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(73) Patenthaver: **Bayer Intellectual Property GmbH, Alfred-Nobel-Str. 10, 40789 Monheim, Tyskland**

(72) Opfinder: **MISSELWITZ, Frank, Wielandtstr. 15, 69120 Heidelberg, Tyskland**
KUBITZA, Dagmar, Hegelstr. 40, 40882 Ratingen, Tyskland
PARK, Son-Mi, Giveonstr. 21, 42287 Wuppertal, Tyskland
WEHLING, Klaus, Am Rohm 121, 42113 Wuppertal, Tyskland

(74) Fuldmægtig i Danmark: **RWS Group, Europa House, Chiltern Park, Chiltern Hill, Chalfont St Peter, Bucks SL9 9FG, Storbritannien**

(54) Benævnelse: **BEHANDLING AF TROMBOEMBOLISKE FORSTYRRELSER MED RIVAROXABAN**

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KUBITZA DAGMAR ET AL: "Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects." BLOOD, vol. 102, no. 11, 16 November 2003 (2003-11-16), page 811a, XP009050847 & 45TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF HEMATOLOGY; SAN DIEGO, CA, USA; DECEMBER 06-09, 2003 ISSN: 0006-4971 cited in the application
KUBITZA DAGMAR ET AL: "Single dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct factor Xa inhibitor in healthy male subjects." BLOOD, vol. 102, no. 11, 16 November 2003 (2003-11-16), page 813a, XP009050848 & 45TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF HEMATOLOGY; SAN DIEGO, CA, USA; DECEMBER 06-09, 2003 ISSN: 0006-4971

DESCRIPTION

[0001] The present invention relates to the field of blood coagulation, more specifically it relates to a method of treating a thromboembolic disorder by administering a direct factor Xa inhibitor once daily in oral dosage form to a patient in need thereof, wherein the factor Xa inhibitor has a plasma concentration half life indicative of a bid or tid administration interval, e.g. of 10 hours or less.

[0002] Blood coagulation is a protective mechanism of the organism which helps to "seal" defects in the wall of the blood vessels quickly and reliably. Thus, loss of blood can be avoided or kept to a minimum. Haemostasis after injury of the blood vessels is effected mainly by the coagulation system in which an enzymatic cascade of complex reactions of plasma proteins is triggered. Numerous blood coagulation factors are involved in this process, each of which factors converts, on activation, the respectively next inactive precursor into its active form. At the end of the cascade comes the conversion of soluble fibrinogen into insoluble fibrin, resulting in the formation of a blood clot. In blood coagulation, traditionally the intrinsic and the extrinsic pathways, which end in a joint reaction path, are distinguished. Here factor Xa, which is formed from the proenzyme factor X, plays a key role, since it connects the two coagulation paths. The activated serine protease Xa cleaves prothrombin to thrombin. The resulting thrombin, in turn, cleaves fibrinogen to fibrin, a fibrous/gelatinous coagulant. In addition, thrombin is a potent effector of platelet aggregation which likewise contributes significantly to haemostasis.

[0003] Maintenance of normal haemostasis - the balance between bleeding and thrombosis - is subject to a complex regulatory mechanism. Uncontrolled activation of the coagulant system or defective inhibition of the activation processes may cause formation of local thrombi or embolisms in vessels (arteries, veins) or in heart cavities. This may lead to serious disorders, such as myocardial infarction, angina pectoris (including unstable angina), vascular re-occlusions and restenoses after angioplasty or aortocoronary bypass, stroke, transitory ischaemic attacks, peripheral arterial occlusive disorders, pulmonary embolisms or deep vein thromboses; herein below, these disorders are collectively also referred to as thromboembolic disorders. In addition, in the case of consumption coagulopathy, hypercoagulability may - systemically - result in disseminated intravascular coagulation.

[0004] These thromboembolic disorders are the most frequent cause of morbidity and mortality in most industrialised countries. Estimates place the annual incidence of VTE in excess of 1 case per 1,000 persons [White, RH. The epidemiology of venous thromboembolism. Circulation 107 (Suppl.1),14-18 (2003)]. About 1.3 - 4.1 persons in 1,000 experience a first stroke [Feigin, V.L., Lawes, C.M., Bennett, D.A., Anderson, C.S. Lancet Neurol. 2, 43-53 (2003)], and about 5 in 1,000 persons a myocardial infarction annually [Fang, J, Alderman, M.H. Am. J. Med 113, 208-214 (2002)].

[0005] The anticoagulants, i.e. substances for inhibiting or preventing blood coagulation, which are known from the prior art have various, often severe disadvantages. Accordingly, in practice, an efficient treatment method or prophylaxis of thromboembolic disorders is very difficult and unsatisfactory.

[0006] In the therapy and prophylaxis of thromboembolic disorders, use is firstly made of heparin, which is administered parenterally (intravenously or subcutaneously). Owing to more favourable pharmacokinetic properties, preference is nowadays more and more given to low-molecular-weight heparin. Since heparin inhibits a plurality of factors of the blood coagulation cascade at the same time, the action is non-selective. Moreover, there is a high risk of bleeding.

[0007] A second class of anticoagulants are the vitamin K antagonists. These include, for example, 1,3-indanediones, and especially compounds such as warfarin, phenprocoumon, dicumarol and other coumarin derivatives which inhibit the synthesis of various products of certain vitamin K-dependent coagulation factors in the liver in a non-selective manner. Owing to the mechanism of action, however, the onset of the action is very slow (latency to the onset of action 36 to 48 hours). It is possible to administer the compounds orally; however, owing to the high risk of bleeding and the narrow therapeutic index, a time-consuming individual adjustment and monitoring of the patient are required.

[0008] Recently, a novel therapeutic approach for the treatment and prophylaxis of thromboembolic disorders has been described. This novel therapeutic approach aims to inhibit factor Xa [cf. WO-A-99/37304; WO-A-99/06371; J. Hauptmann, J. Stürzebecher, Thrombosis Research 1999, 93, 203; S.A.V. Raghavan, M. Dikshit, "Recent advances in the status and targets of antithrombotic agents" Drugs Fut. 2002, 27, 669-683; H.A. Wieland, V. Laux, D. Kozian, M. Lorenz, "Approaches in anticoagulation: Rationales for target positioning" Curr. Opin. Investig. Drugs 2003, 4, 264-271; U.J. Ries, W. Wienen, "Serine proteases as targets for antithrombotic therapy" Drugs Fut. 2003, 28, 355-370; L.-A. Linkins, J.I. Weitz, "New anticoagulant therapy" Annu. Rev. Med. 2005, 56, 63-77]. It has been shown that, in animal models, various both peptidic and nonpeptidic compounds are effective as factor Xa inhibitors.

[0009] In general, oral application is the preferable route of administration of a drug, and a less frequent dose regimen is desirable. In particular, once daily oral application is preferred due to favourable convenience for the patient and for compliance reasons. However, this goal is sometimes difficult to achieve depending on the specific behaviour and properties of the drug substance, especially its plasma concentration half life. "Half life" is the time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50 % (Goodman and Gillmans "The Pharmacological Basis of Therapeutics" 7th Edition, Macmillan Publishing Company, New York, 1985, p 27).

[0010] When the drug substance is applied in no more than a therapeutically effective amount, which is usually preferred in order to minimize the exposure of the patient with that drug substance in order to avoid potential side effects, the drug must be given approximately every half live (see for example: Malcolm Rowland, Thomas N. Tozer, in "Clinical Pharmacokinetics, Concepts and Applications", 3rd edition, Lea and Febiger, Philadelphia 1995, pp 83).

[0011] In the case of multiple dose application the target plasma concentration (approximate steady state) can be reached after 3 to 5 half lives (Donald J. Birkett, in "Pharmacokinetics Made Easy", McGraw-Hill Education: 2000; p 20). At steady state the concentrations of drugs which rise and fall during each interdose interval are repeated identically in each interdose interval (Goodman and Gillmans "The Pharmacological Basis of Therapeutics" 7th Edition, Macmillan Publishing Company, New York, 1985, p 28).

[0012] Surprisingly, it has now been found in patients at frequent medication that once daily oral administration of a direct factor Xa inhibitor with a plasma concentration half life time of 10 hours or less demonstrated efficacy when compared to standard therapy and at the same time was as effective as after twice daily (bid) administration.

[0013] The present invention relates to the use of an oral dosage form of a direct factor Xa inhibitor for the manufacture of a medicament for the treatment of a thromboembolic disorder administered once daily for at least five consecutive days, wherein said inhibitor has a plasma concentration half life of 10 hours or less when orally administered to a human patient.

[0014] In a preferred embodiment, the present invention relates to 5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide (I), a low molecular weight, orally administrable direct inhibitor of blood clotting factor Xa (see WO-A 01/47919) as the active ingredient.

[0015] Compound (I) is an active site directed, competitive, direct factor Xa inhibitor [E. Perzborn, J. Strassburger, A. Wilmen, J. Pohlmann, S. Roehrig, K.-H. Schlemmer, A. Straub; J Thromb Haemost 2005; DOI: 10.1111/j.1538-7836.2005.01166.x]. (I) acts directly on factor Xa, that means independently from a cofactor (such as Antithrombin III, the cofactor of heparins). The antithrombotic effect is attributed to the inhibition of factor Xa.

[0016] Furthermore, (I) binds to the active site of factor Xa in the S1- and S4 pockets [S. Roehrig et al. 228th ACS National Meeting, Philadelphia, August 22-26, 2004, MEDI-156].

[0017] For (I) a plasma concentration half life of 4-6 hours has been demonstrated at steady state in humans in a multiple dose escalation study (D. Kubitza et al, Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of Bay 59-7939, an oral, direct Factor Xa inhibitor, in healthy male subjects. Blood 2003, 102: Abstract 3004)

[0018] In a clinical study in patients undergoing total hip replacement (THR), the efficacy of (I) is measured by the occurrence of deep vein thrombosis (DVT) after THR surgery. According to the Sixth ACCP Consensus Conference on Antithrombotic Therapy (Chest 2001; 119: 132S-175S) the DVT rate (prevalence) after THR surgery is as follows:

	Prevalence (%)	(95 % Confidence intervall)
Placebo	54.2	(50-58)
Low dose heparin	30.1	(27- 33)
LMWH *	16.1	(15-17)
* LMWH = Low Molecular Weight Heparin		

[0019] After 7 to 9 days of once daily administration of 30 mg (I) to 73 patients undergoing THR surgery, a DVT rate of 12.3 % has been observed (LMWH comparator was 16.8 %). Administration of (I) was also safe and well tolerated.

[0020] The once daily dose of (I) was also compared to different doses of (I) which have been administered twice daily (bid). By

comparing the total daily doses administered it could also be demonstrated that after once daily administration efficacy on one hand and major bleeding, an expected side effect on the other hand, match well the expected effects after twice daily administration (for a discussion of further details see the experimental part).

[0021] For the purpose of the present invention as disclosed and described herein, the following terms and abbreviations are defined as follows.

[0022] The term "treatment" includes the therapeutic and/or prophylactic treatment of thromboembolic disorders.

[0023] The term "direct factor Xa inhibitor" means an inhibitor that acts directly on factor Xa, independently of a cofactor (such as Antithrombin III, the cofactor of heparins). The antithrombotic effect is hereby attributed to the inhibition of factor Xa.

[0024] The term "thromboembolic disorders" includes in particular disorders as the acute coronary syndrome spectrum as ST Segment Elevation Myocardial Infarction (STEMI) (also known as Q-wave MI), Non ST Segment Elevation Myocardial Infarction (NSTEMI) (also known as Non Q-wave MI) and unstable angina (UA), as well as stable angina pectoris, vascular re-occlusions and restenoses after angioplasty or aorto-coronary bypass, peripheral arterial occlusion disorders, pulmonary embolisms, or deep vein thromboses, renal thrombosis, transitory ischaemic attacks and stroke, inhibition of tumor growth and development of metastasis, treatment of disseminated intravascular coagulation (DIC) and the so-called "economy class syndrome", especially in patients with risk of venous thrombosis, atherosclerotic diseases, inflammatory diseases, as rheumatic diseases of the musculoskeletal system, Alzheimer's disease, inhibition of old-age macula-degeneration, diabetic retinopathy, diabetic nephropathy and other microvascular diseases.

[0025] Included are also disorders derived from cardiogenic thromboembolism, for instance cerebral ischemic diseases, stroke, systemic embolism and ischemic attacks, especially in patients with acute, intermittent or persistent arrhythmia of the heart such as atrial fibrillation or alongside cardioversion, or in patients with valvular heart disease or artificial heart valves.

[0026] Moreover, included are also disorders derived from thromboembolic complications which can arise within patients with microangiopathic hemolytic anaemia, extracorporal circulation such as hemodialysis, or prosthetic heart valves as well as from thromboembolic complication, e.g. venous thromboembolism in tumor patients, in particular in patients undergoing surgical interventions, chemotherapy or radiotherapy.

[0027] Preferred is the treatment of acute coronary syndrome spectrum as ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI) and unstable angina, reocclusions after angioplasty or aortocoronary bypass, peripheral arterial occlusion disorders, pulmonary embolisms or deep vein thromboses, transitory ischaemic attacks and stroke.

[0028] Particularly preferred is the treatment of acute coronary syndrome spectrum as ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI) and unstable angina, reocclusions after angioplasty or aortocoronary bypass, pulmonary embolisms or deep vein thromboses and stroke.

[0029] The term "oral dosage forms" is used in a general sense to reference pharmaceutical products administered orally. Oral dosage forms are recognized by those skilled in the art to include such forms as liquid formulations, granules, gelcaps, hard gelatine capsules or sachets filled with granules, and tablets releasing the active compound rapidly or in a modified manner.

[0030] Tablets are preferred, in particular tablets rapidly releasing the active compound. In the context of the present invention, rapid-release tablets are in particular those which, according to the USP release method using apparatus 2 (paddle), have a Q value (30 minutes) of 75 %.

[0031] Very particularly preferred are rapid-release tablets containing 5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide as active ingredient. Preparation of such tablets is for example described in PCT/04/01289.

[0032] The amount of active ingredient in the formulation will depend on the severity of the condition, and on the patient to be treated, as well as the compound employed. In the case of (I) as active ingredient, a dose of 1 to 100 mg, preferentially 2 to 50 mg, particularly preferred 5 to 30 mg can be applied.

[0033] The term "once daily" is well known by those skilled in the art and means administration of the drug once a day and includes the administration of one dosage form as well as administration of two or more dosage forms simultaneously or

consecutively within a short time period.

[0034] The invention is illustrated, but in no way limited, by the following example:

Experimental part (clinical trial)

Example 1

[0035] This was a dose guiding study for the direct factor Xa inhibitor (I). Objective of the study was the assessment of safety, tolerability, and efficacy of (I) at different oral doses (bid and od) compared with subcutaneously administered enoxaparin 40 mg in the prevention of venous thromboembolism.

[0036] 642 patients were enrolled in this study and the treatment duration was 7 to 9 days.

[0037] The main inclusion criteria for the study were: men ≥18 years of age and postmenopausal women undergoing elective primary total hip replacement.

[0038] This was a prospective, randomized, open-label, active comparator controlled, multi-center and multi-national trial designed as a proof-of-principle dose-escalating study in patients undergoing elective primary total hip replacement.

[0039] Patients were consecutively to receive within each dose step either (I) or the active comparator drug, enoxaparin:

- one group receiving 2.5 mg (I) bid,
- one receiving 5 mg (I) bid,
- one receiving 10 mg (I) bid,
- one receiving 20 mg (I) bid,
- one receiving 30 mg (I) bid,
- and one receiving 30 mg (I) od.
    1. (I) was administered orally as rapid release tablets.

[0040] The criteria for evaluation were:

1. a) The primary efficacy endpoint was a composite endpoint of
    - Any deep vein thrombosis (DVT) (proximal and/or distal).
    - Non-fatal pulmonary embolism (PE).
    - Death from all causes.

    The primary endpoint was evaluated 5 - 9 days after surgery. The analysis of the primary efficacy endpoint was solely based on the assessments made by the central adjudication committee which was blinded to the treatment allocation.
2. b) The main safety endpoint was the incidence of major bleeding events observed after the first intake of study drug and not later than 2 days after last intake of study drug. Major bleeding observed after this period was assessed separately.
   The analysis of the primary safety endpoint was solely based on the classification made by the Safety Committee and Bleeding Committee which were both blinded to the treatment allocation.

Results:

[0041] The analysis of demographic data can be summarized as follows:

For subjects in the "valid for safety analysis" age ranged from 30 - 92 years, weight from 45 -150 kg, height from 145 -195 cm, and BMI from 17.3 - 52.7 kg/m^2.

For subjects in the "valid for PP (per protocol) analysis" age ranged from 30 - 92 years, weight from 45 - 150 kg, height from 146 - 195 cm, and BMI from 17.3 - 37.7 kg/m^2.

a) Efficacy results:

[0042] An 7 - 9 -day treatment with (I) using a wide, 12-fold dose range [2.5 to 30 mg bid corresponding to total daily doses of 5 to 60 mg (I)] prevented venous thromboembolism (VTE) in adult subjects undergoing elective hip replacement compared with enoxaparin, thus confirming the proof-of-principle of (I) in this indication.

[0043] The reduction of the VTE incidence rates (primary composite endpoint comprising DVT, PE and death) by (I) was dose-dependent in the range from 2.5 to 20 mg bid with incidence rates declining from 22.2 % to 10.2 % compared with 16.8 % in the enoxaparin group. The incidence rate in the 30 mg od dose group was 15.1 % (Table 1-1).

[0044] On the basis of total daily doses the 30 mg once daily dose fits well into the dose dependance observed in the range of 2.5 to 20 mg bid, which corresponds to total daily doses of 5 to 40 mg.

Table 1-1:	**Incidence rate of primary efficacy endpoint and its individual components (PP population)**			
	Dose (I)	Dose (I)	Dose (I)	Dose (I)
	2.5 mg bid	5 mg bid	10 mg bid	30 mg od
	(N = 63)	(N = 63)	(N = 55)	(N = 73)
Primary efficacy, composite endpoint [n(%)]	14 (22.2%)	15(23.8%)	11(20.0%)	11(15.1%)
	Dose (I)	Dose (I)		Enoxaparin
	20 mg bid	30 mg bid		40 mg od
	(N = 59)	(N = 46)		(N = 107)
Primary efficacy, composite endpoint [n(%)]	6 (10.2 %)	8 (17.4 %)		18 (16.8%)

Summary: The above data clearly demonstrate the efficacy of od administration of (I), namely fewer occurrence of composite endpoint events, i.e. fewer cases of DVT, PE or death compared to untreated conditions, and in the range of standard therapy. Furthermore, the od administration is surprisingly perfect in line with bid administration.

b) Safety results:

[0045] The number of post-operative major bleeding events increased with increasing (I) doses indicating a monotonous dose-response (table 1-2). However, it is important to note that there were neither fatal bleeds or bleeds in critical organs, nor clinically significant bleeds that could not be treated. Most bleeds adjudicated as major were related to the surgical site and no wound healing complications were reported in these subjects.

[0046] On the basis of total daily doses the 30 mg once daily dose fits very well into the dose dependence observed in the range of 2.5 to 30 mg bid which corresponds to total daily doses of 5 to 60 mg.

Table 1 - 2: Incidence rates of post-operative bleeding events (safety population)				
	Dose (I)	Dose (I)	Dose (I)	Dose (I)
	2.5 mg bid	5 mg bid	10 mg bid	30 mg od
	(N = 76)	(N = 80)	(N = 68)	(N = 88)
Any major bleeding event [n(%)]	0 (0.0 %)	2 (2.5 %)	2 (2.9 %)	4 (4.5 %)
	Dose (I)	Dose (I)		Enoxaparin
	20 mg bid	30 mg bid		40 mg od
	(N = 77)	(N = 74)		(N = 162)

Table 1 - 2: Incidence rates of post-operative bleeding events (safety population)			
Any major bleeding event [n(%)]	5 (6.5 %)	8 (10.8 %)	0 (0.0 %) *
* For LMWH in similar studies major bleeding rates of 1.5 - 5.3 % have been observed (Sixth ACCP Consensus Conference on Antithrombotic Therapy, Chest 2001; 119: 1325-175S).			

Summary: The above data clearly demonstrate the safety of od administration of (I). The occurrence of any major bleeding events is low, approximately in the range of standard therapy and again perfectly in line with results from bid administration.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

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- Chest, 2001, vol. 119, 132S-175S **[0018]**
- Sixth ACCP Consensus Conference on Antithrombotic TherapyChest, 2001, vol. 119, 1325-175S **[0046]**

Patentkrav

1. Anvendelse af en tablet med hurtig frigivelse af forbindelsen 5-chlor-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophencarboxamid til fremstilling af et medikament til behandling af en tromboembolisk forstyrrelse administreret højst en gang dagligt i mindst fem på hinanden følgende dage, hvor forbindelsen har en halveringstid for plasmakoncentrationen på 10 timer eller mindre, når den administreres oralt til en human patient.

2. Anvendelse ifølge krav 1, hvor den tromboemboliske forstyrrelse er myokardieinfarkt med ST-segmentelevation (STEMI), myokardieinfarkt uden ST-segmentelevation (NSTEMI), ustabil angina, reokklusion efter angioplastik eller aortokoronar bypass, lungeembolier, dybe venetromboser eller apopleksi.

ESC European Society of Cardiology

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ORIGINAL ARTICLE
Thrombosis and antithrombotic therapy

Patients selected for dual pathway inhibition in clinical practice have similar characteristics and outcomes to those included in the COMPASS randomized trial: The XATOA Registry

Keith A.A. Fox[1,*], Victor Aboyans[2], E. Sebastian Debus[3], Uwe Zeymer[4], Martin R. Cowie[5], Manesh Patel[6], Robert C. Welsh[7], Jackie Bosch[8], Alain Gay[9], Kai Vogtländer[10] and Sonia S. Anand[8,11]

[1]Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK; [2]Department of Cardiology, Dupuytren University Hospital, and Inserm U1094, Limoges, France; [3]Department of Vascular Medicine, Vascular Surgery, Angiology, Endovascular Therapy, University of Hamburg-Eppendorf, Hamburg, Germany; [4]Klinikum der Stadt Ludwigshafen, Medizinische Klinik B, and Institut für Herzinfarktforschung, Ludwigshafen am Rhein, Germany; [5]Royal Brompton Hospital and King's College London, London, UK; [6]Division of Cardiology, Duke Clinical Research Institute, Duke University, Durham NC; [7]Mazankowski Alberta Heart Institute and University of Alberta, Edmonton, Alberta, Canada; [8]School of Rehabilitation Science, Chanchlani Research Centre and the Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada; [9]Bayer AG, Berlin, Germany; [10]Bayer AG, Wuppertal, Germany; and [11]Department of Medicine, McMaster University, Hamilton, Ontario, Canada

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Aims To determine the characteristics of patients with coronary artery disease (CAD), peripheral artery disease (PAD), or both, initiating dual pathway inhibition (DPI) using rivaroxaban 2.5 mg twice daily plus aspirin, and to report their clinical outcomes and bleeding rates in clinical practice compared to the COMPASS randomized trial, which provided the basis for using DPI in this patient population.

Methods and results XATOA is a prospective registry of 5532 patients: of which, 72.7% had CAD, 58.9% had PAD, and 31.6% had both. The mean age of patients was 68 years and 25.5% were women. The mean follow-up period was 15 months. The most frequently reported reason for initiating DPI was the presence of existing, worsening or newly diagnosed risk characteristics ($n = 4753$, 85.9%). Before initiating DPI, 75.3% received a single antiplatelet and 18.3% received various antiplatelet combinations. The incidence of major adverse cardiovascular events (MACE), major adverse limb events (MALE) and acute or severe limb ischaemia was 2.26, 3.57, and 1.54 per 100 patient-years, respectively, among the 5532 patients in XATOA. Corresponding rates in COMPASS were 2.18, 0.19, and 0.12 per 100 patient-years, respectively. Major bleeding rates were 0.95 and 1.67 per 100 patient-years in XATOA and COMPASS, respectively.

Conclusion High-risk vascular patients are prioritized for DPI in clinical practice, and rates of MACE are similar to COMPASS, but MALE rates are higher in XATOA, consistent with the greater proportion of PAD patients. Major bleeding rates were lower in XATOA. The findings provide support for favourable net clinical benefit of DPI in high-risk vascular patients.

One-sentence summary The characteristics of patients initiated on dual pathway inhibition (DPI: rivaroxaban 2.5 mg twice daily plus aspirin) have not previously been defined in clinical practice and the XATOA registry findings demonstrate patient outcomes are consistent with those of the COMPASS trial, despite geographic differences in recruitment and the higher proportion of PAD patients.

* Corresponding author. Tel: +44 778 615 8881; Email: k.a.a.fox@ed.ac.uk

Keywords Cardiovascular disease • Coronary artery disease • Peripheral artery disease • Real-world evidence

Introduction

Patients with coronary artery disease (CAD) and/or peripheral artery disease (PAD) are at elevated risk of future atherosclerotic events despite evidence-based recommendations for secondary prevention measures. Current guidelines recommend consideration of additional antithrombotic therapy in certain patients with CAD or PAD to mitigate the risk of cardiovascular events including stroke, myocardial infarction, ischaemic limb events, and cardiovascular death.[1–7]

The COMPASS trial assessed the efficacy and safety of dual pathway inhibition (DPI) with rivaroxaban 2.5 mg twice daily (bid) plus aspirin or rivaroxaban 5 mg bid versus aspirin alone for the prevention of atherothrombotic events in patients with CAD, PAD, or both.[8–11] In a population receiving a high standard of risk factor management, DPI significantly reduced the risk of cardiovascular events (including limb events) compared with aspirin alone, at a cost of increased risk of International Society on Thrombosis and Haemostasis (ISTH) major bleeding, but not intracranial or fatal bleeding.[8–11] Rivaroxaban 5 mg bid did not significantly reduce the risk of cardiovascular events and increased the risk of bleeding events versus aspirin alone.[10]

DPI has now been approved widely by healthcare regulatory authorities (such as the European Medicines Agency) for use in patients with increased vascular risk and CAD, PAD, or both. Several clinical guidelines recommend its use in this setting (e.g. Class IIa recommendation by European Society of Cardiology guidelines for the diagnosis and management of chronic coronary syndromes).[1–7] In some countries, a broader population of patients is approved for DPI compared with the COMPASS trial population.[12,13] However, it is unknown which types of patients with CAD or PAD are prioritized for DPI use in clinical practice. Additionally, the rates of bleeding and clinical events in clinical practice in patients receiving DPI outside of the context of a randomized trial are unknown.

The proportion of patients meeting the qualifying criteria for COMPASS and the characteristics of such COMPASS-eligible patients have been examined in some prior studies.[14–17] However, XATOA differs importantly as patients were initiated on DPI in clinical practice. Clinicians initiating a new antithrombotic regimen may judge risks versus potential benefits differently from the selection criteria of the COMPASS trial.

To address this topic, the international, multicentre, prospective, single-arm XATOA registry study (NCT03746275) enrolled and prospectively followed patients receiving DPI in routine clinical practice.[18] Treatment patterns and clinical characteristics, as well as adjudicated ischaemic and bleeding outcomes, were investigated.[18] This pre-specified analysis reports the main results of XATOA for the overall population and compares them with those reported from the COMPASS trial.

The aim of XATOA was to determine the characteristics of patients with CAD, PAD, or both receiving DPI using rivaroxaban 2.5 mg bid plus aspirin, and to report their clinical outcomes and bleeding rates in clinical practice compared with those in the COMPASS randomized trial.

Methods

The design and methods of the XATOA study have been reported previously.[18] In brief, XATOA is an international, multicentre, prospective, single-arm registry study in adults (aged ≥18 years) with CAD, PAD, or both. Enrolled patients received DPI based on a clinical practice decision. Patients starting DPI within 4 weeks prior to enrolment were included in the registry. All patients met all enrolment criteria and provided informed consent.

Patient population and follow-up

Patients aged ≥18 years with chronic CAD, PAD, or both were eligible in countries where DPI was in clinical use and had regulatory approval. Patients with contraindications according to the locally approved indication for DPI, those receiving chronic anticoagulation therapy, and those participating in an interventional trial were excluded. All treatment decisions were at the discretion of the responsible clinician, including the use of concomitant therapies. Clinicians were asked to consider patients consecutively to minimize the risk of selection bias. The population was limited to patients in countries where DPI was both approved by local healthcare authorities and in clinical use. The countries included in XATOA were intended to represent a population of patients worldwide where DPI was a possible treatment option at the time of this study. Similarly, centres were selected to be representative of patients in each country, as well as factors such as types of healthcare providers, type and size of practice, and geography. The minimum criteria for site selection were availability of suitable patients; availability of data for determining exposures, outcomes, and all other variables relevant to the study objectives; number of patients planned to be included per site experience with electronic data capturing where applicable; and representativeness.

The follow-up period was at least 12 months after enrolment and follow-up visits took place according to routine practice. Patients could withdraw from the XATOA study at any time and substitute patients were not recruited following premature treatment discontinuation. After permanent discontinuation, survival status within 30 days of the end-of-study observation was documented by the treating clinician. An electronic data-capturing system was used for data collection. Data collection took place at baseline and at routine clinical follow-up visits throughout the study. The study complied with the relevant local laws and regulations pertaining to observational studies and data protection.

Study outcomes

The primary objective of the study was to describe clinical characteristics of patients selected for DPI with CAD, PAD, or both, in clinical practice. The clinical outcomes of interest included major adverse cardiovascular events (MACE), defined as the composite of cardiovascular death, myocardial infarction (MI), or stroke; consistent with an

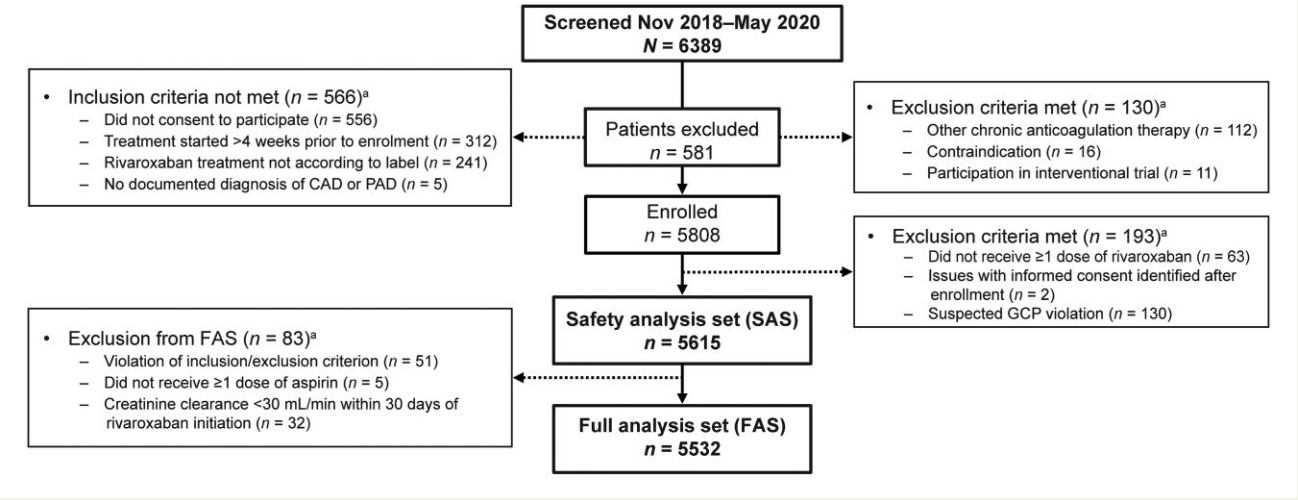

Figure 1 Patient disposition in XATOA. [a]Patients could have more than one reason for exclusion or non-inclusion from the study. CAD, coronary artery disease; FAS, full analysis set; GCP, good clinical practice; PAD, peripheral artery disease; SAS, safety analysis set.

analysis of the COMPASS trial,[19] major adverse limb events (MALE) defined as the composite of acute or severe limb ischaemia (leading to an intervention), chronic limb ischaemia (leading to an intervention), and major amputation (amputation above the forefoot). The safety outcome was ISTH major bleeding, defined as the composite of fatal and/or symptomatic bleeding into a critical organ and/or associated with a ≥2 g/dL reduction in haemoglobin and/or requiring a transfusion of ≥2 units of packed red blood cells or whole blood. Non-major bleeding was defined according to the ISTH criteria (all bleeding events that do not meet the definition of ISTH major bleeding). Outcome definitions were harmonized with those of the COMPASS trial to allow comparisons of the data (Supplementary material online, *Table S1*). Adverse events that occurred within 30 days after the last rivaroxaban or aspirin dose were also documented and reported. Clinical events were centrally adjudicated by an independent external adjudication committee.

Statistical analysis

The full analysis set consisted of all patients who received at least one dose of DPI and the safety analysis set was defined as patients who received at least one dose of rivaroxaban. Treatment-emergent events were defined as events arising or worsening within 2 days after permanent treatment discontinuation. Clinical outcomes were assessed using incidence proportions, cumulative incidences, and incidence rates with 95% confidence intervals (Clopper–Pearson formula). All statistical analyses were descriptive and exploratory as XATOA was a single-arm prospective study. To allow the description of treatment patterns and estimation with adequate precision of clinical outcomes in the overall population, as well as by country and in the main subgroups as per the aim of the study, the inclusion of 5000–6500 patients from at least 300 sites was planned. Incidence proportions of 1%, 5%, and 10% and a study size of 5000 patients would yield corresponding 95% confidence intervals of 0.6%, 1.2%, and 1.7%, respectively. The corresponding characteristics and outcomes of patients in the COMPASS study are presented for reference.[8–10] In XATOA, clinical outcomes were collected through adverse event reporting, whereas clinical events in COMPASS were captured separately. Annualized rates of clinical outcomes and bleeding events are presented.

The COMPASS trial[10,20]

The design and results of the COMPASS trial have been published previously.[10,20] COMPASS was a phase III, double-blind, randomized controlled trial investigating the efficacy and safety of rivaroxaban 2.5 mg bid plus aspirin or rivaroxaban 5 mg bid versus aspirin in patients with chronic CAD or PAD.[10,20] Key inclusion criteria were PAD, or CAD and ≥one of the following: age ≥65 years, or age <65 years and atherosclerosis in ≥2 vascular beds or ≥2 additional risk factors (smoking, diabetes, estimated glomerular filtration rate <60 mL/min/1.73 m^2, heart failure or non-lacunar ischaemic stroke ≥1 month previously). Key exclusion criteria included stroke within 1 month previously, any haemorrhagic or lacunar stroke, severe heart failure with known ejection fraction <30% or NYHA class III or IV symptoms, a need for dual antiplatelet therapy (DAPT), other non-aspirin antiplatelet therapy or oral anticoagulation, or estimated glomerular filtration rate <15 mL/min/1.73 m^2.[10,20]

Results

Patient disposition and follow-up

From November 2018 to May 2020, 6389 patients were screened. Of these, 581 patients were excluded and 5808 were enrolled. Reasons for exclusion are summarized in *Figure 1* and Supplementary material online, *Table S2*. A total of 5615 patients received at least one dose of rivaroxaban and were included in the safety analysis set. The full analysis set consisted of 5532 patients who received at least one dose of DPI with rivaroxaban and aspirin. Of the patients in the full analysis set, 4022 (72.7%) had CAD, 3258 (58.9%) had PAD, and 1748 (31.6%) had both CAD and PAD. The mean observation period in the full analysis set was 15 ± 6 months and 79.1% ($n = 4374$) were followed up for more than 12 months.

Table 1 Baseline characteristics in XATOA and COMPASS

	XATOA (*N* = 5532)	COMPASS (*N* = 27 395)[10]
Demographics		
Age, years, mean ± SD	68.0 ± 9.6	68.2 ± 0.02
Female sex	1413 (25.5)	6020 (22.0)
Race (self-reported)		
White	4773 (86.3)	17 027 (62.2)
Black	13 (0.2)	262 (1.0)
Asian	335 (6.1)	4269 (15.6)
Other	119 (2.2)	5837 (21.3)
Regions[a]		
North America/Canada	853 (15.4)	3918 (14.3)
Latin America/South America	311 (5.6)	6144 (22.4)
Middle East, Western Europe, Australia, or South Africa	3358 (60.7)	8555 (31.2)
Eastern Europe	866 (15.7)	4823 (17.6)
Asia Pacific	144 (2.6)	3955 (14.4)
Clinical characteristics		
BMI, kg/m^2, mean ± SD	28.2 ± 4.9	28.3 ± 0.02
Tobacco use	1343 (24.3)[b]	5867 (21.4)
Family history of vascular disease		
Yes	1636 (29.6)	Not currently available
No	3805 (68.8)	Not currently available
Missing	91 (1.6)	Not currently available
Serum creatinine value available at baseline	1516 (27.4)	Not reported
Serum creatinine, mg/dL, mean ± SD	1.03 ± 0.43	1.03 ± 0.61
eGFR (CKD-EPI), mL/min/1.73 m^2	1516 (27.4)	27 387 (100.0)
eGFR (CKD-EPI), mL/min/1.73 m^2, mean ± SD	73.31 ± 20.01	73.8 ± 17.9
Co-morbidities		
Myocardial infarction	2015 (36.4)	17 028 (62.2)
Heart failure	921 (16.6)	5902 (21.5)
Stroke	319 (5.8)	1032 (3.8)
Intermittent claudication	1916 (34.6)	3829 (14.0)
Diabetes	2130 (38.5)	10 341 (37.7)
Hypertension	4454 (80.5)	20 632 (75.3)
eGFR (CKD-EPI) <60 mL/min/1.73 m^2	407 (26.8)[c]	6276 (22.9)[d]
Prior interventions and revascularizations		
PCI	2295 (41.5)	14 862 (54.3)[e]
CABG	1048 (18.9)	6471 (23.6)
Peripheral arterial intervention	1692 (30.6)	2045 (7.5)[f]
Lower-extremity amputation	129 (2.3)	335 (1.2)
Carotid intervention	277 (5.0)	Not reported separately
Cerebrovascular intervention	32 (0.6)	Not reported separately
Other	199 (3.6)	Not reported separately
Prior medications of interest		
Antidiabetic medications	1615 (29.2)	9890 (36.1)
Lipid-lowering agents	4538 (82.0)	25 727 (93.9)
Beta-blockers	3286 (59.4)	20 682 (75.5)
ACE inhibitors/ARBs	3868 (69.9)	21 628 (78.9)

Table 1 Continued

	XATOA ($N = 5532$)	COMPASS ($N = 27\,395$)[10]
ARN inhibitors	63 (1.1)	Not reported
Mineralocorticoid receptor antagonists	415 (7.5)	Not reported
Diuretics	1372 (24.8)	10 383 (37.9)
Proton pump inhibitors	1437 (26.0)	10 869 (39.7)[g]

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARN, angiotensin receptor–neprilysin; BMI, body mass index; CABG, coronary artery bypass grafting; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; SD, standard deviation.
Values are *n* (%) unless otherwise indicated.
[a]Countries are shown in *Figure 2* and Supplementary material online, *Table S2*.
[b]Current smoking in XATOA.
[c]Based on laboratory values collected before inclusion in XATOA and shown as a proportion of patients with available values at baseline.
[d]eGFR 15–<60 mL/min/1.73 m^2.
[e]Includes percutaneous transluminal coronary angioplasty and atherectomy.
[f]Includes peripheral artery bypass surgery and peripheral percutaneous transluminal angioplasty.
[g]Eligible patients ($n = 17\,598$) who were not receiving a proton pump inhibitor at baseline were randomized to a proton pump inhibitor versus placebo.

Baseline characteristics

Patients were mostly enrolled from outpatient clinics ($n = 3344$, 60.4%) and the remainder ($n = 2188$, 39.6%) from hospitals. A total of 2944 (53.2%) patients were enrolled in cardiology clinics, 815 (14.7%) in vascular medicine clinics, 743 (13.4%) in vascular surgery or other surgery clinics, 684 (12.4%) in internal medicine clinics, and 346 (6.3%) in general medicine clinics.

Baseline characteristics, including laboratory values of patients in XATOA, are shown in *Table 1*, Supplementary material online, *Table S3*, and *Figure 2*. Patients had a mean age of 68 years, and 25.5% were female. Common co-morbidities included hypertension (80.5%), diabetes (37.0%), and prior MI (36.4%). A total of 24.3% were smokers. In XATOA, study sites were asked to capture all available haemoglobin and creatinine values, and this resulted in 76.0% of patients with at least one haemoglobin test and 78.8% with at least one serum creatinine test (*Table 1*). Prior MI was reported in 36.4% of patients, prior acute coronary syndrome (ACS) in 13.5%, and prior percutaneous coronary intervention (PCI) in 41.5%. In these patients, the mean time between the event and the initial study visit was 100, 48, and 70 months, respectively.

The use of secondary prevention treatments is shown in *Table 1*. More than two-thirds of patients were receiving standard secondary prevention therapies including antiplatelet agents, statins, and angiotensin-converting enzyme inhibitors /angiotensin receptor blockers, prior to enrolment. Secondary prevention therapies were used more frequently in CAD than in PAD patients. The most common type of antithrombotic therapy in XATOA patients prior to enrolment was aspirin only ($n = 3910$, 70.7%), followed by DAPT with aspirin and another antiplatelet agent ($n = 900$, 16.3%; *Figure 3*).

Study treatment and indications for initiating DPI

The most frequent reason reported for initiating DPI was existing, worsening, or newly diagnosed vascular risk characteristics ($n = 4753$, 85.9%). Clinicians defined high cardiovascular risk as the reason for initiating DPI in 70.7% of patients (including at least one of the following: history of hypertension, diabetes, hyperlipidaemia, chronic renal dysfunction, smoking, family history of vascular disease, age >65 years, or high body mass index). A total of 794 patients (14.4%) were initiated on DPI following the completion of DAPT. Clinical features leading to DPI initiation are shown in *Table 2*.

The initial daily dose of rivaroxaban was 2.5 mg twice daily in 5523 (99.8%) patients and 2.5 mg once daily in 9 (0.2%) patients. The mean duration of rivaroxaban treatment was 446.4 ± 198.0 days and the mean duration of aspirin treatment was 457.8 ± 186.0 days.

The majority of patients (88.2%) did not receive additional antiplatelet agents during the study, although 9.3% received DAPT.

Clinical events

Clinical outcomes occurred in 425 (7.7%) patients (*Figures 4* and *5*). The incidence of MACE, MALE and acute or severe limb ischaemia was 2.26, 3.57, and 1.54 per 100 patient-years, respectively. Other thrombotic events, such as transient ischaemic attack, amputation, pulmonary embolism, and deep vein thrombosis were very infrequent (rates less than 0.3 per 100 patient-years). ISTH major bleeding occurred at a rate of 0.95 per 100 patient-years and non-major bleeding at a rate of 4.43 per 100 patient-years. Events accrued at a consistent rate during the follow-up period as reflected by the consistent slopes of the event curves (*Figure 5*).

In COMPASS, the rate of MALE was 0.19 per 100 patient-years. Rates of MACE and acute limb ischaemia were 2.18 and 0.12 per 100 patient-years, respectively. The rate of major bleeding was 1.7 per 100 patient-years while the rate of non-major bleeding was 5.11 per 100 patient-years.

In XATOA, a total of 150 patients (2.7%) had died by the end of follow-up. A total of 242 (4.3%) patients had unknown survival status and 217 patients (3.9%) did not have follow-up data. Adjudicated treatment-emergent cardiovascular causes of death occurred in 64.1% and non-cardiovascular causes of death in 35.9%

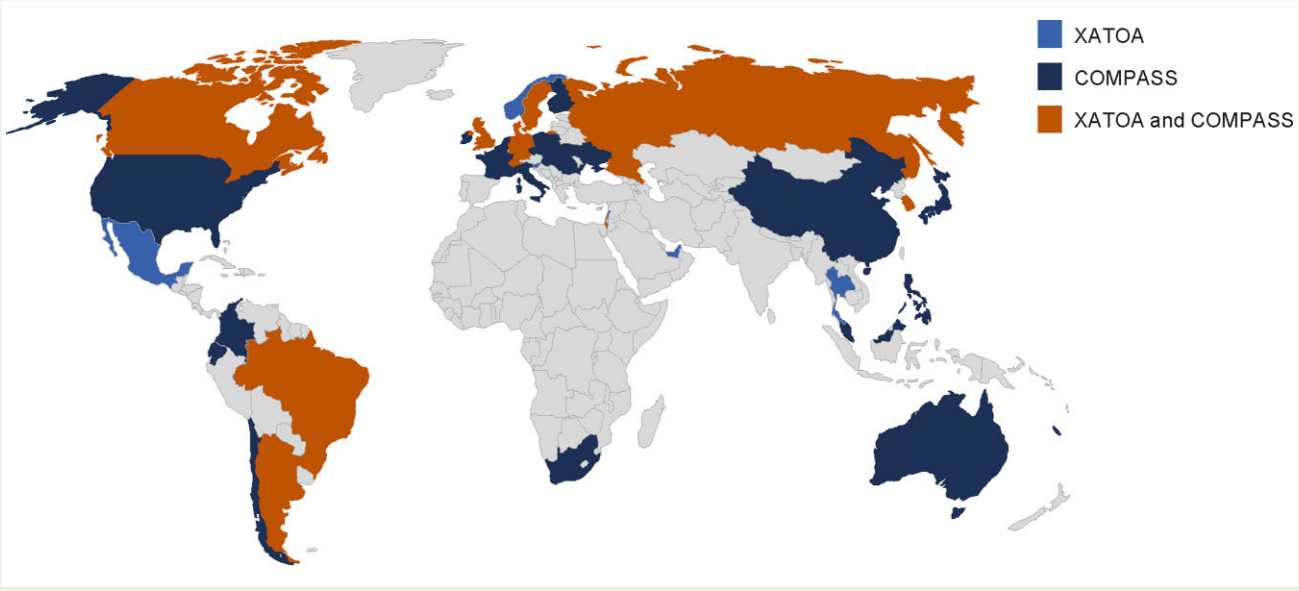

Figure 2 Regions enrolling patients in XATOA and COMPASS.[10]

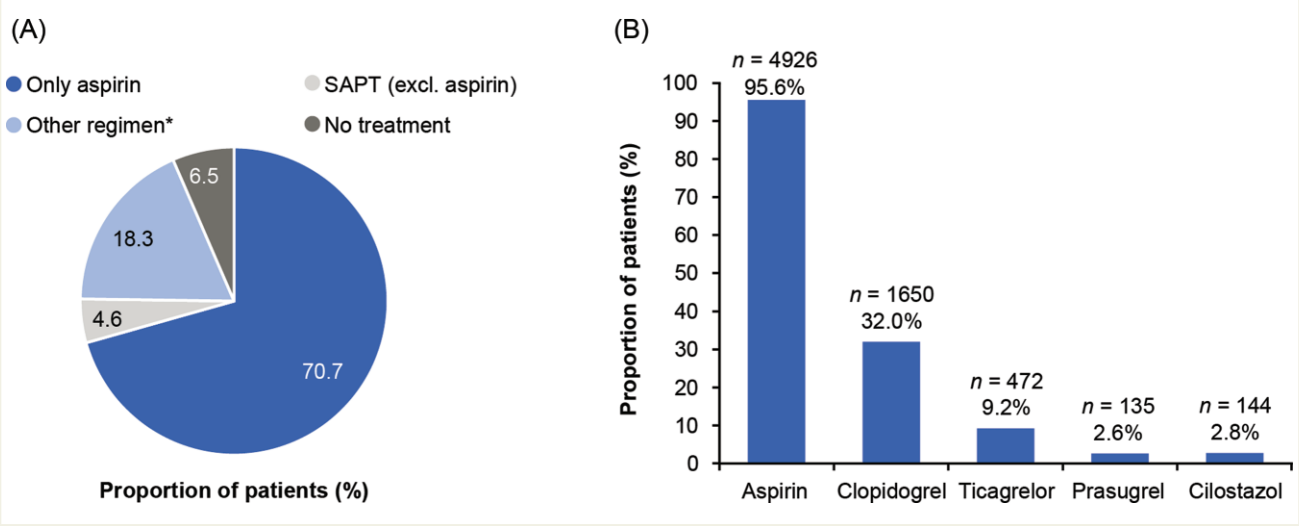

Figure 3 Antithrombotic regimens in XATOA before initiation of DPI *(A)* Antithrombotic regimens. *(B)* Antiplatelet therapy. Values are *n* (%) unless indicated otherwise. Other regimen: only anticoagulant (excluding antiplatelet agents), aspirin plus antiplatelet, aspirin plus anticoagulant, aspirin plus antiplatelet plus antithrombotic, antithrombotic plus antiplatelet, two antithrombotic agents, aspirin plus two antithrombotic agents, two antiplatelet agents, or aspirin plus two antiplatelet agents. DPI, dual pathway inhibition; SAPT, single antiplatelet therapy.

of patients. The incidence rate of all-cause death was 1.95 per 100 patient-years.

