



Bayer AG
Communications
51368 Leverkusen
Germany
Phone +49 214 30-1
media.bayer.com

News Release

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Large real-world study shows benefit of rivaroxaban in patients with nonvalvular atrial fibrillation with type 2 diabetes

- Real-world data contribute to findings from pivotal clinical trial
 - Data show that rivaroxaban was associated with reduced serious complications and death in patients with nonvalvular atrial fibrillation (NVAF) and comorbid type 2 diabetes (T2D) compared to warfarin
 - The findings come from the large study RIVA-DM which evaluated the effectiveness and safety of rivaroxaban versus warfarin in patients with NVAF and T2D, focusing on endpoints including the risk of vascular death, bleeding-related hospitalization, and stroke as well as kidney and limb related complications
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Berlin, May 17, 2021 – Real-world data presented at the American College of Cardiology's 70th Annual Scientific Session & Expo (ACC.21) showed that the oral Factor Xa inhibitor rivaroxaban (Xarelto™) was associated with reduced vascular mortality in patients with nonvalvular atrial fibrillation (NVAF) and comorbid type 2 diabetes (T2D), with fewer bleeding-related hospitalizations versus warfarin. The data contribute to the findings from the pivotal clinical trial ROCKET-AF.

These real-world data build on previous results from two analyses from the same study (RIVA-DM), already presented at the European Heart Rhythm Association (EHRA) congress in April this year, which demonstrated that rivaroxaban was associated with reduced kidney and limb related complications, ophthalmic complications (including ophthalmic bleeding) and death in these same patients compared to warfarin. The RIVA-DM study analyzed electronic health record data of approximately 116,000 patients from the US over several years. ACC.21 takes place virtually from 15-17 May.

The three analyses presented so far from RIVA-DM are as follows:

- Presented at American College of Cardiology's 70th Annual Scientific Session & Expo 2021:
 - o Craig I. Coleman et al., Thromboembolism, Bleeding and Vascular Death in Nonvalvular Atrial Fibrillation Patients with Type 2 Diabetes Receiving Rivaroxaban or Warfarin: An Analysis of Electronic Health Records
- Presented at European Heart Rhythm Association (EHRA) congress 2021:
 - o Olivia S. Costa et al., Ophthalmic complications in patients with nonvalvular atrial fibrillation and type 2 diabetes prescribed rivaroxaban or warfarin
 - o Olivia S. Costa et al., Kidney, Limb and Ophthalmic Complications, and Death in Patients with Nonvalvular Atrial Fibrillation and Type 2 Diabetes Prescribed Rivaroxaban or Warfarin: An Electronic Health Record Analysis

People with T2D are at a 49% increased risk of developing NVAF compared to people without T2D. About one-third of NVAF patients have comorbid diabetes. Furthermore, patients with NVAF and comorbid T2D are at a five times greater risk of stroke/systemic embolism (SSE) or death from vascular causes than NVAF patients without diabetes. Given that the latest estimates put the number of people living with T2D worldwide at approximately 462 million, corresponding to about 6% of the world's population, this poses a significant threat to healthcare services.

“Developing atrial fibrillation can pose a serious health threat to people with T2D,” said Dr. Michael Devoy, Chief Medical Officer and Head of Medical Affairs and Pharmacovigilance at Bayer's Pharmaceuticals Division. “These data show that rivaroxaban has a consistent safety and efficacy profile when treating these patients, providing further reassurance of its ability to be used for patients with this condition.”

NVAF patients typically receive a non-vitamin K oral anticoagulant (NOAC) such as rivaroxaban or a vitamin K antagonist (VKA) such as warfarin for stroke prevention. NOACs have been shown to significantly decrease the risk of clot formation and subsequent morbidity and mortality in patients with NVAF. The RIVA-DM study was conducted to evaluate the effectiveness and safety of rivaroxaban in NVAF patients with T2D compared to warfarin in real-life practice. The study focused on a range of key endpoints including the risk of vascular death, bleeding related hospitalization, stroke, adverse kidney outcomes and adverse limb events.

The analyses found that rivaroxaban was associated with a significantly reduced risk of vascular death and serious complications in comparison to warfarin. Hospitalization for any type of major/clinically relevant nonmajor bleeding was reduced with rivaroxaban versus warfarin as was critical organ and intracranial hemorrhage.

About the analyses

Craig I. Coleman et al., Thromboembolism, Bleeding and Vascular Death in Nonvalvular Atrial Fibrillation Patients with Type 2 Diabetes Receiving Rivaroxaban or Warfarin: An Analysis of Electronic Health Records

This study analyzed Optum® De-Identified electronic health record data from 11/2011–12/2019, looking at adults with NVAF and T2D who were newly started on rivaroxaban or warfarin. It evaluated the incidence rate of developing the composite outcome of SSE or vascular death and hospitalization for major or clinically relevant nonmajor (CRNM) bleeding, as well as each endpoint individually.

32,078 rivaroxaban users and 83,971 warfarin users were included in the study. Rivaroxaban was associated with a reduced risk of SSE or vascular death (the composite outcome, 3.79 vs. 4.19; HR=0.91, 95%CI=0.88–0.95), driven mostly by reductions in vascular death (2.81 vs. 3.18, HR=0.90, 95%CI=0.86–0.95) and systemic embolism (0.13 vs. 0.16; HR=0.82, 95%CI=0.66–1.02).

Hospitalization for major or 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 (including intracranial hemorrhage) (0.35 vs. 0.54; HR=0.63, 95%CI=0.55–0.72). (These safety data apply also to the following two other analyses.)

