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Comparative patterns of use of non-vitamin K antagonist oral anticoagulants and risk of haemorrhage in real life. The Stroke Prevention and Anticoagulants (SPA) study

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Background/Introduction: The pattern of use of non- vitamin K antagonist oral anticoagulants (NOAC) in the management of non-valvular atrial fibrillation (NVAF) and the rates of haemorrhage associated with their use under real-life conditions are still broadly unknown in France.
Purpose: To describe patterns of use for dabigatran, rivaroxaban, apixaban, and VKA as well as to assess the rates of haemorrhage according to OAC therapy.
Methods: Data from patients participating in the PGRx-Atrial fibrillation systematic registry assembled by 118 cardiologists and 32 general practitioners from December 2013 to October 2016 were analysed. A total of 3693 patients with NVAF, who underwent also an interview, were retained for the treatment patterns analysis, of whom 2850 patients treated with anticoagulants over the 12 months prior to recruitment were considered for the study of haemorrhage. Recruiting physicians collected data on diagnosis and comorbidities for enrolled patients. Patients' interviews detailed retrospectively the one-year history of OAC treatment and haemorrhage ahead of study onset.
Results: VKA users were 76.4 [8.7] y.o. on average vs. 73.5 [9.4], 72.1 [9.8] and 73.4 [9.5] y.o. for dabigatran, rivaroxaban and apixaban users, respectively. There were 66.3%, 65.0%, 63.6%, and 61.1% males amongst VKA, dabigatran, rivaroxaban and apixaban users, respectively. NOAC users had permanent NVAF less often than VKA users (41.9%, 30.9%, and 20.5%. respectively, vs. 53.7%). Switching –from and to any OAC drug -rate was low and around 6.9% overall. Incident users were switched to any OAC treatment in 8.3%, 5.5%, 5.8%, and 2.8% of patients respectively for dabigatran, VKA, rivaroxaban, and apixaban. Proportions of switchers across the prevalent OAC Users' subpopulations were similar (7.8%, 8.6%, 5.8%, 4.5%, respectively). OAC were continued in 90% of patients, a percentage that remained unchanged regardless of the drug. Discontinuation at 12 months occurred in 2.9% of patients on average, with no difference across OAC. The incidence rate per 100 patient/year of experiencing a major haemorrhage episode was 2.57 [1.99 - 3.15] overall, with 1.22 [0.00 - 2.45], 1.83 [0.82 - 2.83], 1.32 [0.01 - 2.62], 6.73 [2.59 - 10.87], 2.88 [2.01 - 3.74] respectively in users of dabigatran, rivaroxaban, and apixaban, in switchers, and in VKA users. The HAS-BLED score and any interruption were statistically significant when associated with risk of major haemorrhage, with OAC interruption showing a high OR of 4.47 [2.61 - 7.66].
Conclusion: NOAC were used in younger patients, with a more recent diagnosis of AF and less likely permanent AF than VKA users. On average, switching and discontinuation rates were low. NOAC exhibited lower rates of major bleeding, which may be a reflection of both their mechanism of action and differences in the populations treated.
Acknowledgement/Funding: Study conception and data analyses were conducted independently of Boehringer Ingelheim that subscribed data from PGRx data registry for the SPAstudy

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The extrinsic and intrinsic pathways of coagulation are considerably activated in patients with paroxysmal atrial fibrillation