Any treatment-emergent adverse events related to rivaroxaban occurred in 473 (8.4%) patients and serious adverse events related to rivaroxaban occurred in 108 (1.9%) patients (Supplementary material online, *Table S4*). All-cause fatal adverse events occurred in 110 (2.0%) patients, and COVID-19 occurred in 68 (1.2%) patients, with a fatal outcome in 8 (0.1%) patients (Supplementary material online, *Table S4*).

Discussion

The findings of XATOA in the context of data from the COMPASS trial[10]

XATOA is the first prospective registry study to provide insights into which patients are being selected for treatment with DPI in clinical practice. The majority of patients were only on aspirin prior to enrolment. The main reason for initiating DPI was high or deteriorating vascular risk as assessed by the responsible clinician. In the

Table 2 Reasons and risk features leading to DPI initiation in the XATOA registry

Reason	Number (%) (*N* = 5532)
Risk features (existing, worsening, or newly diagnosed)	4753 (85.9)
High cardiovascular risk profile[a]	3913 (70.7)
CAD	3266 (59.0)
CAD, 1 vessel affected	818 (14.8)
CAD, 2 or 3 vessels affected	2292 (41.4)
MI	1269 (22.9)
ACS	350 (6.3)
PCI	1126 (20.4)
CABG	647 (11.7)
Lower-limb PAD	2467 (44.6)
PAD, lower extremities	2375 (42.9)
PAD, other[b]	88 (1.6)
ABI <0.9	612 (11.1)
Peripheral arterial intervention	847 (15.3)
Symptomatic lower-extremity PAD[c]	1090 (19.7)
Polyvascular disease (≥2 vascular beds affected)	863 (15.6)
Carotid lesion[d]	829 (15.0)
Other cardiovascular conditions[e]	502 (9.1)
High stroke risk[f]	389 (7.0)
Other non-cardiovascular conditions[g]	229 (4.1)
End of DAPT	794 (14.4)
Missing	2 (<0.1)

Values are *n* (%). Responses were chosen by the investigators from a prespecified list. Multiple responses were permitted.
ABI, ankle–brachial index; ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; DPI, dual pathway inhibition; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.
[a]At least one of the following: history of hypertension, diabetes, hyperlipidaemia, chronic renal dysfunction, smoking, family history of vascular disease, age >65 years, or high body mass index.
[b]Not lower-limb or carotid.
[c]Intermittent claudication or lower-extremity amputation.
[d]PAD: carotid disease, carotid intervention, or cerebrovascular interventions.
[e]Atrial fibrillation or chronic heart failure.
[f]Prior transient ischaemic attack or stroke.
[g]Liver cirrhosis, cancer, or other conditions.

COMPASS trial and in XATOA, the MACE rates were similar. However, in XATOA the MALE rate was substantially higher, and the major bleeding rate was substantially lower. Key differences between XATOA and COMPASS include the higher proportion of PAD patients and geographic differences (e.g. a lower proportion of patients from South America and Asia were enrolled in XATOA; *Figure 2*).

Most patients in XATOA were initiated on DPI because of risk characteristics, such as multivessel CAD or lower-extremity PAD, and about 70% of patients had a high cardiovascular risk profile. Factors included in the definition of a high cardiovascular risk profile in XATOA were hypertension, hyperlipidaemia, diabetes, chronic renal dysfunction, smoking, a family history of vascular disease, age >65 years, and a high body mass index. In a subsidiary analysis of the COMPASS trial, polyvascular disease, heart failure, renal insufficiency, and diabetes were identified as the strongest predictors of vascular risk.[21] A higher number of risk factors that are poorly controlled have been shown in the COMPASS trial to be associated with higher incidence of ischaemic events.[22] Fontaine class 3 or 4 PAD, prior peripheral revascularization, or prior amputation were additional co-morbidities associated with increased vascular risk in patients with lower-extremity PAD in COMPASS.[23] Patients with these characteristics were shown to have the largest absolute benefit in terms of vascular risk reduction with DPI versus aspirin.[23–25] Thus, the risk characteristics of patients included in XATOA, and the high proportion of patients with PAD, suggest that patients with the potential for greater absolute benefit with DPI are being selected for this treatment in clinical practice.[21,23,24] Prior MI, ACS, or PCI was given as a reason for initiating DPI in some cases. However, in XATOA, the time between MI, ACS, or PCI, and the initial study visit was 100, 48, and 70 months, respectively. In some cases, the end of DAPT was also listed as the reason for initiating DPI. Therefore, these patients may have been initiated on DPI at the end of their planned period of DAPT for MI, ACS, or PCI.

In XATOA, 72.7% of patients had CAD, 58.9% had PAD, and 31.6% had both CAD and PAD, while in COMPASS, 90.6% of patients had CAD, 27.3% had PAD, and 18.0% had both CAD and PAD. Consistent with prior studies, secondary prevention measures were more widely used in CAD patients than in patients with PAD only. Because of the greater proportion of PAD patients recruited in XATOA than in COMPASS, a higher frequency of limb events would be expected, and this was observed (*Figure 4*). The findings suggest that patients with PAD or polyvascular disease are being prioritized for DPI therapy in clinical practice. In contrast to patients with CAD, where several intensified antithrombotic therapies have been demonstrated to improve outcomes and have been included in guidelines, there is a relative paucity of such evidence-based medical therapies in patients with PAD.[1,4] Overall, a high proportion of patients in XATOA and in COMPASS were receiving secondary prevention therapies at baseline, although not as high a proportion in XATOA as in COMPASS (69.9% and 78.9% of patients in XATOA and COMPASS received angiotensin-converting enzyme inhibitors or ARBs, respectively). Future studies will determine whether these findings are accounted for by the higher proportion of CAD patients in COMPASS.

To account for the different follow-up periods in XATOA (15 months) and COMPASS (23 months),[10] incidence rates of clinical events per 100 patient-years were calculated. Although the studies cannot be compared directly, the annualized incidence rates of MACE in XATOA and the DPI arm of COMPASS were highly consistent. In XATOA, the rate of clinically recognized major bleeding (0.95 per 100 patient-years) was relatively lower than the rate of ischaemic events, such as MACE (2.26 per 100 patient-years). In COMPASS, the rate of major bleeding (1.7 per 100 patient-years) was also lower than the rate of MACE (2.18 per 100 patient-years). In contrast, the rate of non-major bleeding was slightly lower in XATOA (4.43 per 100 patient-years) than in COMPASS (5.11 per 100 patient-years). The lower rates of bleeding in XATOA than in COMPASS could be related to various factors. For example, physicians may have chosen, in clinical practice, to initiate DPI in patients with a lower perceived bleeding risk rather than higher perceived bleeding risk. While the rates of MACE were similar between the

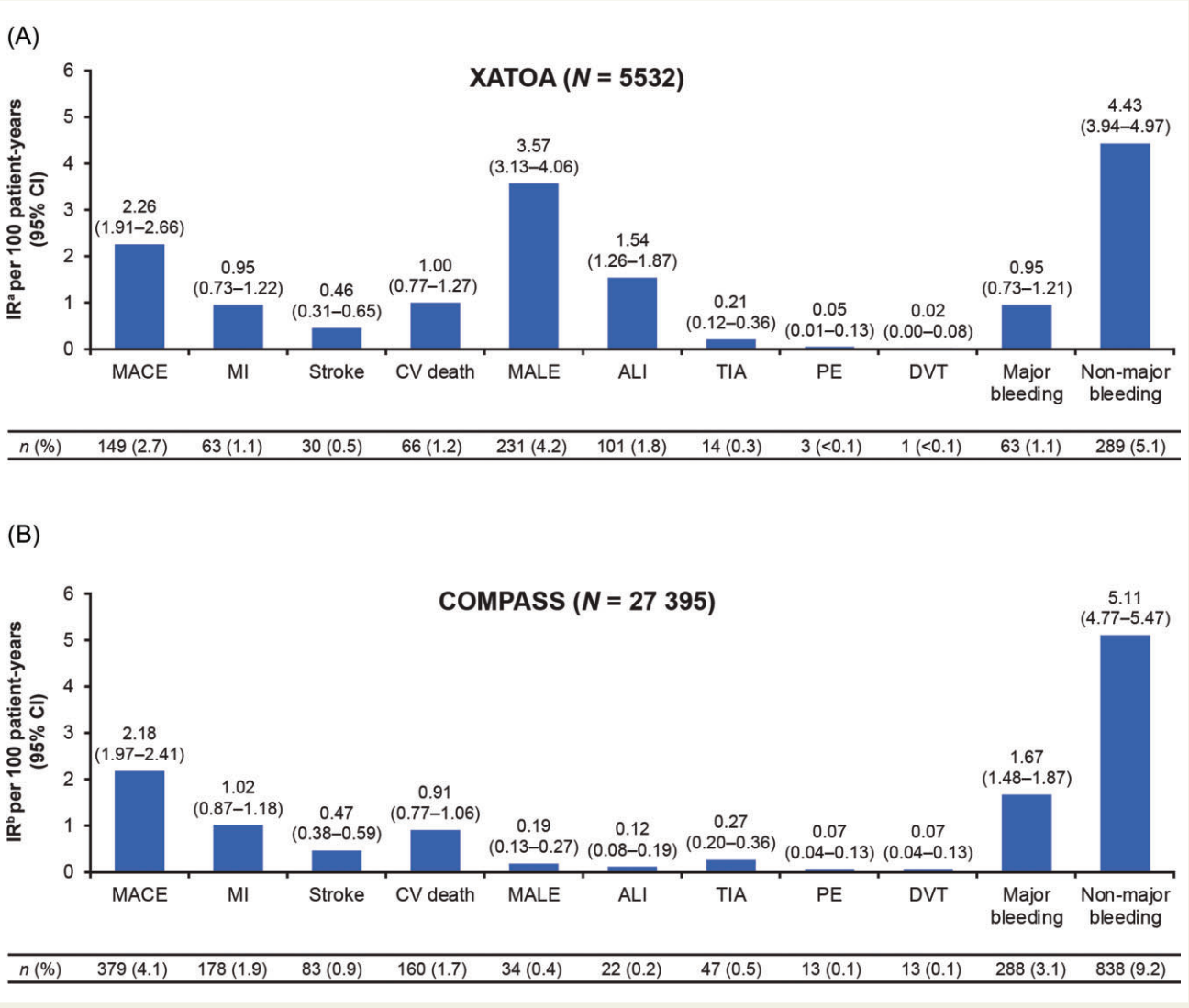

Figure 4 Incidence rates of clinical events in XATOA and in the DPI arm of COMPASS. Event rates in *(A)* XATOA and *(B)* COMPASS for corresponding outcomes. Bleeding in XATOA is shown for the safety analysis set ($N = 5615$). ALI, acute limb ischaemia; CI, confidence interval; CV, cardiovascular; DPI, dual pathway inhibition; DVT, deep vein thrombosis; IR, incidence rate; MACE, major adverse cardiovascular events; MALE, major adverse limb events; MI, myocardial infarction; PE, pulmonary embolism; TIA, transient ischaemic attack. [a]Incidence rate defined as the number of patients with a specific event divided by the total follow-up time over all patients. For patients who had an event, the exposure time was truncated at the time of the first occurrence of the event (or at rivaroxaban treatment start where the date of the event was missing). [b]Incidence rate estimated as the number of patients with incident events divided by the cumulative at-risk time in the reference population, where a subject was no longer at risk once an incident event occurred.

studies, relatively higher annualized rates of acute limb ischaemia (1.54 per 100 patient-years) and MALE (3.57 per 100 patient-years) were observed in XATOA than in COMPASS (0.12 and 0.19 per 100 patient-years, respectively). This is likely due to the enrolment of a higher proportion of patients with PAD in XATOA than in COMPASS. The adverse events associated with DPI in XATOA, including the rates of bleeding, are consistent with previous evidence on the safety profile of rivaroxaban.

The XATOA study highlights the frequency of peripheral vascular events in this vascular risk population, including those with atherothrombotic disease manifesting in both the CAD and PAD territories. Underdiagnosis of PAD in clinical practice and the presence of occult PAD in patients with CAD may all contribute to the future risk of PAD events.[4] Systematic evaluation of PAD and occult PAD is not routine in cardiology clinics. However, PAD assessments in cardiology clinics could be justified to identify high vascular risk patients and the potential for benefit with DPI.

The ongoing XATOC registry (Xarelto + Acetylsalicylic Acid: Treatment Patterns and Outcomes Across the Disease Continuum in Patients With CAD and/or PAD [XATOC] NCT04401761) is expected to include patients from additional countries beyond those included in XATOA and a more ethnically diverse patient population.

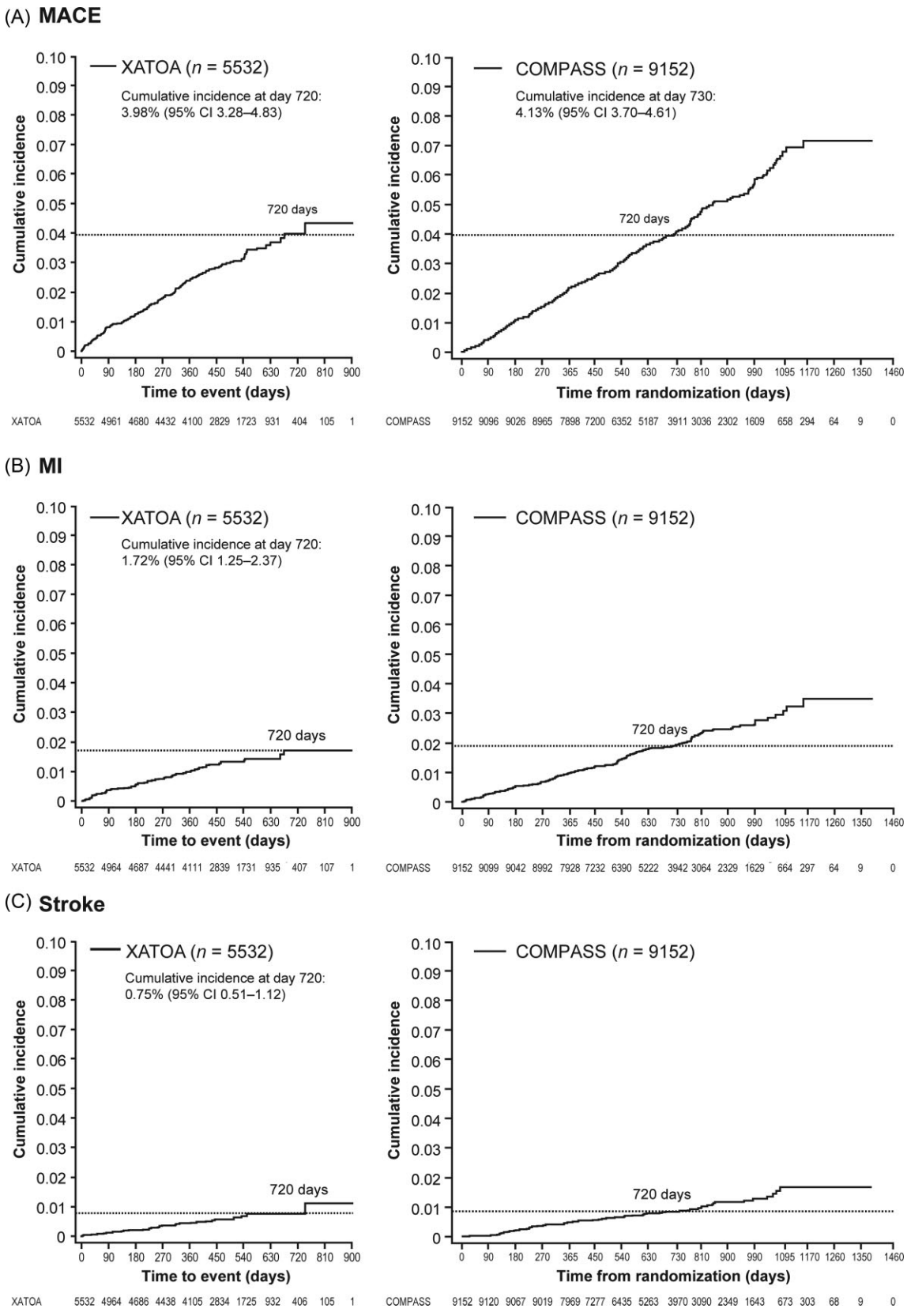

Figure 5 Cumulative incidences of clinical events in XATOA and the DPI arm of COMPASS.[8,10] *(A)* MACE. *(B)* MI. *(C)* Stroke. *(D)* CV death. *(E)* Acute/severe limb ischaemia. *(F)* Major bleeding. Event rates in XATOA and COMPASS are not exactly comparable. *A plot for ALI is not available for COMPASS. The most closely matched values available are shown. Major bleeding in XATOA is shown for the safety analysis set ($N = 5615$). ALI, acute limb ischaemia; CI, confidence interval; CV, cardiovascular; DPI, dual pathway inhibition; MACE, major adverse cardiovascular events; MI, myocardial infarction.

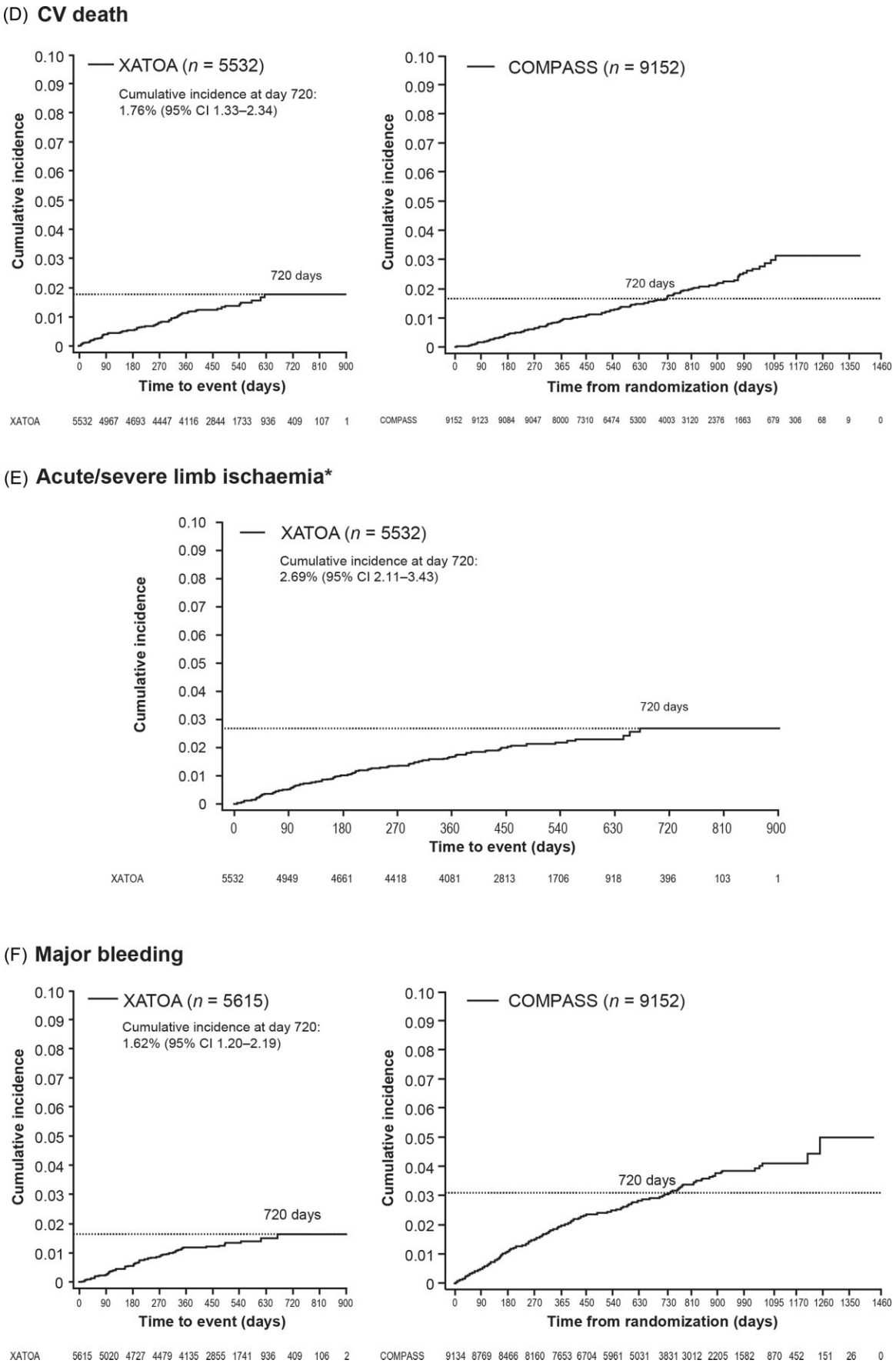

Figure 5 Continued

Limitations

As in other observational studies, there is a possibility of selection bias, but patients were screened consecutively to reduce selection bias. Measures were taken to ensure that the enrolled patients were representative of the population at each study site. Because outcomes were collected in different ways in XATOA and COMPASS, differences between outcomes in the studies are inherent. In an observational study like XATOA, there may be lower ascertainment of bleeding events than in a phase III trial setting. Most patients were male and of White European origin, and although this is consistent with prior studies, it limits the generalizability of the findings to other populations. A large proportion of patients were enrolled in Germany, and this should be taken into account when interpreting the results.

Conclusion

In summary, the XATOA registry shows that high-risk vascular patients are prioritized for DPI therapy in clinical practice. The clinical outcome rates for MACE were similar in XATOA and COMPASS, but MALE rates were higher in XATOA than in COMPASS. This is consistent with the higher proportion of patients in XATOA with PAD. Major bleeding rates were low in XATOA, and this provides support for a favourable net clinical benefit of DPI in vascular risk patients in clinical practice.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Data availability

Data cannot be shared for ethical/privacy reasons.

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MINI-FOCUS ISSUE: BLEEDING, THROMBOSIS, AND ATRIAL FIBRILLATION

ORIGINAL RESEARCH

Effectiveness and Safety of Rivaroxaban and Low Molecular Weight Heparin in Cancer-Associated Venous Thromboembolism

Craig I. Coleman, PharmD,[a] Kimberly Snow Caroti, PharmD,[b] Khaled Abdelgawwad, MSc, MBA,[c] George Psaroudakis, PhD,[c] Samuel Fatoba, PhD,[c] Marcela Rivera, PhD,[c] Bernhard Schaefer, BSc,[c] Gunnar Brobert, PhD,[c] Alok A. Khorana, MD,[d] Cecilia Becattini, MD,[e] Agnes Y.Y. Lee, MD,[f] Anders Ekbom, MD,[g] Marc Carrier, MD,[h] Christopher Brescia, BS,[i] Alexander T. Cohen, MD[j]

ABSTRACT

BACKGROUND Direct-acting oral anticoagulants (DOACs) are alternatives to low molecular weight heparin (LMWH) in most cancer-associated thrombosis (CAT) patients.

OBJECTIVES This study sought to compare the effectiveness and safety of rivaroxaban and LMWH for venous thromboembolism (VTE) treatment in patients with an active cancer type not associated with a high risk of DOAC bleeding.

METHODS An analysis of electronic health records from January 2012 to December 2020 was performed. Patients were adults, had active cancer, experienced an index CAT event, and were treated with rivaroxaban or LMWH. Patients with cancers with an established high risk of bleeding on DOACs were excluded. Baseline covariates were balanced using propensity score–overlap weighting. HRs with 95% CIs were calculated.

RESULTS We identified 3,708 CAT patients treated with rivaroxaban (29.5%) or LMWH (70.5%). The median (25th-75th percentiles) time on anticoagulation was 180 (69-365) and 96 (40-336) days for rivaroxaban and LMWH patients. At 3 months, rivaroxaban was associated with a 31% reduced risk of recurrent VTE vs LMWH (4.2% vs 6.1%; HR: 0.69; 95% CI: 0.51-0.92). No difference in bleeding-related hospitalizations or all-cause mortality was observed (HR: 0.79; 95% CI: 0.55-1.13 and HR: 1.07; 95% CI: 0.85-1.35, respectively). Rivaroxaban reduced the recurrent VTE risk (HR: 0.74; 95% CI: 0.57-0.97) but not bleeding-related hospitalizations or all-cause mortality at 6 months. At 12 months, no difference was observed between cohorts for any of the previously mentioned outcomes.

CONCLUSIONS Among active cancer patients experiencing VTE and not at high risk of bleeding on DOACs, rivaroxaban was associated with a reduced risk of recurrent VTE versus LMWHs at 3 and 6 months but not 12 months. (Observational Study in Cancer-Associated Thrombosis for Rivaroxaban-United States Cohort [OSCAR-US]; NCT04979780) (J Am Coll Cardiol CardioOnc 2023;5:189–200) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]School of Pharmacy, University of Connecticut, Storrs, Connecticut, USA; [b]Evidence-Based Practice Center, Hartford Hospital, Hartford, Connecticut, USA; [c]Bayer AG, Berlin, Germany; [d]Cleveland Clinic and Case Comprehensive Cancer Center, Cleveland, Ohio, USA; [e]Department of Internal and Emergency Medicine, Stroke Unit, University of Perugia, Perugia, Italy; [f]University of British Columbia and BC Cancer, Vancouver, Canada; [g]Unit of Clinical Epidemiology, Department of Medicine,

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CAT = cancer-associated thrombosis

DOAC = direct-acting oral anticoagulant

DVT = deep vein thrombosis

eGFR = estimated glomerular filtration rate

EHR = electronic health record

LMWH = low molecular weight heparin

OLW = overlap weighting

PE = pulmonary embolism

RCT = randomized controlled trial

VTE = venous thromboembolism

The presence of active cancer increases patients' risk of venous thromboembolism (VTE) by approximately 15-fold.[1] Moreover, patients with cancer-associated thrombosis (CAT) have a 3-fold increased risk of recurrent VTE and twice the risk of bleeding.[2,3] Therefore, it is of utmost importance that optimal anticoagulation is used in patients with CAT with the goals of reducing recurrent thrombosis and minimizing bleeding risk.

CAT management guidelines[4,5] endorse direct-acting oral anticoagulants (DOACs) as alternatives (and in some cases preferred) to low molecular weight heparins (LMWHs) for the treatment of VTE in most patients. Pooled data supporting the use of DOACs in CAT treatment derived from 6 randomized controlled trials (RCTs)[6-12] suggest that DOACs significantly lower recurrent VTE risk[10] and improve patient-reported treatment satisfaction and anticoagulation persistence[11] without increasing the risk of major bleeding,[10] although individual RCTs have shown an increased risk of clinically relevant bleeding with DOACs.[9,10,12]

Comparative effectiveness and safety observational studies evaluating rivaroxaban and other DOACs vs LMWHs for CAT treatment have been published but have been limited in sample size, used older data sets, employed heterogeneous definitions of active cancer, lacked laboratory and clinical data, or evaluated types of cancer in which caution is recommended with the use of DOAC treatment according to guidelines (ie, gastrointestinal and urothelial cancers).[13-19] Although RCTs[6-12] have consistently demonstrated the relative efficacy and safety of DOACs compared with LMWHs among a broad cohort of patients with varying cancer types, there are sparse data evaluating the effectiveness and safety of DOACs specifically in CAT patients for whom guidelines endorse DOACs as alternatives. Therefore, we sought to compare the effectiveness and safety of rivaroxaban and LMWHs for the treatment of VTE in patients with an active cancer type not associated with an established high risk of bleeding on a DOAC.[4]

METHODS

DATA SOURCE. This was an analysis of OSCAR-US (Observational Study in Cancer-Associated Thrombosis for Rivaroxaban-United States Cohort; NCT04979780). OSCAR-US is 1 of 3 studies comparing rivaroxaban with LMWH in CAT patients being performed using standardized methodologies, outcomes, and time points in populations drawn from 3 different country data sets (the United States, United Kingdom [NCT05112666], and Sweden [NCT05150938]). Because it was possible that the use of the different oral factor Xa inhibitors in CAT patients likely varied between the 3 countries in the OSCAR program, each country decided to perform an analysis of rivaroxaban vs LMWH for the purposes of standardization. We performed a retrospective cohort analysis using U.S. Optum deidentified electronic health record (EHR) data from January 1, 2012, to December 31, 2020. The database provided longitudinal patient-level medical record data for >95 million patients seen at ~700+ hospitals and ~7,000+ clinics across the United States and includes data on medications both prescribed and self-reported (including over-the-counter medications) entered into the EHR (not prescription fill records), laboratory results, vital signs, body measurements, other clinical observations, and diagnosis and procedure codes.[20] Insured and uninsured patients of all ages are included in the data set. The use of this database does not involve human subjects research and has been determined by the New England Institutional Review Board to be exempt from broad Institutional Review Board approval. All data in the database are deidentified and follow the Health Insurance Portability and Accountability Act of 1996 to preserve patient anonymity and confidentiality.

COHORT SELECTION. The population of interest for this study included adult patients with active primary or metastatic cancer excluding esophageal, gastric, unresected colorectal, bladder, and noncerebral central nervous system cancers and leukemia[4] who were admitted to the hospital, emergency department, or observation unit for acute deep vein thrombosis

Karolinska Institute, Stockholm, Sweden; [h]Department of Medicine, Ottawa Hospital Research Institute at the University of Ottawa, Ottawa, Canada; [i]Freshtech IT, LLC, East Hartford, Connecticut, USA; and the [j]Department of Haematological Medicine, Guy's and St Thomas' National Health Service Foundation Trust, King's College London, London, United Kingdom. Dr Fatoba is now with Bayer U.S. LLC, Whippany, New Jersey, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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(DVT) and/or pulmonary embolism (PE) on or after January 1, 2013 (corresponding with the availability of rivaroxaban for VTE treatment in the United States; rivaroxaban does not have a specific indication for CAT) and were treated with therapeutic VTE doses of rivaroxaban or LMWH per written prescription or patient self-report on day 7 post-acute VTE diagnosis (index date). Patients had to be active in the EHR data set for at least 12 months before the index event and had to have at least 1 provider visit in the 12 months before the acute VTE event (baseline period). We defined active cancer as cancer being actively treated with systemic therapy or surgery within 6 months of the index CAT or metastatic disease regardless of the time from the initial cancer diagnosis or treatment. We excluded patients from this analysis if they had atrial fibrillation or valvular heart disease, were pregnant, or were using anticoagulation during the baseline period.

The primary outcomes for this study included recurrent VTE (defined by the presence of an appropriate inpatient discharge diagnosis code in the primary coding position[21]), any clinically relevant bleeding-related hospitalization (per the Cunningham algorithm[22]), and all-cause mortality during the 3 months after the index date. The 3-month time point was selected as our primary time point a priori because we anticipated potential differences in the duration of treatment between cohorts but with both rivaroxaban and the LMWH cohorts receiving a median of at least 3 months. The secondary study outcomes included the occurrence of these same outcomes at 6 and 12 months after the index date as well as bleeding subtypes, including critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome), intracranial, and extracranial hemorrhage.

Given the retrospective nature of the data analysis, the presence of a comorbid disease diagnosis was made based on billing codes and/or supporting laboratory/observation data. The absence of data suggesting a comorbidity exists was assumed to represent the absence of the disease (no missing data imputation for binary comorbidity disease diagnoses). For continuous laboratory and observation data, missing values were imputed using a "multiple imputation" approach based on a fully conditional specification linear regression model with all other available variables included in the model. No imputation was performed for missing outcomes data.

STATISTICAL ANALYSIS. Baseline characteristics were analyzed using descriptive statistics. Categoric data are reported as percentages and continuous data as mean ± SD or medians with accompanying 25th to 75th percentiles (Q1-Q3) where appropriate. To adjust for potential confounding between the rivaroxaban and LMWH cohorts, propensity scores were calculated using a multivariable logistic regression model. The propensity score model included commonly used variables and accepted risk factors for differential anticoagulation exposure identified at baseline, including demographics, cancer types, VTE risk factors and comorbidities, laboratory values, vital signs, other clinical observations, systemic cancer therapy or surgery, and other medications used (both prescription and over the counter), as depicted in **Table 1**. Propensity scores were used to assign weights to individual patients in the analysis using an overlap weighting (OLW) approach.[23] OLW assigns weights to patients that are proportional to their probability of belonging to the opposite treatment cohort (1 − the propensity score for rivaroxaban and the propensity score for patients with LMWH). By design, OLW results in the exact balance of all variables included in the propensity score model.

After the normalization of OLWs to adjust the weighted (pseudo) sample size to match the initial cohort sample sizes, we fit Cox proportional hazards regression models to compare event rates over time for the rivaroxaban and LMWH cohorts. Because OLW balanced key characteristics of the treatment cohorts, the only independent variable that was included in the Cox regression model was the anticoagulant received. The results of the Cox regression model are reported as HRs with 95% CIs. Statistical analyses were performed using SAS version 9.4 (SAS Institute) and IBM SPSS Statistics version 27.0 (IBM Corp). The proportional hazard assumption was tested based on Schoenfeld residuals and was shown to be valid in all cases. Patients were followed in the Cox models until outcome occurrence, end of EHR activity, end of data availability, or end of follow-up (maximum of 3, 6, or 12 months depending on the analysis). A P value <0.05 was considered significant unless otherwise noted.

Because of the lack of prescription fill/claims data in the data set and the ability of patients to self-report anticoagulation use, it was anticipated that it would be difficult to accurately assess patient time on anticoagulation for a substantial proportion of the study population (when the discontinuation date was available; the date the anticoagulant was listed as discontinued in the EHR may not correspond with the date anticoagulation was stopped by the patient). Therefore, our main analyses used an intention-to-treat approach in which patients were

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TABLE 1 Characteristics of Unweighted and OLW Rivaroxaban and LMWH Patients with Cancer-Associated Thrombosis

	Unweighted			OLW		
	Rivaroxaban (n = 1,093)	LMWH (n = 2,615)	Standardized Difference	Rivaroxaban (n = 1,093)	LMWH (n = 2,615)	Standardized Difference
Age ≤40, y	3.8	3.8	0.00	3.4	3.4	0.00
Age 41-60, y	31.2	30.3	0.02	30.7	30.7	0.00
Age 61-74, y	40.4	40.7	-0.01	39.9	39.9	0.00
Age ≥75, y	24.6	25.2	-0.01	26.1	26.1	0.00
BMI ≤29, kg/m^2	55.7	62.0	-0.13	57.8	57.8	0.00
BMI 30-34, kg/m^2	23.4	19.3	0.10	21.9	21.9	0.00
BMI 35-39, kg/m^2	11.3	9.8	0.05	10.3	10.3	0.00
BMI ≥40, kg/m^2	9.5	8.8	0.02	9.9	9.9	0.00
Female	58.8	57.8	0.02	58.9	58.9	0.00
January 1, 2013, to anticoagulation, d	1,617 ± 711	1,322 ± 768	0.41	1,533 ± 718	1,533 ± 777	0.00
Number of hospitalizations in previous 12 months ≥2	39.6	44.5	-0.10	45.7	45.7	0.00
Active cancer treatment within 4 weeks	54.2	60.9	-0.14	58.9	58.9	0.00
Metastatic	36.7	55.1	-0.38	43.4	43.4	0.00
eGFR <30, mL/min/1.73 m^2	4.5	7.9	-0.16	5.5	5.5	0.00
eGFR 30-59, mL/min/1.73 m^2	11.3	13.5	-0.07	12.6	12.6	0.00
eGFR 60-89, mL/min/1.73 m^2	42.4	41.7	0.01	42.0	42.0	0.00
eGFR >90, mL/min/1.73 m^2	42.0	37.4	0.09	40.4	40.4	0.00
Chronic lung disease	29.7	27.1	0.06	29.4	29.4	0.00
Rheumatic disease	6.0	4.4	0.07	5.1	5.1	0.00
Liver disease	6.4	12.0	-0.23	7.6	7.6	0.00
Heart failure	8.2	7.7	0.02	9.2	9.2	0.00
Stroke or systemic embolism	3.8	5.3	-0.08	4.1	4.1	0.00
Prior myocardial infarction	5.3	6.5	-0.06	6.0	6.0	0.00
Peripheral arterial disease	7.3	6.7	0.03	6.9	6.9	0.00
Hypertension	60.7	61.1	-0.01	61.3	61.3	0.00
Varicose veins	2.0	2.0	0.00	2.0	2.0	0.00
Any prior bleeding	8.3	10.0	-0.06	9.0	9.0	0.00
Pulmonary embolism	42.0	50.4	-0.17	51.9	51.9	0.00
Prior history of VTE	12.0	11.5	0.02	12.6	12.6	0.00
Frailty score ≥16[a]	10.2	12.5	-0.08	11.5	11.5	0.00
Coagulopathy[b]	9.9	15.0	-0.17	11.9	11.9	0.00
Impaired mobility[b]	1.6	2.5	-0.08	1.8	1.8	0.00
$P2Y_{12}$ inhibitor	1.8	2.0	-0.01	2.1	2.1	0.00
Aspirin	17.5	16.2	0.03	17.9	17.9	0.00
NSAID	43.4	39.0	0.09	42.1	42.1	0.00
Statin	35.6	32.4	0.07	35.1	35.1	0.00
PPI or H2-receptor antagonist	54.1	58.9	-0.10	56.3	56.3	0.00
Estrogen	3.6	2.9	0.03	3.5	3.5	0.00

Continued on the next page

evaluated based on the index anticoagulant received at day 7 and were not censored at therapy switch or discontinuation. The time from the index anticoagulant initiation to the end of follow-up was then considered the time at risk. An exploratory analysis limited to patients in whom the time on anticoagulation could be assessed (ie, both the start and stop dates for the index anticoagulant were available for a patient) and implementing an on-treatment approach (ie, censored at outcome occurrence, index anticoagulant switch or discontinuation, end of EHR activity, end of data availability, or end of follow-up) was also undertaken.

SUBGROUP AND SENSITIVITY ANALYSES. We performed subgroup analyses to evaluate the effectiveness and safety of rivaroxaban compared with LMWH in patients ≥65 or <65 years of age; patients with an estimated glomerular filtration rate (eGFR) ≥60, 30 to 59, or <30 mL/min/1.73 m^2;

TABLE 1 Continued

	Unweighted			OLW		
	Rivaroxaban (n = 1,093)	LMWH (n = 2,615)	Standardized Difference	Rivaroxaban (n = 1,093)	LMWH (n = 2,615)	Standardized Difference
Laboratory values						0.00
Alkaline phosphatase, U/L	108.6 ± 104.1	131 ± 144	-0.22	115 ± 121	115 ± 108	0.00
Hemoglobin, g/dL	11.9 ± 2.0	11.3 ± 2.0	0.30	11.6 ± 2.0	11.6 ± 2.0	0.00
Platelets, $\times 10^3/\mu L$	242.2 ± 102.4	243 ± 120	-0.01	241 ± 104	241 ± 110	0.00
Total bilirubin, mg/dL	0.7 ± 0.7	0.7 ± 1.0	-0.07	0.7 ± 0.8	0.7 ± 0.9	0.00
Absolute neutrophil count, <1,500 cells/μL	3.2	4.2	-0.06	3.7	3.7	0.00
Serum albumin, g/dL	3.5 ± 0.6	3.3 ± 0.7	0.37	3.4 ± 0.6	3.4 ± 0.6	0.00
Primary and metastatic cancer type[c]						0.00
Resected colorectal	1.5	1.5	0.00	1.6	1.6	0.00
Lung	18.3	28.4	-0.26	22.5	22.5	0.00
Ovarian	3.8	4.8	-0.05	4.3	4.3	0.00
Brain	2.4	6.7	-0.28	2.8	2.8	0.00
Urologic	4.9	4.3	0.02	4.6	4.6	0.00
Hepatobiliary	11.2	19.6	-0.27	14.0	14.0	0.00
Breast	25.3	19.0	0.15	22.9	22.9	0.00
Gynecologic	9.9	12.7	-0.09	11.3	11.3	0.00
Pancreatic	3.6	8.0	-0.24	5.0	5.0	0.00
Upper gastrointestinal	2.6	2.3	0.02	2.7	2.7	0.00
Lymphoma	9.4	8.0	0.05	9.0	9.0	0.00
Prostate	13.0	10.4	0.08	11.7	11.7	0.00
Kidney	4.5	3.8	0.03	4.4	4.4	0.00
Myeloma	3.3	3.3	0.00	3.4	3.4	0.00
Testicular	0.6	1.0	-0.04	0.9	0.9	0.00
Other	14.7	8.4	0.18	12.2	12.2	0.00
Systemic cancer therapies						0.00
Hormonal therapy	20.6	16.7	0.10	19.5	19.5	0.00
Kinase inhibitors	3.8	4.3	-0.03	4.3	4.3	0.00
Monoclonal antibodies	2.5	3.9	-0.09	2.8	2.8	0.00
Immunomodulating agents	0.1	0.3	-0.06	0.2	0.2	0.00
Miscellaneous	1.1	1.3	-0.02	1.1	1.1	0.00
Antimetabolites	6.4	6.9	-0.02	5.7	5.7	0.00
Alkylating agents	3.4	5.5	-0.12	3.4	3.4	0.00
Antitumor antibiotics	0.4	0.3	0.02	0.4	0.4	0.00
Proteasome inhibitors	1.0	0.9	0.01	0.9	0.9	0.00
Platinum-based chemotherapy	4.1	6.5	-0.12	5.0	5.0	0.00
Anthracyclines	0.0	0.0	0.00	0.0	0.0	0.00
Topoisomerase inhibitors	1.2	1.7	-0.05	1.6	1.6	0.00
Vinca alkaloids	0.2	0.7	-0.12	0.2	0.2	0.00
Bevacizumab	0.0	0.0	0.00	0.0	0.0	0.00
Taxanes	3.3	4.3	-0.06	3.4	3.4	0.00

Values are % or mean ± SD unless otherwise indicated. [a]Frailty was assessed in this study using the Hospital Frailty Risk Score developed and validated by Gilbert T, Neuburger J, Kraindler J, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic health records: an observational study. *Lancet*. 2018;391:1775-1782. The Hospital Frailty Risk Score has been shown to performs at least as well as existing frailty or risk stratification tools. It is derived from International Classification of Diseases codes and implemented into electronic health record and claims data sets. [b]The presence of the coagulopathy and impaired mobility covariates were assessed using International Classification of Diseases codes validated as part of the Elixhauser comorbidity index.[27] [c]Cancer types add up to >100% because both patients' primary and metastatic cancer locations were counted.

BMI = body mass index; eGFR = estimated glomerular filtration rate; LMWH = low molecular-weight heparin; NSAID = nonsteroidal anti-inflammatory drug; OLW = overlap weighted; PPI = proton pump inhibitor; VTE = venous thromboembolism.

patients with a body mass index (BMI) ≥35 or <35 kg/m^2; patients in whom there was a presence or absence of metastatic disease; patients with or without PE (± DVT) as their index CAT; and those being actively treated or not treated for cancer within ±4 weeks of developing CAT. The *P* values for interaction were calculated to test for the presence of statistical interactions. To reduce the chances of obtaining false-positive results (type I error) because of multiple hypothesis testing, we used a

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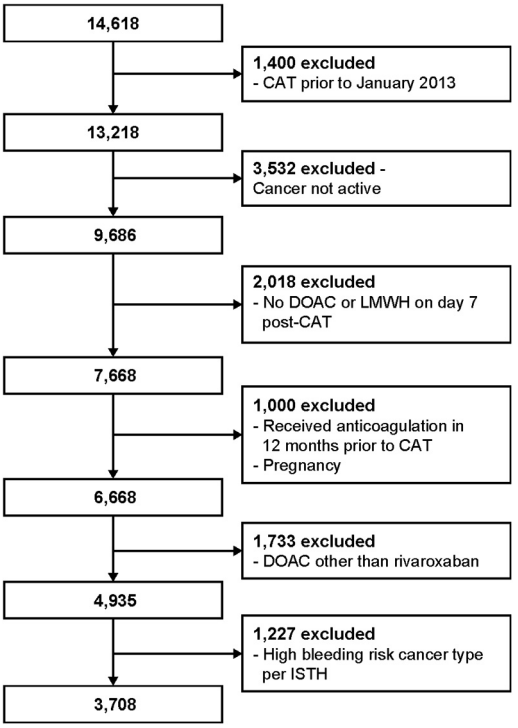
FIGURE 1 Patient Inclusion and Exclusion



Of 14,618 patients with cancer-associated thrombosis (CAT) initially identified, 10,910 were excluded, resulting in a final study population of 3,708 patients with cancer types for which direct-acting oral anticoagulants (DOACs) are recommended according to the International Society on Thrombosis and Haemostasis (ISTH) guidelines and receiving either rivaroxaban or low molecular-weight heparin for inclusion in the analysis.

Bonferroni-corrected P value < 0.003 to indicate a statistically significant interaction. A sensitivity analysis was performed in which a proportional hazards model for the subdistribution of competing risk was fit. Propensity scores and OLWs were recalculated for each subgroup and sensitivity analysis.

RESEARCH REPORTING. This paper was written in accordance with the reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology guidance.[24]

RESULTS

PATIENT CHARACTERISTICS. Our EHR data set included 105,463 patients who had a primary hospital, emergency department, or observation unit billing code for VTE. Of these, 12.5% were adult patients with a diagnosis of cancer and had their VTE on or after January 1, 2013. Approximately 27% of these patients lacked evidence of active cancer (cancer treatment within 6 months or metastatic disease). Additional patients were excluded from the analysis because they were not receiving rivaroxaban or a LMWH on day 7 post-CAT diagnosis, had an alternative indication for full-dose anticoagulation, or were pregnant. This left 4,935 patients with active cancer experiencing CAT and treated with either rivaroxaban or LMWH. Of these, 1,227 patients (286 rivaroxaban and 941 LMWH) were excluded because of the presence of a cancer type associated with a high risk of DOAC bleeding. (Characteristics for these patients are provided in Supplemental Table 1.) In total, 3,708 patients, 29.5% of whom were treated with rivaroxaban and 70.5% were treated with LMWH (99.5% of LMWH patients used enoxaparin at an estimated median dose per administration of 1.02 mg/kg), were included in this analysis (**Figure 1**).

After OLW, the characteristics of patients with active primary or metastatic cancer excluding esophageal, gastric, unresected colorectal, bladder, and noncerebral central nervous system cancers and leukemia[4] and receiving rivaroxaban and LMWH were similar for all covariates included in the propensity score model (**Table 1**). Approximately one-quarter of patients were ≥75 years of age, 58.9% were female, 20.2% of patients had a BMI ≥35 kg/m^2, and 18.1% had an eGFR <60 mL/min/1.73 m^2 at baseline. The qualifying CAT event was PE (with or without DVT) in 51.9% of patients. Nearly 46% of all patients were admitted to the hospital at least twice in the 12 months prior. A total of 43.4% of patients had metastatic disease, and 58.9% had received active cancer treatment within 4 weeks (before or after) of the CAT event. The most common cancers in our study population were breast (22.9%), lung (22.5%), hepatobiliary (14.0%), prostate (11.7%), and gynecologic (11.3%).

RECURRENT VTE, BLEEDING-RELATED HOSPITALIZATIONS, AND ALL-CAUSE MORTALITY. At 3 months, the incidence of recurrent VTE was 4.2% in the rivaroxaban cohort and 6.1% in the LMWH cohort of patients with active primary or metastatic cancer excluding esophageal, gastric, unresected colorectal, bladder, and noncerebral central nervous system cancers and leukemia,[4] corresponding to a 31% relative hazard reduction associated with rivaroxaban use (HR: 0.69; 95% CI: 0.51-0.92) (**Table 2**). No differences in bleeding-related hospitalizations or all-cause

mortality were observed between the 2 cohorts (HR: 0.79; 95% CI: 0.55-1.13 and HR: 1.07; 95% CI: 0.85-1.35, respectively). The 6-month results were consistent with those at 3 months, with rivaroxaban use associated with a significant 26% reduction in patients' risk of recurrent VTE but no significant difference in bleeding-related hospitalizations or all-cause mortality. At 12 months, no significant difference was observed between the 2 treatment groups for any of the 3 primary outcomes.

The results of OLW analysis of the 286 rivaroxaban and 941 LMWH patients with a cancer type associated with a high risk of DOAC bleeding (and thus a priori excluded from the base case analysis) are provided in Table 3. No significant differences between the rivaroxaban and LMWH treatment cohorts were observed for any outcome at any time point assessed.

