Risk of bleeding with non-vitamin K oral antagonists and phenprocoumon in routine care patients with non-valvular atrial fibrillation

Poster-Nr 2608

S.H. Hohnloser[1], M. Näbauer[2], A. Genet[3], T. Windeck[3], F. Volz[3], G. Hack[4], C. Lefevre[5], S. Dheban[6], J. Jacob[6], L. Hickstein[6], F. Leverkus[3]

[1]J. W. Goethe University, Dep. Of Cardiology, Frankfurt, Germany, [2]Ludwig-Maximilians-Universität, Munich, Germany, [3]Pfizer Deutschland GmbH, Berlin, Germany,

[4]Bristol Myers Squibb, Munich, Germany, [5]Bristol Myers Squibb, Rueil-Malmaison, France, [6]Elsevier Health Analytics, Berlin, Germany

Introduction

- Oral anticoagulation therapy (OAC) substantially reduces the risk of stroke in patients with non-valvular atrial fibrillation (NVAF) (1).
- The most important side effect of OAC is bleeding.
- Since 2011 non-vitamin K-oral anticoagulants (NOACs) are available for stroke prevention in patients with NVAF.
- NOACs are easier to use than vitamin-K antagonists (VKA) and have demonstrated equivalent or even superior efficacy and safety in comparison to VKA in large randomized control trials (RCTs) (2).
- The efficacy and safety achieved in RCTs may not necessarily translate into routine practice.
- Phenprocoumon is the predominantly used VKA in Germany.
- This study was conducted under the acronym CARBOS (Comparative risk of major bleeding with new oral anticoagulants (NOACs) and phenprocoumon in patients with atrial fibrillation).

Objectives

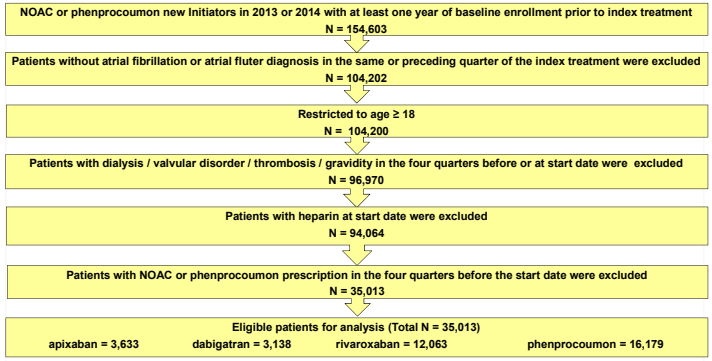
- To compare the risk of major bleeding, gastrointestinal bleeding and any bleeding in daily practice among German NVAF patients newly anticoagulated with apixaban, dabigatran, rivaroxaban or phenprocoumon, respectively.

Methods

Study Population:

- This non-interventional, retrospective study was based on an anonymized research data base from the Health Risk Institute (HRI) (3,4) which contains data of about 4 million statutory health insured subjects in Germany, approximately 5% of the total population.
- The HRI (owned by SpectrumK) offers independent statistical analyses on anonymized claims data for patient-level risk predictions, outcome research, and patient safety.
- All patients ≥18 years with one year of baseline period were included if they were newly prescribed OAC from January 1, 2013 to December 31, 2014 and had a documented NVAF (ICD-10 GM I48.0/I48.1/I48.2/I48.9) diagnosis in the same or the preceding quarter of the treatment initiation.
- Patient selection is presented in **Figure 1**.
- Observation start date: Date of first prescription for oral anticoagulants from Jan 1, 2013 to Dec 31, 2014.

Figure 1: Patient selection criteria



Study endpoints:

- Bleeding on anticoagulant was defined as bleeding documented at hospital discharge any time during the period of drug use or within 30 days from the last supply of treatment prescription.
- Major bleeding: Bleeding consists of emergency admission to hospital and pre-specified ICD10 GM hospital discharge diagnosis.
- Gastro-intestinal (GI) bleeding: Bleeding at any time during exposure time with localization in the GI-tract and documented as hospital discharge diagnosis.
- Any bleeding: Pre-specified primary or secondary ICD10 GM hospital discharge diagnoses at any time.
- Bleeding events that occurred on treatment, defined as the time after the first prescription fill until the end of the study period, discontinuation of treatment, death, end of continuous enrollment, or switching to another OAC were included (whatever occurred first).

Statistical Analysis

- Unadjusted rates of bleeding events were described as number of bleeding events per 100 person-years.
- Cox proportional hazard models were used to estimate the hazard ratios (HR) of major bleeding, gastrointestinal bleeding and any bleeding adjusted for pre-specified baseline demographics and clinical factors.

Sensitivity Analysis

- Analyses with the highest approved doses (2x5mg for apixaban, 2x150 mg for dabigatran, and 1x20 mg for rivaroxaban) were performed.

