Clinical Study Synopsis

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1. Abstract

Acronym/Title	RIVA-DM: Effectiveness and Safety of Rivaroxaban vs. Warfarin in Nonvalvular Atrial Fibrillation and Diabetes Mellitus: Analysis of Electronic Health Record Data
Report version and date **Author**	v 1.0, 05 NOV 2021 1) PPD MetaEvidence, LLC 2) PPD Bayer AG 3) APCER: PPD
Keywords	NVAF, Rivaroxaban, Diabetes Mellitus, Effectiveness, Safety
Rationale and background	Patients with diabetes are at a greater risk of developing nonvalvular atrial fibrillation (NVAF). Comorbid diabetes and NVAF increases the risk of stroke and systemic embolism (SSE), lower extremity arterial disease, and progression to end-stage renal disease (ESRD)
Research question and objectives	What is the comparative effectiveness and safety of rivaroxaban versus warfarin in patients with NVAF and comorbid type 2 diabetes managed in routine clinical practice? The objectives of the study were to compare the effectiveness and safety of rivaroxaban versus warfarin by assessing the risk of major thrombotic adverse events and bleeding-related hospitalization in patients with NVAF and comorbid type 2 diabetes, as well as secondary endpoints (e.g., development of new-onset neurologic impairment, adverse renal outcomes)
Study design	A retrospective cohort study using the Optum EHR database.
Setting	The Optum EHR (electronic health record) database included data on insured and uninsured patients of all ages (≥18 years) to provide a representative sample of US patients with NVAF. Optum EHR data from 01 NOV 2010 to 31 DEC 2019 were used for the study.
Subjects and study size, including dropouts	NVAF patients with comorbid type 2 diabetes and those qualifying for study inclusion were identified in the Optum EHR database and analyzed for primary and secondary outcomes. After applying all of the defined selection criteria, 116,049 patients (32,078 rivaroxaban users and 83,971 warfarin users) were considered to evaluate primary

	outcomes and secondary outcomes (CV and bleeding). Of the 116,049 patients, 83,182 patients (24,912 rivaroxaban users and 58,270 warfarin users) were considered to evaluate secondary outcomes related to kidney, major adverse limb event (MALE), ophthalmic, and all-cause mortality. Of the 116,049 patients, a total of 88,227 patients (26,537 rivaroxaban users and 61,690 warfarin users) were considered to evaluate ophthalmic outcomes/complications (non-traumatic bleeding and/or diabetic retinopathy).
Variables and data sources	Patient baseline characteristics such as age, gender, comorbidities and comedications, stroke and bleeding scores were collected at the index date or from the last recorded value within the baseline period. The primary outcomes were: • Composite outcome of SSE • Major or clinically relevant non-major (CRNM) bleeding events resulting in hospitalization. The secondary outcomes were composite of stroke, systemic embolism, and vascular death; composite of stroke, systemic embolism, myocardial infarction (MI), and vascular death; major adverse cardiovascular event (stroke, MI, and vascular death); ischemic stroke (IS); systemic embolism; need for revascularization or major amputation of the lower limb; intracranial hemorrhage (ICH); critical organ bleeding; any extracranial bleeding; any hospitalization due to intracranial or critical organ bleeding or a bleed in another location associated with either a 2 g/dL drop in hemoglobin or need for transfusion; doubling of the serum creatinine level from baseline; decrease in eGFR>30% or 40%; development of an eGFR<15 mL/min or initiation of dialysis; development of ESRD; development of urine albumin-to-creatinine ratio (UACR) of 30-300 or >300; development of diabetic retinopathy; development of serum potassium > 5.6 or >6 mg/dL; MI; all-cause mortality; vascular mortality; composite stroke, systemic embolism, need for lower limb revascularization or major amputation; and composite of >40% decrease in eGFR from baseline, eGFR<15 mL/min, need for dialysis, renal transplant, MALE, retinopathy or all-cause death. Billing codes were required to identify covariates or outcomes and endorsed and/or validated coding algorithms (e.g., Centers for Medicare & Medicaid Services (CMS), agency for health research and Quality (AHRQ), Elixhauser