For the 71.5% of patients with available anticoagulant duration data, the median (Q1-Q3) time on anticoagulation was 180 (69-365) days for the 933 rivaroxaban patients and 96 (40-336) days for the 1,720 LMWH patients. The results of this exploratory on-treatment analysis were directionally similar to the main intention-to-treat analysis, albeit with more robust effect sizes in favor of rivaroxaban (Supplemental Table 2).

The evaluation of specific bleeding-related hospitalization outcomes suggested that rivaroxaban use was associated with significantly fewer critical organ bleeds vs LMWHs at all 3 time points (HR range: 0.20-0.33) (Table 4). These reductions appear to be driven by lower intracranial hemorrhage rates with rivaroxaban compared with LMWH. No difference in extracranial bleeding was observed between the 2 anticoagulation cohorts at any point during follow-up (HR range: 0.92-0.96).

SUBGROUP AND SENSITIVITY ANALYSES. No statistically significant interactions at a Bonferroni-corrected alpha <0.003 were observed for any outcome at any time point in the age, eGFR, BMI, metastatic disease, and active cancer treatment subgroup analyses (Supplemental Tables 3 to 8). Upon subgroup analysis stratified by the presence or absence of PE at index CAT diagnosis, no significant interaction was noted for recurrent VTE or all-cause mortality. Significant interactions were observed at the 3-, 6-, and 12-month time points for the bleeding-related hospitalization outcome ($P \leq 0.003$ for all), with results suggesting rivaroxaban's relative impact on bleeding was more favorable in patients with PE than those without PE.

When a proportional hazards models for the subdistribution of competing risk was fit, the results for recurrent VTE and bleeding-related hospitalization at 3, 6, and 12 months had a similar direction and magnitude of effect sizes.

TABLE 2 OLW Outcomes in Rivaroxaban and LMWH Cohorts

	Rivaroxaban (n = 1,093)[a]	LMWH (n = 2,615)[a]	OLW HR (95% CI)
0-3 months			
Recurrent VTE	4.2	6.1	0.69 (0.51-0.92)
Bleeding-related hospitalization	2.9	3.7	0.79 (0.55-1.13)
All-cause mortality	7.9	7.4	1.07 (0.85-1.35)
0-6 months			
Recurrent VTE	5.2	6.9	0.74 (0.57-0.97)
Bleeding-related hospitalization	3.9	4.9	0.78 (0.57-1.06)
All-cause mortality	13.0	13.5	0.97 (0.81-1.15)
0-12 months			
Recurrent VTE	6.2	7.7	0.80 (0.63-1.02)
Bleeding-related hospitalization	4.4	5.5	0.78 (0.58-1.05)
All-cause mortality	19.4	22.2	0.87 (0.76-1.00)

Values are % unless otherwise indicated. [a]Not based on the length of follow-up (censoring) or competing risk. Abbreviations as in Table 1.

DISCUSSION

In our study of more than 3,700 patients with active cancer experiencing CAT and having a cancer type for which guidelines endorse the use of a DOAC or LMWH,[4,5] we observed significant 31% and 26% reductions in recurrent VTE at 3 and 6 months of follow-up with rivaroxaban compared with LMWH but not at 12 months (Central Illustration). No significant impact on all-cause mortality or overall bleeding-related hospitalization risk was noted

TABLE 3 Results of OLW Analysis in Cancer Types Considered High Risk for Direct-Acting Oral Anticoagulant Bleeding

	Rivaroxaban (n = 286)[a]	LMWH (n = 941)[a]	OLW HR (95% CI)
0-3 months			
Recurrent VTE	5.6	5.4	1.01 (0.62-1.62)
Bleeding-related hospitalization	3.7	4.2	0.87 (0.49-1.53)
All-cause mortality	7.6	10.7	0.70 (0.48-1.02)
0-6 months			
Recurrent VTE	7.2	6.0	1.19 (0.77-1.84)
Bleeding-related hospitalization	5.3	4.9	1.06 (0.65-1.75)
All-cause mortality	15.2	18.5	0.80 (0.61-1.06)
0-12 months			
Recurrent VTE	9.2	7.7	1.19 (0.81-1.75)
Bleeding-related hospitalization	5.4	5.7	0.95 (0.59-1.53)
All-cause mortality	24.8	26.7	0.91 (0.73-1.14)

Values are % unless otherwise indicated. [a]Not based on the length of follow-up (censoring) or competing risk. Abbreviations as in Table 1.

TABLE 4 Bleeding Outcomes in the OLW Rivaroxaban and LMWH Cohorts

	Rivaroxaban (n = 1,093)[a]	LMWH (n = 2,615)[a]	OLW HR (95% CI)
0-3 months			
Bleeding-related hospitalization	2.9	3.7	0.79 (0.55-1.13)
Critical organ	0.2	1.0	0.20 (0.07-0.62)
Intracranial	0.0	0.3	Not calculable
Extracranial	2.8	2.9	0.96 (0.65-1.40)
0-6 months			
Bleeding-related hospitalization	3.9	4.9	0.78 (0.57-1.06)
Critical organ	0.4	1.2	0.33 (0.15-0.75)
Intracranial	0.2	0.6	0.37 (0.11-1.19)
Extracranial	3.5	3.9	0.92 (0.66-1.28)
0-12 months			
Bleeding-related hospitalization	4.4	5.5	0.78 (0.58-1.05)
Critical organ	0.5	1.4	0.33 (0.15-0.71)
Intracranial	0.3	0.7	0.37 (0.13-1.04)
Extracranial	4.0	4.3	0.92 (0.67-1.26)

Values are % unless otherwise indicated. [a]Not based on the length of follow-up (censoring) or competing risk. Abbreviations as in Table 1.

between the 2 anticoagulant cohorts at any time point. Rivaroxaban use was associated with a significantly reduced risk of critical organ bleeding vs LMWHs at 3, 6, and 12 months (HR range: 0.20-0.33).

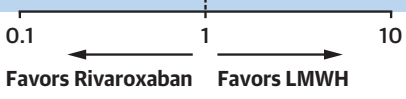
The findings of our present study are generally consistent with the results of the 6 RCTs comparing DOACs with LMWHs in the treatment of acute CAT.[6-12] In the SELECT-D (Anticoagulation Therapy in Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism) trial,[6] 203 patients receiving rivaroxaban and 203 patients receiving dalteparin were randomized and followed for 6 months. Recurrent VTE was observed less frequently in patients randomized to receive rivaroxaban (4% vs 11%; HR: 0.43; 95% CI: 0.19-0.99). This reduction in recurrent VTE was observed without a significant increase in major bleeding between the 2 anticoagulant groups (6% vs 4%; HR: 1.83; 95% CI: 0.68-4.96). A meta-analysis by Planquette et al[10] pooled SELECT-D along with 4 other RCTs comparing a DOAC and LMWH in CAT (CASTA-DIVA [Cancer Associated Thrombosis, a Pilot Treatment Study Using Rivaroxaban] for rivaroxaban,[10] Caravaggio[7] and ADAM-VTE [Apixaban and Dalteparin in Active Malignancy Associated Venous Thromboembolism] trials[8] for apixaban, and the Hokusai VTE Cancer trial[9] for edoxaban) as part of a meta-analysis and found DOACs were associated with a lower VTE recurrence (HR: 0.63; 95% CI: 0.47-0.86) with no significant difference in the risk of major bleeding (HR: 1.26; 95% CI: 0.84-1.90). However, a subanalysis of the Hokusai VTE Cancer trial[9] suggested patients with gastrointestinal and urothelial cancers were substantially more likely to have a bleeding event when treated with edoxaban than with dalteparin (13.2% vs 2.4% for gastrointestinal cancer and 13.2% vs 0% for urothelial cancer). These results were supported by a second meta-regression analysis performed by Sabatino et al,[12] who reported more frequent clinically relevant nonmajor bleeding with DOACs than with LMWHs (relative risk: 1.47; 95% CI: 1.16-1.85), which was potentially driven by patients with gastrointestinal malignancies (meta-regression $P = 0.027$ for the association between the log relative risk for clinically relevant nonmajor bleeding and the percentage of gastrointestinal cancers enrolled in each trial). Based on these data, it is not surprising that CAT guidance/guidelines[4,5] recommend caution when using DOACs (as alternatives to LMWH) in patients with these specific cancer types. It should be noted that our study population excluded patients previously identified in RCTs as being at high risk of DOAC bleeding. Although our study's exclusion of higher-risk bleeding patients makes the comparability of our results to RCTs more complicated, it in return allowed us to address a nuanced clinical question not directly answered by current RCT data (ie, What is the comparative effectiveness and safety of rivaroxaban vs LMWH in CAT patients for which guidelines support rivaroxaban use?) Prior observational studies assessing the comparative effectiveness and safety of DOACs (as a class or individual agents) and LMWH in CAT have been published,[13-19] but these studies have been limited in the sample size of the DOAC arms,[11,13-16] used noncontemporary data (predominantly data before 2019),[13-16,18,19] did not strictly define active cancer,[18] lacked laboratory and/or clinical observation data available to adjust for potential confounders[14,15,18] (that have been shown to have utility in predicting 6-month mortality among patients with cancer[25]), and/or evaluated types of cancer not recommended or caution advised for DOAC treatment.[13,15-19] Although none of the previously mentioned CAT studies demonstrated LMWHs to be superior to DOACs for either recurrent VTE or bleeding, there were some important inconsistencies in their results. Although some studies found DOACs to be associated with both a reduced risk of recurrent VTE and bleeding,[15] others suggested reductions in recurrent VTE with no difference in bleeding rates,[14,18] and others still found no difference between DOACs and LMWHs on either outcome.[13,16,17,19]

Kaplan-Meier curves from the SELECT-D[6] and CARAVAGGIO[7] trials suggest the relative benefit of rivaroxaban and apixaban compared with dalteparin in decreasing rates of recurrent VTE within the first

CENTRAL ILLUSTRATION **Effectiveness and Safety of Rivaroxaban vs Low Molecular-Weight Heparin**

Observational Study in Cancer-Associated Thrombosis for Rivaroxaban - United States Cohort (OSCAR-US)

Outcome	Rivaroxaban, % (n = 1,093)	LMWH, % (n = 2,615)	Overlap-Weighted HR (95% CI)	Overlap-Weighted HR (95% CI)
3 Months				
Recurrent VTE	4.2	6.1		0.69 (0.51-0.92)
Bleeding-related hospitalization	2.9	3.7		0.79 (0.55-1.13)
All-cause mortality	7.9	7.4		1.07 (0.85-1.35)
6 Months				
Recurrent VTE	5.2	6.9		0.74 (0.57-0.97)
Bleeding-related hospitalization	3.9	4.9		0.78 (0.57-1.06)
All-cause mortality	13.0	13.5		0.97 (0.81-1.15)
12 Months				
Recurrent VTE	6.2	7.7		0.80 (0.63-1.02)
Bleeding-related hospitalization	4.4	5.5		0.78 (0.58-1.05)
All-cause mortality	19.4	22.2		0.87 (0.76-1.00)



Coleman CI, et al. J Am Coll Cardiol CardioOnc. 2023;5(2):189–200.

Rivaroxaban was associated with a 31% reduced risk of recurrent venous thromboembolism (VTE) vs low molecular-weight heparin (LMWH) (HR: 0.69; 95% CI: 0.51-0.92) at 3 months. No difference in bleeding-related hospitalizations or all-cause mortality was observed (HR: 0.79; 95% CI: 0.55-1.13 and HR: 1.07; 95% CI: 0.85-1.35, respectively) at 3 months. Rivaroxaban reduced recurrent VTE (HR: 0.74; 95% CI: 0.57-0.97) but not bleeding-related hospitalizations or all-cause mortality at 6 months. At 12 months, no difference was seen between cohorts for any of these 3 outcomes.

few months of anticoagulant therapy initiation. Our finding that rivaroxaban was associated with a reduced hazard of recurrent VTE at 3 months aligns with these previous trials. The present study (as well as the Hokusai VTE Cancer trial,[9] which allowed investigators to stop therapy anytime between 6 and 12 months) also demonstrated that when given the choice, clinicians frequently prefer to stop anticoagulation at or before 6 months. The fact that most patients in both anticoagulant cohorts in our study were no longer receiving treatment after 6 months may explain the loss of statistical significance for reduction in recurrent VTE with rivaroxaban at 12 months (HR: 0.80; 95% CI: 0.63-1.02). Furthermore, it raises an important question of whether a longer duration of anticoagulation (>6 months) after acute CAT would offer a net benefit in patients deemed to be at a lower risk of bleeding.

STUDY LIMITATIONS. Because this study used a retrospective cohort design and was based on routinely collected EHR, various biases may have affected our results.[26] Misclassification bias is always a concern in retrospective analyses.[26] We attempted to attenuate this risk by using validated coding algorithms (whenever possible) to identify active cancer diagnoses, covariates, and outcomes.[21,22,27,28] We

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limited the identification of recurrent VTE to the presence of ≥1 of a validated set of VTE-associated billing codes restricted to the primary coding position during an inpatient hospital encounter. This approach to detecting VTE has previously been shown to have a positive predictive value of ≈95%.[21] Additionally, to identify bleeding-related hospitalizations, we used the validated coding algorithm published by Cunningham et al.[22] Both the VTE and bleeding outcome detection algorithms used in our study have been used previously in real-world studies evaluating the comparative effectiveness of anticoagulants to prevent CAT.[14,18,19] To address the risk of confounding bias, our analysis used propensity score OLW to balance many important baseline covariates between rivaroxaban- and LMWH-treated patients.[23] The OLW method used has the advantage of retaining all patients in the analysis data set (unlike propensity score matching, which would have resulted in the inclusion of only LMWH users who closely resembled rivaroxaban users) and gives less weight to patients with propensity scores close to 0.0 or 1.0 (a concern with inverse probability weighting).[23] Despite our use of propensity score OLW, residual confounding bias from unmeasured covariates (eg, socioeconomic status) in nonrandomized studies can never fully be ruled out.[26] Because we used an EHR data set that did not have corresponding prescription fill records,[20] we were unable to formally assess persistence, adherence, or patient out-of-pocket treatment costs for DOACs vs LMWHs. Of note, a study comparing DOACs vs LMWHs in Optum's Clinformatics Data Mart claims database (not the EHR data set) found that among the 2 propensity score–matched anticoagulant cohorts (1,128 patients per group) being treated for CAT, patient persistence appeared higher with DOACs vs LMWH (median = 116 days [Q1-Q3: 57-231] vs 34 days [Q1-Q3: 30-92]), no significant difference in adherence defined as a proportion of days covered ≥80% was observed between groups (95.6% vs 94.6% adherence with DOACs vs LMWH; $P = 0.33$), and mean anticoagulant prescription copayments for 30 days of treatment were numerically higher for LMWH vs DOAC patients ($154 ± $307 vs $41 ± $33).[29] The choice of using the anticoagulant used on day 7 as the "intention-to-treat" anticoagulant therapy was made to prevent early therapy switching from impacting our results. Future analyses using other data sets with prescription claims data should be performed. Lastly, because we evaluated a U.S. CAT population without cancer types associated with higher bleeding when on DOACs receiving only rivaroxaban (and almost exclusively enoxaparin), our results and conclusions should be viewed as being most generalizable to a U.S. population with CAT in which guidelines support rivaroxaban use as an alternative to enoxaparin.[20,26] It should be noted that only 286 rivaroxaban patients were excluded from our study because they had "any" cancer type associated with a high risk of bleeding on a DOAC (including esophageal [n = 15], gastric [n = 15], unresected colorectal [n = 103], bladder [n = 47], and noncerebral central nervous system [n = 51] cancers and leukemia [n = 59]). Although it is of clinical interest to compare rivaroxaban vs LMWH in CAT patients with specific high-risk bleeding cancer types, the available sample sizes are not yet large enough to perform robust analyses. Additional studies should be performed to evaluate the comparative effectiveness and safety of rivaroxaban vs LMWHs in cancer types associated with a high risk of bleeding on a DOAC when sample sizes become more robust. Finally, the results of subgroup analyses should be interpreted with caution and be considered hypothesis generating only. Although we set a stricter threshold to define statistical significance ($P < 0.003$) to reduce the likelihood of falsely concluding statistical significance, it can also result in less power to detect true differences.[30]

CONCLUSIONS

Guidelines[4,5] endorse DOACs as alternatives (and in some cases preferred) to LMWHs for the treatment of VTE in patients with cancer types not associated with a high risk of bleeding on a DOAC. Among adult patients with active cancer (excluding esophageal, gastric, unresected colorectal, bladder, and most central nervous system cancers and leukemia) and experiencing an acute VTE, rivaroxaban use was associated with significant reductions in recurrent thrombosis risk at 3 and 6 months. No difference in any clinically relevant bleeding-related hospitalization outcome was observed; however, rivaroxaban use was associated with a reduced risk for critical organ bleeding compared with LMWHs. No significant difference in all-cause mortality was noted between the 2 anticoagulants. In conclusion, our study supports the use of rivaroxaban as an alternative to LMWHs (specifically enoxaparin) in patients with CAT and cancer types not associated with a high risk of bleeding when on a DOAC. Future studies may wish to evaluate the comparative effectiveness and safety of individual DOACs in the treatment of CAT.

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ADDRESS FOR CORRESPONDENCE: Dr Craig I. Coleman, School of Pharmacy, University of Connecticut, Hartford Hospital, Evidence-Based Practice Center, 80 Seymour Street, Hartford, Connecticut 06102, USA. E-mail: craig.coleman@hhchealth.org.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among active cancer patients (excluding esophageal, gastric, unresected colorectal, bladder, and most central nervous system cancers and leukemia) experiencing VTE, rivaroxaban was associated with a reduced risk of recurrent VTE versus LMWHs at 3 and 6 months. These data support current CAT guideline recommendations.

TRANSLATIONAL OUTLOOK: Future studies evaluating the comparative effectiveness of rivaroxaban and LMWH in specific cancer types are needed. Comparative studies of the effectiveness and safety of different oral factor Xa inhibitors are also warranted to optimize clinician CAT anticoagulation management decision making.

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KEY WORDS **cancer-associated thrombosis, low molecular-weight heparin, real-world evidence, rivaroxaban, venous thromboembolism**

APPENDIX **For supplemental tables, please see the online version of this paper.**

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EDITED BY
Daniele Pastori,
Sapienza University of Rome,
Italy

REVIEWED BY
Wei Anhua,
Huazhong University of Science and Technology,
China
Li-Nien Chien,
Taipei Medical University,
Taiwan

*CORRESPONDENCE
Eue-Keun Choi
choiek17@snu.ac.kr

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Renal outcomes of rivaroxaban compared with warfarin in Asian patients with nonvalvular atrial fibrillation: A nationwide population-based cohort study

So-Ryoung Lee[1], Eue-Keun Choi[1,2]*, Sang-Hyun Park[3], Kyung-Do Han[4], Seil Oh[1,2], Khaled Abdelgawwad[5] and Gregory Y. H. Lip[2,6,7]

[1]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [2]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea, [3]Department of Medical Statistics, College of Medicine, Catholic University of Korea, Seoul, Republic of Korea, [4]Statistics and Actuarial Science, Soongsil University, Seoul, Republic of Korea, [5]Bayer AG, Berlin, Germany, [6]Liverpool Centre for Cardiovascular Science, Liverpool Chest and Heart Hospital, University of Liverpool, Liverpool, United Kingdom, [7]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Background: Further studies are needed to expand the evidence for the association of rivaroxaban with a lower risk of adverse renal outcomes in patients with atrial fibrillation (AF) as compared with warfarin, especially in Asians.

Objectives: To determine whether there are differences in adverse renal outcomes between rivaroxaban and warfarin-treated AF patients.

Methods: Using the Korean nationwide claims database partly linked to laboratory results, patients with AF who initiated warfarin or rivaroxaban from 1 January 2014 to 31 December 2017 were identified. Inverse probability of treatment weighting (IPTW) was used to balance the baseline characteristics of the two groups. The primary outcome (kidney failure) was defined as the need for maintenance dialysis or having kidney transplantation. For the exploratory analysis in a subset of patients with baseline and follow-up laboratory results, the composite of renal outcomes, including estimated glomerular filtration rate (eGFR) lower than 15 ml/min/1.73 m^2 at follow-up measurement, starting dialysis, or having kidney transplantation, ≥30% decline in eGFR, doubling of serum creatinine level, and acute kidney injury (AKI) were evaluated. The two groups were compared using Cox proportional hazards regression in the weighted population.

Results: We identified 30,933 warfarin users and 17,013 rivaroxaban users (51% of low dose rivaroxaban). After IPTW, the mean age was 70 years, and the mean CHA_2DS_2-VASc score was 3.9 in both groups. During a median follow-up of 0.93 (interquartile ranges 0.23–2.10) years, weighted incidence rates of kidney failure for warfarin and rivaroxaban were 0.83 and 0.32 per 100 person-years, respectively. Compared with the warfarin group, the rivaroxaban group was associated with a lower risk of kidney failure (hazard ratio [HR] 0.389, 95% confidence interval [CI] 0.300–0.499, $p<0.001$). In patients with preexisting chronic kidney disease or eGFR≤60 ml/min/1.73 m^2, rivaroxaban was more beneficial than warfarin in reducing the risk of kidney failure. For the composite of five renal outcomes in the exploratory analysis, the rivaroxaban group showed a lower risk than warfarin (HR 0.798, 95% CI 0.713–0.892, $p<0.001$).

Conclusion: Rivaroxaban was associated with lower risks of renal adverse outcomes than warfarin in Korean patients with AF.

KEYWORDS

warfarin, kidney failure, atrial fibrillation, anticoagulation, rivaroxaban

Introduction

Atrial fibrillation (AF) has been related to an increased risk of chronic kidney disease (CKD) later in life (1). For several decades, warfarin was the only oral anticoagulation (OAC) therapy in preventing thromboembolic events in AF patients. Warfarin-related nephropathy, including the rapid development of renal function decline in CKD patients and the prevalence of acute kidney injury (AKI), has been described among warfarin-treated patients (2, 3).

Since the introduction of non-vitamin K antagonist oral anticoagulants (NOACs), there has been some evidence that NOACs might be associated with improved renal function preservation compared with warfarin (4, 5). According to a post-hoc analysis of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, dabigatran was linked to a reduced risk of creatinine clearance reduction compared with warfarin (4). Several observational studies found that NOACs had similar results to warfarin, but there was variance in the outcomes across NOACs (5–9). Firstly, rivaroxaban and dabigatran consistently outperformed warfarin regarding kidney preservation (5–9). On the other hand, apixaban did not produce consistent findings with statistical significance (5), and there was no information on edoxaban. Secondly, the relationship between NOAC and the likelihood of unfavorable renal outcomes varied depending on the patients' baseline kidney function (10). Finally, between non-Asians and Asians, the protective effect of NOACs versus warfarin on renal outcomes was slightly different (9).

Renal function deterioration is widespread in AF patients treated with OAC (5). As decreased renal function is associated with an increased risk of stroke and bleeding, it is critical to maintain renal function in patients treated with OAC (11, 12). Further studies are needed to examine whether NOACs bring consistent results for preventing progressive renal function decline, especially in Asians who had poor treatment quality of warfarin therapy (13).

This study aims to determine whether there are differences in adverse renal outcomes between rivaroxaban and warfarin-treated AF patients utilizing a nationwide population-based study in South Korea.

Materials and methods

Data source

This retrospective observational nationwide population-based cohort study was conducted using administrative claims data from the Korean National Health Insurance Service (NHIS) and the linked health check-up database of the National Health Insurance Corporation (NHIC) (14, 15). The Korean NHIS provides comprehensive medical care coverage for the entire Korean population (approximately 50 million people). The analysis was based on a randomly selected 50% sample cohort from the Korean NHIS. Supplementary methods provide additional information about the data source. All data have been provided publicly available through the National Health Insurance Data Sharing Service (accessed at: http://nhiss.nhis.or.kr/bd/ab/bada000eng.do). After permission to use the data was obtained, the analysis was performed at the Korean NHIS Big Data Center, Seoul, Republic of Korea.

Study population and study design

The study period was from 1 January 2013 to 31 December 2018. The study's enrollment period ran from 1 January 2014 to 31 December 2017, to allow for at least a 12-month follow-up period. Study enrollment flow is presented in Figure 1. Firstly, we identified adult AF patients prescribed OAC during the enrollment period. AF was defined as at least one hospitalization or outpatient visit with relevant diagnostic codes (I48.0–I48.4, I48.9). To compare the renal outcome between two treatment groups (rivaroxaban versus warfarin), we included patients who were OAC new users (who had no record of OAC use in the prior 12 months) and were newly initiated on rivaroxaban or warfarin. Patients with valvular AF, alternative indications of OAC including pulmonary embolism, deep vein thrombosis, recent joint surgery, and end-stage renal disease (ESRD) were excluded.

The primary analysis included all eligible patients. Additionally, we designed the exploratory analysis to assess renal outcomes estimated by laboratory data, including a subset of patients who received at least two health examinations during the study period. These patients had baseline and follow-up eGFR measurements. As a baseline eGFR, we collected the results of the health examination performed within 2-year from the index date. Among patients with a baseline eGFR value, we included patients with at least one follow-up health examination data during follow-up.

Covariates

Age, sex, co-morbidities including hypertension, diabetes, dyslipidemia, heart failure, prior stroke, prior myocardial infarction, peripheral artery disease, chronic kidney disease, chronic obstructive pulmonary disease (COPD), and cancer, CHA_2DS_2-VASc score, Charlson Comorbidity Index (CCI), and concomitant use of antiplatelet agents were evaluated as covariates. The operational definitions of co-morbidities were based on diagnostic codes, drug dispensing records, and inpatient/outpatient hospital visits within 3 years prior to the index date. Complete definitions of each covariate are presented in Supplementary Tables S1 and S2 (5, 15, 16).

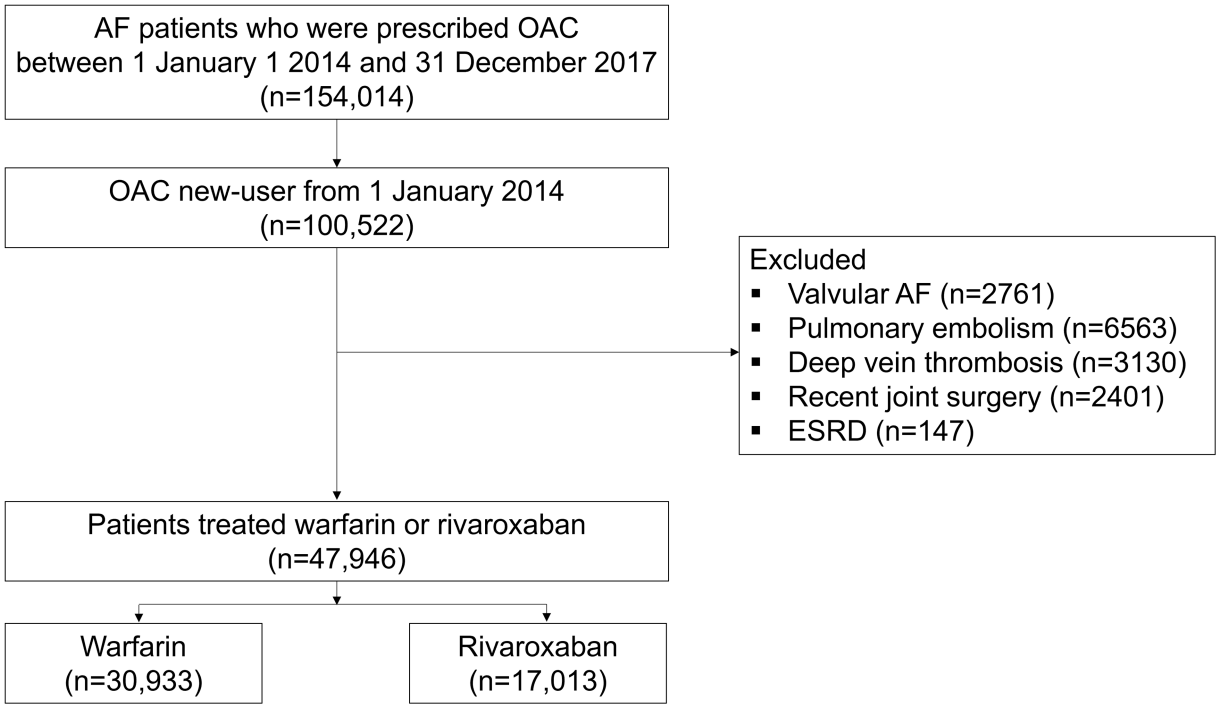


FIGURE 1
Study enrollment flow. AF, atrial fibrillation; ESRD, end-stage renal disease; OAC, oral anticoagulant.

Among the total study population, 67.4% of patients had the data from the baseline national health examination, and 23.4% had the data from both baseline and at least one follow-up national health examination. From the health examination data, body weight, body mass index (kg/m^2), serum creatinine (mg/dL) and eGFR (mL/min/1.73 m^2) were collected. eGFR was calculated by a creatinine-based equation used from Modification of Diet in Renal Disease. In addition, smoking status (never smoker, ex-smoker, or current smoker), alcohol consumption (heavy drinker, ≥30 g/day), and physical activity were also evaluated from the self-reported questionnaires of health examination. Regular exercise was defined as performing moderate-intensity exercise ≥5 times per week or vigorous-intensity exercise ≥3 times per week (17).

Study outcomes and follow-up

The index date was defined as the time when rivaroxaban or warfarin was newly initiated. To evaluate the comparative risk of renal outcome between the two groups, the primary outcome was incident kidney failure, defined as the need for maintenance dialysis or having kidney transplantation (Supplementary Table S3) (5, 18). Secondary outcomes were incident ischemic stroke, intracranial hemorrhage, major gastrointestinal bleeding, major bleeding, and all-cause death (Supplementary Table S3) (16). To assess the outcomes, patients were followed up until 31 December 2018. Patients were censored at the occurrence of each outcome, the end of the study period (31 December 2018), or death, whichever came first. In addition, the main analysis followed the on-treatment approach; therefore, patients were also censored at the discontinuation of index treatment for more than 30 days. The date of discontinuation was defined as the end of exposure, and patients were censored.

For the exploratory analysis, five renal outcomes were assessed; [1] eGFR lower than 15 ml/min/1.73 m^2 at follow-up measurement, [2] starting dialysis or having kidney transplantation, [3] ≥30% decline in eGFR, [4] doubling of serum creatinine level, and [5] AKI (Supplementary Table S3) (5). The 30% decline in eGFR and doubling of serum creatinine defined as changes from baseline (using measurement closest to index date) at any time point during follow-up (5). Because [1, 3, 4] relied entirely on laboratory data, when examining these three outcomes, patients were censored at their last laboratory measurement. AKI was defined as an emergency department visit or hospitalization with a diagnostic code of AKI (N17×) (5, 9). The composite of five renal outcomes was also evaluated.

Statistical analysis

Patients were described at treatment initiation in terms of demographic and clinical variables. Continuous variables are presented as means and standard deviations or medians and interquartile ranges (IQR). The numbers and proportions of patients in each category are presented for categorical variables. Person-years of follow-up were calculated from the index date to the outcome event of interest, discontinuation of the index treatment, death, or the end of the study period, whichever comes first. Incidence rates were calculated as the number of events over the observed person-time and presented as per 100 person-years.

We used the propensity score (PS) methods to compare the rivaroxaban and warfarin groups (19). We utilized stabilized inverse

probability of treatment weighting (IPTW) approach based on the PS to adjust for potential confounding resulting from imbalances in baseline patient characteristics. The objective of IPTW is to create a weighted sample for which the distribution of either the confounding variables or the prognostically important covariates is approximately the same between comparison groups (20). PS is the patient's probability of receiving a treatment under investigation (rivaroxaban) given a set of known patients' baseline characteristics. PS was calculated using multiple logistic regression on all the available covariates, including demographics, co-morbidities, CHA_2DS_2-VASc score, Charlson Comorbidity Index, and concomitant medication. For the exploratory analysis, health examination variables such as body weight, body mass index (BMI), eGFR, smoking, alcohol consumption, and physical activity were additionally included for PS calculation. Detailed methods of IPTW are described in Supplementary methods. After IPTW, we assessed the balance of the two treatment groups by using absolute standardized differences (ASDs). The PSs and stabilized weights distributions were inspected for initial and synthetic samples. An ASD of 0.1 or less was considered as a negligible difference between the two groups. The weighted event numbers and incidence rates were calculated. We compared treatments using weighted Cox proportional hazards regression with IPTW. Results of Cox analyses are reported as hazard ratios (HRs) with 95% confidence intervals (CIs). Each Cox regression was checked to see if the model assumptions were fulfilled. For the exploratory analysis set, weighted cumulative incidences of the composite of five renal outcomes were estimated by the Kaplan–Meier method and log-rank test.

All statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC, United States).

Subgroup analyses

In the main analysis set, for the primary outcome, subgroup analyses were performed for age strata (< 65, 65–74, and ≥ 75 years), sex, hypertension, diabetes, heart failure, CKD (defined by diagnostic codes), CHA_2DS_2-VASc score (< 3, and ≥ 3) and Charlson Comorbidity Index (< 3, and ≥ 3). Among patients with baseline eGFR measurements, subgroup analyses were performed for eGFR ranges (> 60 and ≤ 60 ml/min/1.73 m^2). Subgroup analyses were performed using a multivariable Cox proportional hazards regression model. The variables used in the multivariable Cox analysis were identical to those used in the PS calculation for the main analysis set. Tests for interaction were conducted to evaluate statistically significant ($p < 0.1$) subgroup differences in treatment.

Sensitivity analyses

To provide complementary analyses, we performed sensitivity analyses for the primary outcome as follows: [1] IPTW following the intention-to-treat (ITT) approach, which was not censoring patients at discontinuation or switching the index treatment), [2] multivariable Cox proportional hazards regression models in the study population before IPTW following the on-treatment approach, [3] multivariable Cox analysis following the ITT approach, [4] 5% trimmed IPTW following the on-treatment approach, [5] 5% trimmed IPTW following the ITT approach, [6] a sensitivity analysis among patients with a 6-month or longer follow-up period to evaluate whether the main results are consistent in those who had neither drug discontinuation nor any renal outcome during the first 6 months, [7] a sensitivity analysis restricting the follow-up within 12 months, and [8] an analysis in the subset of patients with baseline eGFR measurements. The sensitivity analyses of [2, 3, 6, 7] were performed using a multivariable Cox proportional hazards regression model, and the variables used in the multivariable Cox analysis were identical to those used in the PS calculation for the main analysis set. For [8], baseline eGFR values were additionally adjusted. In addition, although we included the CHA_2DS_2-VASc score and CCI in the final multivariable Cox analysis, there is a possibility of model overfitting. Therefore, we conducted a sensitivity analysis excluding the CHA_2DS_2-VASc score, CCI, or both of these in the final model. Also, we performed a competing risk analysis with the Fine-Gray methods as a sensitivity analysis (21).

Results

Baseline characteristics

This study comprised a total of 47,946 individuals (mean age 70.1 ± 11.7 years, mean CHA_2DS_2-VASc score 3.9 ± 1.9), with 30,933 patients taking warfarin and 17,013 taking rivaroxaban. Supplementary Table S2 shows the baseline characteristics of the total, warfarin, and rivaroxaban groups. Before PS matching, the rivaroxaban group was older, more likely to be women, and had a higher mean CHA_2DS_2-VASc score than the warfarin group. Co-morbidities such as hypertension, diabetes, dyslipidemia, heart failure, peripheral artery disease, and cancer were more common in the rivaroxaban group. In contrast, prior stroke, prior myocardial infarction, chronic kidney disease, and chronic obstructive pulmonary disease were more prevalent in the warfarin group. Antiplatelet co-use was more common in the warfarin group than in the rivaroxaban group. In the rivaroxaban group, standard dose rivaroxaban (20 mg once daily) was prescribed to 49% of patients, whereas low-dose rivaroxaban (15 mg once daily) was prescribed to 51%.

Primary and secondary outcomes

In the main analysis set, a median follow-up duration was 0.93 (IQR 0.23–2.10) years. Rivaroxaban group showed longer median follow-up duration than warfarin group (1.27 [IQR 0.27–2.35] vs. 0.75 [0.21–1.85], $p < 0.001$). Supplementary Table S4 shows crude event numbers, incidence rates, and unadjusted HRs for primary and secondary outcomes. In Table 1, all baseline variables were well-balanced in the two groups after PS weighting, and all ASDs for the two groups were less than 0.1 (Table 1). PS distribution after weighting is presented in Supplementary Figure S1.

Figure 2 shows weighted incidence rates and weighted HRs for primary and secondary outcomes. Compared with the warfarin group, the rivaroxaban group was associated with a lower risk of kidney failure (HR 0.398, 95% CI 0.300–0.499). For the secondary outcomes, the rivaroxaban group was associated with lower risks of ischemic stroke (HR 0.887, 95% CI 0.797–0.986), intracranial hemorrhage (HR 0.699, 95% CI 0.550–0.883), and all-cause death (HR 0.807, 95% CI

TABLE 1 Baseline characteristics of warfarin and rivaroxaban groups before and after inverse probability of treatment weighting (IPTW).

	Before IPTW			After IPTW		
	Warfarin	Rivaroxaban	ASD	Warfarin	Rivaroxaban	ASD
n	30,933	17,013		30,946	17,006	
Age, years	69.0 ± 12.3	72.1 ± 10.1	0.277	70.2 ± 11.9	70.4 ± 11.2	0.015
< 65 years	9,944 (32.2)	3,468 (20.4)		87,223 (28.2)	4,523 (26.6)	
65 to < 75 years	9,412 (30.4)	5,974 (35.1)		9,700 (31.3)	5,701 (33.5)	
≥ 75 years	11,577 (37.4)	7,571 (44.5)		12,524 (40.5)	6,782 (39.9)	
Sex, male	18,260 (59.0)	9,605 (56.5)	0.052	17,985 (58.1)	9,909 (58.4)	0.003
CHA_2DS_2-VASc	3.8 ± 2.0	4.1 ± 1.7	0.125	3.9 ± 1.9	3.9 ± 1.9	0.010
CHA_2DS_2-VASc ≥ 3	22,494 (72.7)	13,779 (81.0)	0.197	23,446 (75.8)	12,949 (76.2)	0.013
Charlson comorbidity index	4.0 ± 2.5	4.0 ± 2.4	0.006	4.0 ± 2.5	4.0 ± 2.5	0.015
Charlson comorbidity index ≥ 3	21,444 (69.3)	11,978 (70.4)	0.023	21,668 (70.0)	11,900 (70.0)	0.009
Hypertension	25,023 (80.9)	14,582 (85.7)	0.129	25,572 (82.6)	14,050 (82.6)	<0.001
Diabetes	8,067 (26.1)	4,617 (27.1)	0.023	8,213 (26.5)	4,558 (26.8)	0.005
Dyslipidemia	16,290 (52.7)	9,357 (55.0)	0.046	16,563 (53.5)	9,150 (53.8)	0.005
Heart failure	12,550 (40.6)	7,592 (44.6)	0.082	12,988 (42.0)	7,104 (41.8)	0.003
Prior stroke	9,511 (30.8)	4,315 (25.4)	0.120	8,964 (29.0)	5,017 (29.5)	0.011
Prior myocardial infarction	2026 (6.6)	1,004 (5.9)	0.026	1955 (6.3)	1,079 (6.3)	0.001
Peripheral artery disease	6,948 (22.5)	4,355 (25.6)	0.073	7,301 (23.6)	4,025 (23.7)	0.001
Chronic kidney disease	1899 (6.1)	724 (4.3)	0.084	1,699 (5.5)	976 (5.7)	0.010
COPD	2,975 (9.6)	1,372 (8.1)	0.054	2,814 (9.1)	1,578 (9.3)	0.006
Cancer	2003 (6.5)	1,368 (8.0)	0.060	2,177 (7.0)	1,219 (7.2)	0.005
Antiplatelet use						
None	18,790 (60.7)	12,679 (74.5)	0.235	20,305 (65.6)	11,114 (65.4)	<0.001
Aspirin only	6,562 (21.2)	2,137 (12.6)		5,611 (18.1)	3,090 (18.2)	
$P2Y_{12}$ only	1889 (6.1)	902 (5.3)		1800 (5.8)	1,002 (5.9)	
Both	3,701 (12.0)	1,295 (7.6)		3,230 (10.4)	1800 (10.6)	
Rivaroxaban dose						
20 mg once daily	N/A	8,354 (49.1)		N/A	8,022 (47.2)	
15 mg once daily	N/A	8,659 (50.9)		N/A	8,984 (52.8)	

Continuous variables are shown as mean and standard deviation. Categorical variables are presented as numbers (percentages).
ASD, absolute standardized difference; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65–74, female; COPD, chronic obstructive pulmonary disease; IPTW, inverse probability of treatment weighting; N/A, not available.

0.751–0.867) than the warfarin group. The two groups had comparable outcomes for major gastrointestinal bleeding (HR 1.092, 95% CI 0.930–1.279) and major bleeding (HR 0.966, 95% CI 0.858–1.086).

Sensitivity analyses

For the primary outcome we performed various sensitivity analyses that demonstrated results consistent with the main analysis. Rivaroxaban was associated with significant reductions in the risk for kidney failure in all analyses (Supplementary Results, Supplementary Figure S2, and Supplementary Table S5). The results were consistent with the primary findings when we conducted a competing risk analysis that was adjusted for the competing risk of death rather than a censoring event (HR 0.447, 95% 0.344–0.582, $p < 0.001$).

Subgroup analyses

The benefit of rivaroxaban compared with warfarin on the risk of kidney failure was consistently observed across almost all of the examined subgroups (Figure 3). However, wide CI was observed in patients without hypertension due to the small number of patients and low event rates. There were no significant interactions between treatment and all subgroups, except in the subgroup stratified by CKD and eGFR. Rivaroxaban was associated with a greater reduction in the risk of kidney failure in patients with underlying CKD, as defined by diagnostic codes, compared with those without (value of p for interaction < 0.001). There was also a strong trend towards a reduction in the risk of kidney failure in patients with CKD defined as eGFR less than 60 ml/min/1.73 m^2, compared with those with an eGFR greater than 60 ml/min/1.73 m^2.

Outcomes	Number		Event		Weighted IR		IPTW HR (95% CI)	*p*-value
	W	R	W	R	W	R		
Kidney failure	30,946	17,006	316	74	0.83	0.32	0.389 (0.300–0.499)	<0.001
Ischemic stroke	30,946	17,006	1013	528	2.70	2.30	0.887 (0.797–0.986)	0.026
ICH	30,946	17,006	231	100	0.61	0.43	0.699 (0.550–0.883)	0.003
Major GIB	30,946	17,006	401	257	1.05	1.11	1.092 (0.930–1.279)	0.279
Major bleeding	30,946	17,006	772	450	2.04	1.96	0.966 (0.858–1.086)	0.566
All-cause death	30,946	17,006	2327	1114	6.08	4.78	0.807 (0.751–0.867)	<0.001

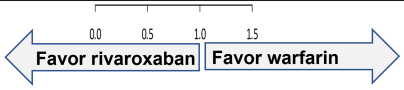


FIGURE 2
Weighted event numbers, incidence rates, and hazard ratios for the primary and secondary outcomes between warfarin and rivaroxaban groups. Incidence rate, per 100 person-years. CI, confidence interval; GIB, gastrointestinal bleeding; ICH, intracranial hemorrhage; IPTW, inverse probability of treatment weighting; IR, incidence rate; R, rivaroxaban; W, warfarin.

Exploratory analysis in patients with baseline and follow-up eGFR measurements

Among the total study population, 11,210 (23.4%) patients were included in the exploratory analysis. Baseline characteristics of the total population, warfarin, and rivaroxaban group are presented in Supplementary Table S6. After IPTW, the two groups were well-balanced in all variables (all ASDs < 0.1). Mean baseline eGFR was 81.6 ml/min/1.73 m^2 in the two groups (ASD < 0.001). The duration from baseline eGFR to index date and baseline eGFR to follow-up eGFR of the two groups did not show statistically significant differences.

During a median follow-up of 2.28 (IQR 1.42–3.19) years, five renal outcomes and the composite of renal outcomes were evaluated in the two groups. Weighted event numbers, incidence rates, and HRs are shown in Figure 4A. Compared with warfarin, the rivaroxaban group was associated with significant 72, 20 and 39% reductions in the risks of developing eGFR lower than 15 ml/min/1.73 m^2 at follow-up measurement, 30% decline in eGFR, and incidence of AKI, respectively. Although there was no statistically significant difference in the risk of serum creatinine doubling, the rivaroxaban group had a lower chance than the warfarin group. During the follow-up period, none of the patients in this exploratory analysis started dialysis or had kidney transplantation. For the composite of five renal outcomes, the rivaroxaban group showed a lower risk than warfarin (HR 0.798, 95% CI 0.713–0.892, $p < 0.001$; Figures 4A,B).

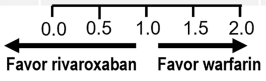
Discussion

In this large-scale observational cohort, we observed very consistent findings that rivaroxaban was associated with a lower risk of renal adverse outcomes than warfarin in Korean patients with AF. Also, consistently with the general consensus, we confirmed that rivaroxaban was associated with a lower risk of ischemic stroke, intracranial hemorrhage, and all-cause death than warfarin. The effect of rivaroxaban on renal preservation was more accentuated in patients with underlying renal function impairment. The strength of this study included a large number of patients with AF treated in diverse clinical practice settings who had linked insurance claims and laboratory results. Also, this analysis allowed us to examine multiple renal outcomes to evaluate the consistency of results across a variety of renal outcomes.

Patients with AF should be aware of the potential deterioration in renal function. Renal impairment puts individuals with AF at greater risk of thromboembolism and bleeding (22). Also, the dose of NOACs may need to be adjusted with renal function decline, or the prescription of NOACs should be discontinued if significant renal impairment develops (23). Since anticoagulation therapy should be continued throughout a patients' entire life for those with AF, preserving renal function has become an important issue for optimal care in patients with AF. From the post-hoc analysis of the RE-LY trial, dabigatran, a direct thrombin inhibitor, firstly showed a protective effect from the progressive renal function decline compared with warfarin (4). Interestingly, warfarin with an increased international normalized ratio (INR) out of the therapeutic range showed a significantly rapid progression of renal function decline than dabigatran. In contrast, warfarin with mainly below therapeutic INR rage showed similar renal function decline to dabigatran (4). Considering poor INR control of Asians, mainly with lower INR than therapeutic ranges (13, 24), we needed additional Asian data to provide a comprehensive comparison of the risk of renal outcome caused by NOAC versus warfarin. Two previous reports from the Taiwanese population were based on the nationwide administrative claims database (6, 9). According to these studies, dabigatran, rivaroxaban, and apixaban were associated with a lower risk of AKI (6, 9). Although these studies included many patients, approximately 6,000–28,000 patients in each NOAC group, the study outcome was only defined by diagnostic codes of AKI without laboratory measurements. The present study, including many Asian patients, showed consistent findings with previous observational studies of non-Asians (5, 7, 8) and Asians (6, 9). Furthermore, in a subset of patients with laboratory results, we first confirmed that rivaroxaban benefited renal preservation in various definitions of renal outcomes in Asian patients with AF.