Results

- Among 35,013 eligible patients, 3,633 (10.38%) were initiated on apixaban, 3,138 (8.96%) on dabigatran, 12,063 (34.45%) on rivaroxaban, and 16,179 (46.21%) on phenprocoumon.
- The mean follow-up for patients initiated on apixaban was 220.79 days, dabigatran was 264.45 days, rivaroxaban was 262.78 days, and phenprocoumon was 284.93 days.
- Patients initiated on apixaban or phenprocoumon were older compared to those initiated on dabigatran or rivaroxaban, had on average a higher CHA2DS2-VASc score, and more comorbidities (**Table 1**).
- Patients initiated on apixaban had greater use of ASA, NSAIDs, antiplatelet drugs and proton-pump-inhibitors compared to patients initiated on phenprocoumon, dabigatran, or rivaroxaban (**Table 1**).

Table 1: Baseline characteristics of Study Population

Characteristic	phenprocoumon (n=16,179)	NOAC (n=18,834)	apixaban (n=3,633)	dabigatran (n=3,138)	rivaroxaban (n=12,063)
Age	76.1 [9.1]	73.7 [11.2]	75.5 [10.8]	72.6 [11.2]	73.4 [11.3]
Male	50.1	51.2	49.2	51.9	51.7
Medical history					
CHA2DS2-VASc-Score	4.1 [1.6]	3.8 [1.8]	4.1 [1.8]	3.8 [1.8]	3.7 [1.8]
HASBLED-Score	2.7 [1.1]	2.7 [1.2]	2.9 [1.2]	2.6 [1.2]	2.6 [1.2]
Charlson Comorbidity Index	3.4 [2.6]	3.1 [2.6]	3.4 [2.7]	2.9 [2.5]	3.0 [2.6]
Number of hospitalizations	1.1 [1.3]	1.2 [1.3]	1.3 [1.3]	1.3 [1.2]	1.2 [1.3]
Number of unique ATC codes	10.9 [5.2]	10.4 [5.4]	10.8 [5.4]	10.1 [5.1]	10.4 [5.4]
Major bleeding	1.3	1.4	2.0	1.6	1.1
Gastrointestinal bleeding	2.1	1.9	2.1	2.1	1.8
Any bleeding event	8.6	8.3	9.7	7.5	8.0
Ischemic stroke or TIA	12.2	16.1	22.4	21.9	12.7
Myocardial Infarction	7.5	5.0	5.6	5.1	4.8
Renal insufficiency	23.9	17.3	21.4	13.3	17.1
Congestive heart failure	40.4	34.6	37.1	31.7	34.6
Coronary heart disease	46.9	37.6	39.7	36.7	37.2
Hypertension	88.5	85.7	88.2	85.0	85.2
Cancer	19.7	18.4	19.2	17.9	18.3
Moderate or severe liver disease	0.5	0.5	0.9	0.2	0.5
Dementia	7.7	8.8	10.7	7.0	8.6
Diabetes	36.8	32.6	34.2	29.9	32.8
Obesity	23.0	23.0	22.2	22.7	23.3
Substance abuse	0.8	0.8	1.1	0.6	0.9
Medication use					
Antiplatelet drugs	22.7	24.7	27.0	25.5	23.7
ASA	17.5	19.7	21.8	19.4	19.2
NSAIDs	34.8	36.9	37.4	36.0	36.9
Proton-pump-inhibitors	43.9	44.1	46.0	44.0	43.6

Mean and standard deviation for continuous variables and proportions for categorical variables are shown.
ATC = Anatomical Therapeutic Chemical Classification System

- After adjusting for baseline characteristics, apixaban was associated with lower risks for major bleeding, gastrointestinal bleeding and any bleeding compared with phenprocoumon (**Figure 2**).
- There was no significant difference in the risk of different types of bleeding between dabigatran and phenprocoumon users (**Figure 2**).
- Rivaroxaban was associated with higher risk of GI bleeding and any bleeding, whereas there was no significant difference in the risk of major bleeding between rivaroxaban and phenprocoumon users (**Figure 2**).