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Background: Clinical interest in the haemostasis profile of patients with paroxysmal atrial fibrillation (PAF), and in particular, in blood coagulation is significant. It is known that blood coagulation is activated in two pathways: extrinsic and intrinsic. The extrinsic pathway is initiated by the tissue factor (TF), which forms a complex with factor VII (F VII) and activates it. The intrinsic pathway is triggered by the contact of factor XII (F XII) with the subendothelial space and its subsequent activation. Regardless of the activation method, the coagulation cascade ends with a final common pathway, in which the activated factor X (FX) is central to the prothrombin complex, responsible for the conversion of prothrombin (factor II (F II)) to thrombin that converts fibrinogen into fibrin.
Purpose: To study the coagulation system in patients with clinical manifestation of PAF$<$24 hours.
Materials and methods: 51 non-anticoagulated patients (26 men, 25 women; mean age 59.84±1.60 years) and 52 controls (26 men, 26 women; mean age 59.50±1.46 years) corresponding in age, gender, comorbidities and conducted treatment, were consequently selected for the study. TF levels and coagulation activity of F II, F VII, F X and F XII were examined in plasma. Enzyme-linked immunoassays and kinetic enzyme tests were used.
Results: All patients were hospitalized between the 2nd and the 24th hour after the onset of the arrhythmia (mean 8.14±0.74 hours). TF values in the patient group were significantly higher (170.21pg/mL±9.18pg/mL vs 268.63pg/mL±12.69pg/mL; $p<0.001$) (fig 1). There was also increased coagulation activity of FII, F VII, FX and FXII in the PAF group compared to the control group (100.43%±5.77% vs 167.81% ± 9.12%, $p<0.001$; 95.17% ± 5.26% vs 170.82% ± 8.32%, $p<0.001$; 116.20% ± 5.86 vs 193.20% ± 11.85, $p<0.001$; 148.41% ± 7.48% vs 218.31% ± 11.77%, $p<0.001$, respectively) (fig 1).
Conclusion: Even in the first twenty-four hours of the clinical presentation of PAF, the plasma levels of TF and the activity of F II, F VII, F X and F XII were substantially increased. This gives grounds to assume that there is an early and considerable activation of blood coagulation in PAF patients. Unidirectional changes in the initiation factors of the extrinsic (elevated plasma levels of TF and F VII activity) and intrinsic (increased F XII activity) pathways suggest considerable activation of both coagulation pathways. Given the fact that heparin indirectly mediates the inhibition of F II, F VII, F X and F XII, our results give grounds to believe that the use of heparin and low molecular weight heparins in order to reduce the embologenic risk in the early hours of PAF is clinically appropriate.

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Incidence of ischemic stroke in a pacemaker population

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Introduction: Dual-chamber pacemakers can detect and store atrial high rate episodes (AHRE). Subclinical episodes of AF identified as AHRE are common, but whether they justify antithrombotic treatment remains incompletely unknown.
Methods: Consecutive patients implanted with a dual-chamber pacemaker due to bradyarrhytmhia were retrospectively studied. Occurrence of AF/AHRE episodes and ongoing/prescribed anticoagulant or antiplatelet treatment, and the incidence of ischemic stroke were analyzed.
Results: Among patients with known AF (n=267) at implant, 3.4% (n=9) suffered an ischemic stroke during 43±17 months follow-up. One stroke was fatal. At the time of stroke eight of them had treatment with warfarin (n=4), aspirin (n=2), clopidogrel (n=1) and low molecular weight heparin (n=1).
In patients with incident AF (n=125), 6.4% (n=8) suffered an ischemic stroke during 47±16 months follow-up. Seven had their AF diagnosis confirmed before the onset of ischemic stroke, while one was diagnosed during the care episode for ischemic stroke via pacemaker diagnostics. The mean time from first AF episode to ischemic stroke were 18.5±18.2 (median 10, range 0–50) months. Two strokes were fatal in patients with ongoing treatment with aspirin. At the time of stroke five patients had treatment consisting of warfarin (n=1), aspirin (n=3) and clopidogrel (n=1).
Among patients without any documented AHRE/AF (n=286), 2.4% (n=7) suffered an ischemic stroke during 39±16 months follow-up. Five patients were on ongoing treatment with warfarin n=3 or aspirin n=2, for other reason than AF.
Conclusion: Although not statistically significant, most probably due to small numbers, we observed a higher incidence of ischemic stroke in patients with incident AF compared to those with known AF and without any documented AHRE/AF. The annual stroke incidence was low in all three groups, 0.9%, 1.6% and 0.7%, respectively. Anticoagulation (warfarin) was present in less than half of the patients with stroke in each group, 4/8, 1/8 and 3/7 patients, and at least in the latter group not due to AF. Larger studies are needed to establish the role of antithrombotic treatment in this patient population.

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Timing of trial stoppage for non-inferiority trials and interpretation: lessons from ROCKET AF

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Background: Analysis of non-inferiority in clinical trials generally uses the per-protocol (PP) cohort to reduce bias towards non-inferiority due to non-compliance. Intention-to-treat (ITT) analysis for superiority includes all patients (on or off study drug) until end of the trial. For event-driven studies evaluating non-inferiority and superiority, whether to stop trials based on the requisite number of accrued events in the PP vs. ITT cohort is not clear.