In previous studies, including three NOACs (rivaroxaban, dabigatran, and apixaban), the results were slightly different among

Subgroup	No. of events/total no. (IR per 100 PY)		Hazard ratio (95% CI)	P-for-interaction
	Warfarin	Rivaroxaban		
Age				0.312
<65 yr	71/9944 (0.51)	6/3468 (0.12)	0.239 (0.103-0.555)	
65-74 yr	104/9412 (0.82)	27/5974 (0.28)	0.509 (0.329-0.787)	
≥75 yr	167/11,577 (1.41)	35/7571 (0.38)	0.381 (0.262-0.553)	
Sex				0.462
Men	224/18,260 (0.97)	42/9605 (0.31)	0.367 (0.262-0.514)	
Women	118/12,673 (0.77)	26/7408 (0.25)	0.496 (0.320-0.769)	
Hypertension				0.213
No	20/5910 (0.28)	6/2431 (0.21)	0.703 (0.269-1.835)	
Yes	322/25,023 (1.03)	62/14,582 (0.30)	0.391 (0.296-0.516)	
Diabetes				0.267
No	160/22,866 (0.55)	39/12,396 (0.22)	0.483 (0.337-0.693)	
Yes	182/8067 (1.89)	29/4617 (0.45)	0.335 (0.225-0.500)	
Heart failure				0.762
No	147/18,383 (0.65)	32/9421 (0.24)	0.442 (0.299-0.654)	
Yes	195/12,550 (1.24)	36/7592 (0.35)	0.387 (0.269-0.557)	
CKD				<0.001
No	166/29,034 (0.46)	57/16,289 (0.25)	0.580 (0.425-0.791)	
Yes	176/1899 (8.41)	11/724 (1.32)	0.169 (0.091-0.311)	
eGFR*				0.065
>60 ml/min/1.73m²	69/16,989 (0.31)	29/9723 (0.20)	0.711 (0.454-1.113)	
≤60 ml/min/1.73m²	119/3570 (2.61)	18/1942 (0.66)	0.372 (0.224-0.618)	
CHA_2DS_2-VASc				0.980
0-2	40/8439 (0.35)	6/3234 (0.13)	0.453 (0.186-1.103)	
≥3	302/22,494 (1.12)	62/13,779 (0.32)	0.404 (0.306-0.534)	
CCI				0.413
0-2	31/9489 (0.24)	10/5035 (0.13)	0.531 (0.252-1.117)	
≥3	311/21,444 (0.12)	58/11,978 (0.36)	0.394 (0.296-0.525)	
Antiplatelet use				
No	131/18,790 (0.58)	39/12,679 (0.22)	0.410 (0.284-0.590)	0.989
Yes	211/12,143 (1.33)	29/4334 (0.50)	0.408 (0.276-0.604)	



*among in patients with baseline eGFR value

FIGURE 3
Subgroup analyses. CCI, Charlson comorbidity index; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IR, incidence rate.

studies (5, 9, 10). Compared with warfarin, rivaroxaban was associated with lower risks of a 30% decline in eGFR, doubling of serum creatinine, and AKI, but dabigatran was only associated with a 30% decline in eGFR and AKI, and apixaban did not show significant risk reduction for the any of the renal outcomes (5). With AKI defined by diagnostic codes, rivaroxaban and dabigatran were associated with a lower risk of AKI than warfarin, but apixaban showed comparable results with warfarin (10). In Asian patients with AF, all three NOACs showed a similar risk reduction of AKI defined by diagnostic codes to warfarin (9). NOACs' renal preservation compared with warfarin is often attributed to warfarin's hazardous effects, such as glomerular microhemorrhage, vascular inflammation, or calcification (4). Further studies are required to discover the difference among NOACs on the renal protection effect, especially edoxaban, and consider the dose–response relationship.

This study highlighted that rivaroxaban reduced the risk of renal failure in patients with CKD compared with those without. In the

A

	Number		Event		Weighted IR		IPTW HR (95% CI)	*p*-value
	W	R	W	R	W	R		
Composite of (1) to (5)	6430	4780	14	4	5.73	5.13	0.798 (0.713-0.892)	<0.001
(1) eGFR <15 mL/min/1.73m²	6430	4780	10	0	0.09	0.04	0.278 (0.060–0.882)	0.052
(2) Dialysis or KTPL	6430	4780	779	467	0.06	0.00	N/A	0.992
(3) eGFR 30%↓	6430	4780	16	8	5.30	4.81	0.811 (0.722–0.909)	<0.001
(4) Serum Cr ≥ 2-fold↑	6430	4780	80	37	0.10	0.08	0.665 (0.274–1.493)	0.337
(5) AKI (N17x)	6430	4780	834	495	0.52	0.36	0.610 (0.408–0.895)	0.013

B

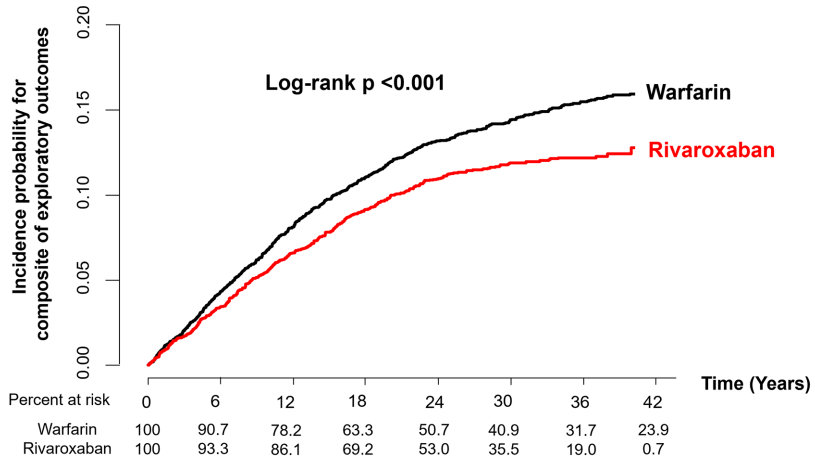


FIGURE 4
Exploratory analysis in patients with baseline and follow-up eGFR measurements. **(A)**. Weighted event numbers, incidence rates, and hazard ratios for five renal outcomes and composite of renal outcomes between rivaroxaban and warfarin groups **(B)**. Weighted Kaplan–Meier curves for the composite of renal outcomes between rivaroxaban and warfarin groups. Incidence rate, per 100 person-years. AKI, acute kidney injury; CI, confidence interval; Cr, creatinine; eGFR, estimated glomerular filtration rate; HR, hazard ratio; KTPL, kidney transplantation; IPTW, inverse probability of treatment weighting; IR, incidence rate; R, rivaroxaban; W, warfarin.

subgroup analyses, patients with underlying CKD and those with baseline eGFR $\leq$ 60 ml/min/1.73 m^2 showed greater relative risk reduction with rivaroxaban than warfarin. Patients who are more vulnerable to the risk of kidney failure might get more benefit from rivaroxaban's kidney protection effect. Kidney failure due to acute tubular injury with microhemorrhage might be more critical in patients with a smaller reservoir because of underlying renal impairment. This finding was consistently observed in previous studies (6, 7, 9). Careful selection of the anticoagulation agent and close follow-up of kidney function should be emphasized in this population. From Korean AF patients with mildly impaired renal function (creatinine clearance 50–60 ml/min), we previously reported that rivaroxaban 15 mg once daily was associated with a lower risk of ischemic stroke, intracranial hemorrhage, and hospitalization for major bleeding than warfarin. Additionally, rivaroxaban 15 mg once daily showed a comparable risk of ischemic stroke, intracranial hemorrhage, and hospitalization for major bleeding with rivaroxaban 20 mg once daily (25).

Recently, consistent results have been updated in various subsets of patients with elderly (26) and those with diabetes (7), and even a meta-analysis has been reported (27); thus, it is quite evident that NOAC is superior to warfarin for renal preservation. Our study supported its reasoning using data from large-scale Asian patients and laboratory data.

Limitations

First, despite careful adjustment using IPTW, our study may still be subject to residual confounding. In database analysis where randomization is not possible, such PS-based methods as matching or IPTW serve to harmonize comparison groups concerning patient characteristics. However, residual confounding was caused by unmeasured factors such as laboratory values (e.g., time in the therapeutic window for warfarin), missing data, miscoding, or tactical coding issues. Second, the application of both on-treatment and ITT analysis in non-randomized studies has different limitations as follows: an on-treatment method leads to a loss of information on the reasons for treatment discontinuation, while an ITT approach would not reflect changes on treatments affecting the primary outcome. In our study, the primary purpose of this study was to compare warfarin and rivaroxaban for the risk of kidney failure in anticoagulated patients with AF. In real-world clinical practice, many patients changed their OAC agents from

warfarin to NOAC (28). The clinical impact of warfarin might widely mix with various NOACs in patients who changed their OAC agents from warfarin to NOAC in ITT analysis. Therefore, we believe it is more appropriate for the main analysis to be an on-treatment manner rather than ITT manner. Furthermore, we analyzed an ITT analysis for a sensitivity analysis. Although there was a slight attenuation on the HRs, the results were largely consistent with the main analysis in an on-treatment manner. Third, to control the possible effect of prior use of warfarin, we only include OAC new users from 1 January 2014. This could result in an overall short-term follow-up duration for both groups. Fourth, in the present study, we did not perform a comprehensive comparison among different NOACs for the risk of kidney failure because of the limitation of dataset. Comparative analysis among DOACs on the risk of kidney failure might be a valuable topic foe patient care. Further research is needed to elucidate the relative risk difference of different NOACs on the risk of kidney failure compared to warfarin or NOACs. Fifth, because of an inherent limitation of the data source, we could not analyze the treatment quality of warfarin using the time in therapeutic range of INR. Furthermore, the results can be generalized only to Korean patients with AF. Informative censoring might exist in patients who discontinued the index treatment. This was evaluated by a sensitivity analysis that follows the ITT approach.

Conclusion

In Korean patients with AF, rivaroxaban was associated with a lower risk of renal adverse outcomes than warfarin. The renal preservation effect of rivaroxaban compared with warfarin was particularly pronounced in patients with preexisting renal impairment. Rivaroxaban should be explored for anticoagulation therapy in AF patients at high risk of renal function decline.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: http://nhiss.nhis.or.kr/bd/ab/bada000eng.do.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

S-RL contributed to the design of the study, interpretation of the results and prepared the manuscript. E-KC, SO, KA, and GL contributed to the design of the study, interpretation of the results and critical revision of the manuscript. S-HP and K-DH contributed to the analysis of data and interpretation of results. All authors contributed to the article and approved the submitted version.

Conflict of interest

E-KC: Research grants or speaking fees from Bayer, Biosense Webster, BMS/Pfizer, Chong Kun Dang, Daiichi Sankyo, Dreamtech Co., Ltd., Jeil Pharmaceutical Co. Ltd., Medtronic, Samjinpharm, Seers Technology, and Skylabs. GL: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, and Daiichi Sankyo. No fees are received personally. KA was employed by Bayer AG. This study was funded by Bayer AG. Bayer AG contributed to the design and conduct of the study; management and interpretation of the data; preparation, review, and approval of the manuscript; and the decision to submit the manuscript for publication.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1040834/full#supplementary-material

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ORIGINAL RESEARCH

Bleeding risk with rivaroxaban compared with vitamin K antagonists in patients aged 80 years or older with atrial fibrillation

Olivier Hanon,[1] Jean-Sébastien Vidal ,[1] George Pisica-Donose,[1,2] Galdric Orvoën,[1] Jean-Philippe David,[3] Edouard Chaussade,[1] Laure Caillard,[1] Laura W de Jong,[4] Nicolas Boulloche,[5] Ulric Vinsonneau,[6] Stéphane Bouée,[7] Pierre Krolak-Salmon,[8] Laurent Fauchier,[9] Pierre Jouanny,[10] Guillaume Sacco,[11] Fabienne Bellarbre,[12] Joël Belmin,[13] François Puisieux,[14] Matthieu Lilamand,[15] Elena Paillaud,[16] Anne Sophie Boureau ,[17] SAFIR study group

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For numbered affiliations see end of article.

Correspondence to
Professor Olivier Hanon, Service de Gérontologie, Hôpital Broca, 75013 Paris, France; olivier.hanon@aphp.fr

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ABSTRACT

Objective Direct oral anticoagulants have been evaluated in the general population, but proper evidence for their safe use in the geriatric population is still missing. We compared the bleeding risk of a direct oral anticoagulant (rivaroxaban) and vitamin K antagonists (VKAs) among French geriatric patients with non-valvular atrial fibrillation (AF) aged ≥80 years.

Methods We performed a sequential observational prospective cohort study, using data from 33 geriatric centres. The sample comprised 908 patients newly initiated on VKAs between September 2011 and September 2014 and 995 patients newly initiated on rivaroxaban between September 2014 and September 2017. Patients were followed up for up to 12 months. One-year risks of major, intracerebral, gastrointestinal bleedings, ischaemic stroke and all-cause mortality were compared between rivaroxaban-treated and VKA-treated patients with propensity score matching and Cox models.

Results Major bleeding risk was significantly lower in rivaroxaban-treated patients (7.4/100 patient-years) compared with VKA-treated patients (14.6/100 patient-years) after multivariate adjustment (HR 0.66; 95% CI 0.43 to 0.99) and in the propensity score–matched sample (HR 0.53; 95% CI 0.33 to 0.85). Intracerebral bleeding occurred less frequently in rivaroxaban-treated patients (1.3/100 patient-years) than in VKA-treated patients (4.0/100 patient-years), adjusted HR 0.59 (95% CI 0.24 to 1.44) and in the propensity score–matched sample HR 0.26 (95% CI 0.09 to 0.80). Major lower bleeding risk was largely driven by lower risk of intracerebral bleeding.

Conclusions Our study findings indicate that bleeding risk, largely driven by lower risk of intracerebral bleeding, is lower with rivaroxaban than with VKA in stroke prevention in patients ≥80 years old with non-valvular AF.

INTRODUCTION

Atrial fibrillation (AF) is a disease of the elderly, with increasing prevalence and incidence among older age groups.[1] AF is with age a major risk factor for ischaemic stroke; hence, stroke prevention with oral anticoagulants is the cornerstone for AF management in the elderly. Although in the elderly, the risk of stroke without oral anticoagulation exceeds the bleeding risk on anticoagulation,[2 3] a significant underuse of anticoagulation is observed in older patients with AF essentially due to fear of bleeding.[4]

Direct oral anticoagulants (DOACs) have been proposed as an alternative to vitamin K antagonists (VKAs) for stroke prevention in patients with non-valvular AF.

Randomised controlled trials have demonstrated that DOACs have a more favourable benefit–risk profile than VKAs,[5] and meta-analyses focused on patients >75 years old found that DOACs are more effective than VKAs in stroke prevention, with a significantly lower risk of intracerebral haemorrhage and a similar risk of major bleeding.[6]

Although DOACs have been extensively evaluated in the general population, only 38% of patients enrolled in the four landmark trials of DOACs in non-valvular AF were aged ≥75 years, and only around 15% were >80 years old.[5 7–10] Moreover, elderly patients in randomised clinical trials are usually a selected group who are relatively healthy with few geriatric conditions such as dementia, falls, malnutrition or disability. Consequently, evidence for the efficacy and safety of DOACs in very old and frail patients is still insufficient.[11]

Given the limited evidence on the risks of bleeding with DOACs in individuals 80 years and older, generating evidence supporting the use of DOACs in this specific geriatric population is critical. Accordingly, the purpose of this large sequential observational prospective cohort study was to compare the bleeding risk of rivaroxaban with that of VKAs among patients with non-valvular AF aged ≥80 years in geriatric settings in France.

METHODS

Study design and study population

This was a balanced sequential cohort study using data from 33 geriatric centres across France. Patients were followed up every 3 months for up to

12 months. The study was conducted under real-life conditions of daily clinical practice and in accordance with the Declaration of Helsinki, the Good Pharmacoepidemiology Practice guidelines, and abided by French laws and regulations. The protocol was approved by the ethics committee of *Ile de France V*. No consent to participate was sought for the subjects in accordance with the French ethics rules because the study was observational and no nominative data were collected.

Study participants

Eligible patients comprised men and women aged 80 years and older, with documented non-valvular AF on ECG or 24-hour Holter monitoring, originating from geriatric settings (hospitals, private practice or nursing homes). Two cohorts of patients were evaluated. One had recently (less than 6 months) initiated VKA and the other rivaroxaban. In order to reduce selection bias, VKA cohort was constituted from September 2011 to September 2014 whereas rivaroxaban cohort was constituted from September 2014 to September 2017. Because rivaroxaban was marketed in France in 2011, prescriptions were more likely to be given to healthier patients for this initial period. Indeed, several observational studies showed that VKAs were more likely used in older comorbid patients whereas DOACs were more likely used in healthier patients.[12] To limit the difference between the two cohorts in terms of comorbidity and age, we decided to include patients in the rivaroxaban group a few years after its marketing in France.

To optimise generalisability of the study findings, exclusion criteria were limited to participation in an interventional clinical trial, and contraindications to VKA or rivaroxaban as described in the summary of product characteristics. All patients were informed about the nature of the study.

Data collection

At baseline, patient and treatment characteristics were collected from the electronic medical record databases of the study centres. These included clinical characteristics, CHA_2DS_2-VASc[13] and HAS-BLED[14] scores, age-adjusted Charlson comorbidity index (ACCI),[15] comprehensive geriatric assessment including cognition (mini-mental state examination (MMSE)),[16] dementia, disability (activities of daily living (ADL)),[17] falls, anaemia according to WHO definition: haemoglobin <130 g/L in men and <120 g/L in women, malnutrition, medications taken and most recent laboratory data (serum creatinine, eGFR (glomerular filtration rate estimated with Cockcroft-Gault formula),[18] haemoglobin, albumin). Labile international normalised ratio (INR) was not included in the HAS-BLED score because it was unavailable in the local centres' databases.

At each 3-month follow-up, all bleeding events, thrombotic events, hospitalisations, anticoagulant discontinuation and deaths were prospectively registered.

Major bleeding was defined according to the International Society on Thrombosis and Haemostasis: clinically overt bleeding associated with any of the following: (1) death; (2) involvement of a critical anatomical site (intracranial, spinal, ocular, pericardial, retroperitoneal, articular or intramuscular with compartment syndrome); (3) drop in haemoglobin concentration ≥2 g/dL; (4) transfusion ≥2 U of whole blood or red blood cells.[19]

Statistical analysis

Baseline characteristics were analysed in the two cohorts in terms of means and SD for continuous variables, and in terms of counts and percentages for categorical variables and compared with t-tests and χ^2, respectively. Missing data were not imputed, and patients were left censored from analysis at the point of loss to follow-up (see online supplemental table 1). Kaplan-Meier curves were drawn for major bleedings, intracerebral and gastrointestinal haemorrhages, and ischaemic strokes in the two cohorts. Cox proportional-hazard models were used to calculate HR and 95% CI for the incidence of bleeding and ischaemic events in rivaroxaban-treated patients as compared with those treated with VKAs. For each comparison, we fit three sets of Cox models: unadjusted (crude); adjusted for age, sex, eGFR and ACCI (model 1); and adjusted for various variables selected based on univariate p values <0.10, including model 1+malnutrition (albumin <35 g/L), anaemia, falls, use of antiplatelets, amiodarone, proton-pump inhibitors (PPIs) and selective serotonin reuptake inhibitors (SSRIs) (model 2). In both adjusted models, dementia was not included as a covariate because it is already taken into account in the ACCI. A sensitivity analysis was performed for major bleedings with adjustment for HAS-BLED with age, sex and Charlson comorbidity index score, even though both scores include some identical variables. Also we performed three logistic regression models with the same adjustment for major bleedings.

The proportional-hazard assumption was checked graphically for all covariates and using Schoenfeld residuals. Log-linearity was also tested for all covariates. Because proportional-hazard assumption was marginally broken in the crude Cox model for ischaemic strokes (p=0.064), we built three logistic regression models with the same adjustment for ischaemic strokes.

A propensity score matching method (GenMatch package in R) was also used to balance patients' characteristics between the two cohorts. The propensity score was calculated on characteristics significantly different regarding haemorrhagic events (ie, age, sex, Charlson comorbidity index, eGFR, haemoglobin, albumin, antiplatelets) (see online supplemental table 2). One participant treated with VKA was matched to one participant treated with rivaroxaban without replacement with a calliper of 0.8 SD in standardised unit. This sample comprised 760 subjects, 380 in the VKA cohort and 380 in the rivaroxaban group. The power to detect a difference similar to that of the overall sample was 73.1%.

The balance of measured covariates between matched rivaroxaban and VKA users was assessed using standardised mean differences that were all ≤0.1 (10%) indicating a negligible difference between the cohorts[20] (online supplemental table 2).

A two-sided p value <0.05 was considered statistically significant. All statistical analyses were performed using R.[21]

RESULTS

Patient characteristics

For the rivaroxaban cohort, 1045 consecutive patients were enrolled. Of these patients, 995 (95.2%) had at least 6 months of follow-up (mean age=86.0 (4.3), including 23% aged 90 years and older) and mean follow-up was 322 (89) days.

For the VKA group, 924 consecutive patients were enrolled from the same 33 geriatric centres across France. Of these patients, 908 (98.2%) had at least 6 months of follow-up (mean age=86.4 (5.2), including 27% aged 90 years and older) and mean follow-up was 286 (117) days.

Compared with VKA-treated patients (see table 1), rivaroxaban-treated patients were slightly younger, more often male and heavier. They had significantly less comorbidity, higher eGFR and were less likely to receive antiplatelets, amiodarone, PPIs and SSRIs. CHA_2DS_2VASc score was similar in the two

Table 1 Baseline characteristics among rivaroxaban and VKA cohorts

General characteristics, M (SD)	VKA n=908	Rivaroxaban n=995	P value*
Age (years)	86.4 (5.2)	86.0 (4.3)	0.06
Women, % (n)	66.4 (603)	61.1 (608)	0.02
Weight (kg)	64.5 (15.8)	67.2 (14.8)	0.0002
Body mass index (kg/m^2)	24.8 (5.6)	25.1 (4.9)	0.16
Haemorrhagic and thrombotic scores			
CHA_2DS_2VASc (score)	4.58 (1.39)	4.58 (1.39)	0.96
HAS-BLED (score)	2.15 (0.85)	1.99 (0.93)	0.003
Charlson comorbidity index (score)	8.59 (2.65)	6.68 (2.02)	<0.0001
Geriatric parameters			
Dementia, % (n)	55.3 (446)	38.5 (382)	<0.0001
Mini-mental state examination (score)	20.1 (6.8)	21.5 (6.9)	<0.0001
Activity of daily living (score)	2.47 (1.83)	4.42 (1.87)	<0.0001
Falls (more than 2 the previous year), % (n)	47.6 (374)	27.0 (265)	<0.0001
Malnutrition (albumin <35 g/L), % (n)	76.5 (657)	54.7 (465)	<0.0001
Anaemia†, % (n)	64.5 (578)	40.8 (396)	<0.0001
Biological characteristics			
Serum creatinine (µmol/L)	98.7 (59.8)	80.4 (23.1)	<0.0001
eGFR (mL/min)	47.2 (26.0)	53.1 (16.4)	<0.0001
Haemoglobin (g/dL)	11.7 (1.6)	12.6 (1.6)	<0.0001
Treatment, % (n)			
Antiplatelets	16.1 (128)	11.6 (114)	0.007
Amiodarone	19.4 (154)	15.1 (150)	0.02
Proton-pump inhibitors	46.3 (377)	35.0 (348)	<0.0001
Serotonin reuptake inhibitors	30.6 (244)	19.7 (196)	<0.0001

M (SD), mean (standard deviation); % (n), percentage (count).
*T-test or χ^2 test.
†Anaemia according to WHO definition: haemoglobin <130 g/L in men and <120 g/L in women.
eGFR, glomerular filtration rate estimated with Cockcroft-Gault formula; VKA, vitamin K antagonist.

groups. HAS-BLED score was significantly lower in the rivaroxaban group.

In the rivaroxaban cohort, 65% of patients were prescribed rivaroxaban as initial anticoagulant therapy, while 35% switched from VKA. Thirty-six per cent of patients were prescribed 20 mg of rivaroxaban once daily, 63% 15 mg and 1% 10 mg. In patients with a baseline eGFR 30–50 mL/min, 84.5% were prescribed rivaroxaban 15 mg once daily. In patients with a baseline eGFR ≥50 mL/min, rivaroxaban was prescribed 20 mg once daily in 54.6% and 15 mg once daily in 45.4% of patients.

Figure 1 shows the Kaplan-Meier cumulative probability of being free from major, intracerebral and gastrointestinal haemorrhages and from ischaemic strokes in rivaroxaban and VKA cohorts.

Major bleeding

During the 1-year follow-up, major bleeding occurred in 63/995 (6.3%) rivaroxaban-treated patients (7.4 events/100 patient-years) and in 102/908 (11.2%) VKA-treated patients (14.6 events/100 patient-years) (figures 1–3 and table 2).

Major bleeding rate was significantly lower in the rivaroxaban cohort than in the VKA cohort in the crude Cox model (HR (95% CI)), and model 1 (adjusted for age, sex, eGFR and CCI)

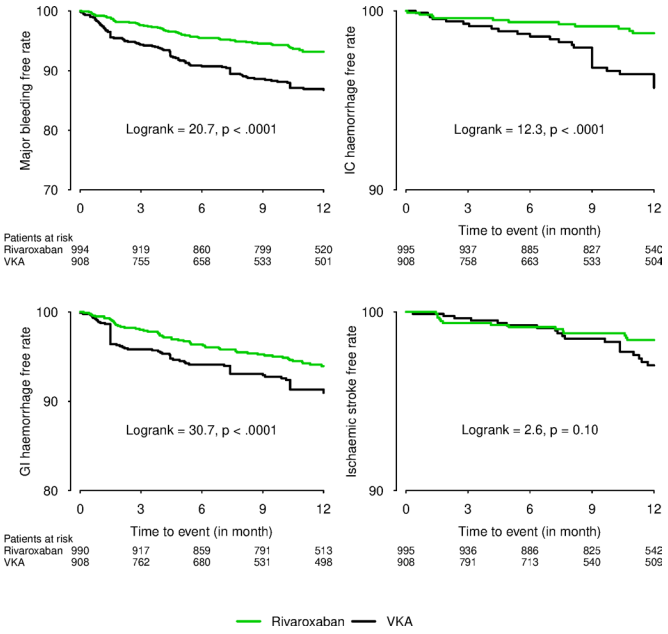

Figure 1 Major bleeding, intracerebral (IC) and gastrointestinal (GI) haemorrhages and ischaemic stroke in vitamin K antagonist (VKA) and rivaroxaban cohorts.

and model 2 (model 1 adjusted for malnutrition, anaemia, falls, antiplatelets, amiodarone, PPI and SSRI use) (HR (95% CI) 0.66 (0.43 to 0.99)).

In the propensity score–matched sample, the difference between rivaroxaban and VKA groups was also significant (HR 0.53 (0.33 to 0.85), p=0.009).

Fatal bleeding occurred in 9/995 (0.9%) rivaroxaban-treated patients (1.0/100 patient-years) and in 21/908 (3.3%) VKA-treated patients (3.0/100 patient-years). Fatal bleedings were significantly different in the two cohorts in the crude Cox model and model 1 (HR 0.42 (0.18 to 0.99), p=0.04), but not in model

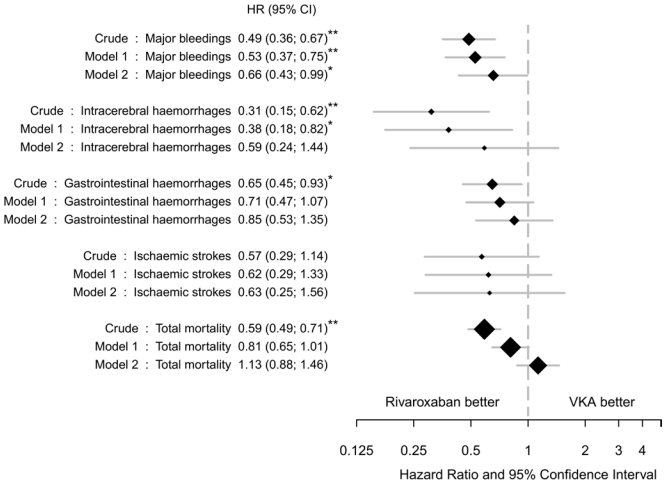

Figure 2 Comparison of rate of events between rivaroxaban and vitamin K antagonist (VKA). Diamonds are sized proportionally to the number of events. Model 1: Cox model adjusted for age, sex, estimated glomerular filtration rate and Charlson comorbidity index. Model 2: model 1+ malnutrition, anaemia, falls, use of antiplatelets, use of amiodarone, proton-pump inhibitors and serotonin reuptake inhibitors. *p<0.05 **p<0.001.

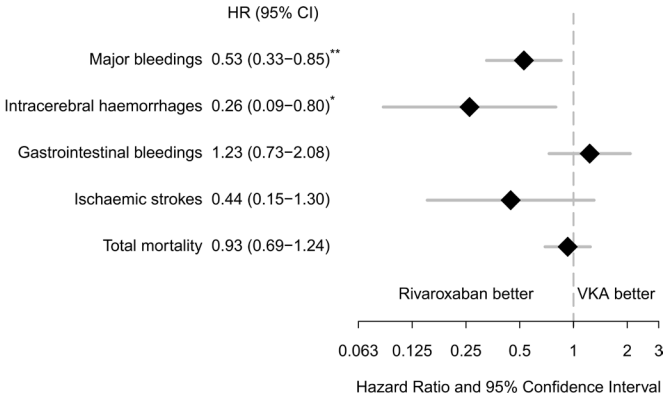

Figure 3 Comparison of rate of events between rivaroxaban and vitamin K antagonist (VKA) in the propensity score–matched sample. *p<0.05 **p<0.01.

2 (HR 0.48 (0.15 to 2.07), p=0.21). Two-thirds (20/30) of the fatal bleeding were related to intracerebral haemorrhages.

In a sensitivity analysis, HAS-BLED score was added in the model with age, sex and Charlson comorbidity index score. Likewise, major bleeding rate was lower in rivaroxaban-treated patients than in VKA-treated patients (HR 0.61 (0.37 to 1.00), p=0.05).

In the three logistic regression models, major bleeding rate was significantly lower in the rivaroxaban cohort than in the VKA cohort (online supplemental table 3).

Intracerebral haemorrhages

Intracerebral haemorrhages occurred in 11/995 (1.1%) rivaroxaban-treated patients (1.3 events/100 patient-years) and 28/908 (3.1%) VKA-treated patients (4.0 events/100 patient-years). Intracerebral haemorrhage rate was significantly lower in rivaroxaban cohort than in VKA cohort in the crude Cox model and model 1 but not in model 2 (table 2 and figures 1–3)

In the propensity score–matched sample, intracerebral haemorrhage rate was significantly lower in the rivaroxaban cohort than in the VKA cohort.

Gastrointestinal haemorrhages

Gastrointestinal haemorrhage occurred in 26/995 (3.0%) in the rivaroxaban cohort (3.0 events/100 patient-years) compared with 34/908 (3.7%) in the VKA cohort (4.9 events/100 patient-years). The difference of gastrointestinal haemorrhage rate was significant in the crude Cox model but not in the adjusted models and in the propensity score–matched sample (table 2 and figures 1–3).

Ischaemic strokes

Ischaemic stroke occurred in 14/995 (1.4%) rivaroxaban-treated patients (1.6 events/100 patient-years), while it occurred in 19/908 (2.1%) patients in the VKA cohort (2.7 events/100 patient-years). The difference between the two cohorts was not significantly different in any of the Cox models or in the propensity score–matched sample (table 2 and figures 1–3).

In all three logistic regression models, ischaemic strokes were not significantly different in the two cohorts.

All-cause mortality

In the rivaroxaban cohort, 178/995 (17.9%) patients (20.3/100 patient-years) died during the follow-up whereas 241/908 (26.5%) patients (34.5/100 patient-years) died in the VKA cohort (table 2 and figures 2 and 3).

The mortality rate was significantly lower among rivaroxaban-treated patients than in VKA-treated patients in the crude Cox model but not in the adjusted models.

Factors associated with major bleedings

In the rivaroxaban cohort, compared with those without a major bleeding (n=932), patients with a major bleeding (n=63) were older, more often male and treated with antiplatelets and amiodarone and had more often anaemia, dementia and lower eGFR; meanwhile, HAS-BLED was not associated with major bleeding events (table 3). When all those variables were simultaneously entered into a multivariate logistic model, age, male sex, lower eGFR and anaemia remained significantly associated with major bleedings (table 4).

In the VKA cohort, compared with those without a major bleeding (n=806), patients with a major bleeding (n=102) were more often male and treated with antiplatelets and PPIs, had more often anaemia and lower eGFR, and had a higher HAS-BLED score (table 3). When all those variables were simultaneously entered into a multivariate logistic model (table 4), male sex and lower eGFR remained significantly associated with major bleedings.

DISCUSSION

To our knowledge, this is the first large observational prospective study in geriatric patients with AF comparing data on bleeding complications between rivaroxaban and VKA.

The 1-year rate of major bleedings was 7.4 per 100 person-years for rivaroxaban, suggesting that major bleeding risk with rivaroxaban is higher in older frail patients than in younger ones. In the ROCKET-AF trial involving patients with AF with a median age of 73 years, major bleeding risk was 3.6 events per 100 patient-years.[8] In the XANTUS study with a mean age of

Table 2 Events during the follow-up period among rivaroxaban and VKA groups

	Rivaroxaban		VKA		
Event	n (%)	/100 person-years	n (%)	/100 person-years	HR (95% CI)
Major bleedings	63 (6.3)	7.4	102 (11.2)	14.6	0.49 (0.36 to 0.67)
Fatal bleedings	9 (0.9)	1.0	21 (3.3)	3.0	0.34 (0.16 to 0.76)
Intracerebral haemorrhages	11 (1.1)	1.3	28 (3.1)	4.0	0.65 (0.45 to 0.93)
Gastrointestinal haemorrhages	26 (3.0)	3.0	34 (3.7)	4.9	0.82 (0.53 to 1.28)
Ischaemic strokes	14 (1.4)	1.6	19 (2.1)	2.7	0.57 (0.29 to 1.14)
All-cause mortality	178 (17.9)	20.3	241 (26.5)	34.5	0.59 (0.49 to 0.72)

n (%), count (percentage); HR (95% CI), hazard ratio (95% confidence interval)

VKA, vitamin K antagonist.

Table 3 Characteristics of patients with and without major bleeding events among rivaroxaban and VKA cohorts

	Rivaroxaban			Vitamin K antagonist		
	No major bleeding	Major bleeding		No major bleeding	Major bleeding	
General characteristics, M (SD)	n=932	n=63	P value*	n=806	n=102	P value*
Age (years)	85.9 (4.2)	87.5 (4.8)	0.003	86.3 (5.3)	86.7 (5.0)	0.46
Women, % (n)	61.9 (577)	49.2 (31)	0.06	67.4 (543)	58.8 (60)	0.11
Weight (kg)	67.2 (14.9)	65.9 (13.2)	0.49	64.5 (15.9)	64.3 (15.4)	0.89
Height (cm)	164 (29)	164 (8)	0.99	162 (10)	162 (10)	0.75
Body mass index (kg/m^2)	25.2 (5.0)	24.4 (4.0)	0.22	24.8 (5.6)	24.5 (6.1)	0.64
Activity of daily living (score)	4.40 (1.88)	4.69 (1.69)	0.23	2.49 (1.83)	2.32 (1.78)	0.4
Mini-mental state examination (score)	21.4 (7.0)	22.8 (6.6)	0.14	20.1 (6.9)	20.0 (6.6)	0.87
Charlson comorbidity index (score)	6.68 (2.03)	6.66 (1.83)	0.92	8.60 (2.67)	8.52 (2.50)	0.78
Anaemia†, % (n)	39.9 (362)	54.0 (34)	0.04	63.7 (508)	71.4 (70)	0.16
Falls (more than 2 the previous year), % (n)	26.8 (247)	28.6 (18)	0.88	47.2 (329)	51.1 (45)	0.56
Dementia, % (n)	39.1 (364)	28.6 (18)	0.12	55.7 (398)	51.6 (48)	0.52
Biological characteristics						
Serum creatinine (µmol/L)	80.0 (23.0)	86.4 (23.0)	0.03	97.9 (60.9)	105 (50)	0.26
eGFR mL/min	53.5 (16.5)	47.6 (14.7)	0.006	47.9 (26.6)	42.0 (19.1)	0.04
Haemoglobin (g/dL)	12.7 (1.6)	12.0 (1.7)	0.0009	11.7 (1.6)	11.5 (1.5)	0.19
Treatment, % (n)						
Antiplatelets	11.2 (103)	17.5 (11)	0.20	15.0 (106)	25.9 (22)	0.02
Amiodarone	14.6 (136)	22.2 (14)	0.15	20.1 (142)	14.1 (12)	0.24
Proton-pump inhibitors	35.2 (328)	31.7 (20)	0.68	45.3 (330)	54.7 (47)	0.12
Serotonin reuptake inhibitors	19.7 (184)	19.0 (12)	0.99	30.6 (218)	31.0 (26)	0.99
Haemorrhagic and thrombotic scores						
HAS-BLED	1.98 (0.93)	2.12 (0.97)	0.29	2.10 (0.83)	2.67 (0.93)	0.0001
CHA_2DS_2VASc	4.56 (1.41)	4.84 (1.21)	0.18	4.59 (1.40)	4.41 (1.24)	0.32

M (SD), mean (standard deviation); % (n), percentage (count).
*T-test or χ^2 test.
†Anaemia according to WHO definition: haemoglobin <130 g/L in men and <120 g/L in women.
eGFR, glomerular filtration rate estimated with Cockcroft-Gault formula; VKA, vitamin K antagonist.

Table 4 Multivariable analysis of factors associated with major bleedings in the rivaroxaban and VKA cohorts

	HR (95% CI)	P value
Rivaroxaban cohort		
Age (years)	1.07 (1.00 to 1.13)	0.04
Male sex	1.79 (1.06 to 3.01)	0.03
eGFR	0.67 (0.48 to 0.94)	0.02
Anaemia*	1.68 (1.00 to 2.82)	0.05
History of bleeding	1.46 (0.81 to 2.62)	0.21
Dementia	0.66 (0.38 to 1.14)	0.13
Medication		
Antiplatelets	1.55 (0.79 to 3.06)	0.20
Amiodarone	1.64 (0.90 to 3.00)	0.11
Vitamin K antagonist cohort		
Male sex	1.56 (0.97 to 2.49)	0.06
eGFR	0.74 (0.55 to 0.99)	0.04
Anaemia*	1.31 (0.79 to 2.19)	0.30
Medication		
Antiplatelets	1.55 (0.90 to 2.63)	0.11
Proton-pump inhibitor	1.37 (0.87 to 2.17)	0.18

HR (95% CI), hazard ratio (95% confidence interval)
*Anaemia according to WHO definition: haemoglobin <130 g/L in men and <120 g/L in women.
eGFR, glomerular filtration rate estimated with Cockcroft-Gault formula (HR for an increase of 1 SD); VKA, vitamin K antagonist.

71.5 years, major bleeding risk was 2.1 events per 100 patient-years.[22] Meanwhile, our results are consistent with a retrospective study including AF octogenarians showing a rate of 9.0% of bleeding in subjects treated with DOACs.[23] Similarly, our study showed a high rate of major bleeding in the VKA group (14.6 per 100 person-years) consistent with previous studies.[23 24]

The 1-year rate of major bleeding events was significantly lower in the rivaroxaban group than in the VKA group. The difference remained significant even after adjustment for all potentially confounding factors and in a propensity score–matched sample. The difference in major bleedings was largely driven by the difference in intracerebral haemorrhages and also explained the difference in fatal bleedings. In European registries in patients aged ≥75 years, major bleedings were less frequent in patients treated with DOAC than VKAs.[3] Our results are also consistent with a meta-analysis including elderly patients that finds a lower rate of bleedings in the DOAC group compared with VKA[25] but not with others that show similar rates of major bleedings in DOAC and VKA groups.[6 26 27]

There was a lower rate of intracerebral haemorrhages in the rivaroxaban group. The difference remained significant after adjustment in model 1 and in the propensity score matching sample but not in model 2 possibly because of lack of power. However, the HR was still 0.59. In most studies, DOAC is associated with a significantly lower risk of intracerebral haemorrhages in elderly patients (≥75 years old) compared with VKA.[6 28] There are only few studies in patients >80 years old especially with a prospective design. Retrospective data found

intracerebral haemorrhage rate similar to ours (0.89%/person-years)[29] and lower risk among patients with AF ≥90 years of age.[28]

Major bleedings in patients treated with rivaroxaban were associated with age, male sex, low eGFR and anaemia and interestingly were not associated with geriatric features like falls, dementia, malnutrition and co-medication.

HAS-BLED score was not associated with major bleedings in the rivaroxaban group whereas it was highly significantly related to major bleedings in the VKA group. HAS-BLED was created to predict major bleedings in patients treated with VKA and not with DOAC. This result shows the need for a specific bleeding score for patients treated with DOAC.

There was no difference in gastrointestinal haemorrhages between the two groups in the adjusted models. In randomised studies, gastrointestinal haemorrhages were more frequent with rivaroxaban than with VKA. Our results could be related to a selection bias from investigators: patients with higher risk of gastrointestinal haemorrhage might not have been treated by geriatricians with rivaroxaban.

There was no difference in ischaemic strokes between the two cohorts. This result is consistent with the ROCKET-AF study, especially the sub-analysis in elderly ≥75 years old.[30] However, the number of events was small (19 in the VKA group and 14 in the rivaroxaban group) and a longer follow-up would be necessary to better analyse this outcome.

Our study has some limitations. Despite the time lag between the two including periods, the two cohorts were not totally comparable. As it has already been shown in other studies,[12] patients treated with VKA usually have more comorbidity. To take into account these issues, we adjusted for all potentially confounding factors and also ran the analyses in a propensity score–matched sample. Meanwhile, despite the use of advanced statistical methods to account for differences between cohorts, we cannot make causal inference. No data on INR control in VKA-treated patients were available, lessening the strength of the study. Investigators calculated and entered HAS-BLED and CHA_2DS_2VASc scores directly and variables contained in these scores were not recorded. Lastly, this study only analysed rivaroxaban and not the other DAOCs because apixaban and edoxaban were not yet marketed in France at the time of study inception and dabigatran was not widely used in the geriatric population because of its renal elimination.

The strength of our study lies in its very old population, characterised by high Charlson comorbidity index and geriatric syndromes such as dementia, falls and malnutrition, and which profile is never included in randomised controlled studies. To our knowledge, this is the largest observational prospective study on a geriatric population comparing DOAC and VKA medication in patients with AF. We evaluated cardiologic determinants of bleeding and stroke risks and also comprehensive geriatric assessment that are usually not assessed in randomised and observational studies. Furthermore, the study's prospective design allowed for greater completeness of data and potentially better data quality compared with retrospective designs. Loss to follow-up was low for a prospective study in geriatric patients (7%). Finally, drugs potentially interacting with rivaroxaban and frequently prescribed in elderly patients such as antiplatelets, PPIs, SSRIs and amiodarone were monitored.

This study shows that, compared with VKAs, rivaroxaban use is associated with a lower risk of major bleeding and intracerebral haemorrhage in very old geriatric patients with AF treated in clinical practice. Our findings are consistent with evidence-based data and indicate that rivaroxaban can be used for stroke prevention in geriatric patients with non-valvular AF.

Key messages

What is already known on this subject?

- Direct oral anticoagulants have been proposed as an alternative to vitamin K antagonists (VKAs) for stroke prevention in patients with non-valvular atrial fibrillation (AF). However, proper evidence for their safe use is still missing in the geriatric population with dementia, falls, anaemia, malnutrition and disability.

What might this study add?

- During the 1-year follow-up, major bleeding occurred significantly less often in rivaroxaban-treated patients, 63/995 (6.3%) (7.4 events/100 patient-years), than in VKA-treated patients, 102/908 (11.2%) (14.6 events/100 patient-years). That result was significant in crude model, in adjusted Cox model and in propensity-matched sample.

How might this impact on clinical practice?

- Our study findings indicate that bleeding risk is lower with rivaroxaban than with VKA in stroke prevention in patients ≥80 years old with non-valvular AF.

Author affiliations
[1]Hôpital Broca, Service de Gérontologie, Assistance Publique – Hopitaux de Paris and EA 4468, Université de Paris, F-75013 Paris, France
[2]Medalice, F-78560 Le Port Marly, France
[3]Hôpital Henri Mondor, Service de Gériatrie, Assistance Publique – Hopitaux de Paris and Inserm U955, Université Paris Est Créteil (UPEC), F-94000 Créteil, France
[4]Service de Radiologie, Groupe hospitalier Sainte-Anne, F-75014 Paris, France
[5]Centre Hospitalier de Montauban, F-82000 Montauban, France
[6]Service de Cardiologie, Hôpital d'Instruction des Armées Clermont-Tonnerre, F-29240 Brest, France
[7]CEMKA, F-92340 Bourg-la-Reine, France
[8]Centre de Recherche Clinique Vieillissement Cerveau - Fragilité, CHU Lyon, F-69000 Lyon, France
[9]Service de Cardiologie, Hôpital Trousseau and Université François-Rabelais, F-37170 Chambray-les-Tours, France
[10]Centre Champmaillot, Service de Médecine Interne Gériatrie, CHU de Dijon, F-21000 Dijon, France
[11]Hôpital de Cimiez, Pole de Gérontologie, CHU de Nice, F-06003 Nice, France
[12]Hôpital de la Milétrie, Service de Gériatrie, CHU de Poitiers, F-86000 Poitiers, France
[13]Hôpital Charles Foix, Service de Gériatrie, Assistance Publique – Hôpitaux de Paris and Université de Paris, F-94400 Ivry-sur-Seine, France
[14]Hôpital Gériatrique Les Bateliers, Pôle de gérontologie, CHRU de Lille, F-59000 Lille, France
[15]Hôpital Bichat, Service de Gériatrie, Assistance Publique – Hôpitaux de Paris and Université de Paris, F-75018 Paris, Paris
[16]Hôpital Européen Georges Pompidou, Service de Gériatrie, Assistance Publique – Hôpitaux de Paris and Université de Paris, F-75015 Paris, France
[17]Hôpital Bellier, Pole Hospitalo-Universitaire de Gérontologie Clinique, CHU de Nantes, F-44000 Nantes, France

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Contributors OH: conception and design, acquisition of data, interpretation of data; drafting the article; final approval of the version to be published. J-SV: analysis and interpretation of data; drafting the article; final approval of the version to be published. GP-D: conception and design; revising the article critically for important intellectual content; final approval of the version to be published. GO: acquisition of data; revising the article critically for important intellectual content; final approval of the version to be published. J-PD: acquisition of data; revising the article critically for important intellectual content; final approval of the version to be published. EC: acquisition of data; revising the article critically for important intellectual content; final approval of the version to be published. LC: acquisition of data; revising the

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Author note SAFIR study group: bleeding risk in elderly Subjects Aged more than 80 years in atrial FIbrillation treated by Rivaroxaban

ORCID iDs
Jean-Sébastien Vidal http://orcid.org/0000-0001-6770-0720
Anne Sophie Boureau http://orcid.org/0000-0002-2224-2014

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ORIGINAL ARTICLE
Atrial fibrillation

Head-to-head efficacy and safety of rivaroxaban, apixaban, and dabigatran in an observational nationwide targeted trial

Yeela Talmor-Barkan [1,2,3,4,†], Nancy-Sarah Yacovzada [3,5,6,†], Hagai Rossman [3,4], Guy Witberg [1,2], Iris Kalka [3,4], Ran Kornowski [1,2,‡] and Eran Segal [3,4,*,‡]

[1]Department of Cardiology, Rabin Medical Center, Petah Tikva 4941492, Israel; [2]Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv 69978, Israel; [3]Department of Computer Science and Applied Mathematics, Weizmann Institute of Science, Rehovot 7610001, Israel; [4]Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot 7610001, Israel; [5]Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 7610001, Israel; and [6]Department of Molecular Neuroscience, Weizmann Institute of Science, Rehovot 7610001, Israel

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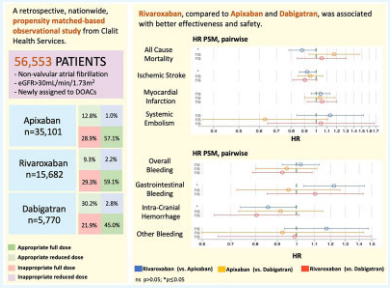
Aims The advantages of direct oral anticoagulants (DOACs) over warfarin are well established in atrial fibrillation (AF) patients, however, studies that can guide the selection between different DOACs are limited. The aim was to compare the clinical outcomes of treatment with apixaban, rivaroxaban, and dabigatran in patients with AF.

Methods and results We conducted a retrospective, nationwide, propensity score-matched-based observational study from Clalit Health Services. Data from 141 992 individuals with AF was used to emulate a target trial for head-to-head comparison of DOACs therapy. Three-matched cohorts of patients assigned to DOACs, from January-2014 through January-2020, were created. One-to-one propensity score matching was performed. Efficacy/safety outcomes were compared using KaplanMeier survival estimates and Cox proportional hazards models. The trial included 56 553 patients (apixaban, $n = 35\,101$; rivaroxaban, $n = 15\,682$; dabigatran, $n = 5\,770$). Mortality and ischaemic stroke rates in patients treated with rivaroxaban were lower compared with apixaban (HR,0.88; 95% CI,0.78–0.99; *P*,0.037 and HR 0.92; 95% CI,0.86–0.99; *P*,0.024, respectively). No significant differences in the rates of myocardial infarction, systemic embolism, and overall bleeding were noticed between the different DOACs groups. Patients treated with rivaroxaban demonstrated lower rate of intracranial haemorrhage compared with apixaban (HR,0.86; 95% CI,0.74–1.0; *P*,0.044). The rate of gastrointestinal bleeding in patients treated with rivaroxaban was higher compared with apixaban (HR, 1.22; 95% CI,1.01–1.44; *P*, 0.016).