Sensitivity Analysis:

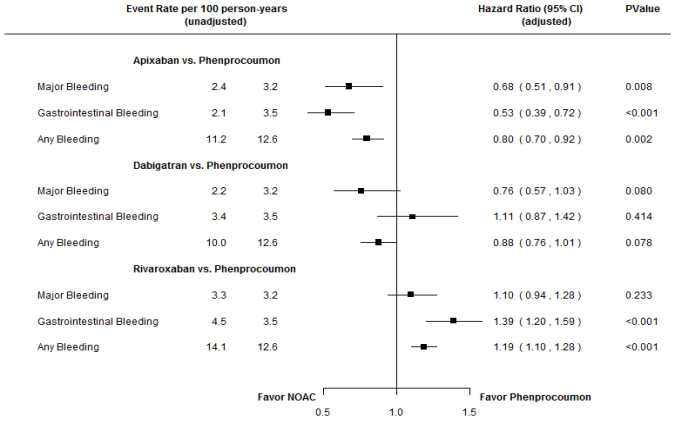
- Patients treated with the highest approved dose of apixaban n=2,231 (61%), dabigatran n=1,496 (48%) and rivaroxaban n= 8,379 (69%) were analysed, respectively.
- The results of sensitivity analysis for apixaban and rivaroxaban were consistent with the main analysis.
- Contrary to the main analysis dabigatran 2x150mg dose users had significantly lower risk of major bleeding and any bleeding compared with phenprocoumon users (**Table 2**).

Table 2: Adusted hazard ratios with 95% confidence intervals (CI) for each pairwise comparison (apixaban, dabigatran, and rivaroxaban each vs phenprocoumon) for highest approved doses of NOACs.

	apixaban (2x5 mg) vs. phen (HR, 95% CI)	dabigatran (2x150 mg) vs. phen (HR, 95% CI)	rivaroxaban (1x20 mg) vs. phen (HR, 95% CI)
Major Bleeding	**0.56** [0.36; 0.87]	**0.50** [0.27; 0.95]	1.07 [0.88; 1.29]
Gastrontestinal Bleeeding	**0.50** [0.32; 0.79]	0.88 [0.54; 1.42]	**1.33** [1.12; 1.58]
Any Bleeding	**0.75** [0.61; 0.91]	**0.70** [0.54; 0.90]	**1.15** [1.05; 1.27]

phen = phenprocoumon

Figure 2: Unadjusted event rates (per 100 person-years) and adjusted hazard ratios with 95% confidence intervals for each pairwise comparison (apixaban, dabigatran, and rivaroxaban each vs phenprocoumon)



Limitations

- As with all observational study, there remains the possibility of residual confounding.
- As is the case with any claims data , there is a potential for coding errors and missing data.
- A potential bias may be caused by uncertainties regarding patients' compliance.
- This study concentrated on bleeding events that were treated in hospitals.

Conclusions

- This is the first evaluation related to bleeding events comparing different NOACs and phenprocoumon in daily clinical practice in Germany.
- Our results indicate that treatment with apixaban is associated with a significantly reduced risk for bleeding events compared to phenprocoumon. Bleeding risk with dabigatran was comparable to phenprocoumon but bleeding risk with rivaroxaban seemed to be higher.
- Sensitivity analyses (e.g. subgroup of highest approved doses of NOACs) were consistent with the primary findings in demonstrating the better safety profile of apixaban vs. phenprocoumon in this real world setting.

Disclosure

- This analysis was funded by Bristol-Myers Squibb and Pfizer. Srirangan Dheban, Josephine Jacob and Lennart Hickstein are employees of Elsevier Health Analytics who received payment from Bristol-Myers Squibb and Pfizer to conduct this analysis. Professor Hohnloser serves as a consultant for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi Sankyo and Jansen. Professor Näbauer receives lecture fees from Bayer, BMS/Pfizer, Boehringer Ingelheim and Daiichi Sankyo.

References

1. Wolf, P.A., R.D. Abbott, and W.B. Kannel, *Atrial fibrillation as an independent risk factor for stroke: the Framingham Study.* Stroke, 1991. **22**(8): p. 983-988, 2012
2. 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.
3. Swart E, Gothe H, Geyer S, Jaunzeme J, Maier B, Grobe TG, Ihle P; German Society for Social Medicine and Prevention; German Society for Epidemiology. [Good Practice of Secondary Data Analysis (GPS): guidelines and recommendations]. Gesundheitswesen. 2015 Feb;77(2):120-6.
4. Andersohn F, Walker J. Characteristics and external validity of the GermanHealthRisk Institute (HRI) Database. Pharmacoepidemiol Drug Saf. 2016 Jan;25(1):106-9
5. Mohr W; et al.., *Vorhofflimmern - Herz aus dem Takt*, K.V. e.V., Editor. 2013.
6. Kannel, W.B. and E.J. Benjamin, Status of the epidemiology of atrial fibrillation. Medical Clinics of North America, 2008. 92(1): p. 17-40.
7. Mercaldi, C.J., et al., Long-term costs of ischemic stroke and major bleeding events among Medicare patients with nonvalvular atrial fibrillation. Cardiology research and practice, 2012.
8. Miller, C.S., et al., Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. The American journal of cardiology, 2012. 110(3): p. 453-460.

Remarks:
ESC CONGRESS 2016, 28 Aug 2016, Rome, Italy