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Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Title
REal-life aNticoaGulants comparative bEnefit-risk in nonvalvular atrial fibrilLation in France

Keywords
Nonvalvular Atrial Fibrillation, VKA, Direct Oral Anticoagulant, comparative effectiveness, comparative risk, Arterial Thrombotic Event, Bleeding, Acute coronary syndrome, Death, claims and hospitalisation database

Rationale and background
The benefit-risk of the 3 direct oral anticoagulants (DOAC) for nonvalvular atrial fibrillation (NVAF) was considered better than that of vitamin K antagonists (VKA) in premarketing clinical trials. However, health authorities have questioned the generalization of these results to current practice, where the physicians, the patients, drug prescription and use are not the same as those of the clinical trials. The ENGEL 2 study is an analysis using the whole French national health insurance database, starting six months after the beginning of DOAC launch in the NVAF indication. The aim is to compare the one-year, two-year and three-year benefit-risk (major bleeding, arterial thrombotic events, myocardial infarction (MI), death) between patients starting a DOAC and patients starting a VKA for NVAF in 2013, for the two DOAC marketed at this time in this indication (Pradaxa® versus VKA, and Xarelto® versus VKA), using matching on the main known risk factors, as well as propensity score to take into account potential unknown confounders.

Research question and objectives
The research question is to compare the one-year and long-term benefit-risk between each DOAC (Pradaxa®, Xarelto®) and VKA for new users in NVAF. The main objective is to compare the 1-year risk of major bleeding, risk of arterial thrombotic events (stroke, systemic embolism), risk of MI and risk of death for each DOAC (Pradaxa®, Xarelto®) versus VKA in NVAF during drug exposure. The secondary objective is to compare the long-term risk of major bleeding, risk of arterial thrombotic events (stroke, systemic embolism), risk of MI and risk of death for each DOAC (Pradaxa®, Xarelto®) versus VKA in NVAF during drug exposure (not done at this time).

Study design
Historical cohort study in a healthcare claims and hospitalisation database including new users of DOAC or VKA in NVAF in 2013 with a follow-up of at least one year (primary outcome); and a long-term follow-up (up to 4 years) (secondary outcomes).

Setting
New users of DOAC, dabigatran (Pradaxa®), rivaroxaban (Xarelto®) or VKA for NVAF, identified and followed in a claims and hospitalisation database (apixaban (Eliquis®) was marketed in this indication after the inclusion period, January 2014).

Subjects and study size, including dropouts

Among the 371 539 patients identified in the nationwide SNIIRAM database with a first DOAC or VKA dispensing in 2013, without DOAC or VKA dispensing for the last 3 years, 103 101 were included in the NVAF specific study population: 27 060 (26.2%) in the dabigatran group, 31 388 (30%) in the rivaroxaban group, and 44 653 (43%) in the VKA group, and 144 220 in the NVAF sensitive study population: 37 222 (26%) in the dabigatran group, 46 882 (33%) in the rivaroxaban group, and 60 116 (42%) in the VKA group. Patients of the specfic population had AF diagnosis from LTD or hospitalisation history, without valvular disease history. The sensitive population included the specific population, plus patients having a high probability to have an AF, based on an AF disease score.

From them, 20 489 patients per group were matched (1:1) on gender, age at index date (±1 year), hdPS (± 0.05 caliper) for the dabigatran versus VKA comparison in the specific population and 28 118 per group in the sensitive population (76% and 76% of dabigatran patients, respectively). For the rivaroxaban versus VKA comparison, 23 053 patients per group were matched in the same way

in the specific population, and 32 803 per group in the sensitive population (73% and 70% of rivaroxaban, respectively).

Variables and data sources

The SNIIRAM database is the nationwide claims and hospital database with individual anonymous information on all reimbursed outpatient claims linked to the national hospital-discharge summaries database system (PMSI) and the national death registry. It currently includes more than 98% of the French population of 65 million persons from birth (or immigration) to death (or emigration), even if a subject changes occupations or retires. It contains individual anonymised information on:

- Demographic characteristics: gender, date of birth, area of residence;
- Date of death;
- Long-term disease (LTD and associated ICD-10 codes) registration for full insurance coverage (with start and end dates);
- Outpatient reimbursed healthcare expenditures with dates and codes (but not the medical indication nor result): visits, medical procedures, lab tests, drugs and medical devices, etc;
- Hospital discharge summaries from hospital discharge summaries database (PMSI): ICD-10 diagnosis codes (primary, linked and associated diagnoses) for all medical, surgery and obstetrics hospitalisations, with the date and duration, medical procedures and cost coding system.