Conclusion We demonstrated significant differences in outcomes between the three studied DOACs. The results emphasize the need for randomized controlled trials that will compare rivaroxaban, apixaban, and dabigatran in order to better guide the selection among them.

* Corresponding author: Eran Segal, Weizmann Institute of Science, Herzl St 234, Rehovot 7610001, Israel; Tel: +972-54-2239989; Email: Eran.Segal@weizmann.ac.il
† These authors contributed equally to this work.
‡ These authors jointly supervised this work.

Graphical Abstract



Six-years follow-up of 56,553 patients who were treated with apixaban, rivaroxaban or dabigatran for non-valvular atrial fibrillation.

Keywords Apixaban • Rivaroxaban • Dabigatran • Stroke • Intracranial haemorrhage

Key questions

- What are the differences in efficacy and safety outcomes between rivaroxaban, apixaban, and dabigatran?

Key findings

- Treatment with rivaroxaban was associated with decreased rates of all-cause mortality, ischaemic stroke, and intracranial bleeding compared with apixaban.
- Rivaroxaban compared with dabigatran demonstrated decreased rate of all-cause mortality and ischaemic stroke in patients under the age of 70 years, and decreased rate of intracranial haemorrhage in patients aged 80 years or above.
- Rivaroxaban was associated with increased gastrointestinal bleeding compared with apixaban.

Take-home message

- The differences in efficacy and safety outcomes between rivaroxaban, apixaban and dabigatran warrant further randomized controlled trials.

Introduction

Atrial fibrillation (AF) is a common heart arrhythmia that is associated with an increased risk of mortality and embolic events, mainly stroke.[1] The prevention of stroke in patients with AF is obtained by anticoagulant treatment.[2] Direct oral anticoagulants (DOACs) have several advantages over warfarin including fewer drug interactions, more predictable pharmacological profiles, and an absence of major dietary effects. In addition, data from randomized controlled trials (RCTs) showed that DOACs were non-inferior to warfarin with respect to the risk of thromboembolic and bleeding events in AF patients.[3–5] Therefore, treatment with DOACs has become widespread in clinical practice.[6–8]

Currently, there are limited data to guide the selection between rivaroxaban, apixaban, and dabigatran. To date, the comparison between the different DOACs for the treatment of AF was not examined under RCTs and the data is based on retrospective analysis from different cohorts.[7–11] The majority of studies demonstrate similar efficacy and safety among agents. For example, in a nationwide cohort of patients with AF from Denmark, no overall statistically significant differences were observed in stroke, systemic embolism or major bleeding in apixaban, rivaroxaban, and dabigatran.[12] Additionally, apixaban, rivaroxaban, and dabigatran appear to have similar effectiveness, although apixaban may be associated with lower bleeding risk and rivaroxaban may be associated with elevated bleeding risk.[13] A recent study from Iceland showed that rivaroxaban was associated with higher gastrointestinal (GI) bleeding rates than apixaban and dabigatran regardless of treatment indication.[14]

Larger and more representative observational data sets with longer follow-up may add important information to guide the selection between the different DOACs in patients suffering from AF. Therefore, by using observational data from the largest Health Care Organization (HCO) in Israel, we designed a target trial[15,16] and then emulated its protocol to compare the effectiveness and safety between apixaban, rivaroxaban, and dabigatran in patients with AF.

Methods

Data source

The study was based on the database of Clalit Health Services (CHS), the largest HCO in Israel, encompassing over 19 years of full administrative and clinical data. This health care system provides care for 4.7 million patients, with a membership that is approximately representative of the Israeli population with respect to both socioeconomic status and prevalence of coexisting diseases.[17] The database that we used in this study has been described previously.[18] Medical records include International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes, and ICD-9 procedure codes. The study was approved by the institutional review board at Clalit Health Services approval number 0195–17-COM2, and by the Ethics Committee of Rabin Medical Center, approval number 0096–20-RMC. Since the study was based on retrospective data, it was exempt from the provision of patients' written informed consent.

Study design

An observational study was designed to emulate a target trial of the effect of different DOACs treatment on the outcomes of patients with AF.[15,16,19] Participant's time zero is determined when the participants meet the eligibility criteria and are assigned to a treatment strategy (as enforced in randomized trials). Eligibility criteria included individuals between the age of 20 and 100 years, with a diagnosis of AF that issued a prescription for apixaban, rivaroxaban or dabigatran from 1 January 2014 to 1 January 2020, and being a member of the HCO during the previous 12 months. Additionally, only patients fulfilling the continuity of care criteria were eligible in the study (see online methods; Study Exposures). Exclusion criteria included previous heart transplantation, mitral stenosis, mechanical valve, and renal failure with estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 m^2 or below.

Table 1 Baseline Characteristics of 1:1 Propensity Score-based Matched Cohorts (a) Apixaban vs. Rivaroxaban (b) Dabigatran vs. Apixaban (c) Dabigatran vs. Rivaroxaban

	Apixaban (n = 15 668)	Rivaroxaban (n = 15 668)	SMD
(a) Apixaban vs. Rivaroxaban			
Age, yrs	76.2 (9.6)	76.2 (9.6)	0
Male (%)	7 547 (48.2%)	7 523 (48.0%)	0.004
BMI (kg/m^2)	29.8 (5.9)	29.9 (5.9)	−0.017
Hb (g/dl)	13.0 (1.7)	13.0 (1.6)	0
Bilirubin mg/dL	0.7 (0.3)	0.7 (0.3)	0
AST (U/L)	23.8 (14.4)	23.5 (12.8)	0.022
ALT (U/L)	21.1 (20.0)	20.4 (15.7)	0.039
ALP (IU/L)	85.5 (39.7)	84.5 (41.6)	0.025
PLTs (mcL)	229.9 (76.9)	228.6 (73.4)	0.017
LDL cholesterol (mg/dL)	90.3 (31.6)	90.8 (30.7)	−0.016
Creatinine (μ mol/L)	1.0 (0.3)	1.0 (0.3)	0
HbA1C (%)	6.4 (1.1)	6.4 (1.1)	0
eGFR (ml/min/1.73 m^2)	76.3 (23.1)	76.2 (23.2)	0.004
CHA2DS2-VASc Score	4.1 (1.5)	4.1 (1.5)	0
HAS-BLED Score	2.9 (0.7)	2.9 (0.7)	0
Diabetic (%)	7 537 (48.1%)	7 521 (48.0%)	0.002
Previous hypertension (%)	14 067 (89.8%)	14 005 (89.4%)	0.013
Previous total-bleeding (%)	1 508 (9.6%)	1 517 (9.7%)	−0.003
Previous GI-bleeding (%)	581 (3.7%)	567 (3.6%)	0.005
Previous bleeding-ICH (%)	723 (4.6%)	700 (4.5%)	0.005
Previous bleeding-other (%)	273 (1.7%)	317 (2.0%)	−0.022
Previous MI (%)	2 546 (16.2%)	2 539 (16.2%)	0
Previous CAD (%)	2 698 (17.2%)	2 559 (16.3%)	0.024
Previous stroke (%)	1 193 (7.6%)	1 163 (7.4%)	0.008
Previous TAVI (%)	93 (0.6%)	52 (0.3%)	0.045
Previous prosthetic valve (%)	442 (2.8%)	303 (1.9%)	0.059
CHF (%)	4 701 (30.0%)	4 768 (30.4%)	−0.009
PAD (%)	2 509 (16.0%)	2 399 (15.3%)	0.019
Cirrhosis (%)	127 (0.8%)	123 (0.8%)	0
Previous VTE (%)	822 (5.2%)	867 (5.5%)	−0.013
Alcohol abuse (%)	94 (0.6%)	97 (0.6%)	0
Coumadin use (%)	6 509 (41.5%)	8 127 (51.9%)	−0.21
Statins use (%)	13 367 (85.3%)	13 234 (84.5%)	0.022
NSAIDs use (%)	14 729 (94.0%)	14 729 (94.0%)	0
PPIs use (%)	12 386 (79.1%)	12 223 (78.0%)	0.027
H2 Blockers use (%)	7 757 (49.5%)	8 144 (52.0%)	−0.05
antiplatelets use (%)	4 430 (28.3%)	4 451 (28.4%)	−0.002
Appropriate full dose (%)	10 165 (0.6%)	9256 (0.6%)	0
Appropriate reduced dose (%)	1406 (0.1%)	1458 (0.1%)	0
Inappropriate full dose (%)	142 (0.0%)	358 (0.0%)	0
Inappropriate reduced dose (%)	3955 (0.3%)	4596 (0.3%)	0
	Apixaban (n = 5 767)	**Dabigatran (n = 5 767)**	**SMD**
(b) Dabigatran vs. Apixaban			
Age, yrs	74.5 (9.8)	74.5 (9.8)	0
Male (%)	2 887 (50.1%)	2 916 (50.6%)	−0.01
BMI (kg/m^2)	29.9 (6.0)	29.9 (5.9)	0
Hb (g/dl)	13.1 (1.7)	13.1 (1.6)	0

Table I Continued

	Apixaban (n = 5 767)	Dabigatran (n = 5 767)	SMD
Bilirubin mg/dL	0.7 (0.4)	0.7 (0.4)	0
AST (U/L)	23.9 (12.1)	23.8 (11.7)	0.008
ALT (U/L)	21.6 (19.2)	21.5 (22.9)	0.005
ALP (IU/L)	85.4 (39.7)	83.9 (35.6)	0.04
PLTs (mcL)	231.9 (79.7)	229.0 (72.5)	0.038
LDL cholesterol (mg/dL)	89.4 (31.9)	89.6 (30.9)	−0.006
Creatinine (μ mol/L)	6.4 (1.1)	6.4 (1.0)	0
HbA1C (%)	0.9 (0.3)	0.9 (0.2)	0
eGFR (ml/min/1.73 m^2)	79.1 (22.3)	79.3 (22.9)	−0.009
CHA2DS2-VASc Score	3.9 (1.5)	3.9 (1.5)	0
HAS-BLED Score	2.9 (0.7)	2.9 (0.8)	0
Diabetic (%)	2 721 (47.2%)	2 659 (46.1%)	0.022
Previous Hypertension (%)	5 049 (87.5%)	5 018 (87.0%)	0.015
Previous Total-Bleeding (%)	590 (10.2%)	602 (10.4%)	−0.007
Previous GI-Bleeding (%)	218 (3.8%)	225 (3.9%)	−0.005
Previous Bleeding-ICH (%)	287 (5.0%)	301 (5.2%)	−0.009
Previous Bleeding-Other (%)	115 (2.0%)	99 (1.7%)	0.022
Previous MI (%)	1 014 (17.6%)	1 000 (17.3%)	0.008
Previous CAD (%)	1 075 (18.6%)	1 014 (17.6%)	0.026
Previous Stroke (%)	512 (8.9%)	535 (9.3%)	−0.014
Previous TAVI (%)	28 (0.5%)	27 (0.5%)	0
Previous prosthetic valve (%)	157 (2.7%)	131 (2.3%)	0.026
CHF (%)	1 591 (27.6%)	1 549 (26.9%)	0.016
PAD (%)	851 (14.8%)	805 (14.0%)	0.023
Cirrhosis (%)	43 (0.7%)	38 (0.7%)	0
Previous VTE (%)	176 (3.1%)	190 (3.3%)	−0.011
Alcohol abuse (%)	49 (0.8%)	38 (0.7%)	0.012
Coumadin use (%)	2 308 (40.0%)	2 809 (48.7%)	−0.176
Statins use (%)	4 959 (86.0%)	4 921 (85.3%)	0.02
NSAIDs use (%)	5 458 (94.6%)	5 446 (94.4%)	0.009
PPIs use (%)	4 534 (78.6%)	4 481 (77.7%)	0.022
H2 Blockers use (%)	2 825 (49.0%)	2 689 (46.6%)	0.048
antiplatelets use (%)	1 789 (31.0%)	1 739 (30.2%)	0.017
Appropriate full dose (%)	4097 (0.7%)	2597 (0.5%)	0.417
Appropriate reduced dose (%)	381 (0.1%)	1745 (0.3%)	−0.516
Inappropriate full dose (%)	47 (0.0%)	162 (0.0%)	
Inappropriate reduced dose (%)	1242 (0.2%)	1263 (0.2%)	0
	Dabigatran (n = 5 766)	**Rivaroxaban (n = 5 766)**	**SMD**
(c) Dabigatran vs. Rivaroxaban			
Age, years	74.5 (9.8)	74.5 (9.8)	0
Male (%)	2 916 (50.6%)	2 946 (51.1%)	−0.01
BMI (kg/m^2)	29.9 (5.9)	29.9 (5.9)	0
Hb (g/dl)	13.1 (1.6)	13.1 (1.7)	0
Bilirubin mg/dL	0.7 (0.4)	0.7 (0.4)	0
AST (U/L)	23.8 (11.7)	23.5 (9.9)	0.028
ALT (U/L)	21.3 (14.7)	21.0 (14.0)	0.021
ALP (IU/L)	83.9 (35.7)	84.0 (35.6)	−0.003
PLTs (mcL)	229.0 (72.5)	228.3 (72.9)	0.01

Table I Continued

	Dabigatran ($n = 5\,766$)	Rivaroxaban ($n = 5\,766$)	SMD
LDL cholesterol (mg/dL)	89.6 (30.9)	90.7 (30.6)	−0.036
Creatinine (μ mol/L)	6.4 (1.0)	6.4 (1.1)	0
HbA1C (%)	0.9 (0.2)	0.9 (0.3)	0
eGFR (ml/min/1.73 m^2)	79.3 (22.9)	79.1 (22.2)	0.009
CHA2DS2-VASc Score	3.9 (1.5)	3.9 (1.6)	0
HAS-BLED Score	2.9 (0.8)	2.9 (0.8)	0
Diabetic (%)	2 657 (46.1%)	2 663 (46.2%)	−0.002
Previous Hypertension (%)	5 016 (87.0%)	5 038 (87.4%)	−0.012
Previous total-bleeding (%)	602 (10.4%)	595 (10.3%)	0.003
Previous GI-Bleeding (%)	225 (3.9%)	213 (3.7%)	0.01
Previous bleeding-ICH (%)	301 (5.2%)	292 (5.1%)	0.005
Previous bleeding-other (%)	99 (1.7%)	116 (2.0%)	−0.022
Previous MI (%)	1 000 (17.3%)	987 (17.1%)	0.005
Previous CAD (%)	1 013 (17.6%)	957 (16.6%)	0.027
Previous stroke (%)	535 (9.3%)	536 (9.3%)	0
Previous TAVI (%)	27 (0.5%)	19 (0.3%)	0.032
Previous prosthetic valve (%)	131 (2.3%)	110 (1.9%)	0.028
CHF (%)	1 548 (26.8%)	1 585 (27.5%)	−0.016
PAD (%)	805 (14.0%)	841 (14.6%)	−0.017
Cirrhosis (%)	38 (0.7%)	40 (0.7%)	0
Previous VTE (%)	189 (3.3%)	177 (3.1%)	0.011
Alcohol abuse (%)	38 (0.7%)	48 (0.8%)	−0.012
Coumadin use (%)	2 809 (48.7%)	2 921 (50.7%)	−0.04
Statins use (%)	4 919 (85.3%)	4 849 (84.1%)	0.033
NSAIDs use (%)	5 445 (94.4%)	5 434 (94.2%)	0.009
PPIs use (%)	4 479 (77.7%)	4 496 (78.0%)	−0.007
H2 Blockers use (%)	2 688 (46.6%)	2 907 (50.4%)	−0.076
antiplatelets use (%)	1 738 (30.1%)	1 693 (29.4%)	0.015
Appropriate full dose (%)	2596 (0.5%)	3791 (0.7%)	−0.417
Appropriate reduced dose (%)	1745 (0.3%)	360 (0.1%)	0.516
Inappropriate full dose (%)	162 (0.0%)	88 (0.0%)	
Inappropriate reduced dose (%)	1263 (0.2%)	1527 (0.3%)	−0.232

Values are mean (±SD) or *n* (%). BMI, body mass index; Hb, haemoglobin; AST, aspartate transaminase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; PLTs, platelets; LDL, low-density lipoproteins; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; ICH, intra cranial haemorrhage; MI, myocardial infarction; CAD, coronary artery disease; TAVI, transcatheter aortic valve replacement; CHF, congestive heart failure; PAD, peripheral artery disease; VTE, venous thromboembolism; NSAIDs, nonsteroidal anti-inflammatory drugs; PPIs, proton-pump inhibitors.

Follow-up started at first eligible DOACs prescription and ended at an outcome event including death, treatment discontinuation, disenrollment from Clalit HCO, end of follow-up (6 years after index event), or the end of the study (May 1, 2020), whichever occurs first. All DOACs recipients were matched in a 1:1 ratio for the following variables: age, sex, creatinine, eGFR, haemoglobin (Hb), alanine aminotransferase (ALT), c A1C (HbA1C), CHA2DS2-VASc and HAS-BLED scores, hypertension, previous overall bleeding, previous ischaemic stroke, previous myocardial infarction (MI), coronary artery disease (CAD), peripheral artery disease (PAD), diabetes mellitus (DM), congestive heart failure (CHF), previous venous thromboembolism (VTE), cirrhosis and use of antiplatelet drugs (aspirin/plavix/effient/brilinta). Dabigatran was the first DOAC to be introduced into clinical practice in Israel followed by rivaroxaban, and apixaban. Edoxaban is not marked in Israel and therefore, was not included in the study. Therefore, treatment assignment was identified by index prescription only after January 2014, when the use of all three drugs was available (Supplementary *eFigure 20*). The target trial emulation protocol is described in Supplementary *eTable 1*, as accepted in other observational emulation frameworks.[20]

DOACs dosage

AF treatment guidelines recommend using the lower dose of DOACs in certain clinical conditions.[8] For apixaban, a low dose is recommended for patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg or serum creatinine ≥1.5 mg/dL. For rivaroxaban low dose is recommended for patients with eGFR <50 mL/min/1.73 m^2. For dabigatran, a low dose is recommended for patients with at least 1 of the following characteristics: age > 80 years, concomitant treatment with verapamil, or eGFR 15-30 mL/min/1.73m^2.[8,21–23] Patients prescribed 20 mg of rivaroxaban, 5 mg of apixaban bid, or 150 mg of dabigatran bid were considered to be receiving a standard dose; Rivaroxaban 15 mg, apixaban 2.5 mg bid and dabigatran 110 mg bid were considered as reduced doses. We considered patients as receiving an appropriate dose when they received the recommended dose according to current guidelines. We considered patients as receiving inappropriate low doses while according to current guidelines they should have received a full dose, but in practice, they received a low dose. Finally, we considered patients as receiving an inappropriate full dose when patients should have received a low dose but in practice received a full dose (see Supplementary material).

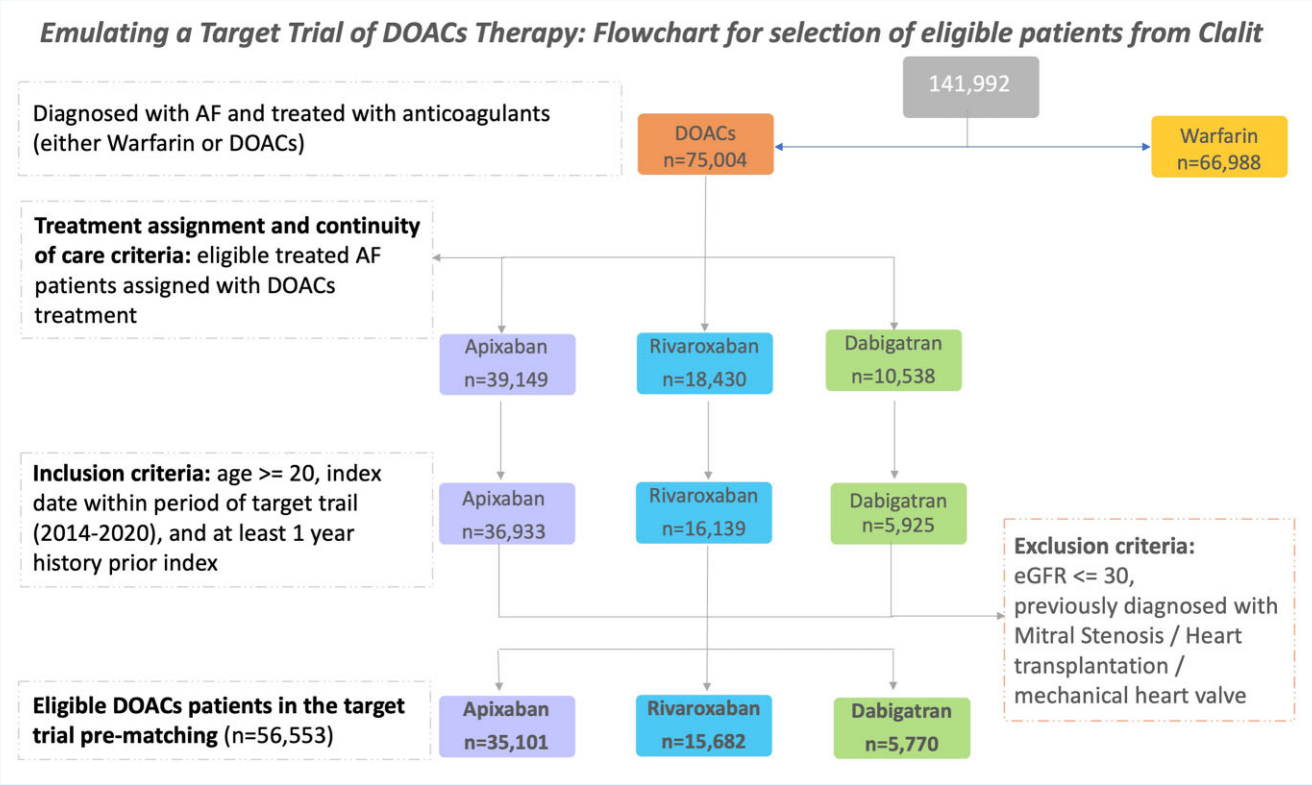


Figure 1 Flowchart for cohort selection. AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; DOACs, direct oral anticoagulants.

Evaluated outcomes

The efficacy outcomes were mortality, ischaemic stroke, myocardial infarction, or systemic embolism. The safety outcomes were gastrointestinal (GI) bleeding, intracranial haemorrhage (ICH), bleeding from other sites, and overall bleeding (GI bleeding, ICH, and bleeding from other sites). Regarding ICH, we included bleeding events that were not triggered by trauma or by ischaemic stroke, to exclude haemorrhagic transformation of ischaemic stroke. The ICD-9 codes used are listed in Supplementary *eTable 3* (see Supplementary material).

Sensitivity analysis

We performed two sensitivity analyses: (1) According to 3 different age groups (<70 years, 7080 years, 80 years and above), (Supplementary *eFigures 4–10*); (2) according to renal function (eGFR between 30 to 50 mL/min/1.73 m^2, eGFR≥ 50 mL/min/1.73 m^2), (Supplementary *eFigures 11–17*).

Negative controls

The validity of the observational associations and detection of unmeasured confounding was examined by a falsification hypothesis (negative control) by using the same observational matched cohorts and replicating the analytic approach. The prerequisite to proper falsification analyses was satisfied by identifying a hypothesis that tests a putative mechanism of potential bias.[24] Propensity Score Matching (PSM) based cohorts were tested for a potential mechanism of confounding, by running the analysis on a herpes zoster outcome (Supplementary *eFigure 3*), a relatively common diagnosis in adults unrelated to DOACs treatment, providing additional confidence that selection bias is not reflected among DOACs groups.

Statistical analysis

Study cohorts were generated following a PSM strategy (see online methods). The matched covariate distributions across each pair of treatment groups are shown in *Table 1* and Supplementary *eFigure 19*. KaplanMeier survival analysis of the three comparator DOACs cohorts was used to estimate the cumulative survival and time-to-event curves. Significance of the difference between survival functions was assessed using a log-rank test. We estimate the Average Treatment Effect (ATE) on several cardiac morbidities and mortality. Cox Proportional Hazards models were used to compare the outcome event risk of the comparator DOACs in each of the three matched cohorts. The hazard ratio (HR) and 95% confidence intervals (CIs) for each outcome of interest were calculated. All statistical tests were two-tailed.

Data extraction, pre-processing, and analytical approach were implemented using Python (version 3.63), Lifelines package,[25] (version 0.27.0), and causallib package (version 0.8.1).[26]

Results

Study population

Between 2010 and 2020, a total of 141 992 CHS members were treated with anticoagulants due to AF (*Figure 1*, Supplementary *eTable 2*). Of them, 68 450 patients were prescribed DOACs and 68 117 were assigned with an approved DOACs dosage for AF and therefore were eligible for the study. A total of 10 120 patients were excluded due to the target trial period, age, and an insufficient history of Clalit membership. Additionally, patients with a diagnosis of mitral stenosis ($n = 874$), heart transplantation ($n = 12$), insertion of mechanical valve ($n = 418$) or eGFR ≤ 30 ($n = 1\,222$) were excluded. Finally, 56 553 patients who received DOACs were eligible for the

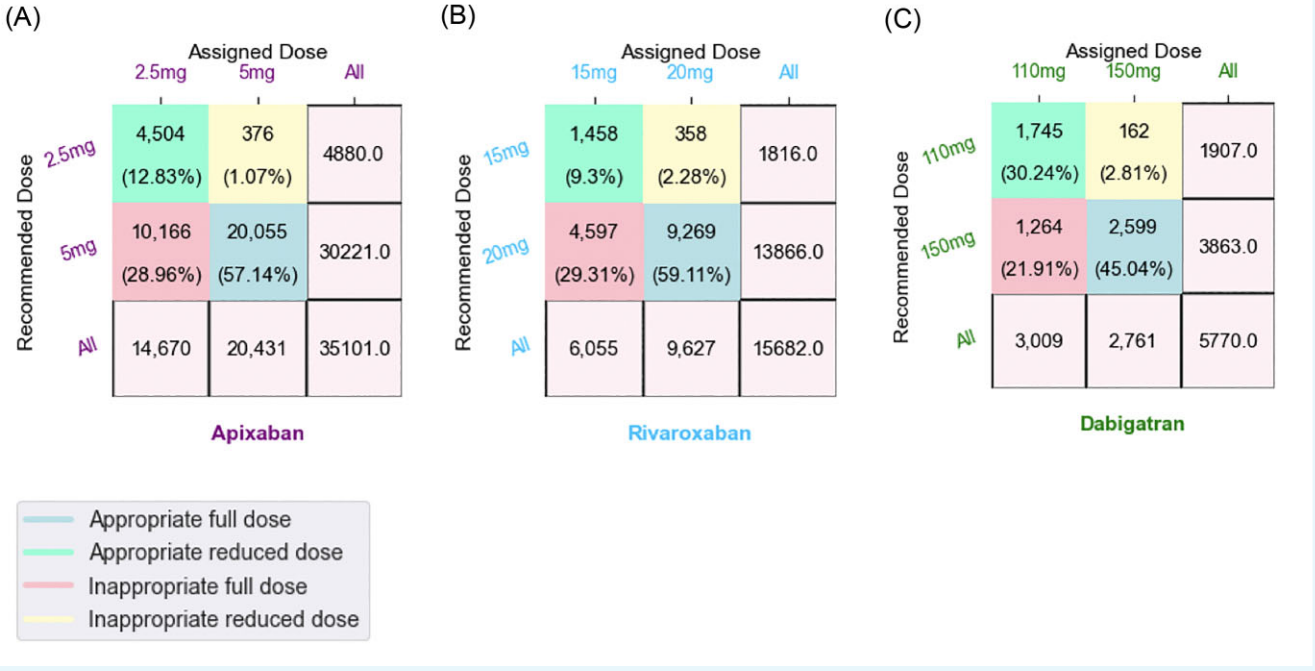


Figure 2 Recommended DOACs doses versus assigned doses. A contingency matrix of (*A*) apixaban, (*B*) rivaroxaban and (*C*) dabigatran treatment groups, displaying (x-axis) the frequency of patients by the dose they received ('assigned') and (y-axis) the distribution of patients by the recommended dose (as if dose assignment was according to guidelines). Patients prescribed 20 mg of rivaroxaban, 5 mg of apixaban, or 150 mg of dabigatran were considered to be receiving a 'full dose'; Rivaroxaban 15 mg, apixaban 2.5 mg and dabigatran 110 mg were considered as 'reduced doses'. Diagonal values showing the proportion of patients that received an 'appropriate dose' (full/reduced dose). Off diagonal values showing the percentage of patients receiving an 'inappropriate dose'. Patients that should have received a full dose, but in practice they received a low dose, are considered as 'inappropriate reduced dose'. Inappropriate full dose—when patients should have received a low dose but in practice received a full dose. Blue—appropriate full dose. Green—appropriate reduced dose. Pink—inappropriate full dose. Green—inappropriate reduced dose.

study (*Figure 1*). Protocol for Target Trial Emulation is presented in Supplementary *eTable 1*.[20]

Apixaban is more widely used in Israel, and is being prescribed for older patients with lower eGFR and higher CHA2DS2-VASc score (Supplementary *eTable 2*). Following a 1:1 propensity score matching of the treatment groups, a total of 31 336 (mean age 76.2 years), 11 534 (mean age 74.5 years), and 11 532 (mean age 74.5 years) patients were included in the apixaban/rivaroxaban, dabigatran/apixaban, and rivaroxaban/dabigatran comparison analyses, respectively. Baseline characteristics following 1:1 propensity score matching of the study groups are presented in *Table 1*.

Seventy-five percent of the patients assigned for dabigatran received appropriate doses (full/reduced) compared with lower rates of appropriate doses of 68.4 and 69.9% in both apixaban and dabigatran groups, respectively (*Figure 2*). The rates of inappropriate reduced doses were found to be higher than the rates of inappropriate full doses in all the studied groups. Inappropriate full doses of apixaban were lower (1%) compared with both rivaroxaban (2.2%) and dabigatran (2.8%) (*Figure 2*).

Study outcomes

The all-cause mortality rate in the rivaroxaban group was lower compared with apixaban (15.7 vs. 17.5 events per 1000 person-years; HR,0.88; 95% CI, 0.78–0.99; *P*,0.037; Supplementary *eFigure 1*, *Figure 3*A). The differences in the mortality rate, in favor of rivaroxaban, commenced in the third year of follow-up and was more pronounced in the younger subgroup (<70 years) (*P*,0.018; Supplementary *eFigure 4A*). There was no significant difference in all-cause mortality while comparing dabigatran with apixaban (12.3 vs. 14.0 events per 1000 person-years; HR,1.18; 95% CI, 0.94 – 1.48; *P*,0.158; Supplementary *eFigure 1*, *Figure 3*B) and dabigatran to rivaroxaban (13.0 vs. 12.3 events per 1000 person-years; HR,1.05; 95% CI, 0.84–1.31; *P*,0.654; Supplementary *eFigure 1*, *Figure 3*C).

Treatment with rivaroxaban compared with apixaban presented a lower rate of ischaemic stroke events (49.3 vs. 55.8 events per 1000 person-years; HR, 0.92; 95% CI, 0.86–0.99; *P*,0.024; Supplementary *eFigure 1*, *Figure 4*A). In subgroup analysis according to age, the results were significant in the age group of 70–80 years (*P*,0.002; Supplementary *eFigure 5A*). In addition, subgroup analysis according to eGFR demonstrated significant differences in favor of rivaroxaban in patients with eGFR≥ 50 mL/min/1.73 m^2 (*P*,0.027; Supplementary *eFigure 12A*). The results in patients with eGFR between 30 to 50 mL/min/1.73 m^2 were not significant (*P*,0.7; Supplementary *eFigure 12A*). In patients below the age of 70 years, similar superiority of rivaroxaban was noted compared with dabigatran (*P*,0.037; Supplementary *eFigure 12C*). The differences are overt even at short term follow-up (Supplementary *eFigure 12C*).

No significant differences in the rates of MI and systemic embolism were noticed between the different DOACs groups (*Figure 5*, Supplementary *eFigure 1*).

During six years of follow-up, no significant differences were observed in the rates of overall bleeding (*Figure 6*A, E, I). However, in subgroup analysis according to eGFR, in patients with impaired renal

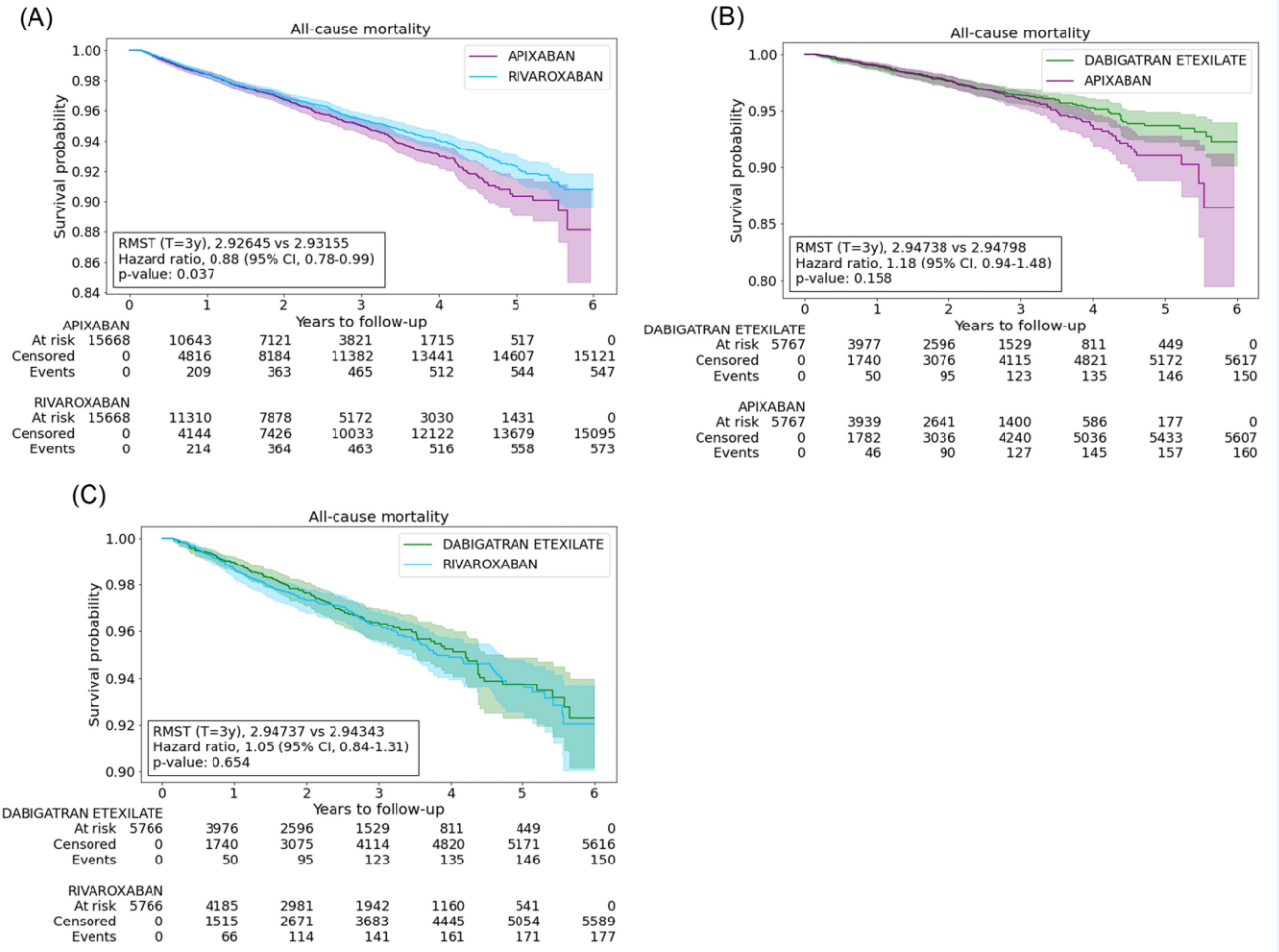


Figure 3 Propensity score matched KaplanMeier curves for all-cause mortality in patients with atrial fibrillation treated with DOACs. A six-year follow-up of (*A*) Apixaban vs. Rivaroxaban (*B*) Dabigatran vs. Apixaban (*C*) Dabigatran vs. Rivaroxaban. Right-censoring upon treatment discontinuation or due to loss to follow-up. Cohort size, proportion of outcomes and censor events reported in the target trial are detailed. RMST represents the average survival time from baseline to time t = 3 (years). Hazard ratio [95% CI] estimated by univariate cox modeling (significance assessed using log rank test). Green line—Dabigatran, purple line—Apixaban, blue line—Rivaroxaban. RMST, restricted mean survival time.

function with eGFR between 30 to 50 mL/min/1.73 m^2, the rate of overall bleeding events was higher in the dabigatran group compared with both apixaban and rivaroxaban ($P < 0.001$, Supplementary *eFigure 14B*, $P = 0.039$, Supplementary *eFigure 14C*; respectively).

The risk of ICH with rivaroxaban was lower compared with apixaban (9.4 vs. 11.6 events per 1000 person-years; HR,0.86; 95% CI, 0.74–1.0; *P*,0.044; *Figure* 6B). While comparing the rate of ICH events between rivaroxaban and dabigatran there was a trend in favor of rivaroxaban, however the results were not significant (10.25 vs. 13.3 events per 1000 person-years; HR, 0.81; 95% CI, 0.64–1.02; *P*, 0.06; Supplementary *eFigure 2*, *Figure* 6J). Nevertheless, in subgroup analysis according to age, the superiority of rivaroxaban was demonstrated compared with dabigatran, in the age group of 80 years and above (*P*,0.05; Supplementary *eFigure 8C*). The risk of GI bleeding was higher in the rivaroxaban group compared with the apixaban group (7.9 vs. 9.5 per 1000 person-years; HR, 1.22; 95% CI, 1.03–1.44; *P*, 0.016; Supplementary *eFigure 2*, *Figure* 6C). The results were significant even at a shorter follow-up period of 2 years (HR(t = 2), 1.34; $P < 0.005$), similar to a previous study by Ingason *et al.*[14] The differences in GI bleeding were pronounced in the older subgroup of patients, aged 80 years and above (*P*,0.036; Supplementary *eFigure 9A*) as well as in patients with eGFR≥ 50 mL/min/1.73 m^2 (*P*,0.023; Supplementary *eFigure 9A*). The risk of GI bleeding did not differ in a comparison between rivaroxaban and dabigatran (Supplementary *eFigure 2*, *Figure* 6K) and dabigatran vs. apixaban (Supplementary *eFigure 2*, *Figure* 6G). However, in subgroup analysis according to renal function, a favorable effect of apixaban compared with dabigatran was observed in patients with eGFR between 30 and 50 mL/min/1.73 m^2 (*P*,0.006; Supplementary *eFigure 16B*).

Negative control analysis showed a similar rate of herpes zoster infection in all three different DOACs groups (Supplementary *eFigure 3*).

Discussion

The current nationwide retrospective study, which included a total of 56 553/141 992 (39.8%) of patients treated with anticoagulants for AF, demonstrated significant differences in outcomes between the three different DOACs, rivaroxaban, apixaban and dabigatran, in the present

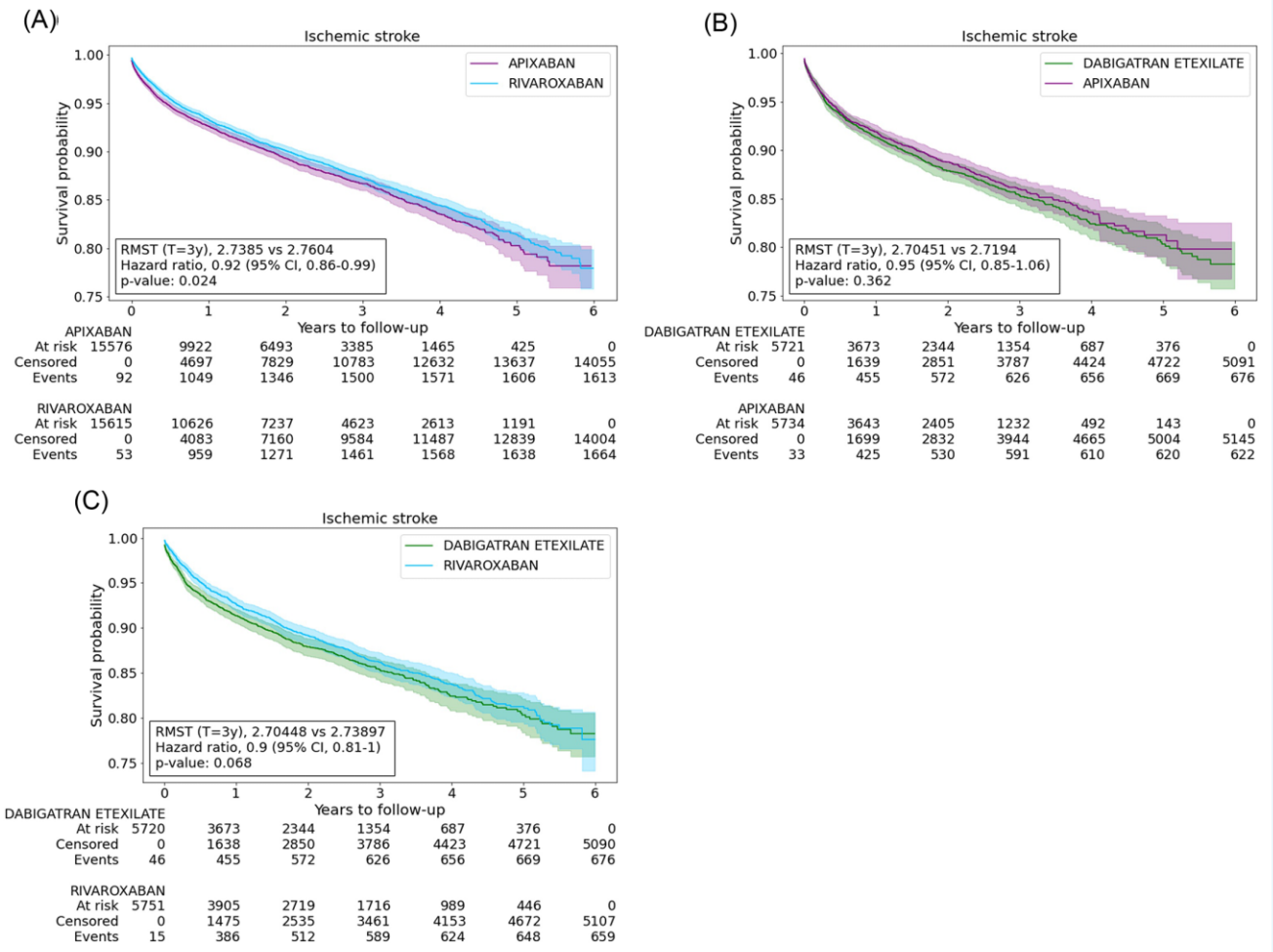


Figure 4 Propensity score matched KaplanMeier curves for ischaemic stroke in patients with atrial fibrillation treated with DOACs. A six-year follow-up of (*A*) Apixaban vs. Rivaroxaban (*B*) Dabigatran vs. Apixaban (*C*) Dabigatran vs. Rivaroxaban. Right-censoring in the event of death, upon treatment discontinuation or due to loss to follow-up. Cohort size, proportion of outcomes and censor events reported in the target trial are detailed. RMST represents the average survival time from baseline to time t = 3 (years). Hazard ratio [95% CI] estimated by univariate cox modeling (significance assessed using log rank test). Green line—Dabigatran, purple line—Apixaban, blue line—Rivaroxaban. RMST, restricted mean survival time.

cohort from Clalit database, as emphasized by the following main findings: (a) All-cause mortality risk was decreased in the rivaroxaban group compared with apixaban. We note that differences in survival were apparent after 3 years of follow-up. In age subgroup analysis, the reduced mortality risk of rivaroxaban compared with apixaban was significant at the younger age group of <70 years. (b) Ischaemic stroke risk in the rivaroxaban group was lower compared with apixaban. The risk for ischaemic stroke in the rivaroxaban group was also lower compared with dabigatran in the younger subgroup of patients <70 years. (c) Overall bleeding rate was higher in the dabigatran group, compared with both rivaroxaban and apixaban, in patients with impaired renal function (eGFR between 30 to 50 mL/min/1.73 m^2). (d) The risk for ICH among patients in the rivaroxaban group was significantly lower compared to apixaban. Decreased rate of ICH in the rivaroxaban group compared with dabigatran, was observed in age group of 80 years and above. (e) The risk for GI bleeding was lower in the apixaban group compared with the rivaroxaban group. The differences were pronounced at the older subgroup of patients (≥80 years). In addition, in patients with impaired renal function (eGFR between 30 and 50 mL/min/1.73 m^2), lower rate of GI bleeding was observed in apixaban compared with dabigatran.

Additionally, the present study showed that in the real world, >24% of AF patients are treated with DOACs off-label doses, with the majority being under-dosed. Patients treated with dabigatran demonstrated better dose adherence to guidelines compared with both apixaban and rivaroxaban. Dose adherence to the guideline was found to be associated with improved clinical outcomes in patients with AF, compared with off-label dosing which is expressed by under/overtreatment and associated with increased rate of adverse outcomes.[27,28] Therefore, this finding may have a favorable effect on both efficacy and safety outcomes rates in the dabigatran group.

Even though several previous retrospective cohort studies have already examined the comparative effectiveness and safety of DOACs in AF, the present study has several strengths and thus adds important evidence and some conflicting results that justify the need for future RCTs, in order to better guide the selection of different DOACs in clinical practice. First, we used the Clalit database, which is the largest

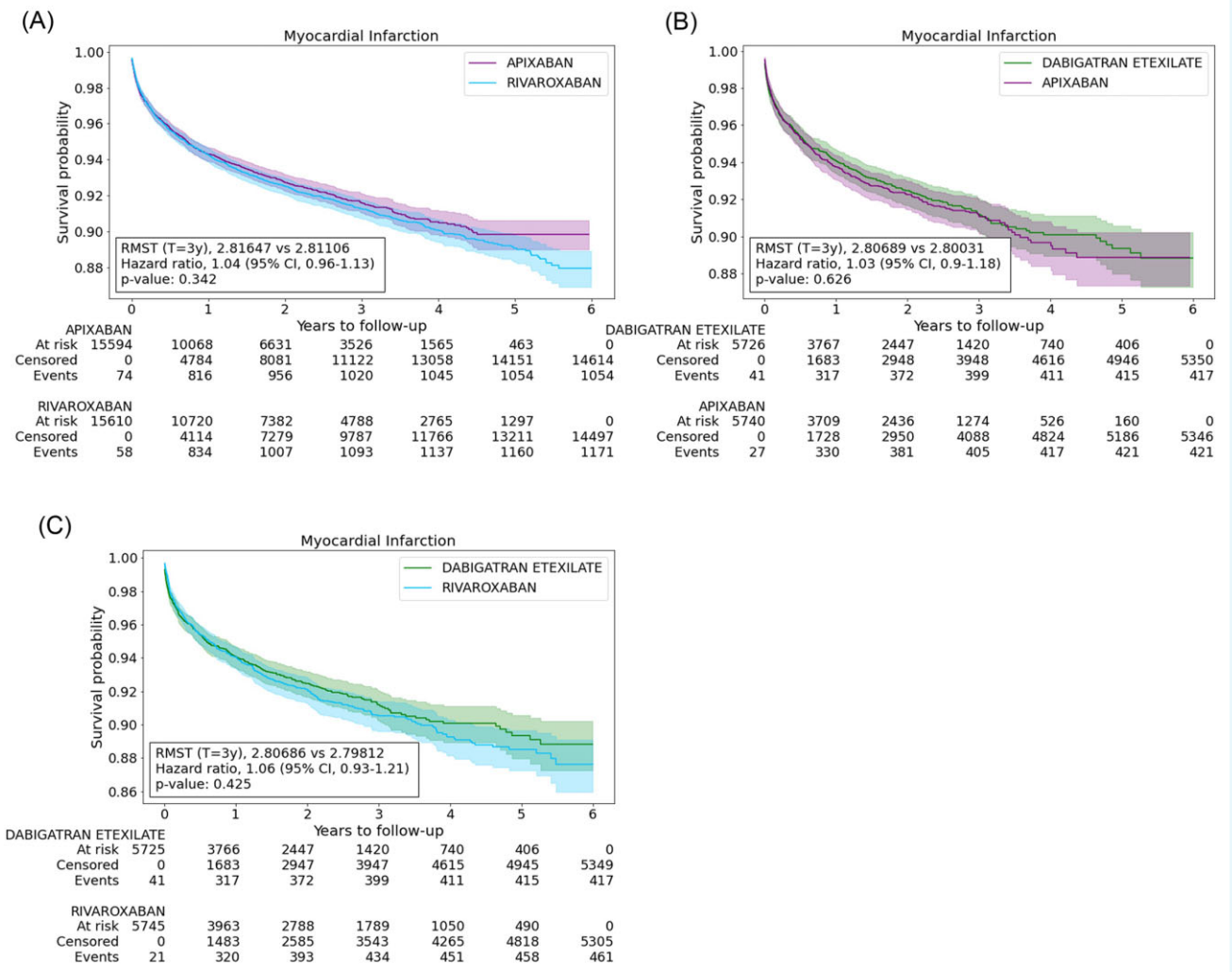


Figure 5 Propensity score matched KaplanMeier curves for myocardial infarction in patients with atrial fibrillation treated with DOACs. A six-year follow-up of (*A*) Apixaban vs. Rivaroxaban (*B*) Dabigatran vs. Apixaban (C) Dabigatran vs. Rivaroxaban. Right-censoring in the event of death, upon treatment discontinuation or due to loss to follow-up. Cohort size, proportion of outcomes and censor events reported in the target trial are detailed. RMST represents the average survival time from baseline to time t = 3 (years). Hazard ratio [95% CI] estimated by univariate cox modeling (significance assessed using log rank test). Green line—Dabigatran, purple line—Apixaban, blue line—Rivaroxaban. RMST, restricted mean survival time.

of four health organizations in Israel. Clalit provides medical services to ~52% of Israel's highly diverse population (4.7 million) and routinely digitizes curated health records to a single database. It maintains a community network of ~1600 clinics located throughout the country and also owns and operates a third of Israel's general hospital beds.[29] Previous studies that provided comparison assessment of the available DOACs often used an administrative claims database, which indeed included larger numbers of patients, yet the information per patient was limited in terms of confounders and follow-up data.[30] Second, the prescription entries in the database indicate medications dispensed by the patient de facto, which may proxy adherence of treatment and allow more accurate estimation of treatment effect. Third, the long follow-up period of 6 years revealed differences in mortality rates that are associated with prolonged use of the drugs, and probably therefore were not demonstrated in previous studies.[7–11] Fourth, we implemented a robust search technique, on the entire database of AF patients (hospitalized and outpatient clinic), to identify relevant ICD-9 codes of cardiovascular and bleeding events, and identified mortality events by integrating with the national death registry data.