The study concluded that in NVAF patients with T2D, rivaroxaban was associated with an ~10% relative reduction in vascular mortality and fewer bleeding-related hospitalizations versus warfarin.

Oliva S. Costa et. Al., Ophthalmic complications in patients with nonvalvular atrial fibrillation and type 2 diabetes prescribed rivaroxaban or warfarin

This study sought to evaluate ophthalmic complications in patients with NVAf and T2D prescribed rivaroxaban or warfarin for stroke prevention, using Optum® de-identified electronic health record (EHR) data from 11/2010-3/2020. Adults with NVAf and T2D who were newly started on rivaroxaban or warfarin were included. The primary outcome was the incidence rate of any ophthalmic complication including non-traumatic bleeding (choroidal, intraocular, retinal, vitreous) or diabetic retinopathy. Ophthalmic bleeds typically associated with trauma (hyphema, orbital) were excluded from our outcomes. The study included 26,537 rivaroxaban and 61,690 warfarin patients. The average age of patients was 69±9 years, CHA2DS2VASc score was 4.1±1.5 and HASBLED 1.5±0.9.

Rivaroxaban was associated with a 15% (95%CI=8-21%) relative hazard reduction of any ophthalmic complication (incidence rate= 1.25 vs. 1.46%/year), driven by reductions in both ophthalmic bleeding (HR=0.80) and diabetic retinopathy (HR=0.85).

Olivia S. Costa et al., Kidney, Limb and Ophthalmic Complications, and Death in Patients with Nonvalvular Atrial Fibrillation and Type 2 Diabetes Treated Prescribed Rivaroxaban or Warfarin: An Electronic Health Record Analysis

This study evaluated the rate of kidney, limb and ophthalmic complications, and death in patients with both NVAf and T2D who were prescribed rivaroxaban or warfarin for stroke prevention, by analyzing Optum® de-identified electronic health record data from 11/2010-12/2019. Adults with NVAf and T2D were included if they were newly initiated on rivaroxaban or warfarin. It evaluated the incidence rate of developing a composite outcome of >40% decrease in estimated glomerular filtration rate (eGFR) from baseline, an eGFR<15 mL/minute/1.73 m², need for dialysis or kidney transplant, limb revascularization or major amputation, diabetic retinopathy or death. The study included 24,912 rivaroxaban and 58,270 warfarin users.

Rivaroxaban was associated with a reduced hazard of the composite outcome (-19.7 events/1000 person-years; HR=0.93, 95%CI=0.91 to 0.95) versus warfarin. Rivaroxaban was also associated with significant reductions in the relative hazard of a >40% decrease in eGFR from baseline, need for dialysis or renal transplant, and limb revascularization or

major amputation (HR=0.96, 0.81, and 0.85, respectively). Death occurred at a lower incidence rate among rivaroxaban (-10.3 events/1000 person-years; HR=0.92, 95%CI=0.89 to 0.95) versus warfarin users.

The study concluded that rivaroxaban was associated with reduced incidence rates of kidney and limb complications, and death in NVAf patients with T2D.

About Rivaroxaban (Xarelto™)

Rivaroxaban is the most broadly indicated non-vitamin K antagonist oral anticoagulant (NOAC) worldwide and is marketed under the brand name Xarelto. Xarelto is approved for more venous and arterial thromboembolic (VAT) conditions than any other NOAC:

- The prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) with one or more risk factors
- The treatment of pulmonary embolism (PE) in adults
- The treatment of deep vein thrombosis (DVT) in adults
- The prevention of recurrent PE and/or DVT in adults
- The prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip replacement surgery
- The prevention of VTE in adult patients undergoing elective knee replacement surgery
- The prevention of atherothrombotic events after an Acute Coronary Syndrome in adult patients with elevated cardiac biomarkers when co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine
- The prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk for ischaemic events when co-administered with acetylsalicylic acid (ASA)
- Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years after at least 5 days of initial parenteral anticoagulation treatment

Xarelto is approved in more than 130 countries, although the approved labelling, including the number of indications may differ from country to country. Since launch in 2008, more than 82 million patients have been treated.

Rivaroxaban was discovered by Bayer, and is being jointly developed with Janssen Research & Development, LLC. Xarelto is marketed outside the U.S. by Bayer and in the

U.S. by Janssen Pharmaceuticals, Inc. (Janssen Research & Development, LLC and Janssen Pharmaceuticals, Inc. are part of the Janssen Pharmaceutical Companies of Johnson & Johnson).

Anticoagulant medicines are therapies used to prevent or treat serious illnesses and potentially life-threatening conditions. Before initiating treatment with anticoagulant medicines, physicians should carefully assess the benefit and risk for the individual patient.

Responsible use of Xarelto is a very high priority for Bayer, and the company has developed a Prescribers Guide for physicians and a Xarelto Patient Card for patients to support best practice.

To learn more about thrombosis, please visit www.thrombosisadviser.com and www.vascularadviser.com

To learn more about Xarelto, please visit www.xarelto.com

About Bayer

Bayer is a global enterprise with core competencies in the life science fields of health care and nutrition. Its products and services are designed to help people and planet thrive by supporting efforts to master the major challenges presented by a growing and aging global population. Bayer is committed to drive sustainable development and generate a positive impact with its businesses. At the same time, the Group aims to increase its earning power and create value through innovation and growth. The Bayer brand stands for trust, reliability and quality throughout the world. In fiscal 2020, the Group employed around 100,000 people and had sales of 41.4 billion euros. R&D expenses before special items amounted to 4.9 billion euros. For more information, go to www.bayer.com.

Contact for media inquiries:

Richard Breum, phone +49 30 468-17112

Email: richard.breum@bayer.com

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Forward-Looking Statements

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