Results

The description of patients at index date showed large differences between dabigatran and VKA patients, as well as between rivaroxaban and VKA patients. In particular, DOAC patients were younger, with fewer comorbidities, hospitalisations before index date, stroke and bleeding risk factors. These differences were obvious from the hdPS distribution, with however a large common area, allowing a 1:1 matching for about 3/4 of the DOAC patients (the smaller group) to VKA patients with a very good hdPS overlapping for the matched patients. Futhermore, crude standardized differences between groups decreased drastically or even disappeared after hdPS adjustment and matching.

The most common first prescriber of dabigatran was a cardiologist for 36% of patients, followed by hospital physicians (33%), and GPs (20%). The same was true for rivaroxaban, 40% of cariologists, 28% of hospital physicians and 23% of GPs, while VKA were more prescribed by hospital physicians (40%), followed by general practitioners (28%), and cardiologists represented only 17% of the prescribers. For the first dabigatran dispensing, the higher dose (150 mg) was less prescribed than lower dose (110 mg), 58% and 40% respectively, with a few patients (3%) receiving the lowest dose (75 mg), which does not have the indication in NVAF. For rivaroxaban, it was the opposite with 60% higher dose (20 mg), 36% lower dose (15 mg), and a few patients (4%) receiving the lowest dose (10 mg), which does not have the indication for NVAF.

The main analysis was done for the specific population with a grace period of 30 days for drug discontinuation defintion. The 1-year cumulative incidence of discontinuation or switch was 60.9% (95% CI [60.3; 61.4]) with dabigatran (about 2/3 discontinuations and 1/3 switches) and 60.3% [59.8; 60.7] with VKA (82% discontinuations and 18% switches). Switches were mainly towards VKA (46.4%), rivaroxaban (32.1%) or heparins (20.2%) for dabigatran, and towards heparins (40%), rivaroxaban (38%), or dabigatran (20.2%) for VKA. The mean exposure duration was about 7 months for both treatment groups for all and matched patients. The number of person-years (PY) during first drug expose was 15 903 and 27 242 PY, respectively for all dabigatran and VKA patients, and 12 067 and 12 794 PY, respectively for matched patients, with a Medication Possession Ratio (MPR) greater than 80% for 97% for all and matched patients for both treatment groups.

For the rivaroxaban compared to VKA, the 1-year cumulative incidence of discontinuation or switch was 53.7% (95% CI [53.1; 54.2]) with rivaroxaban (about 2/3 discontinuations and 1/3 switches, similar to dabigatran). Switches were mainly towards VKA (50.5%), heparins (24.0%), or dabigatran (23.0%) for rivaroxaban. The mean exposure duration was about 7.5 months for both treatment groups for all and matched patients. Total exposure was 19 681 and 27 242 PY, respectively for all

rivaroxaban and VKA patients, and 14 559 and 14 333 PY, respectively for matched patients, with a MPR greater than 80% for 97% for all and matched patients for both treatment groups.

The overall incidence of the composite criterion (death, CRB, ATE, ACS) was 9.7 [95% CI: 9.2; 10.1] per 100 PY for dabigatran, 11.8 [11.4; 12.3] for rivaroxaban and 21.9 [21.4; 22.4] for VKA ; death was the most frequent event and represented between 43.2% and 59.8% of the composite criterion according to treatment groups, followed by clinically relevant bleeds (CRB) (27.8% to 33.9% of the composite criterion) and then arterial thrombotic events (ATE) (14.2% to 17.8%) and acute coronary syndromes (ACS) (9.6% to 14.4%); patient with several events were counted only once for the first one in the composite criterion.

The risk of all main outcomes (ATE, CRB and major bleeding, ACS, death and the composite criterion) was significantly lower with dabigatran compared to VKA for matched patients. For ATE, the risk with dabigatran was 25% lower [95% CI: 12% to 37%] than for VKA, 23% [5% to 37%] for ischemic or undefined stroke and 33% [11% to 50%] for systemic arterial embolism. For bleeding, the risk was lower by 42% [34% to 49%] for CRB, 78% [64% to 86%] for haemorrhagic stroke, 52% [31% to 67%] for other critical organ or site bleeding, 41% [17% to 58%] for urogenital bleeding, 63% [52% to 72%] for other bleeding, 45% [34% to 54%] for major bleeding (ISTH definition, Schulman 2005), but not difference for GI bleeding (HR: 0.98 [0.80 to 1.19]). For ACS, the risk was 21% lower [5% to 35%], 24% [2% to 40%] for unstable angina, but not significant for STEMI and NSTEMI (HR: 0.75 [0.53 to 1.07] and 0.80 [0.49 to 1.32], respectively). For death and composite criterion, the risk was lower by 26% [18% to 33%] and 29% [24% to 34%], respectively. Results were similar for all patients with gender, age and hdPS adjustment.