Finally, we used the target trial framework to explicitly emulate an observational trial while taking into account lack of randomization (by propensity score matching) and confounding (via falsification endpoint study). To overcome adherence issues, we synchronized study 'time zero', eligibility criteria specification, and the treatment assignment by estimating analog of the per-protocol effect.[31] Such strategy also aims to reduce common biases such as selection and immortal time bias in the effect estimates.[16]

Our study has several limitations. The main limitation is the observational nature of the study, even though we used the target trial framework, and as such might still experience residual confounding even after adjustment for key patient covariates. Furthermore, the dabigatran group was significantly smaller compared with the rivaroxaban and apixaban groups, causing the head-to-head matched population with dabigatran to be smaller and less representative. The

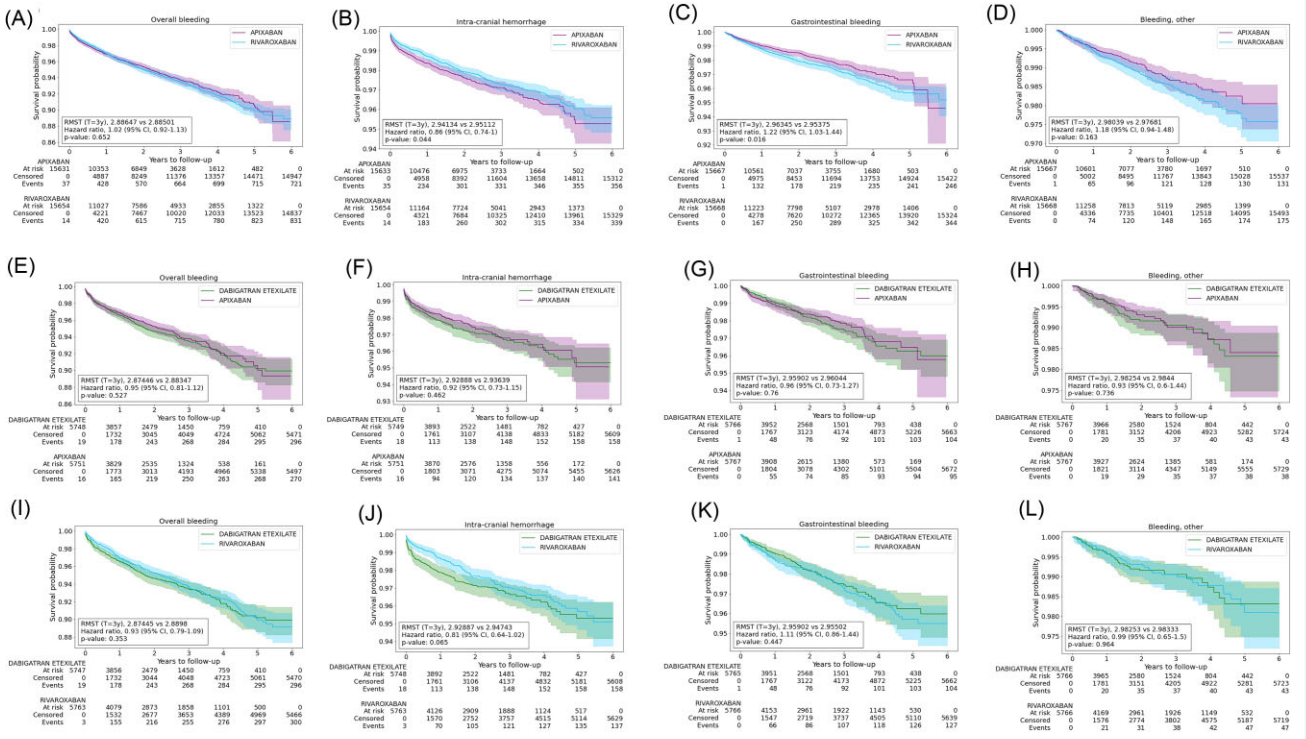


Figure 6 Propensity score matched KaplanMeier curves for total bleeding, intra-cranial haemorrhage, gastrointestinal bleeding and other bleeding in patients with atrial fibrillation treated with DOACs. A six-year follow-up of (*A, B, C, D*) Apixaban vs. Rivaroxaban (*E, F, G, H*) Dabigatran vs. Apixaban (*I, J, K, L*) Dabigatran vs. Rivaroxaban. Right-censoring in the event of death, upon treatment discontinuation or due to loss to follow-up. Cohort size, proportion of outcomes and censor events reported in the target trial are detailed. RMST represents the average survival time from baseline to time t = 3 (years). Hazard ratio [95% CI] estimated by univariate cox modeling (significance assessed using log rank test). Green line—Dabigatran, purple line—Apixaban, blue line—Rivaroxaban. RMST, restricted mean survival time.

differences in cohort sizes may also reflect the natural bias of clinicians in Israel towards a specific drug. Finally, a recent observational study among Medicare beneficiaries aged 65 years or older with AF showed that treatment with rivaroxaban compared with apixaban was associated with a significantly increased risk of major ischaemic or haemorrhagic events in the apixaban group in a 4 years follow-up;[32] Seemingly, these findings are inconsistent with the present study, however, our results showed that both age and follow-up period may affect the risk for ischaemic stroke and bleeding, respectively, and our cohort is not aligned with the Medicare cohort accordingly. In addition, unlike the present study, Ray *et al.* combined both efficacy and safety outcomes.[32]

To conclude, the present study from Clalit database demonstrated differences in outcomes between all available DOACs in Israel (apixaban, rivaroxaban, and dabigatran). The long follow-up data of 6 years may reveal differences in mortality risk in favor of rivaroxaban that were not demonstrated in previous studies in which the follow-up period was shorter. We showed that the differences in mortality and ischaemic stroke are age-related. In addition, the bleeding rates were higher in the dabigatran group in patients with impaired renal function and in elderly (80 years and above). A comparison between apixaban and rivaroxaban revealed decreased GI bleeding in the apixaban group, and on the other hand, decreased ICH in the rivaroxaban group. We believe that the present study emphasizes the need for future RCTs that will compare apixaban, rivaroxaban and dabigatran in order to better guide the use of the different DOACs in clinical practice.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Conflict of interest: The authors have nothing to declare.

Data availability

The data that support the findings of this study originate from Clalit Healthcare Services. All data analyses were conducted on a secured, de-identified dedicated server within the Clalit Healthcare environment. Requests for access to all of parts of the Clalit datasets should be addressed to Clalit Healthcare Services, via the Clalit Research Institute.

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Prevalence and Predictors of Nonadherence to Direct Oral Anticoagulant Treatment in Patients with Atrial Fibrillation

Sabine F. B. van der Horst[1,*] Tim A.C. de Vries[2,3,4,*] Gordon Chu[1,5] Roisin Bavalia[6,7] Helen Xiong[8] Kayleigh M. van de Wiel[8] Kelly Mulder[8] Hanne van Ballegooijen[8] Joris R. de Groot[2,3] Saskia Middeldorp[9] Frederikus A. Klok[1] Martin E.W. Hemels[4,10] Menno V. Huisman[1]

[1] Department of Thrombosis and Hemostasis, Leiden UMC, Leiden, The Netherlands
[2] Department of Clinical and Experimental Cardiology and Cardiothoracic Surgery, Amsterdam UMC location University of Amsterdam, Heart Center, Amsterdam, The Netherlands
[3] Amsterdam Cardiovascular Sciences, Heart Failure and Arrhythmias, Amsterdam, The Netherlands
[4] Department of Cardiology, Hospital Rijnstate, Arnhem, The Netherlands
[5] Department of Internal Medicine, Alrijne Hospital, Leiden, The Netherlands
[6] Department of Vascular Medicine, Amsterdam UMC location University of Amsterdam, The Netherlands
[7] GGD Amsterdam, Amsterdam, The Netherlands
[8] IQVIA Netherlands, Amsterdam, The Netherlands
[9] Department of Internal Medicine, Radboudumc, Nijmegen, The Netherlands
[10] Department of Cardiology, Radboudumc, Nijmegen, The Netherlands

Address for correspondence Sabine F. B. van der Horst, MD, Department of Medicine—Thrombosis and Hemostasis, Leiden University Medical Center, Albinusdreef 2, 2300 RC Leiden, The Netherlands (e-mail: s.f.b.van_der_horst@lumc.nl).

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Abstract

Background For most patients with newly diagnosed atrial fibrillation (AF), direct oral anticoagulants (DOACs) are preferred over vitamin K antagonists. However, there is concern that the lack of monitoring may impair therapy adherence and therefore the anticoagulant effect.

Objective To assess 1-year DOAC nonadherence in patients with AF and a treatment indication of at least 1 year in the Dutch health care setting, and to identify predictors of nonadherence.

Methods We performed a near-nationwide historical cohort study in patients with a novel DOAC indication for AF. Data were obtained from a pharmacy database, covering 65% of all outpatient prescriptions dispensed in the Netherlands. The 1-year nonadherence was assessed by the proportion of days covered; the threshold was set at $<80\%$. Robust Poisson regression analyses were performed to identify predictors of nonadherence.

Results A total of 46,211 patients were included and the 1-year nonadherence was 6.5%. We identified male sex (risk ratio [RR] 1.23, 95% confidence interval [CI]: 1.15–1.33), younger age (age $\geq$60 to $<$70 years: RR: 1.15, 95% CI: 1.00–1.33, age $<$60 years: RR: 2.22, 95% CI: 1.92–2.57; reference age $\geq$85 years), a reduced DOAC dose (RR: 1.10, 95% CI: 1.00–1.22), a twice-daily dosing regimen (RR: 1.21, 95% CI: 1.12–1.30), and treatment with apixaban (RR: 1.16, 95% CI: 1.06–1.26, reference rivaroxaban) or dabigatran (RR: 1.25, 95% CI: 1.14–1.37) as independent predictors of 1-year nonadherence.

Keywords
- direct oral anticoagulant
- anticoagulants
- medication adherence
- atrial fibrillation

[*] *Co-first authorship.*

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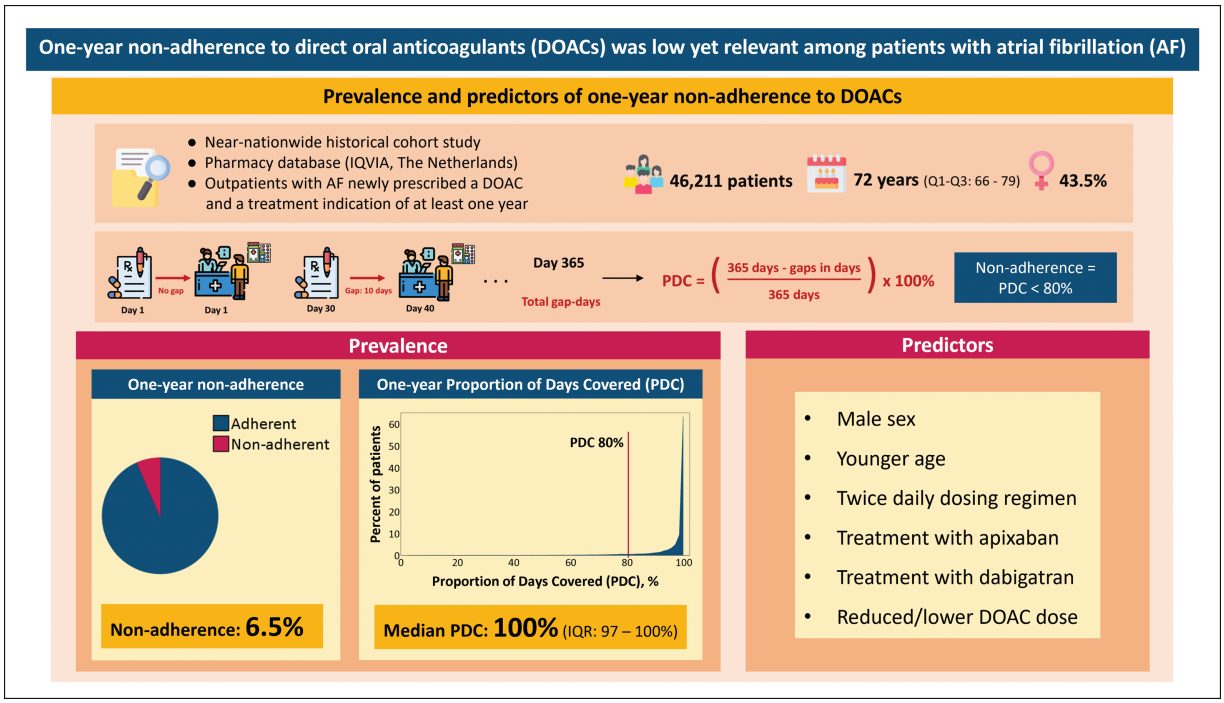
Conclusion One-year nonadherence to DOACs was low yet relevant in patients with AF newly prescribed a DOAC. Understanding the predictors for nonadherence may help identify patients at risk.



Introduction

Direct oral anticoagulants (DOACs) are indicated for the prevention of thrombotic complications in patients with atrial fibrillation (AF) and are preferred over vitamin K antagonists (VKAs) as anticoagulant treatment in most anticoagulation-naïve patients with this arrhythmia.[1] This is because DOACs, compared to VKA targeted at an international normalized ratio of 2.0 to 3.0, were are at least as effective and had a better safety profile.[2–5] In a meta-analysis, DOACs reduced the endpoint of stroke or systemic embolism by 19%, showed a strong trend toward fewer major bleedings, and mortality was significantly lower as compared to VKAs.[6] Moreover, DOACs have an improved ease of use due to the fixed dosing regimen, obviating the need for routine laboratory monitoring.

Yet, there is concern that the lack of monitoring may impair therapy adherence. Two systematic reviews and meta-analyses suggest that roughly 30% (range: 5–59%) of patients treated with a DOAC are nonadherent within the first year of treatment, defined as medication possession ratio (MPR) or proportion of days covered (PDC) of <80%.[7,8] As a consequence of therapy nonadherence, the risk of thromboembolic complications could potentially increase.[9] The increased thrombotic risk might be enhanced by the shorter plasma elimination half-life and concomitant limited duration of anticoagulant effect of DOACs compared to VKAs. Identifying the patients at risk of becoming nonadherent and implementing strategies to reinforce adherence may therefore further optimize anticoagulant care. Since several studies show that education, reminders, and active monitoring improve adherence in patients using a DOAC, it is important to identify those patients who could benefit from such interventions.[10,11] Previous research has focused on elucidating predictors for nonadherence, and adherence was found to vary significantly between patients using various DOACs. There is evidence that patients treated with twice-daily dosed DOACs, especially dabigatran, are less likely to adhere to treatment, with studies showing that nonadherence (PDC/MPR < 80%) is present in up to half of these patients.[12–17]

Nonetheless, most prior studies on DOAC nonadherence in patients with AF did not consider the indicated treatment duration when assessing the prevalence of 1-year nonadherence. Among patients with AF, temporary treatment indications with a DOAC, such as cardioversion or ablation, are common. When these patients are included in 1-year nonadherence assessments, PDC decreases leading to an inadvertent increase in the nonadherence prevalence. To get a better understanding of nonadherence among AF patients who receive long-term treatment with a DOAC, it is important to evaluate 1-year nonadherence in patients who actually have a treatment indication for at least 1 year.

To this end, we performed a historical cohort study using dispensing data from a Dutch representative nationwide pharmacy database. We aimed to determine the prevalence

of therapy nonadherence to DOACs in outpatients with AF newly initiated on a DOAC for at least 1 year, and to identify potential predictors of such nonadherence at the time DOAC treatment was initiated in these patients.

Methods

Study Design and Data Source

We performed a historical cohort study using data from IQVIA's Xtrend Real-World Data Longitudinal Prescription database (Xtrend-LRx, Amsterdam, The Netherlands). This dataset comprises prescription records, including patient characteristics (age, sex), dispensing details (pharmacy, prescription, and dispensing data) and medication specifics (name, dose, strength, therapy duration). All data in the database were provided by pharmacies and were first pseudonymized by a third party before being incorporated into the dataset. The database covers approximately 65% of all prescriptions filled by outpatients in the Netherlands, represented by retail pharmacies, outpatient hospital pharmacies, and dispensing general practitioners (►**Supplementary Fig. S1**). Per October 1, 2014, patients were given a unique identifier ensuring longitudinal follow-up for each patient, even if those who collected prescriptions at different affiliated pharmacies during the study period. Data of pharmacies that failed to provide uninterrupted data for the entire study duration were excluded from the dataset.

Study Population

All patients who filled their first DOAC prescription between November 1, 2014 and October 31, 2019 were identified from the Xtrend-LRx database. The European Pharmaceutical Market Research Association Anatomical Classification System (EPHMRA ATC, 2018) was used to identify the DOACs of interest: apixaban (ATC B01AF02), dabigatran (ATC B01AE07), edoxaban (ATC B0AF03), and rivaroxaban (ATC B01AF01).[18] Patients were eligible for inclusion if they were newly starting a DOAC (i.e., no DOAC prescription fill within the 12 months prior to the initial fill) and had a treatment indication of at least 1 year (i.e., a prescription fill of the same DOAC 12 months after the initial fill). To this end, a look-back and look-forward period of 12 months was implemented and only patients with an initial prescription fill between November 1, 2015 and October 31, 2019 were included. Patients who met any of the following criteria were excluded: (1) those aged <18 years; (2) patients who collected more than one type of oral anticoagulation at the time of the initial DOAC prescription fill; and (3) patients with an initial DOAC treatment indication other than AF or with a dosing regimen not approved for AF. A decision tree model was developed, based on dosing regimen, treatment duration, and pretreatment with low-molecular-weight heparin, to estimate the most probable indication for treatment with a DOAC (►**Supplementary Table S1**, ►**Supplementary Fig. S2**).[19–21]

Baseline Characteristics and Outcome

We collected baseline data on demographics (i.e., age and sex) and on the initially filled DOAC prescription (i.e., type, dose, dosing frequency, clinical field of the prescriber, prescription date, number of pills). DOAC dosing regimens were classified as either standard dose, reduced dose based on clinical characteristics (for apixaban, edoxaban, and rivaroxaban), or lower dose (dabigatran 110 mg twice daily), in accordance with The European Heart Rhythm Association Practical Guide (►**Supplementary Table S1**).[19] Baseline was defined as the day of the first filled DOAC prescription.

The primary outcome of the study was 1-year nonadherence, defined as <80% of days per year covered by filled prescriptions of the index DOAC. We calculated the PDC as follows: total number of days covered by index medication, divided by 365 days. The first DOAC prescription was defined as index medication and the date the prescription was filled as the index date. The estimated duration of DOAC prescriptions was calculated based on the prescription date, days of supply, and the dosing regimen. Subsequent dispensing data were assessed to identify gaps in DOAC treatment. If the prior prescription ended prior to the subsequent dispensing date, it was considered a gap. An overlap, defined as a prior prescription extending past the subsequent dispensing date resulting in a surplus, was considered to carry-over to the subsequent prescription.

Statistical Analysis

The demographic and clinical characteristics of the study population at baseline were expressed as either frequencies and percentages, means with standard deviations (SD), or medians with interquartile intervals (Q1–Q3), for the overall group, adherent patients (PDC $\geq$ 80%), and nonadherent patients (PDC $<$ 80%). The Kruskal–Wallis test and the chi-square test were used to compare the PDC and nonadherence rates across the different DOACs, respectively. A p-value less than 0.05 was considered statistically significant. The dataset did not contain any missing values.

Univariable and multivariable robust Poisson regression analyses were performed to identify predictors of nonadherence and to calculate risk ratios (RRs) and their corresponding 95% confidence intervals (95% CIs). The following potential predictors of nonadherence were selected based on existing evidence and expert opinion: age, sex, type of DOAC, dosing regimen, and dose reduction. To avoid multicollinearity, we performed two separated multivariable regression analyses, with either the specific DOACs used or dosing regimen (i.e., once or twice daily [QD/BID]) as potential predictors for nonadherence.[22] In the analysis by DOAC type, rivaroxaban was considered as a reference category due to the once-daily dosing regimen and group size. To allow for a nonlinear relationship with the outcome of interest (nonadherence), age was modelled using a restricted cubic spline function. The knot locations were kept standard and were based solely on the number of knots of the optimal fit, defined as the model with the lowest Bayesian Information Criterion value. Age was categorized based on these knot locations and clinical applicability. All statistical analyses were conducted using R (version 4.1.2.) within RStudio (version 2022.07.2) or SPSS (version 25.0).

Results

Patient Selection and Baseline Characteristics

Overall, a total of 147,719 patients filled their first DOAC prescription between November 1, 2015 and October 31, 2019. After excluding patients with a treatment indication or follow-up duration of less than 1 year ($n = 90,674$), those aged <18 years ($n = 7$), those who were prescribed more than one type of anticoagulation at the time of the initial DOAC prescription fill ($n = 20$), those with a treatment indication other than AF based on the decision tree ($n = 7,494$), and those with a dosing regimen not approved for AF ($n = 3,313$), a total of 46,211 patients were included in the analysis (►**Fig. 1**). The baseline characteristics are presented in ►**Table 1**. The median age was 72 years (Q1–Q3: 66–79 years) and the majority of patients were male (56.5%). The most commonly initially collected DOAC was rivaroxaban (35.8%), followed by apixaban (33.3%), dabigatran (24.1%), and edoxaban (6.8%). A reduced or lower DOAC dose was prescribed to 20.6% of patients.

Nonadherence

The overall median PDC was 100% (Q1–Q3: 97–100%). Using a PDC threshold of <80%, 6.5% of the patients were nonadherent after 1 year of treatment. Nonadherent patients were younger (median age: 70 years vs. 73 years) and more often male (62.9 vs. 56.1%). Moreover, a twice-daily dosing regimen of DOACs (62.9 vs. 58.5%) was more common among nonadherent patients (►**Table 1**). The 1-year prevalences of nonadherence were 6.6, 7.4, 5.6, and 5.9% ($p < 0.001$) for apixaban, dabigatran, edoxaban, and rivaroxaban, respectively (►**Table 2**).

Predictors of Nonadherence

In multivariable robust Poisson regression analysis, male sex (RR: 1.23, 95% CI: 1.15–1.33), age ≥60 to <70 years (RR: 1.15, 95% CI: 1.00–1.33; reference age ≥85 years), age <60 years (RR: 2.22, 95% CI: 1.92–2.57), dabigatran (RR: 1.25, 95% CI: 1.14–1.37, reference rivaroxaban), apixaban (RR: 1.16, 95% CI: 1.06–1.26), and a reduced or lower dose (RR: 1.10, 95% CI: 1.00–1.22) were independent predictors of nonadherence.

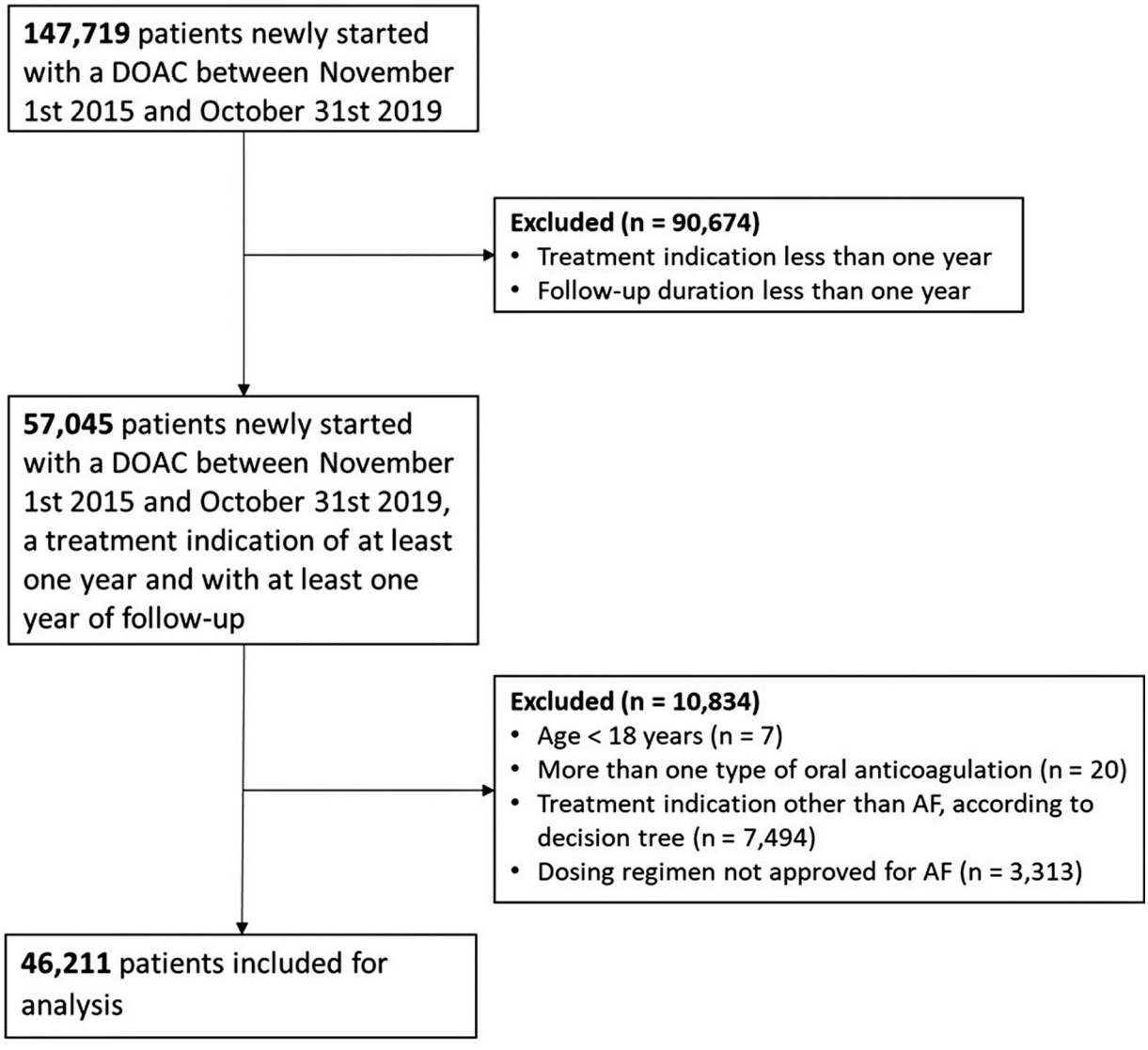


Fig. 1 Flow diagram of patient inclusion and exclusion.

Table 1 Clinical characteristics of the enrolled patients

Characteristics	Overall ($n = 46,211$)	Adherent ($n = 43,205$)	Non-adherent ($n = 3,006$)
Age at index in years, median (Q1 - Q3)	72 (66–79)	73 (66–80)	70 (61–78)
Age category at index in years, *n* (%)			
<60	5,468 (11.8)	4,805 (11.1)	663 (22.1)
≥60 to <70	12,057 (26.1)	11,300 (26.2)	757 (25.2)
≥70 to <85	23,429 (50.7)	22,133 (51.2)	1,296 (43.1)
≥85	5,257 (11.4)	4,967 (11.5)	290 (9.6)
Male, *n* (%)	26,126 (56.5)	24,235 (56.1)	1,891 (62.9)
Type of DOAC, *n* (%)			
Apixaban	15,757 (34.1)	14,710 (34.0)	1,047 (34.8)
Dabigatran	11,422 (24.7)	10,578 (24.5)	844 (28.1)
Edoxaban	3,437 (7.4)	3,243 (7.5)	194 (6.5)
Rivaroxaban	15,595 (33.7)	14,674 (34.0)	921 (30.6)
DOAC dosing frequency, *n* (%)			
Once daily	19,032 (41.2)	17,917 (41.5)	1,115 (37.1)
Twice daily	27,179 (58.8)	25,288 (58.5)	1,891 (62.9)
DOAC dosing, *n* (%)			
Standard dose	36,700 (79.4)	34,292 (79.4)	2,408 (80.1)
Reduced/lower dose	9,511 (20.6)	8,913 (20.6)	598 (19.9)
Adherence			
Number of gaps, median (Q1 - Q3)	0.0 (0.0–1.00)	0.0 (0.0–1.0)	2.0 (1.0–3.0)
Gaps in days, median (Q1 - Q3)	0.0 (0.0–10.0)	0.0 (0.0–7.0)	116 (90.0–164.0)
PDC in %, median (Q1 - Q3)	100 (97–100)	100 (98–100)	68 (55–75)
Adherent, *n* (%)	43,205 (93.5)	43,205 (100)	0 (0.0)
Nonadherent, *n* (%)	3,006 (6.5)	0 (0.0)	3,006 (100)

Abbreviations: DOAC, direct oral anticoagulant; n, number; PDC, proportion of days covered; SD, standard deviation.
Note: Data are presented as mean (SD) or number (%).

Table 2 Proportion of days covered (PDC) and nonadherence by type of direct oral anticoagulant (DOAC)

	Overall	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	*p*-Value
PDC in %, median (Q1 - Q3)	100 (97–100)	100 (97–100)	100 (96–100)	100 (98–100)	100 (98–100)	<0.001
Nonadherence, %	6.5%	6.6%	7.4%	5.6%	5.9%	<0.001

Note: *p*-Values were calculated by Kruskal–Wallis test (PDC) and chi-square test (nonadherence).

When including dosing regimen instead of specific DOAC into the multivariable model, a twice-daily dosing regimen was an independent predictor of nonadherence (RR: 1.21, 95% CI: 1.12–1.30) (►**Table 3**).

Discussion

We performed this near-nationwide historical cohort study to determine the prevalence of therapy nonadherence to DOACs in outpatients with AF, and to identify potential predictors of such nonadherence at the time DOAC treatment was initiated.

Nonadherence is supposed to be a major concern among patients using DOACs. The absence of immediate and observable benefits from thromboembolic prophylaxis may lead to a lack of motivation to continue taking oral anticoagulation as prescribed. Additionally, the long-term treatment indication may make it difficult for patients to maintain adherence over time. The lack of need for routine monitoring may further contribute to nonadherence in patients using DOACs, since monitoring can serve as an active reminder for patients to take their anticoagulant. Moreover, missing one or a few doses may reduce the anticoagulant effect of DOACs more than it would of VKAs

Table 3 Univariable and multivariable logistic regression analyses to identify predictors of nonadherence

	Univariable analysis	Multivariable analysis by type of DOAC	Multivariable analysis by dosing regimen
	RR (95% CI)	RR (95% CI)	RR (95% CI)
Age—in years			
≥85	Reference (1.00)	Reference (1.00)	Reference (1.00)
≥70 to <85	1.00 (0.89–1.13)	1.01 (0.89–1.16)	1.02 (0.90–1.17)
≥60 to <70	1.14 (1.00–1.30)	1.15 (1.00–1.33)	1.17 (1.01–1.35)
<60	2.20 (1.92–2.51)	2.22 (1.92–2.57)	2.25 (1.95–2.60)
Sex, male	1.30 (1.21–1.40)	1.23 (1.15–1.33)	1.24 (1.15–1.33)
Type of DOAC			
Rivaroxaban	Reference (1.00)	Reference (1.00)	N.a.
Edoxaban	0.96 (0.82–1.11)	0.95 (0.82–1.10)	N.a.
Dabigatran	1.25 (1.14–1.37)	1.25 (1.14–1.37)	N.a.
Apixaban	1.13 (1.03–1.23)	1.16 (1.06–1.26)	N.a.
DOAC dosing frequency			
Once daily	Reference (1.00)	N.a.	Reference (1.00)
Twice daily	1.19 (1.11–1.28)	N.a.	1.21 (1.12–1.30)
DOAC dosing			
Standard dose	Reference (1.00)	Reference (1.00)	Reference (1.00)
Reduced/lower dose	0.96 (0.88–1.05)	1.10 (1.00–1.22)	1.13 (1.02–1.24)

Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; N.a., not applicable; RR, risk ratio.
Note: Univariable and multivariable robust Poisson regression analyses were performed to identify predictors of nonadherence and to calculate risk ratios (RRs) and their corresponding 95% confidence intervals (95% CIs).

because of two reasons. First, the administered dose of VKAs is adjusted based on the measured anticoagulant activity, whereas for DOACs the anticoagulant is not routinely assessed. Second, DOACs have a more rapid onset and offset of effect than VKAs due to differences in their mechanism of action and elimination half-lives. Being able to identify patients at risk of becoming nonadherent to implement targeted adherence, reinforcing strategies may contribute to the optimalization of anticoagulant care and the prevention of thromboembolic events.

In the 46,211 AF patients newly prescribed a DOAC and receiving at least 1 year of treatment in the Netherlands, the prevalence of 1-year nonadherence was 6.5%. We identified male sex, younger age, a twice daily dosing regimen, treatment with apixaban or dabigatran, and a reduced or lower DOAC dose as independent predictors of 1-year nonadherence.

Prevalence of 1-Year Nonadherence

The treatment nonadherence found in our study is in line with that of a previous pharmacy-based study in Swedish (nonadherence percentage: 5.5%, mean MPR: 96.0% ± 7.8) and Dutch AF patients (nonadherence percentage: 7.4%, mean MPR: 95.1% ± 10.1) using DOACs.[23] Interestingly, another study showed significantly lower nonadherence rates in cohorts of AF patients in the Netherlands (1-year nonadherence: QD/BID users 6%/9%; mean PDC: QD 96% ± 10, BID 95% ± 13) compared to cohorts in Italy (1-year nonadherence: QD/BID: 11%/12%) and Germany (1-year nonadherence: QD/BID: 18%/38%).[24] However, higher nonadherence estimates have been described in the literature as well. Even though median MPR (95.2%, interquartile range: 87.8–99.7%) was still high in a pharmacy-based Belgian study ($n = 766$ patients), the percentage of nonadherent patients (13%) was higher compared to our study.[25] Other studies found 1-year mean PDCs/MPRs of around 85% and nonadherence percentages of approximately 25%, with (similar to our results) even worse adherence in patients prescribed dabigatran.[9,12,26–29]

Given that follow-up duration and the criteria used to define nonadherence (PDC or MPR <80%) in both our study and the aforementioned studies were comparable, it is plausible that there are additional factors contributing to the variations in nonadherence estimations. First, the availability of a unique patient identifier allowed us to follow up patients even when they switched to another pharmacy. Second, the 12-month look-forward period enabled us to only include those patients with a treatment indication for the specific DOAC for at least 1 year. Most prior studies on nonadherence to DOAC therapy did not take into account the indicated treatment duration. As a result, patients without a DOAC indication for at least 1 year, but a need for anticoagulation prior to electrical cardioversion or ablation, may have been included in these studies and could have inadvertently increased the number of nonadherent patients. For instance, a large population-based study in the Netherlands

($n = 43{,}910$) reported a nonadherence percentage of 24%. However, when excluding patients who completely discontinued treatment within the first year ($n = 23{,}098$), the nonadherence rate was 3% with a mean PDC of 0.97.[29] Additionally, upon excluding patients who discontinued treatment (no refill 12 months after the initial prescription), our study population consisted of patients who were more likely to adhere to treatment, potentially leading to overestimation of adherence. Lastly, the observed discrepancies could potentially be attributed to differences in the methodologies utilized for gathering data on adherence. For instance, in the study by Banerjee et al, dispensing data (data on actual prescription fills) were lacking and adherence was estimated from the available prescription data.[12] Consequently, the results relating to adherence may be relatively less accurate when compared to our study.

Although the prevalence of 1-year nonadherence to DOACs of 6.5% may appear low, our findings indicate that a relevant proportion of patients with AF remain at risk of thromboembolic events for a notable part of the year. With a PDC threshold of 80%, patients classified as being nonadherent did not have their DOAC stocked at home for at least 73 days of the year. Additionally, the presence of medication at home does not guarantee (proper) intake. Thus, it is reasonable to assume that the actual prevalence of AF patients at risk of thromboembolic events due to inappropriate DOAC intake is likely higher. Therefore, the topic of therapy adherence, particularly among patients at risk of becoming nonadherent, warrants special attention in the outpatient setting.

Predictors of 1-Year Nonadherence

While some studies, including our own, reported that men are more likely to be nonadherent, the majority of earlier performed studies did not report any sex-related differences in adherence or even elucidated female sex as a predictor for nonadherence.[12,30,31] Previous studies have shown that women with AF are older, have more comorbidities, and have a greater risk of thromboembolic events.[32] This apparent sex-related difference could be, partially, attributed to these factors instead, as comorbidities and a higher stroke risk have been found to be associated with higher adherence.[28] Moreover, findings from prior reports suggest that men may have a four times increased risk of poor self-care compared to women, which may impair adherence to DOAC therapy as well.[33]

In accordance with existing literature, twice-daily compared with once-daily dosing regimens and the two corresponding DOACs apixaban and dabigatran were associated with an increased prevalence of nonadherence.[12–17,23,24] Nonadherence is often unintentional, and it is understandable that the risk of forgetting a dose is higher with a twice-daily dosing regimen.[34] This was previously reported in patients prescribed other cardiovascular medication as well, where adherence declined with increasing number of doses per day.[35] Another explanation for nonadherence in patients prescribed dabigatran could be the presence of adverse effects, mainly dyspepsia, which is reported to occur more often in patients using this specific DOAC.[2,36]

A reduced or lower DOAC dose was another predictor of nonadherence. Depending on the DOAC prescribed and the guideline adhered to, dose reduction is recommended in patients with a history of bleeding. It is reasonable to hypothesize that such patients are more aware of the risk of bleeding complications associated with anticoagulant therapy, and even minor bleeding complications may make these patients hesitant to take their DOAC as prescribed. Additionally, patients who are prescribed a reduced or lower dose, mostly based on comorbidities, may be more likely to experience intercurrent hospital admissions, which can lead to gaps in the uptake of medication and (inadvertent) higher rates of nonadherence.

Moreover, younger patients were found to be less adherent to treatment in our study, consistent with previous research.[8,29,34] This finding is surprising, given that the elderly population is often assumed to be more susceptible to forgetfulness of medication intake. However, comorbidities and thromboembolic complications of AF are more prevalent in patients over 60 years of age.[37] Thus, older patients may have a greater appreciation for the beneficial effects of oral anticoagulant therapy compared to younger patients, who may be relatively free of comorbidities and less aware of the risks of nonadherence. Additionally, polypharmacy is more common among patients aged 60 years or older. These patients may therefore be more accustomed to taking medication; medication might play a greater role in their lives as compared with patients who do not have concomitant drug use. In line with this, there is evidence that the earlier mentioned dosage related decline in adherence becomes less apparent with increasing age.[35] Both increasing age and polypharmacy might be factors supporting the implementation of measures to improve medication management and therapy adherence, such as enhanced social control, medication rolls, and pillboxes. In our study, however, data on supportive measures for medication intake were not available.

Strengths and Limitations

The population-based study design allowed us to investigate adherence in a large population of unselected participants receiving a DOAC. The main strengths of our study are its large sample size, the availability of a unique patient identifier providing individual patient linkage between different affiliated pharmacies, and the selection of patients with a treatment indication for at least 1 year. In contrast to most previous studies, dispensing information remained available even when patients switched pharmacies. Consequently, our study's dispensing data and derived adherence calculation were comparatively more accurate than those of prior investigations. Additionally, excluding patients with temporary indications for anticoagulant therapy allowed us to focus on nonadherence over a 1-year period among patients with an actual treatment indication for at least 1 year. Lastly, by excluding data of pharmacies that failed to provide uninterrupted data for the entire study duration, we increased the validity of our results.

However, our study has also limitations. First, adherence was based on dispensing data and PDC. On one hand, medication refill does not equate to medication consumption, hence missing doses may remain unnoticed. On the other hand, a gap between refills was automatically regarded as sub-optimal medication intake; reasonable explanations such as peri-operative discontinuation or an intercurrent hospital admission were not taken into account. Therefore, adherence could have been both overestimated and underestimated. However, other available nonadherence measurement tools, such as adherence questionnaires, have disadvantages as well, as they rely on subjective patient-reported nonadherence rates. Similarly, announced "pill counting" methods can disrupt daily practice and potentially lead to overestimation of adherence due to socially desirable behavior or "pill dumping." The PDC measurement tool allowed us to objectively assess therapy nonadherence in daily clinical practice within a near-nationwide cohort. Moreover, it is important to note that the PDC, along with the 80% threshold, is endorsed as the standard and most appropriate method for medication adherence calculation by the Pharmacy Quality Alliance. Therefore, this approach has been widely used in other studies within this field, including research involving patients treated with DOACs.[38] Second, it is worth noting that the pharmacy database used in our study did not contain data regarding the reasons for nonadherence or clinical outcomes, such as ischemic events. Nonetheless, understanding the underlying causes and potential clinical implications of nonadherence is of utmost significance, and we recognize it as a valuable avenue for future research. Additionally, patients without an indication for DOAC treatment for at least 1 year could have been included in this study. Theoretically, patients undergoing an electrical cardioversion or ablation at the start and at 12 months, without an indication for anticoagulant therapy in between, did fulfill inclusion criteria for the current analysis. This could have resulted in lower estimated than actual adherence. Lastly, direct data on the primary indication for DOAC treatment were unavailable. Instead, a decision tree based on dosing regimens approved for AF was used. Even though the criteria were most sensitive to patients with AF, we cannot rule out that we may have excluded some patients being treated with a DOAC because of AF or included some patients with a different indication in our analyses.

Conclusion

In this near-nationwide cohort of AF patients newly initiated on a DOAC for at least 1 year, the prevalence of 1-year nonadherence was low yet relevant. Male sex, younger age, a twice daily dosing regimen, treatment with apixaban or dabigatran, and a reduced DOAC dose were independent predictors of nonadherence. These predictors may help identify patients at risk for becoming nonadherent. In order to reduce thromboembolic complications, interventions to reinforce adherence, such as recurrent counseling sessions and medication-taking reminders, might be specifically targeted at these patients.

What Is Known about This Topic?

- Among patients with atrial fibrillation (AF) who are prescribed direct oral anticoagulants (DOACs), previous studies have reported highly variable rates of nonadherence within the first year of treatment (5–59%).
- There is a gap in current research on DOAC nonadherence in patients with AF, as most prior studies have not accounted for the indicated treatment duration when assessing 1-year nonadherence rates.

What Does This Paper Add?

- In this near-nationwide study, the prevalence of 1-year nonadherence was 6.5% among patients with AF newly prescribed a DOAC and receiving at least 1 year of treatment.
- Independent predictors for 1-year nonadherence were: male sex, younger age, a twice daily dosing regimen, treatment with apixaban or dabigatran, and a reduced or lower DOAC dose.
- Due to therapy nonadherence a relevant proportion of patients with AF remain at risk of thromboembolic events for a notable part of the year. We recommend that clinicians give special attention to this issue in the outpatient clinic.

Author Contributions
All authors have contributed to the concept and design of the study. S.F.B.v.d.H., T.A.C.d.V. and G.C. conducted the analyses. S.F.B.v.d.H., T.A.C.d.V., G.C., H.X., K.M.v.d.W., H.v.B., and M.V.H. contributed to the interpretation of data. S.F.B.v.d.H. wrote the first draft of the manuscript. T.A.C.d.V., G.C., R.B., H.X., K.M.v.d.W., K.M., H.v.B., J.R.d.G., S.M., F.A.K., M.E.W.H., and M.V.H. contributed to critical revision of the manuscript for important intellectual content and gave approval of the final version to be published. M.V.H. was the study supervisor.

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Conflict of Interest
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ORIGINAL RESEARCH

Rivaroxaban vs Vitamin K Antagonist in Patients With Atrial Fibrillation and Advanced Chronic Kidney Disease

Reinhold Kreutz, MD, PhD,[a] Gilbert Deray, MD, PhD,[b] Jürgen Floege, MD,[c] Marianne Gwechenberger, MD, PhD,[d] Kai Hahn, MD, PhD,[e] Andreas R. Luft, MD, PhD,[f,g] Pontus Persson, MD, PhD,[h] Christoph Axthelm, MD, PhD,[i] Juerg Hans Beer, MD,[j,k] Jutta Bergler-Klein, MD,[d] Nicolas Lellouche, MD, PhD,[l] Jens Taggeselle, MD, PhD,[m] Craig I. Coleman, PharmD, PhD,[n,o] Jan Beyer-Westendorf, MD, PhD,[p] XARENO registry

ABSTRACT

BACKGROUND Treatment with vitamin K antagonists (VKAs) has been linked to worsening of kidney function in patients with atrial fibrillation (AF).

OBJECTIVES XARENO (Factor XA-inhibition in RENal patients with non-valvular atrial fibrillation Observational registry; NCT02663076) is a prospective observational study comparing adverse kidney outcomes in patients with AF and advanced chronic kidney disease receiving rivaroxaban or VKA.

METHODS Patients with AF and an estimated glomerular filtration rate (eGFR) of 15 to 49 mL/min/1.73 m^2 were included. Blinded adjudicated outcome analysis evaluated adverse kidney outcomes (a composite of eGFR decline to <15 mL/min/1.73 m^2, need for chronic kidney replacement therapy, or development of acute kidney injury). A composite net clinical benefit outcome (stroke or systemic embolism, major bleeding, myocardial infarction, acute coronary syndrome, or cardiovascular death) was also analyzed. HRs with 95% CIs were calculated using propensity score overlap weighting Cox regression.

RESULTS There were 1,455 patients (764 rivaroxaban; 691 VKA; mean age 78 years; 44% females). The mean eGFR was 37.1 ± 9.0 in those receiving rivaroxaban and 36.4 ± 10.1 mL/min/1.73 m^2 in those receiving VKA. After a median follow-up of 2.1 years, rivaroxaban was associated with less adverse kidney outcomes (HR: 0.62; 95% CI: 0.43-0.88) and all-cause death (HR: 0.76, 95% CI: 0.59-0.98). No significant differences were observed in net clinical benefit.