	or Charlson comorbidity indices, Cunningham bleeding algorithm) were utilized, whenever possible. United States Optum® de-identified EHR database that capture longitudinal patient-level medical record data for ~97 million patients at ~700 hospitals and ~7,000 clinics across the United States (US) were utilized for this study. This EHR database included patients from different geographical areas of the US and captured commercially insured, Medicare, Medicaid, and uninsured patients, providing a more accurate reflection of the general population than a traditional administrative claims data set.
Results	Rivaroxaban was associated with a reduced risk of SSE or vascular death (3.79 vs. 4.19; HR=0.91, 95% CI: 0.88, 0.95), driven mostly by 10% relative risk reduction (RRR) in vascular death (2.81 vs 3.18, HR=0.90, 95% CI: 0.86, 0.95) and 18% RRR in systemic embolism (0.13 vs. 0.16; HR=0.82, 95% CI: 0.66, 1.02). Major/CRNM bleeding was less frequent with rivaroxaban versus warfarin (2.17 vs. 2.31; HR=0.94, 95% CI: 0.89, 0.99) due to decreased critical organ bleeding (37% RRR) and intracranial hemorrhage (28% RRR). These findings remained consistent across subgroups such as baseline HbA1c level, with statistical interactions seen only when comparing the 20 mg versus 15 mg dosing subgroups for the SSE/vascular death outcome (an interaction based more on magnitude than direction of effect) and among patients with a well-controlled INRs (TTR≥75%). These findings also remained robust upon changes in confounding adjustment methodology employed and upon capping follow-up at a maximum of 2-years. The effectiveness and safety of rivaroxaban relative to warfarin remained consistent across older and younger patient subgroups for the outcomes of SSE or vascular death (HR=0.93 vs. 0.91), and hospitalization for major or CRNM bleeding (HR=1.06 vs. 0.90). Rivaroxaban was associated with a reduced hazard of the composite outcome of >40% decrease in eGFR from baseline, eGFR<15 mL/minute/1.73 m^2, need for dialysis or kidney transplant, MALE, diabetic retinopathy or death (HR=0.93, 95%CI: 0.91, 0.95) versus warfarin. Rivaroxaban was also associated with significant reductions in the relative hazard of a >40% decrease in eGFR from baseline (HR=0.96), need for dialysis or renal transplant (HR=0.81), and limb revascularization or major amputation (HR=0.85). Death occurred at a lower incidence rate with rivaroxaban

	(HR=0.92, 95%CI: 0.89, 0.95). These findings remained consistent across subgroups stratified by age, eGFR, HbA1c, morbid obesity, and antiplatelet use; as well as, when follow-up was capped at 2-years and 1:1 propensity score matching or sIPTW was alternatively used for between cohort confounder adjustment. Rivaroxaban was associated with a 15% (95%CI: 8%, 21%) relative hazard reduction of any ophthalmic complication (incidence rate=1.25 vs. 1.46 per 100 person years), driven by reductions in both ophthalmic bleeding (HR=0.80) and diabetic retinopathy (HR=0.85).
Discussion	In NVAF patients with T2DM, rivaroxaban was associated with an ~10% relative risk reduction in vascular mortality and fewer bleeding-related hospitalizations versus warfarin, including a significant 37% relative risk reduction in critical organ bleeding and a 28% relative risk reduction in intracranial hemorrhage. Rivaroxaban was associated with a significant 19.7 event/1,000 person years reduction in the composite outcome of >40% decrease in eGFR from baseline, eGFR<15 mL/minute/1.73 m^2, new need for dialysis or renal transplant, limb revascularization or major amputation, development of diabetic retinopathy, or all-cause mortality. These reductions in adverse events were due to reduced incidence rates of kidney and limb complications, as well as all-cause death. Rivaroxaban was associated with a reduction in ophthalmic complications compared to warfarin. The effectiveness and safety of rivaroxaban relative to warfarin remained consistent across older and younger patient subgroups, supporting rivaroxaban as an alternative for elderly NVAF patients with concomitant type 2 diabetes. The findings of the present study should provide clinicians with additional confidence in selecting rivaroxaban in NVAF patients with comorbid T2DM.
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