Clinical Study Synopsis

This Clinical Study Synopsis is provided for patients and healthcare professionals to increase the transparency of Bayer's clinical research. This document is not intended to replace the advice of a healthcare professional and should not be considered as a recommendation. Patients should always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document or on the related website should not be considered as prescribing advice.
The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

1. Abstract

Acronym/Title	**A**dverse Re**N**al Ou**T**com**E**s in patients with **N**o**N**-Valvular **A**trial fibrillation treated with Rivaroxaban or Vitamin K Antagonists (**ANTENNA**)
Report version and date **Author**	v 1.0 27 APR 2021 PPD PPD Spain
Keywords	Acute kidney injury; End-stage renal disease; renal function; chronic kidney disease; oral anticoagulants
Rationale and background	Atrial fibrillation (AF) and chronic kidney disease (CKD) are both common conditions that become more prevalent with advancing age, and they frequently co-exist. Most patients with AF are at high risk of stroke and therefore require preventative therapy with long-term anticoagulation. Patients with both AF and CKD have a further increased risk of thromboembolic events, and they are also at higher risk of bleeding – risks that are higher with progressively declining renal function. For patients with non-valvular AF (NVAF), international guidelines recommend direct oral anticoagulants (DOACs) as the preferred OAC, yet vitamin-K antagonists (VKAs) are still extensively used in clinical practice, including among patients with concomitant CKD. Anticoagulant-related nephropathy (ARN) is a complication associated with the use of anticoagulants that has been reported in recent years, especially in patients on warfarin. Anticoagulant-related nephropathy accelerates the progression of CKD and is a significant risk factor for mortality within the first two months of diagnosis. Previous observational studies among patients with NVAF have shown that use of vitamin K antagonists, such as warfarin, is associated with higher risks of adverse renal outcomes – both long-term (declining renal function) and acute (acute kidney injury) – than rivaroxaban. The rationale for this present study was that further observational evidence demonstrating a differential effect between rivaroxaban and VKAs on adverse renal outcomes in

	patients with NVAF in other settings would help prescribers make more informed benefit–risk decisions regarding choice of anticoagulant therapy for their patients.
Research question and objectives	**Primary objective:** to estimate the magnitude of renal decline, incidence of end-stage renal disease (ESRD) and acute kidney injury (AKI) in patients with NVAF treated with rivaroxaban and those treated with a VKA according to the presence of CKD and its severity at the start of OAC therapy in UK primary care. **Secondary objective**: to evaluate the primary objective among specific risk groups reflecting known risk factors for CKD progression: • patients with/without diabetes • patients with/without heart failure
Study design	Retrospective cohort study using secondary data collection. A new user design was used – patients with NVAF newly initiated on OAC therapy with either rivaroxaban or a VKA were identified and followed up to identify adverse renal outcomes.
Setting	United Kingdom primary care: IQVIA Medical Research Data UK (IMRD-UK) database.
Subjects and study size, including dropouts	The study cohorts included 6903 initiators of rivaroxaban (15 mg, N=1156; 20 mg, N=5747), and 7586 initiators of warfarin.
Variables and data sources	**Exposure:** the first OAC prescribed – either rivaroxaban or warfarin. The main analysis used an intention-to-treat: any change in exposure during follow-up was ignored and we assumed that patients remain on the OAC they initiated for the entire follow-up. **Renal outcomes:** • 100% increase (doubling) of serum creatinine (SCr) from OAC initiation any time during follow-up (confirmed by a subsequent measurement) • ≥20%, ≥30%, ≥40%, and ≥50% increase in SCr from baseline at any point during follow-up (confirmed by a subsequent measurement).

	• ≥20%, ≥30%, ≥40% and ≥50% decline in estimated glomerular filtration rate (eGFR) from baseline at any time during follow-up confirmed by a subsequent measurement • ESRD • Rate of eGFR decline during follow-up • AKI: two case identification methods were used. Method A used coded entries for AKI only, and Method B used recorded SCr values based on a previously reported AKI phenotyping algorithm **Co-variates:** demographics, comorbidities, comedications, health care use, lifestyle variables
Results	**Renal decline and ESRD** After a mean follow-up of 2.5 years, the number of cases with renal outcomes ranged from 3040 for the mildest renal decline endpoint (≥20% decline in eGFR) and 98 for the most severe endpoint (ESRD). The crude incidence rates of renal decline events, i.e. changes in creatinine clearance and eGFR from the baseline, (per 10,000 person-years) were consistently lower among rivaroxaban initiators (ranging from 22.1 for ≥20% decline in eGFR to 983.4 for ESRD depending on the cut-offs) than among warfarin initiators (ranging from 30.5 for ≥20% decline in eGFR to 1050.6 for ESRD). After adjustment for potential confounders, compared with individuals initiating warfarin, those initiating rivaroxaban experienced a reduced risk of renal decline outcomes that ranged from 14% (95% CI: 8%–20%) for ≥20% decline in eGFR to 28% (95% CI: 12%–41%) for ≥50% decline in eGFR. Furthermore, the estimated mean loss in renal function during the study period was 1.82 ml/min/1.73 m^2 per year among warfarin initiators and 1.37 ml/min/1.73 m^2 per year among rivaroxaban initiators (p<0.01). **AKI** The crude incidence rate of AKI using Method A was 88.1 per 10,000 person-years among initiators of rivaroxaban and 69.9 per 10,000 person-years among initiators of warfarin respectively. The corresponding incidence rates for AKI using Method B were 194.4 per 10,000 person-years among initiators of rivaroxaban and 234 per 10,000 person-years.

	After adjusting for confounders, HRs for AKI with rivaroxaban vs. warfarin use were 1.26 (95% CI: 0.99-–1.60) using Method A, and 0.80 (95% CI: 0.69–0.93) using Method B.
Discussion	Our results support the results of previous observational studies that patients with NVAF using rivaroxaban have a significantly reduced risk of renal decline than those using warfarin. Our results also indicate that identifying AKI in the IMRD-UK primary care database is challenging, but when using the most sensitive definition (Method B), rivaroxaban is associated with a significantly reduced risk of AKI when compared with warfarin. Further observational research and evidence from randomized controlled trials would provide the final word regarding this interesting effect of these drugs.
Marketing Authorization Holder(s)	Bayer AG, 51368 Leverkusen
Names and affiliations of principal investigators	PPD and PPD PPD PPD , Spain