CONCLUSIONS In patients with AF and advanced chronic kidney disease, those receiving rivaroxaban had less adverse kidney events and lower all-cause mortality compared to those receiving VKA, supporting the use of rivaroxaban in this high-risk group of patients. (JACC Adv 2024;3:100813) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

From the [a]Charité - Universitätsmedizin Berlin, Institute of Clinical Pharmacology and Toxicology, Berlin, Germany; [b]Department of Nephrology, Pitié-Salpêtrière Hospital, Paris, France; [c]Division of Nephrology and Clinical Immunology, RWTH Aachen University Hospital, Aachen, Germany; [d]Division of Cardiology, University Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria; [e]Nephrologische Praxis, Dortmund, Germany; [f]Klinik für Neurologie, Universitätsspital Zürich, Zürich, Switzerland; [g]Cereneo, Center for Neurology and Rehabilitation, Vitznau, Switzerland; [h]Institut für Vegetative Physiologie, Charité - Universitätsmedizin Berlin, Berlin, Germany; [i]Cardiologicum Pirna & Dresden, Dresden, Germany; [j]Department Innere

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ABBREVIATIONS AND ACRONYMS

ASD = absolute standardized difference

CKD = chronic kidney disease

DOAC = direct oral anticoagulant

eGFR = estimated glomerular filtration rate

KRT = kidney replacement therapy

OAC = oral anticoagulation

OLW = overlap weighting

VKA = vitamin k antagonist

The prevalence of both atrial fibrillation (AF) and chronic kidney disease (CKD) increases with advanced age and these patients are at increased risk for both thrombotic and bleeding events.[1,2] Nevertheless, long-term oral anticoagulation (OAC) is utilized in most patients with AF and CKD to prevent thromboembolic stroke and systemic embolism. As CKD increases bleeding risk, patients with AF and advanced CKD stages ≥4 represent a high-risk population for which treatment decisions for or against OAC are especially challenging.[3,4]

OAC with vitamin K antagonists (VKAs) has been associated with accelerated calcification of coronary and extra-coronary arteries[5,6] as well as cardiac valves.[7,8] A systematic review and meta-analysis revealed a significantly elevated OR (1.8, IQR: 1.43-2.24) for extra-coronary calcifications in patients treated with a VKA as compared to patients without anticoagulation or receiving other anticoagulants.[9] The observed accelerated decline of kidney function in patients with AF and CKD treated with VKA[10] has also been attributed to these vascular side effects of VKA. However, there are additional concerns about the risk of anticoagulation nephropathy[11,12] during VKA treatment, although this condition may develop in response to any anticoagulant.[13] It has been specifically associated with overdosing of VKA with international normalized ratio levels above the therapeutic range.[10-12] However, studies have demonstrated that, compared to VKA, OAC with direct oral anticoagulants (DOACs) has less impact on renal function decline.[14-19] DOACs including rivaroxaban may not only lack a detrimental effect on arterial calcification but may even induce kidney sparing or preserving effects attributable to inhibition of protease-activated receptor-mediated pro-inflammatory effects in the vasculature[20] and in early vascular aging in CKD.[21]

Available large registries assessing the effectiveness and safety of OAC in patients with AF included only a small proportion of patients with concomitant advanced CKD. Hence, in the large GARFIELD-AF (Global Anticoagulant Registry in the Field-Atrial Fibrillation) registry, physicians classified 10.9% of patients as having moderate-to-severe CKD,[22] while only a minor group (1.7%) of the overall population (564 from 33,024 patients) were diagnosed with advanced CKD 4 or 5 (ie, with estimated glomerular filtration rates [eGFRs] <30 mL/min/1.73 m^2). Similarly, the large PREFER (PREvention oF Thromboembolic Events-European Registry in Atrial Fibrillation) multicenter registry of 6,412 AF patients included only a small portion of 842 (13.1%) patients with chronic kidney failure, while CKD stages were not further classified.[3] The XARENO registry (Factor XA-inhibition in RENal patients with non-valvular atrial fibrillation Observational registry) is the first prospective registry specifically focused on AF patients with advanced stages of CKD receiving rivaroxaban or VKA with an adjudicated blinded analyses of outcomes.

METHODS

STUDY DESIGN. XARENO was an investigator-initiated, multicenter, prospective, noninterventional study conducted in Europe (Germany, Austria, Switzerland, France, Belgium, and Luxembourg).[23] Management of patients was at the discretion of the participating physicians. The study was registered with clinical trials.gov (NCT02663076).

Inclusion criteria were a diagnosis of AF as diagnosed by the participating physicians, adult age (≥18 years), and an eGFR between 15 and 49 mL/min/1.73 m^2 as estimated by the Chronic Kidney Disease Epidemiology Collaboration equation[24] and an indication for anticoagulation. The XARENO protocol was approved by all responsible independent ethic committees and informed consent was obtained for all recruited patients. The study protocol has been reported (Supplemental Appendix).[23] To be included, patients had to be treated with rivaroxaban or VKA for at least 3 months prior to enrollment. Patients continued their ongoing anticoagulation

Medizin, Kantonsspital Baden, Baden, Switzerland; [k]Center of Molecular Cardiology, University of Zürich, Zürich, Switzerland; [l]Service de Cardiologie 1, Centre Hospitalier Universitaire Henri Mondor, Créteil, France; [m]Praxis Dr med. Jens Taggeselle, Markkleeberg, Germany; [n]Department of Pharmacy Practice, University of Connecticut School of Pharmacy, Storrs, Connecticut, USA; [o]Evidence-Based Practice Center, Hartford Hospital, Hartford, Connecticut, USA; and the [p]Department of Medicine I, Division Thrombosis & Hemostasis, University Hospital Carl Gustav Carus Dresden, Dresden, Germany.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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treatment regimen when consented into XARENO (Supplemental Figure 1). Prespecified follow-up was at least 12 months followed by a planned extended data collection period for 1 up to 2 additional years.

OUTCOMES. The primary outcome of interest was the absolute change in eGFR in mL/min/1.73 m^2 (as estimated by the Chronic Kidney Disease Epidemiology Collaboration equation)[24] at 12 months. Clinical outcomes including any adverse kidney outcome, a composite of chronic kidney replacement therapy (KRT), an eGFR <15 ml/min/1.73 m^2, or acute kidney injury, net clinical benefit, a composite of stroke or other thromboembolic events, major bleeding, and all-cause mortality, and each composite's individual component. Baseline characteristics were analyzed using descriptive statistics. Categorical variables were reported as percentages and continuous variables as mean ± SD or median (IQR), where appropriate.

PROPENSITY SCORE OVERLAP WEIGHTING ANALYSIS. To adjust for imbalances in patient characteristics between the rivaroxaban and VKA arms at baseline, we calculated propensity scores[25] based upon multivariable logistic regression using 42 distinct demographic, comorbidity, laboratory, and concurrent medication variables known to be risk factors for differential OAC exposure (**Table 1**, Supplemental Appendix). Estimated propensity scores were subsequently used to weight patients for analysis using overlap weighting (OLW).[26] Propensity score OLW assigns weights to patients proportional to their probability of belonging to the opposing treatment cohort (ie, rivaroxaban patients were weighted by the probability of receiving VKA (or 1−the propensity score) and VKA patients were weighted by the probability of receiving rivaroxaban (the propensity score). OWL was chosen as the primary method for confounder adjustment because it allows for all eligible patients to be included in the analysis (unlike propensity score matching which typically results in sample size reduction in one or both cohorts), it assigns greater weight to patients in which treatment cannot be predicted and lesser weight to patients with extreme propensity scores preventing outliers from dominating the analysis and decreasing precision (a concern with inverse probability weighting) and because overlap weighting has the favorable property of resulting in the exact balance (absolute standardized differences [ASDs] = 0%) for all variables included in the multivariable logistic regression model used to derive propensity scores.

STATISTICAL ANALYSIS. All analyses used the intention-to-treat dataset. The difference in mean change in eGFR from baseline between groups was compared using a Student's *t*-test. Clinical outcomes were compared between groups using a propensity score OWL Cox proportional hazards regression model using a robust estimator. Patients were censored in the Cox models at the time of outcome occurrence, death, or end of study follow-up. Results are presented as HRs and corresponding 95% CIs. The proportionality assumption was assessed by evaluating Schoenfeld residuals and was not significant for any outcome. As a post hoc sensitivity analysis, we constructed a Fine and Gray competing risk regression model for the outcome of any adverse kidney outcome controlling for death. All database management and statistical analysis were performed using SAS version 9.4 (SAS Institute). No statistical adjustments for multiple hypothesis testing were performed. The modest sample size precluded meaningful subgroup analyses according to patient characteristics. A strength of the study was its prospective design with blinded adjudicated outcome analyses.

RESULTS

PATIENT CHARACTERISTICS BEFORE AND AFTER OLW. Overall 1,455 patients receiving either rivaroxaban (N = 764) or a VKA (N = 691) were included in the study and available for propensity score OLW outcome analysis (**Figure 1**). Patient characteristics including demographics, comorbidities, and comedications prior and following OLW are summarized in **Table 1**. Patients in rivaroxaban and VKA arms differed as evidenced by multiple variables with an ASD >10% prior to OLW, while patient characteristics were well-balanced (ASD = 0%) for all covariates entered in the propensity score model after OLW.

Prior to OLW, the mean age of patients in the VKA group was 78.5 ± 7.6 years and somewhat higher as compared to rivaroxaban patients 77.7 ± 7.4 years. At baseline, 94% of patients had eGFR values below 45 mL/min/1.73 m^2, that is, were in CKD stage ≥3b. Mean eGFR after OLW at baseline was 37.1 ± 9.0 in the rivaroxaban and 36.4 ± 10.1 mL/min/1.73 m^2 in the VKA group. After 12 months, the mean eGFR change from baseline in the rivaroxaban group was +0.46 ± 9.46 mL/min/1.73 m^2 and +0.27 ± 8.66 mL/min/1.73 m^2 in the VKA group (group difference 0.19; 95% CI: −1.70 to 2.08 mL/min/1.73 m^2; $P = 0.85$). Following OLW, the distribution of comorbidities including hypertension, diabetes, myocardial infarction, heart failure, and a history of stroke was similar between groups. Accordingly, the median CHA_2DS_2-VASc scores were 4 (IQR 3-5) in both

TABLE 1 Patient Characteristics Prior to and Following Propensity Score Overlap Weighting

	Prior OLW			Following OLW		
	Rivaroxaban (n = 764)	VKA (n = 691)	ASD %	Rivaroxaban (n = 764)	VKA (n = 691)	ASD %
Demographics						
Age, y	77.7 ± 7.4	78.5 ± 7.6	**10.7**	78.2 ± 7.2	78.2 ± 7.5	0
Age ≥75 y	70.7%	74.7%	9.0	73.2	73.2	0
Male	54.3%	57.5%	6.3	56.3	56.3	0
Ethnicity, White	98.4%	99.0%	4.9	99.0	99.0	0
AF type						
Persistent/permanent	48.4%	57.0%	**17.3**	54.2	54.2	0
Paroxysmal	48.7%	41.5%	**14.4**	43.9	43.9	0
Unknown	2.9%	1.4%	9.9	2.0	2.0	0
Time since AF diagnosis						
<2 y	34.2%	21.0%	**29.8**	26.5	26.5	0
2 to <5 y	32.1%	34.2%	4.4	32.5	32.5	0
≥5 y	31.8%	42.7%	**22.7**	38.7	38.7	0
Unknown	2.0%	2.2%	1.5	2.3	2.3	0
Time since CKD diagnosis						
<2 y	55.2%	44.6%	**21.4**	50.0	50.0	0
≥2 y	42.3%	52.8%	**21.2**	47.4	47.4	0
Country						
Germany	61.9%	56.4%	**11.1**	61.9	61.9	0
France	24.2%	30.8%	**14.8**	25.8	25.8	0
Austria	8.5%	6.9%	5.8	7.0	7.0	0
Belgium	4.1%	3.2%	4.7	3.3	3.3	0
Switzerland	1.3%	2.6%	9.4	2.0	2.0	0
Unknown	2.5%	2.6%	0.7	2.6	2.6	0
Alcohol use						
None	75.1%	76.3%	2.6	76.4	76.4	0
Yes	17.8%	19.4%	4.1	18.3	18.3	0
Unknown	7.1%	4.3%	**11.8**	5.3	5.3	0
Smoker						
Never	65.1%	63.2%	3.8	64.6	64.6	0
Former	28.0%	31.3%	7.1	29.1	29.1	0
Current	3.3%	3.2%	0.5	3.3	3.3	0
Unknown	3.7%	2.3%	7.9	3.0	3.0	0
BMI						
<30 kg/m^2	58.6%	62.7%	8.2	61.6	61.6	0
30-39.9 kg/m^2	36.3%	31.5%	**10.0**	32.8	32.8	0
≥40 kg/m^2	3.7%	4.6%	4.8	4.3	4.3	0
Unknown	1.4%	1.2%	2.5	1.3	1.3	0
eGFR						
<15 mL/min/1.73 m^2	0.1%	1.3%	**13.9**	0.3	0.3	0
15-19.9 mL/min/1.73 m^2	1.7%	8.1%	**30.0**	3.3	3.3	0
20-29.9 mL/min/1.73 m^2	11.1%	26.5%	**40.1**	17.5	17.5	0
30-39.9 mL/min/1.73 m^2	33.1%	25.6%	**16.5**	31.1	31.1	0
40-49.9 mL/min/1.73 m^2	35.2%	21.7%	**30.3**	29.1	29.1	0
≥50 mL/min/1.73 m^2	7.1%	3.9%	**13.9**	5.0	5.0	0
Unknown	11.6%	12.9%	3.8	13.6	13.6	0

Continued on the next page

TABLE 1 Continued

	Prior OLW			Following OLW		
	Rivaroxaban (n = 764)	VKA (n = 691)	ASD %	Rivaroxaban (n = 764)	VKA (n = 691)	ASD %
Comorbidities						
Hypertension	79.7%	80.6%	2.2	79.8	79.8	0
Diabetes	39.3%	41.7%	4.9	40.9	40.9	0
Any coronary artery disease	28.0%	32.1%	9.0	30.5	30.5	0
Myocardial infarction	11.9%	14.3%	7.2	11.6	11.6	0
Percutaneous coronary intervention	16.0%	18.1%	5.6	17.2	17.2	0
Coronary bypass grafting	7.1%	10.7%	**12.8**	9.3	9.3	0
Ischemic stroke	8.2%	7.1%	4.3	7.3	7.3	0
Intracranial hemorrhage	0.4%	0.7%	4.4	0.7	0.7	0
Heart failure	21.7%	22.7%	2.4	22.5	22.5	0
Peripheral artery disease	8.8%	9.1%	1.2	8.6	8.6	0
Prior venous thromboembolism	5.9%	8.4%	9.7	7.3	7.3	0
Chronic lung disease	11.0%	10.4%	1.9	11.0	11.0	0
Cancer	12.2%	9.7%	7.9	10.6	10.6	0
Anemia	3.8%	7.4%	**15.7**	5.0	5.0	0
Liver dysfunction	3.3%	4.3%	5.6	4.0	4.0	0
Osteoporosis	2.7%	2.2%	3.7	2.3	2.3	0
Comedications						
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	69.9%	66.3%	7.8	69.2	69.2	0
Beta-blocker	78.3%	79.7%	3.6	79.7	79.7	0
Calcium channel blocker	31.9%	30.1%	4.0	31.6	31.6	0
Diuretic	76.4%	85.4%	**22.9**	82.7	82.7	0
Amiodarone	21.1%	19.7%	3.5	20.3	20.3	0
Other anti-arrhythmic medication	6.8%	3.6%	**14.4**	4.6	4.6	0
Statin	54.5%	56.9%	4.9	55.8	55.8	0
Low-dose aspirin	7.9%	11.4%	**12.1**	9.6	9.6	0
P2Y12 inhibitor	8.1%	6.4%	6.7	7.3	7.3	0
Nonsteroidal anti-inflammatory	5.0%	5.5%	2.4	5.3	5.3	0
Insulin	19.2%	20.1%	2.2	19.6	19.6	0
Other diabetic medication	22.1%	21.1%	2.4	22.2	22.2	0
Erythropoietin	1.6%	4.8%	**18.4**	2.3	2.3	0
Vitamin D supplementation	18.3%	23.3%	**12.3**	19.9	19.9	0

Values are mean ± SD or %. ASD values of at least 10% are given in **bold**.

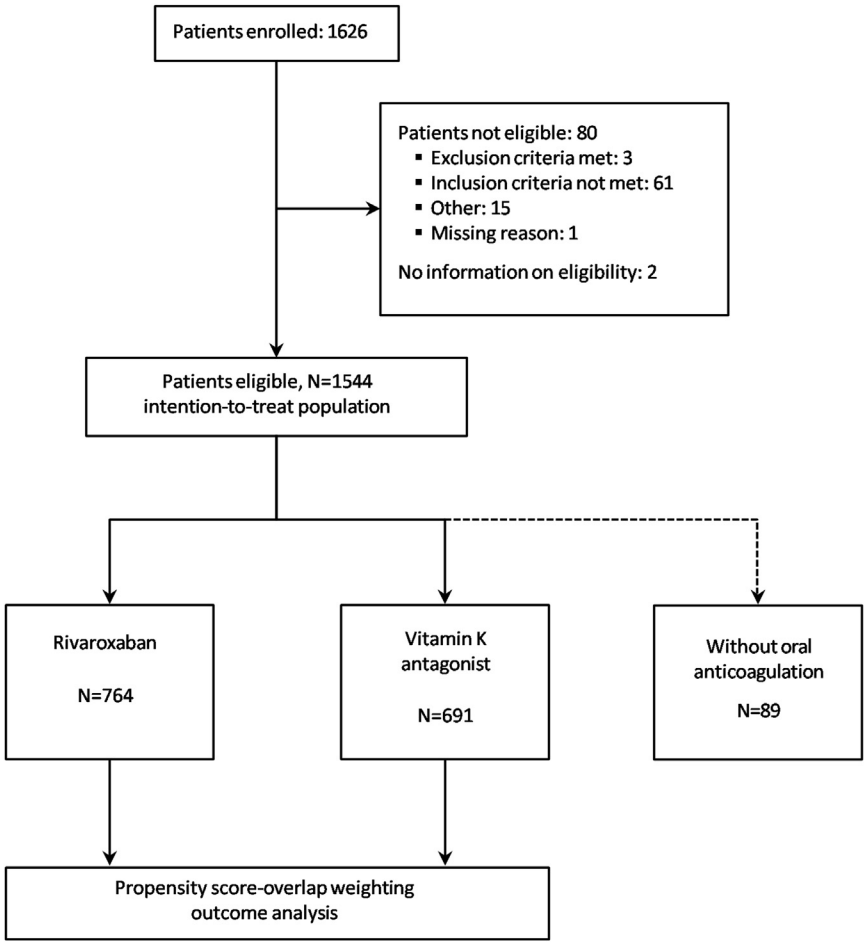
AF = atrial fibrillation; ASD = absolute standardized difference; BMI = body mass index; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; OLW = overlap weighting; VKA = vitamin K antagonist.

rivaroxaban and VKA groups. The median mHAS-BLED scores were 2 (IQR 1-2) in both groups. The median time of follow-up was 757 (IQR 444-1,043) days for the total study population and 777 (IQR 497-1,083) days for rivaroxaban vs 745 (IQR 389-1,022) days for VKA.

MEDICATION USE. Of the 764 patients who received rivaroxaban, 610 patients (79.8%) received the 15 mg and 117 patients (15.3%) the 20 mg dose (Table 2). Different VKA agents were used in the VKA group, reflecting known differences in clinical practice in participation countries. The median (25%, 75% range) time-in-therapeutic range for the 691 VKA patients was 62.6% (35.7%, 82.0%). The use of any antiplatelet drugs (either low-dose aspirin or a P2Y12 inhibitor was similar between groups.

OUTCOMES. Weighted Cox regression analyses showed that rivaroxaban as compared to VKA was associated with significant reductions in adverse kidney outcomes (Table 3) including a significant 38% hazard reduction for the composite of any adverse kidney outcome (HR: 0.62; 95% CI: 0.43-0.88), a 61% reduction in the need for chronic KRT (HR: 0.39; 95% CI: 0.17-0.89) (Central Illustration), and a 49% reduction in the hazard of renal decline to an eGFR <15 mL/min/1.73 m^2 (HR: 0.51; 95% CI: 0.35-0.76) (Table 3, Figure 2). No significant difference in acute kidney injury was observed between the

FIGURE 1 Flow Diagram With Patient Disposition in the XARENO Registry



The flow of patients who particpated in the registry is shown, including the number originally enrolled, and eligible participants included into the intention-to-treat population. The small group of 89 patients that were not treated with anticoagulation at the discretion of participating physicians were according to the study protocol[23] not included in the propensity score overlap weighting outcome analysis. XARENO = Factor XA-inhibition in RENal patients with non-valvular atrial fibrillation Observational registry.

TABLE 2 Oral Anticoagulant Treatment

	Rivaroxaban (n = 764)	Vitamin K Antagonist (n = 691)
Rivaroxaban dose		NA
15 mg	610 (79.85)	
20 mg	117 (15.3)	
VKA type	NA	
Acenocoumarol		26 (3.8)
Fluindione		124 (17.9)
Phenprocoumon		452 (65.4)
Warfarin		89 (12.9)

Values are n (%).
NA = not applicable; VKA = vitamin K antagonist.

rivaroxaban and VKA arms (HR: 0.74; 95% CI: 0.40-1.34). Similarly, no significant differences were found for the composite net clinical benefit outcome (HR: 0.97; 95% CI: 0.72-1.31) or any of the individual component outcomes including no significant difference between groups for cardiovascular death (HR: 0.82; 95% CI: 0.54-1.25) (Table 3). However, all-cause mortality was found to be reduced with rivaroxaban compared to VKA (HR: 0.76; 95% CI: 0.59-0.98) (Table 3, Figure 2, Central Illustration). Taking rivaroxaban on the initial study visit was associated with a 24% lower relative hazard of discontinuing the anticoagulation therapy compared to VKA (HR: 0.76; 95% CI: 0.62-0.92) (Table 3). Our sensitivity analysis

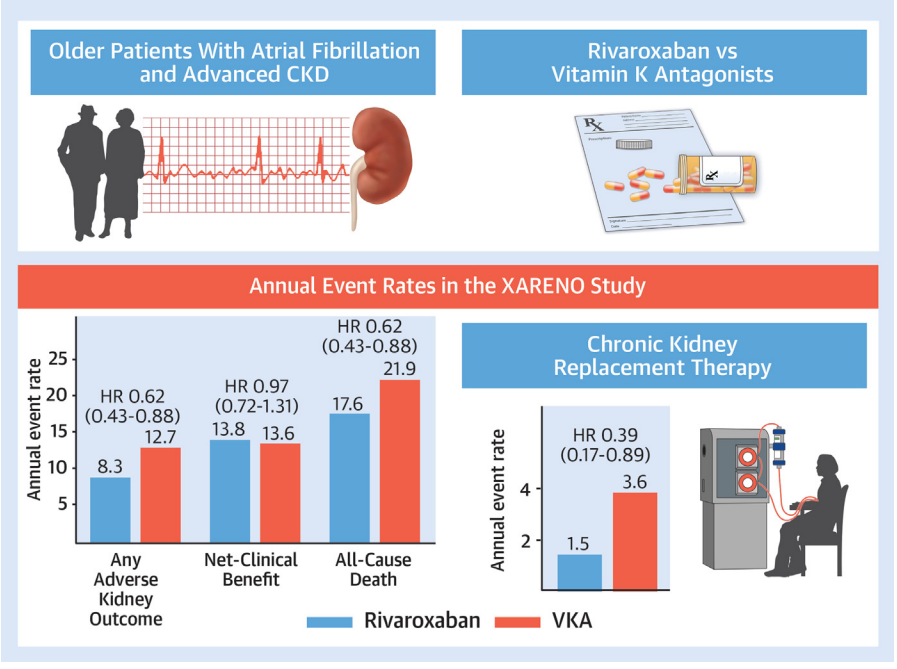
TABLE 3 Propensity Score Overlap-Weighted Outcomes

	Rivaroxaban (n = 764)	VKA (n = 691)	HR (95% CI)
Any adverse kidney outcome	8.3	12.7	0.62 (0.43-0.88), $P = 0.01$
Chronic kidney replacement therapy[a]	1.5	3.6	0.39 (0.17-0.89), $P = 0.03$
eGFR<15 mL/min/1.73 m^2[a]	6.5	12.1	0.51 (0.35-0.76), $P = 0.001$
Acute kidney injury[a]	2.8	3.6	0.74 (0.40-1.34), $P = 0.32$
Net clinical benefit	13.8	13.6	0.97 (0.72-1.31), $P = 0.84$
Stroke/systemic embolism or cardiovascular death	8.0	8.8	0.88 (0.61-1.29), $P = 0.52$
Stroke/systemic embolism[b]	1.7	1.4	1.19 (0.50-2.79), $P = 0.69$
Stroke/TIA/systemic embolism	2.3	2.4	0.92 (0.44-1.94), $P = 0.83$
Cardiovascular death[b]	6.4	7.5	0.82 (0.54-1.25), $P = 0.36$
Myocardial infarction or acute coronary syndrome[b]	2.3	1.3	1.68 (0.68-4.13), $P = 0.26$
Major bleeding[b]	5.3	4.9	1.05 (0.65-1.71), $P = 0.84$
All-cause death	17.6	21.9	0.76 (0.59-0.98), $P = 0.03$
Initial anticoagulant discontinuation	32.4	39.6	0.76 (0.62-0.92), $P = 0.005$

Values are %/y unless otherwise indicated. Annual event rates and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for the comparison between rivaroxaban and vitamin K antagonist (VKA) after propensity score overlap weighting outcome analysis. [a]Individual components of any adverse kidney outcome. [b]Individual components of net clinical benefit.

eGFR = estimated glomerular filtration rate; TIA = transient ischemic attack.

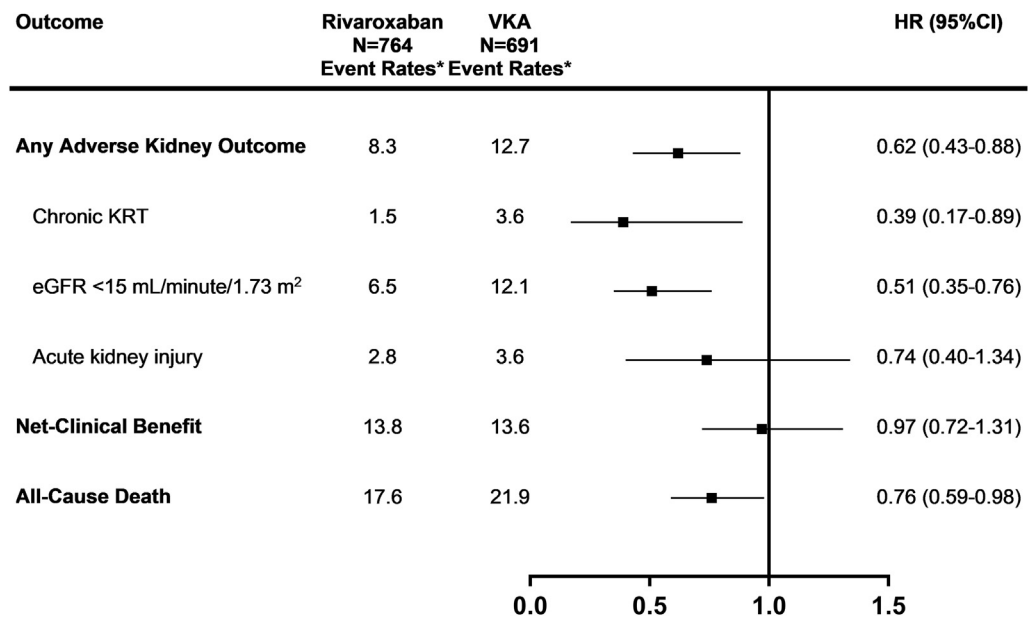
CENTRAL ILLUSTRATION Rivaroxaban vs Vitamin K Antagonist in Patients With Atrial Fibrillation and Advanced Chronic Kidney Disease



Kreutz R, et al. JACC Adv. 2024;3(2):100813.

Annual event rates and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for the comparison between rivaroxaban and vitamin K antagonist (VKA) after propensity score overlap-weighted outcome analysis. CKD = chronic kidney disease; XARENO = Factor XA-inhibition in RENal patients with non-valvular atrial fibrillation Observational registry.

FIGURE 2 Main Outcomes



Annual event rates, and adjusted HR (95% CI) for the comparison between rivaroxaban and vitamin K antagonist (VKA) after propensity score overlap weighting outcome analysis. *Event rates per 100 patient-years. eGFR = estimated glomerular filtration rate; KRT = kidney replacement therapy.

showed that the hazard for the composite of any adverse kidney outcome with death as a competing risk was similar to the main finding (sub-HR: 0.60; 95% CI: 0.36-0.99).

DISCUSSION

KIDNEY OUTCOMES. In the current study, rivaroxaban use in AF patients with comorbid CKD was associated with a 38% reduction in the hazard of experiencing an adverse kidney outcome, including a 61% reduction in need for chronic KRT and a 49% reduction in progression of kidney function decline to an eGFR <15 mL/min/1.73 m^2 vs a VKA. The kidney benefits of rivaroxaban vs VKA observed in XARENO are consistent with previous retrospective real-world database studies.[15-17] It is unclear whether the higher risk of adverse kidney outcomes with VKA compared to rivaroxaban observed in the current and prior real-world evidence studies[15-17] is due to a detrimental effect of VKAs on vascular injury and calcification,[5,9,27] kidney sparing or preservation effects of rivaroxaban possibly attributable to reduced protease-activated receptor-mediated inflammation[20,27] or some combination of both.

THROMBOEMBOLIC AND BLEEDING OUTCOMES. In respect to thrombotic and major bleeding outcomes, no significant difference in the composite net clinical benefit outcome or any of the individual component outcomes was observed when comparing rivaroxaban and VKA in agreement with the ROCKET-AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) randomized controlled trial.[28]

XARENO did not aim and was not powered to show reductions in thrombotic or bleeding outcomes in patients with advanced CKD.[23] However, a recent patient-level network meta-analysis of the RCTs that compared DOACs with warfarin indicated that, compared with warfarin, standard-dose DOAC use was more effective to reduce the risk for stroke/systemic embolism across the spectrum of kidney function above CrCl of at least 25 mL/min.[29] Another recent network meta-analysis in patients with AF and CKD (overall 19 studies)[30] including both subgroup

analysis data from these RCTs (5 studies) and observational studies (14 studies) found that all 4 DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) led to significant risk reductions for stroke or thromboembolism as compared to warfarin in CKD patients. Additionally, except for dabigatran, all 3 Factor Xa inhibitors reduced the risk of major bleeding. For separate analysis in advanced CKD with CrCl below 30 ml/min, only 5 studies were available for inclusion and among DOAC patients those specified as rivaroxaban users dominated the analysis (n = 2,677) over apixaban users (n = 135). While hazards were numerically lower for both rivaroxaban and apixaban no significant risk reduction in stroke or thromboembolism was observed in comparison to warfarin. Kidney outcomes were not considered in this network meta-analysis.[30]

PATIENTS OF OLDER AGE WITH AF AND ADVANCED CKD. Of interest, a randomized controlled trial in patients with AF aged 80 years or older (mean age 86.6 years) included also patients with advanced CKD (inclusion criterion CrCl ≥15 mL/min; mean CrCl 36.3 mL/min).[31] In this trial, active low-dose treatment with edoxaban 15 mg once daily, a dose which is currently not approved for clinical use as monotherapy in AF, was compared to placebo in overall 984 patients of whom 681 patients completed the trial.[31] OAC resulted in a significant risk reduction (HR: 0.34; 95% CI: 0.19-0.61; $P < 0.001$) in the rate of stroke and systemic embolism as compared to placebo, while the risk for major bleeding was numerically but not statistically significantly higher (HR: 1.87; 95% CI: 0.90-3.89; $P = 0.09$) in the OAC group and death rates were similar between groups.[31] However, the question whether low-dose treatment with the Factor Xa inhibitor edoxaban as compared to patients without OAC would impact on kidney outcomes was not addressed in this study.[31]

Annual mortality was high in the XARENO study population which is in agreement with the mean age of about 78 years and the inclusion of a high-risk AF population in which the presence of advanced CKD contributed further to mortality.[32] All-cause mortality was found to be reduced with rivaroxaban compared to VKA, but cardiovascular mortality was not. Whether the reduction in all-cause mortality was a downstream effect of slowing the decline in kidney function or due to residual confounding specific to all-cause mortality or noncardiovascular death (~7 of 10 AF patients die of cardiovascular causes)[33] in XARENO is unclear. Finally, rivaroxaban was associated with better persistence to therapy than VKA; a finding that mirrors observations from prior real-world studies.[34]

STUDY LIMITATIONS. This study has limitations worth discussion. The protocol prespecified that only patients with at least 3 months OAC pretreatment could be included, which limits generalizability of our findings to newly treated patients. However, this mandatory pretreatment phase was important to reduce the risk of selection bias at the time of enrollment, since OAC selection was already done as part of clinical routine and independent from the study procedures. Furthermore, thromboembolic and bleeding end points as well as treatment discontinuations for side effects are known to occur at a higher rate during the early phase of anticoagulant treatment.[35,36] For newly treated patients, the need to establish a stable international normalized ratio at the beginning of VKA therapy (when subtherapeutic and supratherapeutic effects are common) would have clearly biased the study in favor of rivaroxaban. Therefore, the mandatory pretreatment phase was an important measure to reduce confounding within our study. Moreover, although data on measurements of serum creatinine or estimation of GFR were prospectively collected every 3 months during follow-up, due to the noninterventional design of the study, the data set was heterogeneous and measurements occurred inconsistently over time and could have been additionally influenced by restrictions during the COVID-19 pandemic.[37] Thus, the power to assess outcomes such as absolute decline of eGFR over time or other established outcomes based on serum creatinine measurements such as doubling in serum creatinine or >30% decreases of eGFR was limited. On the other hand, while these are reasonable kidney outcomes to evaluate, they are only surrogate in nature. Outcomes such as the need for chronic KRT arguably carry greater clinical relevance. Regardless of the optimization of the methodology and the number of covariates used in propensity score analysis, residual confounding cannot be fully excluded.[38] The number of patients analyzed in XARENO seems modest, however, the registry included largely patients with at least CKD stage 3b (94%) and the sample size is still comparable with the number of patients with advanced CKD that were included in other large registries.[3,22]

CONCLUSIONS

Among patients with AF and CKD, use of rivaroxaban was associated with a reduction in patients' risk of

adverse kidney outcomes including the need for chronic KRT and a decline to an eGFR <15 mL/min/1.73 m^2, when compared to use of VKA. This occurred against a similar risk for net clinical benefit including stroke and thromboembolism and major bleeding events. XARENO thus provides important prospective observational evidence on the effectiveness and safety of rivaroxaban and VKA therapy when used in routine practice within the vulnerable group of patients with AF and advanced CKD.

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ADDRESS FOR CORRESPONDENCE: Dr Reinhold Kreutz, Institute of Clinical Pharmacology and Toxicology, Charitéplatz 1, 10117 Berlin, Germany. E-mail: reinhold.kreutz@charite.de.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In addition to the focus on prophylaxis against thromboembolic events, particularly stroke, nephroprotection has additional clinical significance in the management of older patients with AF and advanced CKD. In this respect, OAC with rivaroxaban may offer better protection than therapy with VKA, including a reduced risk of kidney failure.

TRANSLATIONAL OUTLOOK: The potential benefit of treatment with DOACs such as rivaroxaban to reduce adverse kidney outcomes including kidney failure should be explored in larger prospective studies and with longer follow-up.

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KEY WORDS bleeding, elderly, kidney failure, oral anticoagulation

APPENDIX For supplemental methods and a figure as well as a list of additional investigators in the XARENO registry, please see the online version of this paper.

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ORIGINAL ARTICLE

Pooled Analysis of Rivaroxaban therapy for acute venous thromboembolism in FIRST registry, SWIVTER and DRESDEN NOAC registry

Stephanie Müller MD[1] | Luise Tittl BSc[1] | Victoria Speed PhD[2,3] | Lara Roberts MD[2] | Jignesh Patel MD[2,3] | Raj Patel MD[2] | Roopen Arya MD[2] | Nils Kucher MD[4] | David Spirk MD[5] | Kurtulus Sahin DSc[6] | Jan Beyer-Westendorf MD[1]

[1]Department of Medicine I, Universitätsklinikum "Carl Gustav Carus", Dresden, Germany

[2]Department of Haematological Medicine, King's College Hospital NHS Foundation Trust, King's Thrombosis Centre, London, UK

[3]King's College London, UK Institute of Pharmaceutical Sciences, London, UK

[4]Clinic of Angiology, University Hospital Zurich, Zurich, Switzerland

[5]University of Bern, Institute of Pharmacology, Bern, Switzerland

[6]ClinStat GmbH, Institute for Clinical Research and Statistics, Cologne, Germany

Correspondence
Jan Beyer-Westendorf, Thrombosis Research Department of Medicine I, Division Haematology, University Hospital "Carl Gustav Carus," Technical University Dresden, Fetscherstrasse 74, 01307 Dresden, Germany.
Email: jan.beyer@uniklinikum-dresden.de

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Abstract

Background: The direct factor Xa inhibitor rivaroxaban is approved for the treatment of venous thromboembolism (VTE), based on the results of large phase III trials.

Objectives: To confirm rivaroxaban's effectiveness and safety in routine clinical care of patients with VTE.

Methods: Data were obtained from prospective, noninterventional registries: the FIRST registry (United Kingdom), DRESDEN NOAC registry (Germany), and SWIVTER (Switzerland). Baseline characteristics of these registries and effectiveness and safety outcome rates for the FIRST and DRESDEN NOAC registries were compared.

Results: A total of 1841 rivaroxaban-treated patients with acute VTE (57.9% male, 76.6% deep vein thrombosis [DVT]; 23.4% pulmonary embolism ± DVT; median age, 61 years) were included: 1217 from the FIRST registry, 418 from the DRESDEN NOAC registry, and 206 from SWIVTER. Median time between VTE diagnosis and initiation of rivaroxaban was 1.4 ± 1.81 days (25th–75th percentile 1–1; range, 0–15 days). On-treatment outcome rates for the FIRST and DRESDEN NOAC registries were 0.74 per 100 patient-years (95% confidence interval [CI], 0.35–1.54) versus 0.96 per 100 patient-years (95% CI, 0.46–2.01) for VTE recurrence; 1.16 per 100 patient years (95% CI, 0.64–2.09) versus 2.51 per 100 patient-years (95% CI, 1.58–3.98) for ISTH major bleeding and 1.69 per 100 patient-years (95% CI, 1.21–2.35) versus 1.73 per 100 patient-years (95% CI, 1.27–2.36) for all-cause mortality (intention-to-treat analysis), respectively.

Conclusion: Overall treatment outcomes were consistent with the results of the phase III rivaroxaban trials in VTE treatment, indicating that the use of rivaroxaban offers acceptable treatment results also in routine care. However, we observed significant differences in patient characteristics and management patterns across Switzerland, the

United Kingdom, and Germany, limiting direct comparisons of unadjusted outcome event rates between registries.

KEYWORDS
anticoagulant, hemorrhage, registries, rivaroxaban, venous thromboembolism

Essentials

- Registries are data collection tools for verifying results from clinical trials in daily routine.
- Thrombosis therapy with rivaroxaban was compared in three registries from the United Kingdom, Switzerland, and Germany.
- Treatment results in registries were comparable to results of clinical trials.
- Differences in methodologies indicate a need for standardization of observational registries.

1 | INTRODUCTION

Compared to vitamin K antagonists (VKAs), direct oral anticoagulants (DOACs) are characterized by a better dose–response relationship and fewer interactions with food or comedications and, therefore, do not require routine monitoring and frequent dose adjustments.[1] Today, DOACs have become the standard anticoagulation therapy for patients with deep vein thrombosis (DVT) and pulmonary embolism (PE). The DOAC rivaroxaban, a direct factor Xa inhibitor, demonstrated noninferior efficacy to VKAs in two large phase III trials, the EINSTEIN DVT and the EINSTEIN PE, leading to approval for venous thromboembolism (VTE) treatment.[2,3] In a pooled analysis of the two trials, rivaroxaban demonstrated superior safety over VKAs based on an absolute risk reduction for major bleeding of 0.8%, corresponding to a relative risk reduction of 46%.[4]

Current guidelines of the American Society of Hematology, American College of Chest Physicians (ACCP), and the European Society of Cardiology recommend an anticoagulation duration of 3 months in patients with provoked VTE.[5–7] Extended duration should be considered for patients with a first episode of an unprovoked proximal DVT or PE and low bleeding risk, as well as in patients with persistent risk factors such as ongoing cancer. Anticoagulation treatment of indefinite duration is recommended in patients with a second episode of unprovoked proximal DVT or PE and in those with permanent major risk factors.

However, implementation of guideline recommendations into daily practice is not without challenges, and observational studies such as prospective registries can be used to assess adherence to guidelines. Furthermore, registries can evaluate the external validity of phase III trials in unselected populations treated in routine "real-world" clinical practice.

Several national registries with different designs have been set up, each reporting primarily on rivaroxaban use in VTE[8–16] and, moreover, on different types of DOACs including rivaroxaban and approved anticoagulation for VTE treatment. However, these observational studies differ considerably in design, patient selection, duration of follow-up, and outcome definitions, limiting generalizability of conclusions. We therefore set out to investigate the methodological and clinical differences across three prospective regional noninterventional registries: the Follow-up in Rivaroxaban Patients in Setting of Thromboembolism (FIRST) registry in the United Kingdom,[16,17] the Register for New Oral Anticoagulants (DRESDEN NOAC) registry in Germany[12,18] and the Swiss Venous Thromboembolism Registry (SWIVTER) in Switzerland.[13] We assessed the overall effectiveness and safety of acute VTE treatment with rivaroxaban. In addition, we examined differences in VTE treatment patterns and approaches among the United Kingdom, Germany, and Switzerland.

2 | METHODS

2.1 | Subjects

For this project, data from subjects enrolled in either the FIRST registry, the DRESDEN NOAC registry, or SWIVTER were pooled.

The FIRST registry[16] is a United Kingdom–only prospective, noninterventional, investigator-led, multicenter, single-cohort registry. The FIRST registry enrolled patients with acute DVT and/or symptomatic PE confirmed at the site by appropriate diagnostic imaging, which were treated with rivaroxaban. Enrollment, follow-up, and data collection were managed by 22 individual sites locally. The frequency of follow-up visits or patient contact was planned in accordance with the routine clinical practice at each participating site. For all patients, contacts (visits or phone calls) took place at regular intervals that reflect normal clinical practice. When patients were not returning to the hospital, follow-up took place annually by phone call.

The DRESDEN NOAC Registry[12,18] is an ongoing prospective registry in the administrative district of Dresden (Saxony), Germany, including both patients with atrial fibrillation and VTE. Patients were enrolled by a network of more than 240 physicians from private practices and hospitals and prospectively followed up by phone calls from the central registry office to collect data on the efficacy, safety, and management of DOAC therapy in daily care.

The prospective SWIVTER[13] enrolled in- and outpatients with VTE from academic and nonacademic primary–tertiary care

hospitals in Switzerland. Inclusion criteria were age 18 years or older and objectively confirmed acute DVT or PE by diagnostic imaging; this included compression ultrasound or venography for DVT, and contrast-enhanced chest computed tomography, ventilation–perfusion scan, or conventional pulmonary angiography for PE, and complete follow-up at 90 days. No exclusion criteria were applied. The diagnosis and management of acute VTE was performed according to the standard of care at each participating hospital.[19]

The study synopses for each of the three registries are outlined in Tables S1–S3 in Appendix S1.

All three registries have similar aims but different approaches. They differ in structure and data collection. All three have included a relevant number of patients with VTE treated with rivaroxaban. Participating physicians were not subject to any instructions with regard to the diagnosis and therapy of their patients in all three registries. Each treatment was carried out within clinical routine at the discretion of the physician and according to existing treatment guidelines.

The categorization of the index VTE event as provoked or unprovoked was performed according to ACCP guidelines[20]:

- VTE provoked by major surgery/major trauma within the past 3 months (a major transient risk factor)
- VTE provoked by a nonsurgical transient risk factor (e.g., estrogen therapy, pregnancy, nonfracture leg injury, flight of greater than 8 h)
- Cancer-associated VTE (defined as cancer diagnosed within the previous 6 months; recurrent, regionally advanced, or metastatic cancer; cancer for which treatment had been administered within the previous 6 months; or hematologic cancer that was not in complete remission)[21]
- Unprovoked VTE

All three registries used different definitions for "active cancer" (Table S4).

2.2 | Objectives

The primary objective was to evaluate the effectiveness and safety of rivaroxaban in acute VTE treatment in a pooled analysis of the FIRST registry, DRESDEN NOAC registry, and SWIVTER.

Although the statistical analysis plan intended to include SWIVTER data in the pooled outcome assessment, this was not possible due to the lack of data granularity with regard to treatment type and duration for specific time points. In SWIVTER, anticoagulant treatment duration was collected only in categories, for example, "less than 3 months, greater than 3 to less than 6 months, greater than 6–12 months, and >12–24 months," and documentation of treatment type in the database allowed for entry of several anticoagulants per time interval, making censoring or association of outcome events to a specific treatment impossible. Finally, the starting date for rivaroxaban treatment was not specifically collected so that the exact date was not available for patients switching from initial non-rivaroxaban therapies to rivaroxaban only later. Therefore, the pooled analysis of all three registries was performed only for comparisons of baseline characteristics, and the pooled outcome analysis was restricted to patients enrolled in the FIRST and DRESDEN NOAC registries.

To assess the effectiveness of rivaroxaban therapy in VTE, we evaluated the annualized rate of the recurrent VTE. The main safety outcome was the annualized rate of major bleeding according to the ISTH definition.[22] Further safety outcomes were rates of ISTH clinically relevant nonmajor (CRNM) bleeding[23] and all-cause mortality.

The secondary objective was to describe and compare the design and methodology of the registries and differences in VTE treatment patterns and approaches between the United Kingdom and Germany. Furthermore, we compared the baseline characteristics of patients with acute VTE treatment of the FIRST registry, DRESDEN NOAC registry, and SWIVTER.

2.3 | Treatment duration

In the DRESDEN NOAC and FIRST registries, reasons for stopping anticoagulation were collected in detail. Termination of rivaroxaban therapy was classified as "scheduled end of treatment" if the attending physician or site staff regarded rivaroxaban therapy no longer necessary for treatment of the index VTE event. All other treatment discontinuations were classified as "premature stop," and the reasons for this decision were collected from patients and attending physicians. All patients who did not prematurely stop rivaroxaban treatment were defined as persistent. For patients who switched their anticoagulant treatment, date of discontinuation and duration of rivaroxaban treatment were collected.

For time-to-event analysis and for calculation of the treatment duration, the following formula was used:

$$\text{Duration in days} = \text{event or stop date of treatment} - \text{start date of rivaroxaban} + 1$$

For follow-up and treatment duration, median with 25th and 75th percentiles were calculated.

2.4 | Statistical Analysis

Statistical analysis was performed for all patients in the FIRST, DRESDEN NOAC, and the SWIVTER registries together as a pooled descriptive and comparative analysis among the respective registries. All patients who were anticoagulated with rivaroxaban for DVT and/or PE and followed up for at least 3 months were included in the analysis.

For comparison among the three registries, the baseline characteristics of each registry are presented as absolute and relative frequencies, mean and standard deviation, or median with interquartile range as difference between 25th and 75th percentile, where

appropriate. Missing values were left blank and not imputed. All *p* values presented are exploratory in nature; thus, no adjustment of type I error for multiple testing was conducted. A *p* value of 0.05 or less was considered to be statistically significant. For categorical variables, the overall *p* value is calculated using a generalized chi-squared test for the comparison among the registries. For continuous variables, the overall *p* value is calculated using a one-way analysis of variance for the comparison among the registries assuming normal distribution. For pairwise comparisons the chi-squared test is used for categorical variables and the unpaired *t* test for continuous variables.

For the outcome event analysis of the FIRST and DRESDEN NOAC registries, two different analysis sets were defined and evaluated:

a. The overall rate of recurrent VTE and all-cause mortality rate were evaluated in the intention-to-treat (ITT) analysis. All effectiveness outcome events were included that occurred throughout the follow-up period, including those occurring at any time during or after temporary interruption or discontinuation of rivaroxaban.
b. The on-treatment analysis also included all patients with VTE enrolled in the rivaroxaban group at baseline, but only outcome events that occurred during rivaroxaban treatment were included in the calculation of outcome event rates for recurrent VTE events, ISTH major bleeding, and CRNM bleeding.

