0.89 – 1.49).

Discussion:

This nationwide cohort study, including 8,686 propensity score matched patients showed no significant difference regarding major bleeding events in patients with AF treated with amiodarone in combination with apixaban versus warfarin.

In this study, there was a non-significant numerically lower rate of intracranial bleeding with apixaban versus warfarin in patients treated with amiodarone. Similar findings have been reported in observational studies of dronedarone with concomitant use of apixaban and warfarin. Also, the ARISTOTLE trial reported that the risk for intercranial bleeding in patients on apixaban versus warfarin was statically lower with or without amiodarone.10 In contrast to the current study, earlier studies have reported higher rate of gastrointestinal bleeding with other NOACs other than apixaban compared to warfarin.

The main strength of the current study was the large sample size representing real-world patients nationwide with no loss to follow-up. The Swedish national registries also provide unique opportunities to collect data and to combine registries, minimizing missing data. For estimating medical therapy over time, the National Prescribed Drug Register was utilized. However, adherence to prescribed and collected medication cannot be ascertained. Due to the observational design of the study no evidence of causation could be established, and the definition of major bleeding was based on ICD-10 codes not defined by the International Society of Thrombosis and Hemostasis (ISTH). Although the definition of major bleeding used in this study has been validated, no clinical event adjudication was made.14 Another limitation of the study was the short follow-up. Due to the extracardiac toxicity of amiodarone, the treatment duration is often kept short, resulting in most patients only receiving short amiodarone prescriptions. Further limitations include confounding factors and a potential selection bias despite propensity score matching.

Lastly, the primary outcome was a composite endpoint where patients were censored at the time of an event leaving room for competing risk.

Conclusion:

In real-life patients with AF treated with apixaban versus warfarin and with concomitant use of amiodarone, there were no significant differences in risk of major bleeding. Thus, apixaban appears to be at least as safe as warfarin in terms of major bleeding, in patients with AF concomitantly treated with amiodarone, however, as previous studies have demonstrated the rate of intracranial bleeding is lower, although it did not reach statistical significance.

Marketing Authorization Holders:

Bristol-Myers Squibb/ Pfizer Limited

Names and Affiliations of Principal Investigators:

Angelo Modica, MD PhD
IM Medical Lead
NI Study Lead
Internal Medicine Medical Affairs, Pfizer AB
Solnavägen 3h, 113 63 Solna, Sweden, Sweden
Tel: +4676-889 2404
Email: angelo.modica@pfizer.com

Gorav Batra, MD, PhD
Ass. Professor
Consultant Cardiology
Inst. Medical Sciences,
Cardiology and Uppsala
Clinical Research Center
(UCR), Uppsala University

Christina Christersson, MD, PhD
Ass. Professor
Consultant Cardiology
Inst. Medical Sciences,
Cardiology, Uppsala
University
Sjukhusvägen 7
753 09 Uppsala, Sweden

Claes Held, MD, PhD
Professor
Consultant Cardiology
Inst. Medical Sciences,

Cardiology and Uppsala
Clinical Research Center
(UCR), Uppsala
University
UCR
Dag Hammarskjölds väg 38
751 83, Uppsala, Sweden