For rivaroxaban, the risk of CRB and major bleeding, death and the composite criterion was significantly lower than VKA for matched patients. For bleeding, the risk with rivaroxaban compared to VKA was 17% [8% to 25%] lower for CRB, 32% [21% to 42%] for major bleeding, 35% [13% to 51%] for haemorrhagic stroke, 30% [15% to 43%] for other bleeding, without difference for GI bleeding and urogenital bleeding, HR: 1.08 [0.90 to 1.30] and 1.0 [0.78 to 1.28], respectively. For death and composite criterion, the risk was lower by 23% [16% to 29%] and 16% [11% to 21%], respectively. The risk of ATE was not different between rivaroxaban and VKA (HR: 0.98 [0.85 to 1.14]) and for ACS the risk was of threshold significance (HR: 0.84 [0.71 to 1.0]). Results were similar for all patients with gender, age and hdPS adjustment.

Dabigatran versus VKA, and rivaroxaban versus VKA results were almost unchanged for the sensitive population, as well as with a grace period of 60 days for treatment discontinuation definition.

Discussion

The SNIIRAM is a national healthcare claims database linked to the national hospital discharge summaries database that covers about 99% of the French population. It is therefore fully representative of the French population. It provided a unique opportunity to identify new users of DOAC or VKA for NVAF in 2013, with exhaustive information about reimbursed outpatient healthcare resources including reimbursed drugs, as well as all public and private hospitalisations, excuding selection and information biases. The main limit is that it was built for administrative and reimbursement purposes with a lack of clinical information that could impact the patients' prognosis. An hdPS was built to matched patients 1:1 for each comparison, as well as to adjust analysis of all patients, in order to control confounding bias.

The study confirms a better risk-benefit of dabigatran compared to VKA in real-life, and than in the RE-LY randomized control trial (Connoly 2009), especilally for all bleeding, ACS and death. It could be explained by the VKA used in France, mainly fluindione whereas warfarin was the comparator in the RE-LY trial and the most used in most other countries, but might also be explained by poorer drug surveillance in real life than in a strict randomized control trial, especially for INR surveillance and VKA dose adjustment, as well as several potential VKA interactions. However, the study shares outcome results with several of post approval dabase studies.

The study confirms also a better risk-benefit of rivaroxaban compared to VKA in real-life, but with some discrepancies with the ROCKET-AF randomized control trial: no ATE risk difference, lower risk of bleeding, similar result for ACS and somewhat lower for death. However, the study shares similar outcome results with several other post approval database studies.

Generalizability to the French population was built into the study: patient selection was based on a whole population database, without any sampling. Patients are therefore fully representative of the patients with NVAF diagnosis from LTD or hospitalisation diagnosis, as well as those with probable AF based on study AF disease score. These results are set within a specific healthcare system in which the most used VKA was fluindione, and might or not apply to other countries.

From the conditions of use described in France, DOAC and VKA are prescribed preferentially to rather different patients, which could explain the very different crude risks. When patients are compared with similar patients in our matched groups, or from adjusted analyses, the study shows a significantly overall better benefit-risk of DOAC versus VKA including for death, major bleeding and intracranial bleeding, without increased risk of gastrointestinal bleeding. The risk of all main outcomes was significantly lower with dabigatran than with VKA. For the rivaroxaban, the risks of CRB and major bleeding, death and the composite criterion were significantly lower than for VKA.

Because there is no indication of dose in VKA users, and there was no way to adjust for INR, all doses or rivaroxaban or dabigatran were pooled. Any differences in patient profiles was taken into account in the matched populations.

This study therefore confirms the superior effectiveness of both dabigatran and rivaroxaban over VKA, within the limits expressed above, as used in real life in 2013 and subsequent years in the French population.

Marketing Authorisation Holder(s)
Boehringer Ingelheim France

Names and affiliations of principal investigators
Dr [redacted],