Outcome event rates for the ITT and the on-treatment analysis set were calculated and performed using Kaplan–Meier estimation for time to first event. In addition, event rates were assessed on the basis of the following two approaches:

- The cumulative incidence risk was estimated at different points in time using the Kaplan–Meier method separately for each registry and overall.
- The incidence rate per 100 subject-years was also determined separately for each registry.

For calculation of event rates per 100 subject-years and their 95% confidence intervals (CIs), the following formula was used:

Event rate = total number of events of interest / total time subjects were under risk (defined as the sum of all days from start rivaroxaban treatment until day of first event divided by 100 × 365 days and 100 patient – years as its unit).

All statistical analyses were carried out using the software package SAS release 9.4 or higher (SAS Institute Inc.).

2.5 | Ethics

The study protocol of the FIRST registry (NCT02248610), the DRESDEN NOAC registry (NCT01588119), and SWIVTER complied with the principles and requirements of the Declaration of Helsinki. Written informed consent, including a data protection waiver, was provided or waived by all patients before enrollment, according to local regulations.

3 | RESULTS

3.1 | Patients

Since the start of the respective study period of the three registries (DRESDEN NOAC registry from December 2011 to July 2016; FIRST registry from December 2014 to October 2018; SWIVTER from June 2012 to January 2015) until October 31, 2018, a total of 1841 rivaroxaban-treated patients with acute VTE and completed 3 months of follow-up, including 1217 patients from the FIRST registry, 418 from the DRESDEN NOAC registry, and 206 from SWIVTER were enrolled (Table 1). Of these, 1411 (76.6%), were treated for acute DVT and 430 (23.4%) for PE as the index event. The proportion of DVT only versus PE ± DVT was similar in the three registries: 80.6% versus 19.4% in DRESDEN NOAC registry, 75.1% versus 24.9% in the FIRST registry, and 77.7% versus 22.3% in SWIVTER.

Proportions of unprovoked index VTE were different across registries. In the DRESDEN NOAC registry, 60.8% of patients had an unprovoked index VTE event compared to SWIVTER (66%) and the FIRST registry (71.1%). Overall, 57.9% (n = 1066) were male, and two patients (0.1%) were transgender. The FIRST registry and the SWIVTER enrolled more male than female patients (61.9 and 53.9% male, respectively), whereas female patients dominated in the DRESDEN NOAC registry (48.3% male). Overall, median age was 61 years (25th–75th percentile, 48–71 years) with a range from 14 up to 95 years, but age distributions differed considerably among registries: highest median age was observed in the DRESDEN NOAC registry (64 years), followed by the FIRST registry (61 years) and SWIVTER (58 years). The median body mass index (BMI; 25th–75th percentile) was 28.3 kg/m^2 (25.0–32.2 kg/m^2) with a median BMI of 27.4 kg/m^2 (24.7–30.7 kg/m^2) in the DRESDEN NOAC registry and 28.6 kg/m^2 (25.3–32.8 kg/m^2) in the FIRST registry. BMI was not available for 322 patients, including all 206 patients from SWIVTER. Proportions of patients weighing more than 120 kg also varied among the three registries (6.1% of patients in the FIRST registry versus 2.2% in the DRESDEN NOAC registry vs. 0.5% in SWIVTER).

Concomitant diseases at baseline were documented differently in all three registries, with very limited information recorded in the FIRST registry. Overall, 120 patients were reported to have concomitant malignant disease, but information on active cancer versus history of cancer was captured inconsistently. Proportions of patients with malignant disease were 47 (11.2%) for the DRESDEN NOAC registry, 55 (4.5%) for the FIRST registry, and 18 (8.7%) for SWIVTER, respectively. In addition, cutoffs for "impaired renal function" were

TABLE 1 Patient characteristics at baseline in FIRST registry, DRESDEN NOAC registry and SWIVTER

	All patients ($n = 1841$)	FIRST registry ($n = 1217$)	DRESDEN NOAC registry ($n = 418$)	SWIVTER ($n = 206$)
Index VTE event				
PE, *n* (%)	430/1841 (23.4)	303/1217 (24.9)	81/418 (19.4)	46/206 (22.3)
DVT, *n* (%)	1411/1841 (76.6)	914/1217 (75.1)	337/418 (80.6)	160 /206(77.7)
Proximal DVT, *n* (%)	889/1406 (63.2)	550/914 (60.2)	234/332 (70.5)	105/160 (65.6)
Distal DVT, *n* (%)	517/1406 (36.8)	364/914 (39.8)	98/332 (29.5)	55/160 (34.4)
Male, *n* (%)	1066/1841 (57.9)	753/1217 (61.9)	202/418 (48.3)	111/206 (53.9)
Median age, years (25th–75th percentile)	61 (48–71)	61 (48–70)	64 (49–74)	58 (45–70)
Median BMI, kg/m (25th–75th percentile) [2]	28.3 (25–32.2)	28.6 (25.3–32.8)	27.4 (24.7–30.7)	Not registered
Mean time between VTE diagnosis and initiation of Rivaroxaban, days ± SD	1.4 ± 1.8	1 ± 0	2.8 ± 3.4	1 ± 0
Unprovoked event VTE, *n* (%)	1255/1841 (68.2)	865/1217 (71.1)	254/418 (60.8)	136/206 (66.0)
Recurrent VTE event, *n* (%)	447/1837 (24.3)	275/1213 (22.7)	128/418 (30.6)	44/206 (21.4)
Malignant disease, *n* (%)	120/1841 (6.5)	55/1217 (4.5)	47/418 (11.2)	18/206 (8.7)
Active cancer, *n* (%)	61/117 (52.1)	39/52 (75.0)	11/47 (23.4)	11/18 (61.1)
Chronic lung disease, *n* (%)	13/206 (6.3)	Not registered	Not registered	13/206 (6.3)
Congestive heart failure, *n* (%)	34/624 (5.4)	Not registered	20/418 (4.8)	14/206 (6.8)
History of stroke, *n* (%)	23/624 (3.7)	Not registered	16/418 (3.8)	7/206 (3.4)
Renal dysfunction, *n* (%)	100/1743 (5.7)	CrCl ≤50 ml/min: 5/1119 (4.9)	eGFR ≤50 ml/min: 35/418 (8.4)	eGFR <30 ml/min: 10/206 (4.9)
Hepatic Impairment, *n* (%)	3/624 (0.5)	Not registered	1/418 (0.2)	2/206 (1)
Diabetes mellitus, *n* (%)	85/624 (13.6)	Not registered	72/418 (17.2)	13/206 (6.3)
Hypertension, *n* (%)	280/624 (44.9)	Not registered	230/418 (55)	50/206 (24.3)

Note: In each field, the denominator represents the number of patients with available data.

Abbreviations: BMI, body mass index; CrCl, creatinine clearance; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.

set differently: creatinine clearance of 50 ml/min or less in the FIRST registry; estimated glomerular filtration rate (eGFR) of 50 ml/minor less in the DRESDEN NOAC registry, and eGFR less than 30 ml/min in SWIVTER (Table 1).

Comparisons between the DRESDEN NOAC registry and SWIVTER revealed that cardiovascular risk factors were more prevalent in the DRESDEN NOAC registry compared to SWIVTER (diabetes, 17.2% vs. 6.3%; $p = 0.0002$; hypertension, 55% vs. 24.3%; $p < 0.0001$). More details on baseline characteristics are presented in Table 1.

When the available baseline data of all three registries were compared to the exclusion criteria in the respective phase III trials EINSTEIN DVT/PE, we found that a large proportion of the registry patients would not have been eligible to participate in the EINSTEIN trials: 517 had distal DVT, 45 underwent VTE recanalization, 19 had a creatinine clearance less than 30 ml/min, and 6 were younger than 18 years (Table S5). In addition, a relevant proportion had parenteral pretreatment for longer than 36 h.

3.2 | Follow-up

The overall median follow-up was 746 days (25th–75th percentile, 318–1462.5 days), with a median follow-up of 541 days (25th–75th percentile, 185–1075 days) in the FIRST registry and 2074.5 days (25th–75th percentile, 1708–2764 days) in the DRESDEN NOAC registry. Data on exact follow-up duration were not available from SWIVTER.

3.3 | VTE treatment

Median time between VTE diagnosis and initiation of rivaroxaban was 1 day (25th–75th percentile, 1–1; range, 0–15 days). The overall median treatment duration was 169 days (25th–75th percentile, 86–390 days), with a median treatment duration of 144 days (25th–75th percentile, 85–337 days) in the FIRST registry and 214 days (25th–75th percentile, 105–640 days) in the DRESDEN NOAC registry. Data on exact duration of rivaroxaban treatment were not available

from SWIVTER. Patients with PE received longer anticoagulant therapy compared to patients with DVT (202 days for PE vs. 122 days for DVT; $p = 0.0007$). Similarly, patients with malignant disease received longer anticoagulant therapy compared to patients without cancer (172.50 days vs. 169 days; $p = 0.18$). However, within the cancer population, treatment durations differed across the registries: In the FIRST registry, patients with malignant diseases had a median rivaroxaban exposure of 89 days compared to 372 days in the DRESDEN NOAC registry ($p = 0.0002$).

3.4 | Clinical outcomes

In the ITT population, 144 of 1635 patients developed a recurrent VTE, which translated into an overall crude incidence of 8.81% (95% CI, 7.48–10.29). Crude incidence rate was numerically higher in the DRESDEN NOAC (14.83% [95% CI, 11.56–18.61]) compared to the FIRST registry (6.74% [95% CI, 5.39–8.29]). Annualized incidence rates for recurrent VTE were 3.49 per 100 patient-years (95% CI, 2.96–4.11), with a nonsignificant trend toward higher rates in the FIRST registry (4.08/100 patient-years [95% CI, 3.28–5.06]) compared to the DRESDEN NOAC registry (2.93/100 patient-years [95% CI, 2.28–3.76]) (Figure 1A; Table S6).

The event rate in the group of patients with DVT as the index event (3.96/100 patient-years [95% CI, 3.33–4.72]) was significantly higher compared to patients with PE as the index event (1.9/100 patient years [95% CI, 1.2–3.02]; $p = 0.004$). For patients with provoked versus unprovoked VTE and proximal versus distal DVT, crude incidences of VTE recurrence are provided in Table S7.

A total of 14 patients developed recurrent VTE during active treatment with rivaroxaban (7 in the DRESDEN NOAC registry and 7 in the FIRST registry). In the on-treatment analysis, this corresponded to a pooled annualized incidence rate of 0.83 per 100 patient-years (95% CI, 0.49–1.40), with comparable incidence rates for the DRESDEN NOAC registry (0.96/100 patient-years [95% CI, 0.46–2.01]) and the FIRST registry (0.74/100 patient-years [95% CI, 0.35–1.54]; Figure 1B).

ISTH major bleeding during active treatment with rivaroxaban was experienced by a total of 29 patients (crude incidence rate, 1.77% [95% CI, 1.19–2.54]). This translated into an annualized incidence rate of 1.74 per 100 patient-years (95% CI, 1.21–2.5). ISTH major bleeding was more frequently reported in the DRESDEN NOAC registry ($n = 18/418$; 4.31%) compared to the FIRST registry ($n = 11/1217$; 0.9%), with corresponding annualized incidence rates of 2.51 per 100 patient-years (95% CI, 1.58–3.98) and 1.16 per 100 patient-years (95% CI, 0.64–2.09), respectively (Figure 2). In both registries, major bleeding was much more frequent in patients with malignant disease (DRESDEN NOAC registry annualized incidence rates, 6.27/100 patient-years [95% CI, 2.82–13.95] vs. FIRST registry, 3.22/100 patient-years [95% CI, 0.45–22.88]) compared to patients without cancer (DRESDEN NOAC registry annualized incidence rates, 1.93/100 patient-years [95% CI, 1.1–3.4] vs. FIRST registry, 1.09/100 patient-years [95% CI, 0.59–2.02]; Figures S1, S2).

CRNM bleeding events occurred in 96 cases in the DRESDEN NOAC registry (22.97% [95% CI, 19.02–27.3]), which translated into an annualized incidence rate of 17.62 per 100 patient-years (95% CI, 14.43–21.53). In comparison, only 68 cases reported CRNM bleeding in the FIRST registry, corresponding to a crude incidence of 5.59% (95% CI, 4.36–7.03) and an annualized incidence rate of 7.42 per 100 patient-years (95% CI, 5.85–9.41; Figure 3).

Overall, 75 patients died, which translated into an all-cause mortality event rate of 1.71 per 100 patient-years (95% CI, 1.36–2.14). Event rates were considerably higher in the DRESDEN NOAC registry (crude incidence rate, 9.57% [95% CI, 6.92–12.80]; 1.73/100 patient-years [95% CI 1.27–2.36]) compared to the FIRST registry (crude incidence rate, 2.88% [95% CI, 2.01–3.98]; 1.69/100 patient-years [95% CI, 1.21–2.35]).

4 | DISCUSSION

In this project, we aimed to pool data from three different VTE registries, collecting data on rivaroxaban treatments in Germany, the United Kingdom, and Switzerland.

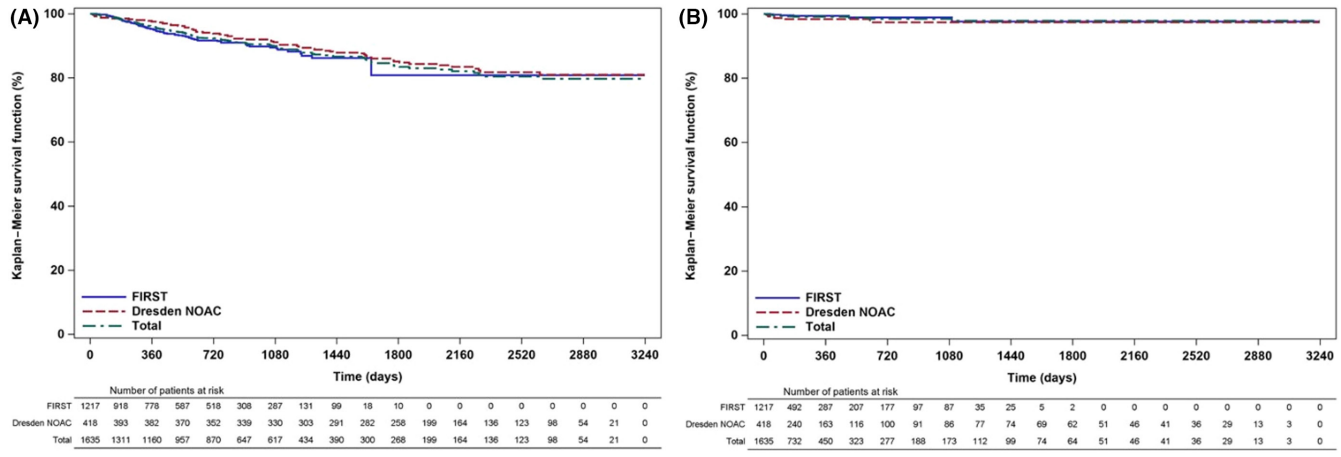

FIGURE 1 Kaplan–Meier event-free survival curves for recurrent VTE in the DRESDEN NOAC and FIRST registries. (A) Intention-to-treat analysis; (B) on-treatment analysis

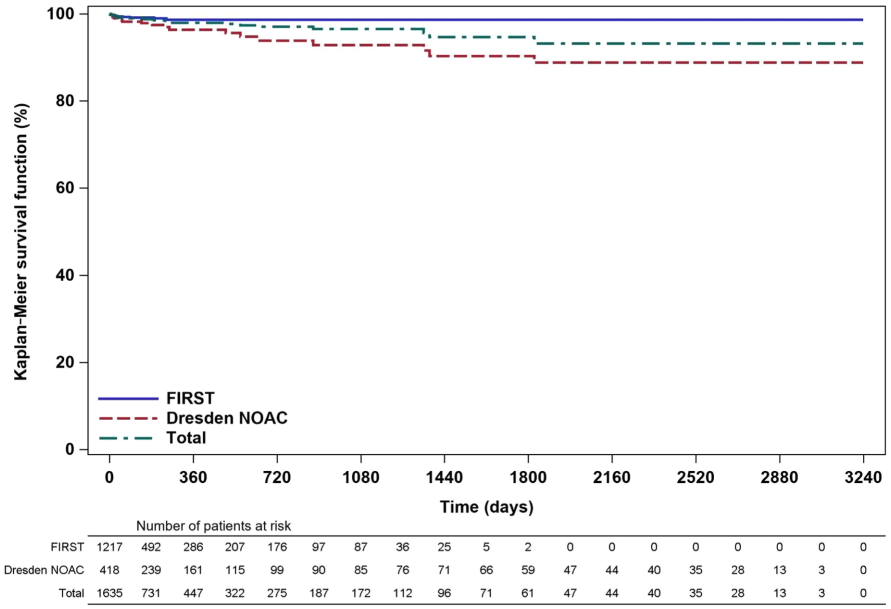

FIGURE 2 On-treatment Kaplan–Meier event-free survival curves for ISTH major bleeding in the DRESDEN NOAC and FIRST registries

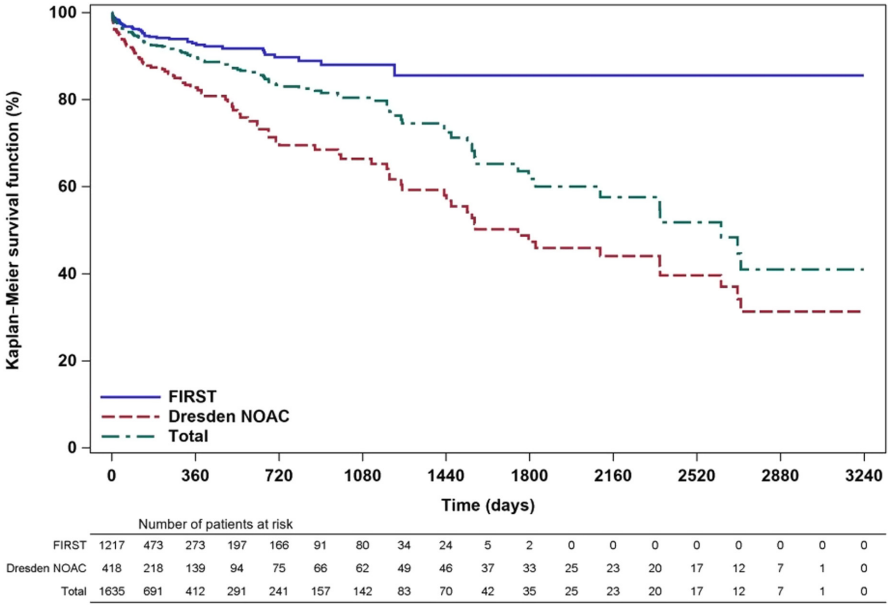

FIGURE 3 On-treatment Kaplan–Meier event-free survival curves for ISTH nonmajor clinically relevant bleeding in the DRESDEN NOAC and FIRST registries

At first glance, methodologies (prospective data collection in consecutive patients treated with rivaroxaban for acute VTE) and some of the baseline characteristics were strikingly similar among the three registries: 75%–80% DVT, with two thirds proximal DVT; median age, 58–64 years; median BMI, 27–28 kg/m^2. However, some baseline characteristics showed pronounced differences (unprovoked VTE much more frequent in the UK registry compared to the Swiss data set; highest rate of recurrent VTE and of malignant disease in the German registry but lowest rate of "active cancer" in this data set). In addition, cutoffs for "impaired renal function" and definitions of "active cancer" were not similar, and data on concomitant diseases were collected differently among the three registries. Finally, the comparison of treatment durations and clinical outcomes revealed differences among the three registries that limited comparison, especially with the Swiss data set. The first major finding of our analysis therefore is that comparisons across different registries suffer from relevant limitations, whereas generalizability of single registries may also be limited. As a consequence, data collection in prospective registries should be better standardized and should define detailed methodologies.[24] Checklists and guidance documents such as Strengthening the Reporting of Observational Studies in Epidemiology[25] are an important step toward such standardization but are often applied to the reporting of research results only and not necessarily in the planning phase of observational studies.

Although we conclude from the differences in baseline characteristics that postbaseline comparisons among the three registries need to be handled with caution, we did observe interesting management patterns across the registries. Probably the most striking difference was related to the median rivaroxaban treatment

duration, which overall was 169 days but considerably shorter in UK patients in the FIRST registry (144 days) compared to German patients from the DRESDEN NOAC registry (214 days). This finding cannot be explained by a higher proportion of patients at high risk for VTE recurrence for whom guidelines recommend extended therapy. In fact, the proportion of patients with an unprovoked index VTE event was somewhat lower in the DRESDEN NOAC registry (61%) compared to the FIRST registry (71%). The most likely explanation for the shorter rivaroxaban treatment in the FIRST registry could be that 40% of patients in the FIRST registry had distal DVT (approximately 80% of those unprovoked) and therefore stopped treatment after 3–6 months. In addition, the DRESDEN NOAC registry applied a much longer follow-up (up to 5 years), enhancing the rivaroxaban exposure with long-term treatments.

Finally, in the pooled outcome analysis of the DRESDEN NOAC registry and FIRST registry, we found that during active rivaroxaban therapy the overall rate of VTE recurrence was as low as 0.86% and affected only 14 of 1635 patients undergoing follow-up. Even in the absence of a comparator arm, it seems reasonable to conclude that this finding across two prospective observational registries performed in two different Western European countries confirms the high efficacy of rivaroxaban seen in the EINSTEIN phase III trials. This confirmation is especially important, since patients in the DRESDEN NOAC registry and FIRST registry were not selected by predefined inclusion and exclusion criteria and tended to be slightly older (mean age, 59 years) than patients in the EINSTEIN trials (mean age, 57 years).[4]

Some of the patients with malignancy were enrolled into one of the three registries before trial evidence or guidelines supported the use of rivaroxaban for the management of cancer-associated thrombosis (CAT). Accordingly, confounding among the patients treated with a DOAC for CAT has to be considered. Unfortunately, within our methodology and the available data, we are unable to speculate on the impact of such a confounder, and also because the definitions of "active cancer" were not consistent among the registries.

It is not surprising that the overall rate of VTE recurrence in the ITT analysis of our cohort (8.8%; n = 144/1635) exceeded the ITT event rate reported in the EINSTEIN phase III trials (2.1% for patients treated for 3–12 months). First, most of the observed events occurred after discontinuation of rivaroxaban therapy, and such events would not have been counted in EINSTEIN phase III trials, where patients were censored after stopping rivaroxaban. Second, although the three registries included a large proportion of patients with distal DVT, ITT event rates were only slightly lower than for patients with proximal DVT. Although recurrent VTE was rarely observed during active rivaroxaban therapy, the guideline-recommended short treatment of distal DVT (maximum, 3 months) and the high rate of VTE recurrence after treatment discontinuation contributed a relevant number of recurrent VTE events to the presented data set. Third, it should also be taken into account that the rate of recurrent VTE events in the ITT population in the EINSTEIN trials refers to a maximum follow-up period of 12 months. In our cohort, only 36.8% (n = 53/144) of recurrent VTE events occurred within the first 360 days after enrollment. Therefore, the considerably longer follow-up period in our cohort is an important reason for the higher rate of recurrent VTE events in the ITT population.

Similar considerations apply to the safety signals in our pooled analysis. During rivaroxaban treatment, 29 of 1635 (1.77%) patients in the DRESDEN NOAC registry and FIRST registry reported major bleeding complications. In addition, CRNM bleeding events were reported in our cohort during rivaroxaban treatment, with a crude incidence of 10.03%. In the EINSTEIN phase III trials, absolute rates of ISTH major bleeding events of 1.0% and absolute rates of CRNM bleeding events of 8.6% were reported for patients treated for 3–12 months. In our cohort, 24.1% (n = 7/29) of ISTH major bleeding events and 31.1% (n = 51/164) CRNM bleeding events occurred after the first 360 days after study inclusion. Again, the significantly longer follow-up period in our cohort could be an important reason for a numerically higher rate of ISTH major and CRNM bleeding events during active treatment with rivaroxaban. Therefore, we conclude that, even in the absence of a comparator arm, our findings confirm the generalizability of safety findings in the large EINSTEIN phase III program.

5 | LIMITATIONS

The results of our work should be interpreted in the context of their limitations. First of all, our study cohort evaluating clinical outcomes consisted of a total of 1841 patients. However, 1217 patients from the FIRST registry and only 418 patients from the DRESDEN NOAC registry were included in the outcome analyses. Outcome data could not be derived from SWIVTER. Thus, treatment effects in our pooled analysis are strongly driven by UK patients from the FIRST registry. In addition, the potential for selection bias cannot be avoided in noninterventional registries, where local physicians are not instructed which type or dosage of treatment patients should receive. In addition, data on race/ethnicity were not available for the DRESDEN NOAC registry and SWIVTER. Therefore, our results may not be generalizable to other settings or cohorts, especially since selection patterns may vary across regional or cultural settings.

Assessment of potential outcome events is based predominantly on patient contacts and patient-derived information. Although all suspected outcome events were adjudicated on the basis of available source documents, it is possible that some events were not reported or were misclassified. Outcome analyses were also not adjusted for competing risks. However, in the DRESDEN NOAC registry and FIRST registry, overall mortality was low (1.71/100 patient-years) and consistent between both registries (1.73 and 1.69/100 patient-years, respectively). As such, death as the most important competing risk was not considered relevant here.

Another limitation is the lack of a direct randomized comparator group. Nevertheless, over the past decade, many large observational studies of VTE treatment with other anticoagulants (VKA, parenteral drugs, DOACs other than rivaroxaban) have been published, enabling the reader to reflect on potential differences in treatment

patterns and outcomes, although indirect comparison in observational research face severe potential for confounding.

Despite all these limitations, the large size of our total cohort of 1841 patients with VTE treated with rivaroxaban and the prospective evaluation of patients from three different registries in three different countries are important strengths of our work. In addition, the long follow-up duration and the central adjudication of suspected outcome events in all three registries are important features to support the generalizability of the EINSTEIN trials.

6 | CONCLUSION

In different prospective observational registries, we found that recurrent VTE and major bleeding are rare events during active rivaroxaban therapy in VTE treatment, which supports the findings from the large EINSTEIN trials. However, our data also indicate significant differences in patient characteristics, management patterns, and outcome data collection across Switzerland, the United Kingdom, and Germany, limiting direct comparisons of unadjusted outcome event rates among registries.

AUTHOR CONTRIBUTIONS

JBW, RA, RP, NK, and DS designed the study and wrote the protocol. SM, LT, LR, JP, and VS collected the data, and KS performed analyses. JBW, SM, and LT wrote the first draft of the manuscript. All authors reviewed and revised the manuscript and approved the submission.

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RELATIONSHIP DISCLOSURE

LR has received speaker fees and travel grant from Bayer, and investigator-initiated research grant and travel grant from Sanofi. RP has received speaker fees from Bayer. RA reports grants from Bayer; personal fees from Bayer, Cardinal Health, and Sanofi; and nonfinancial support from Bayer and Sanofi. JP has received an investigator-initiated research grant from Bayer. VS has received speaker fees from Bayer. NK reports grants from Concept Medical, Bard, and Bayer; and personal fees from Bayer, Bard, Medtronic, Boston Scientific, BTG, and Pfizer, outside the submitted work. DS reports employment by Sanofi-Aventis (Suisse) SA, outside the submitted work. JB-W has received honoraria and research support from Bayer AG, Boehringer Ingelheim, Daiichi Sankyo, and Pfizer. LT has received honoraria and travel support from Bayer and Daiichi Sankyo. KS received payments from GWT-TUD GmbH in Dresden, Germany, for statistical analysis. None of the other authors declared a conflict of interest with regard to the NOAC registry or this manuscript. All authors declare that these companies and institutions had no influence on the study design, conduct of the study, data collection, statistical analysis, or preparation of the manuscript.

ORCID

Stephanie Müller https://orcid.org/0000-0002-7318-3173
Luise Tittl https://orcid.org/0000-0001-5784-1570
Victoria Speed https://orcid.org/0000-0001-5064-9375
Lara Roberts https://orcid.org/0000-0003-3871-8491
Raj Patel https://orcid.org/0000-0002-4404-6647
Roopen Arya https://orcid.org/0000-0001-5630-7990
Kurtulus Sahin https://orcid.org/0000-0002-1810-7362
Jan Beyer-Westendorf https://orcid.org/0000-0002-6983-9993

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Short Communication

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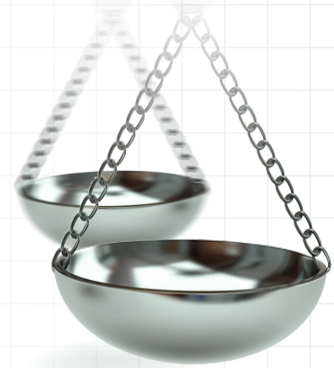

Journal of **Comparative Effectiveness Research**

Thromboembolic and bleeding events with rivaroxaban in clinical practice in Spain: impact of inappropriate doses (the EMIR study)

Marcelo Sanmartín Fernández*[1], Francisco Marín[2], Carles Rafols[3], Fernando Arribas[4], Vivencio Barrios[5], Juan Cosín-Sales[6] & Manuel Anguita Sánchez[7]

[1]Department of Cardiology, Hospital Ramón y Cajal, Madrid, Spain
[2]Department of Cardiology, Hospital Clínico Universitario Virgen de la Arrixaca, IMIB-Arrixaca, University of Murcia, CIBERCV, Murcia, Spain
[3]Department of Medical Affairs, Bayer Hispania, Barcelona, Spain
[4]Department of Cardiology, Hospital Universitario 12 de Octubre; Department of Medicine, Facultad de Medicina, Universidad Complutense de Madrid (UCM); Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12); CIBERCV, Madrid, Spain
[5]Department of Cardiology, Hospital Ramón y Cajal; Alcalá University, Madrid, Spain
[6]Department of Cardiology, Hospital Arnau de Vilanova, Valencia, Spain
[7]Department of Cardiology, Hospital Universitario Reina Sofia, IMIBIC, University of Córdoba, Córdoba, Spain
*Author for correspondence: msanfer@me.com

Aim: To analyze the frequency and variables related to inappropriate rivaroxaban dosage in clinical practice and its impact on outcomes after 2 years. **Materials & methods:** Postauthorization, observational, multicenter study, in which atrial fibrillation patients, treated with rivaroxaban ≥6 months were included. **Results:** A total of 1421 patients (74.2 ± 9.7 years, CHA_2DS_2-VASc 3.5 ± 1.6) were included. Overall, 22.9% received rivaroxaban 15 mg. The proper dose of rivaroxaban was taken by 83.3% (9.7% underdosed, 7.0% overdosed). Older age and renal insufficiency were associated with inadequate rivaroxaban dosage. There was a trend toward higher all-cause mortality among underdosed patients (adjusted hazard ratio 1.39; 95% CI 0.75–2.58), and more bleedings in overdosed patients (2.29 vs 0.80 events/100 patient-years; p = 0.14). **Conclusion:** In clinical practice, rivaroxaban is properly dosed in most patients.

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Keywords: atrial fibrillation • dosage • major bleeding • overdosage • rivaroxaban • stroke • underdosage

Most patients with nonvalvular atrial fibrillation (NVAF) require anticoagulation therapy to reduce the risk of ischemic stroke and systemic embolism [1]. Direct oral anticoagulants (DOACs) have a wide therapeutic window and provide a predictable anticoagulant effect [2]. Clinical trials have shown that DOACs have a better risk–benefit profile than vitamin K antagonists (VKAs) [3].

Given the potentially major differences between 'real-life' patients and those included in clinical trials [4,5], it is mandatory to ascertain whether the results observed in clinical trials can be extended to everyday practice and whether these drugs are properly used [6–13]. In fact, data from a meta-analysis suggest that the effectiveness and safety of DOACs in clinical practice may differ not only between the drugs themselves, but also in terms of the results of their respective pivotal clinical trials [14]. This could be associated, at least in part, with inappropriate dosage of DOACs, which could in turn lead to more frequent thromboembolic or bleeding events [6–13]. As a result, it is necessary to determine the factors underlying incorrect prescription of DOACs and their impact on clinical outcomes [15].

The dosage of DOACs depends on various clinical characteristics, with rivaroxaban being the simplest to adjust, as it relies only on renal function [2]. The aims of this study were to analyze the use of rivaroxaban in clinical practice and to determine the frequency and predictors of inappropriate dosing, along with its possible impact on thromboembolic and bleeding events after 2 years of follow-up.

Future Medicine

Materials & methods

EMIR (**E**studio observacional para la identificación de los factores de riesgo asociados a eventos cardiovasculares **mayores** en pacientes con **fi**brilación auricular no valvular tratados con un anticoagulante oral directo [**R**ivaroxaban] ["Observational study to identify risk factors associated with major cardiovascular events in patients with NVAF treated with a DOAC [rivaroxaban]") was a postauthorization, observational and multicenter study aimed at ascertaining the predictors of major cardiovascular events in NVAF patients treated with rivaroxaban for at least 6 months by different specialists in Spain. Patients were followed up for 2.5 years. In this study, the appropriateness of the dosage of rivaroxaban and the related outcomes (thromboembolic events and major bleeding) were analyzed after 2 years of follow-up. Overdosage was defined as creatinine clearance (Cockcroft–Gault) <50 ml/min with rivaroxaban 20 mg and underdosage as creatinine clearance ≥50 ml/min with rivaroxaban 15 mg.

The study population comprised NVAF patients aged ≥18 years of both sexes who had been treated with rivaroxaban for at least 6 months before being enrolled. The study population excluded patients participating in a clinical trial, patients starting treatment with rivaroxaban after the inclusion period and patients with severe cognitive impairment, chronic infectious disease, systemic autoimmune disease, active cancer or significant liver insufficiency. All patients gave their written consent prior to enrollment. The study was approved by each participating Institutional Review Board.

Baseline data were recorded using a specific electronic case report form and included biodemographic data (age, sex, level of dependency, type of atrial fibrillation [AF]), physical examination (weight, BMI, heart rate, blood pressure), thromboembolic data ($CHADS_2$ [congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA or thromboembolism (doubled)] and CHA_2DS_2-VASc [congestive heart failure, hypertension, age ≥75 years [doubled], diabetes mellitus, prior stroke or TIA or thromboembolism [doubled], vascular disease, age 65–74 years, sex category]), bleeding data (HAS-BLED [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR [international normalized ratio], elderly, drugs/alcohol]), cardiovascular risk factors (hypertension, dyslipidemia, diabetes, smoking status), concomitant structural or vascular disease (heart failure, ischemic heart disease, renal insufficiency, prior cerebrovascular disease, peripheral artery disease, aortic plaque, venous thromboembolic disease and prior systemic embolism). Conditions that increase the risk of bleeding (e.g., labile INR in patients taking VKAs before starting rivaroxaban, alcohol intake, falls) were also recorded. Dependency was classified as autonomous (no dependency), partial dependency to daily activities or complete dependency to daily activities.

Previous antithrombotic treatment before starting rivaroxaban therapy, current dose of rivaroxaban, and the appropriateness of this dose (correct dose, overdosage or underdosage) were analyzed. For the purpose of this analysis, overdosage was considered to have occurred when a patient with a Cockcroft–Gault creatinine clearance <50 ml/min was taking rivaroxaban 20 mg and underdosage when a patient with a Cockcroft–Gault creatinine clearance ≥50 ml/min was taking rivaroxaban 15 mg. Factors associated with prescribing inadequate doses of rivaroxaban, underdosage and overdosage were also analyzed.

Thromboembolic events (stroke, transient ischemic attack, systemic embolism or myocardial infarction), and major bleeding (following International Society of Thrombosis and Haemostasis definition) [16]. In addition, during this period, all-cause death and cardiovascular death that included sudden cardiac death and death from heart failure, myocardial infarction, arrhythmia or percutaneous or surgical coronary revascularization were analyzed. Outcomes were analyzed according to the appropriateness of the rivaroxaban dosage.

Statistical methods

Categorical variables were expressed as absolute (n) and relative frequencies (%). Continuous variables were expressed as mean and standard deviation. Categorical variables were compared using the chi-square test or the Fisher exact test when appropriate. When 2 means were compared, the t-test or the Mann–Whitney test was used, as applicable. A bivariate logistic regression analysis was performed to evaluate which factors were associated with an inadequate dose. The analysis also included age, sex, previous major bleeding, diabetes, type of AF (paroxysmal vs permanent), ischemic heart disease, coronary revascularization, use of aspirin or clopidogrel, renal insufficiency, prior stroke and the level of dependency. A bivariate logistic regression analysis was performed to evaluate which factors were associated with underdosage or overdosage. The analysis included age, sex, previous major bleeding, diabetes, type of AF (permanent vs paroxysmal), ischemic heart disease, coronary revascularization, concomitant use of aspirin or clopidogrel, prior stroke, dependency, anemia (baseline hemoglobin <12 g/dl), falls in the previous

year, and treatment with verapamil, dronedarone or amiodarone. Those factors with a p-value < 0.150 in the bivariate analysis were included in the multivariate analysis through automatic forward stepwise selection.

The analysis was based on events during the 2 years of follow-up after the baseline visit. Follow-up time in years from the date of the baseline visit to the last follow-up (maximum 2 years) was calculated. The event rate was calculated using the following formula: rate = event/time (years)*100. The Fisher exact test was used to compare events between patients who received the appropriate dosage and those who did not (underdosage and overdosage).

Unadjusted and adjusted Cox models were constructed to estimate event rates at 2 years. The time in years from the baseline visit to the first recorded event or to last follow-up visit in cases of not presenting the event (maximum 2 years), was calculated. To calculate variables associated with overdosing/underdosing, a logistic regression was performed, with 16 factors included for over/underdosing and 13 factors for inadequate dosing. All representative factors were included in the analysis. Hazard ratios were adjusted for age, sex, type of AF, diabetes, hypertension, previous major bleeding, ischemic stroke + systemic embolism + transient ischemic attack, congestive heart failure, vascular disease (peripheral artery and/or aortic plaque), smoking, alcohol use and renal insufficiency (glomerular filtration rate <60 ml/min). Hazard ratios with 95% CIs were presented. Missing data or lost values were not imputed to avoid information bias. Missing data for important variables were controlled by filters when data were collected from the electronic case report form. A level of statistical significance of 0.05 was applied in all the statistical tests. The data were analyzed using the statistical package SPSS (v18.0 or superior).

Results

A total of 1503 patients were initially enrolled in the study. After excluding 82 patients because of lack of data or inconsistent data, 1421 patients were finally analyzed.

Table 1 shows the baseline clinical characteristics of the study population. Mean age was 74.2 ± 9.7 years, 55.5% of patients were men, and total or partial dependency was reported in 9.9% of patients. The mean CHA_2DS_2-VASc score was 3.5 ± 1.6 and the mean HAS-BLED score was 1.6 ± 1.0. Major comorbidities were common, such as heart failure in 22.7%, ischemic heart disease in 16.5%, renal insufficiency in 15.8% and prior cerebrovascular disease in 12.5%.

A total of 1096 patients (77.1%) were taking rivaroxaban 20 mg and 325 (22.9%) were taking rivaroxaban 15 mg. At baseline, 238 patients (16.7%) were taking an inadequate dose of rivaroxaban, namely, underdosage in 138 (9.7%) and overdosage in 100 (7.0%), according to the Cockcroft–Gault equation. If estimated glomerular filtration rate is taken into consideration, the percentage of patients underdosed and overdosed would have been, respectively, 14.8 and 3.7% according to the MDRD-4 formula and 12.1 and 5.4% according to CKD-EPI. After 2 years of follow-up, mean creatinine clearance (Cockcroft–Gault) increased slightly from 76.0 ± 30.5 ml/min at baseline to 77.0 ± 33.8 ml/min (p = 0.014). The number of overdosed patients decreased from 100 (7.0%) to 47 (3.3%) during the study period.

At baseline, compared with patients taking the proper dose of rivaroxaban, underdosed patients were older (78.4 ± 8.7 vs 73.0 ± 9.6 years; p < 0.001) and less autonomous (77.9 vs 91.9%; p < 0.001) and had a higher thromboembolic risk (CHA_2DS_2-VASc score: 4.0 ± 1.7 vs 3.4 ± 1.5; p < 0.001), a higher bleeding risk (HAS-BLED score: 2.0 ± 1.0 vs 1.5 ± 1.0; p < 0.001) and more frequent renal insufficiency (31.9 vs 12.9%; p < 0.001). Compared with patients taking the proper dose of rivaroxaban, overdosed patients were older (82.3 ± 5.6 vs 73.0 ± 9.6 years; <0.001) and less autonomous (82.7 vs 91.9%; p = 0.003) and had lower weight (67.4 ± 9.7 vs 80.7 ± 15.9 Kg; p < 0.001), a higher thromboembolic risk (CHA_2DS_2-VASc score: 4.2 ± 1.3 vs 3.4 ± 1.5; p < 0.001), and a higher bleeding risk (HAS-BLED score: 1.9 ± 0.9 vs 1.5 ± 1.0; p < 0.001) and more frequent renal insufficiency (28.0 vs 12.9%; p < 0.001). However, diabetes was less frequent in this group (16.0 vs 27.5%; p = 0.013; Table 1).

Factors associated with the prescription of an inadequate dose of rivaroxaban are reported in Table 2. In the bivariate analysis, older age, female sex, renal insufficiency, prior cerebrovascular disease and partial or total dependency were associated with inappropriate dosage. Of note, labile INR did not have any impact on dosage. However, in the multivariate analysis, the only remaining independent factors were age (OR 1.09; 95% CI 1.07–1.11; p < 0.001) and renal insufficiency (OR 2.00; 95% CI 1.41–2.84; p < 0.001). Variables associated with underdosage and overdosage are reported in Table 3. In the bivariate analysis, older age, permanent AF (versus paroxysmal AF), dependency (versus autonomous) and anemia were associated with underdosage. However, in the multivariate analysis, the only remaining independent factors were age (OR 1.04; 95% CI 1.02–1.07; p < 0.001) and dependency (OR 2.13; 95% CI 1.43–3.18; p = 0.003). In the bivariate analysis, old age, female sex, absence

Table 1. Clinical characteristics of the study population at baseline (n = 1421).

Clinical characteristics	Total (n = 1421; 100%)	Proper dose (n = 1183; 83.3%)	Underdosed (n = 138; 9.7%)	p-value (underdosage vs proper dose)	Overdosed (n = 100; 7.0%)	p-value (overdosage vs proper dose)
Biodemographic data						
Age (years)	74.2 ± 9.7	73.0 ± 9.6	78.4 ± 8.7	**<0.001**	82.3 ± 5.6	**<0.001**
Sex (men), n (%)	788 (55.5)	673 (56.9)	74 (53.6)	0.464	41 (41.0)	**0.002**
Level of dependency, n (%) – No dependency – Partial dependency – Total dependency	 1,249 (87.9) 126 (8.9) 14 (1.0)	 1,066 (91.9) 88 (7.6) 6 (0.5)	 102 (77.9) 21 (16.0) 8 (6.1)	 <0.001	 81 (82.7) 17 (17.3) 0	 0.003
Type of AF, n (%) – Paroxysmal – Persistent – Long-standing persistent AF – Permanent	 569 (40.0) 259 (18.2) 53 (3.7) 532 (37.4)	 481 (40.9) 218 (18.5) 46 (3.9) 431 (36.6)	 48 (34.8) 22 (15.9) 3 (2.2) 65 (47.1)	 0.103	 40 (40.4) 19 (19.2) 4 (4.0) 36 (36.4)	 0.998
Physical examination						
Systolic blood pressure (mmHg)	131.5 ± 16.4	131.8 ± 16.2	128.1 ± 16.8	**0.031**	132.5 ± 17.2	0.763
Diastolic blood pressure (mmHg)	76.2 ± 10.5	76.6 ± 10.6	73.8 ± 10.1	**0.007**	75.0 ± 9.4	0.231
Heart rate (bpm)	71.9 ± 14.8	71.7 ± 14.9	71.8 ± 14.0	0.835	75.4 ± 14.8	**0.008**
Weight (kg)	79.7 ± 15.8	80.7 ± 15.9	80.3 ± 15.2	0.579	67.4 ± 9.7	**<0.001**
BMI (kg/m^2)	29.1 ± 4.9	29.3 ± 4.9	29.3 ± 5.3	0.693	26.0 ± 3.7	**<0.001**
Risk stratification						
$CHADS_2$ score	2.0 ± 1.2	1.9 ± 1.2	2.4 ± 1.4	**<0.001**	2.3 ± 1.1	**<0.001**
CHA_2DS_2-VASc score	3.5 ± 1.6	3.4 ± 1.5	4.0 ± 1.7	**<0.001**	4.2 ± 1.3	**<0.001**
2MACE score	2.4 ± 1.0	2.4 ± 1.0	2.6 ± 1.2	0.060	2.4 ± 0.7	0.155
HAS-BLED score	1.6 ± 1.0	1.5 ± 1.0	2.0 ± 1.0	**<0.001**	1.9 ± 0.9	**<0.001**
Cardiovascular risk factors						
Hypertension, n (%) – Systolic blood pressure >160 mmHg, n (%)	1,119 (78.7) 51 (3.6)	938 (79.3) 41 (4.4)	104 (75.4) 4 (3.8)	0.285 0.999	77 (77.0) 6 (7.8)	0.589 0.161
Dyslipidemia, n (%)	784 (55.2)	664 (56.1)	68 (49.3)	0.125	52 (52.0)	0.425
Diabetes, n (%)	381 (26.8)	325 (27.5)	39 (28.3)	0.844	16 (16.0)	**0.013**
Smoking, n (%) – Current – Ex-smoker <1 year – Ex-smoker >1 year	119 (8.4) 72 (5.1) 24 (1.7) 23 (1.6)	109 (9.2) 63 (5.4) 23 (1.9) 23 (1.9)	7 (5.1) 6 (4.3) 1 (0.8) 0	0.104 0.492	3 (3.0) 3 (3.0) 0 0	**0.035** **0.567**
Vascular disease						
Heart failure, n (%)	323 (22.7)	260 (22.0)	42 (30.4)	0.104	21 (21.0)	0.724
Ischemic heart disease, n (%) – Revascularization, n (%)	235 (16.5) 183 (12.9)	196 (16.6) 153 (12.9)	28 (20.2) 21 (15.2)	0.634 0.453	11 (11.0) 9 (9.0)	0.095 0.256
Renal insufficiency,† n (%) – Severe renal insufficiency	225 (15.8) 14 (1.0)	153 (12.9) 14 (9.2)	44 (31.9) 0	**<0.001** **0.043**	28 (28.0) 0	**<0.001** **0.132**
Prior cerebrovascular disease, n (%)	177 (12.5)	137 (11.6)	24 (17.4)	**0.048**	16 (16.0)	0.190
Peripheral artery disease, n (%)	58 (4.1)	47 (4.0)	8 (5.8)	0.310	3 (3.0)	0.792
Aortic plaque, n (%)	46 (3.2)	35 (3.0)	4 (2.9)	0.999	7 (7.0)	**0.039**
Venous thromboembolic disease, n (%)	32 (2.3)	26 (2.2)	4 (2.9)	0.545	2 (2.0)	0.999
Prior systemic embolism, n (%)	14 (1.0)	13 (1.1)	0	0.383	1 (1.0)	0.999
Other conditions						
Labile INR, n (%)	372 (26.2)	304 (25.7)	44 (31.9)	0.118	24 (24.0)	0.709
Drugs or alcohol, n (%)	129 (9.1)	121 (10.2)	3 (2.2)	**0.002**	5 (5.0)	0.092
Medication usage predisposing to bleeding‡, n (%)	119 (8.4)	93 (7.9)	20 (14.5)	**0.008**	6 (6.0)	0.503
Cancer, n (%)	83 (5.8)	61 (5.2)	14 (10.1)	**0.017**	8 (8.0)	0.226
Falls in the last year, n (%)	86 (6.1)	65 (5.5)	10 (7.2)	0.400	11 (11.0)	**0.025**

†Glomerular filtration rate <60 ml/min (investigator assessment).
‡Nonsteroidal anti-inflammatory drugs or antiplatelets at least once a week.
Bold terms indicate significant p-values.
AF: Atrial fibrillation; eFGR: Estimated glomerular filtration rate; INR: International normalized ratio.

Table 1. Clinical characteristics of the study population at baseline (n = 1421) (cont.).

Clinical characteristics	Total (n = 1421; 100%)	Proper dose (n = 1183; 83.3%)	Underdosed (n = 138; 9.7%)	p-value (underdosage vs proper dose)	Overdosed (n = 100; 7.0%)	p-value (overdosage vs proper dose)
Previous major bleeding, n (%) – Gastrointestinal – Intracranial – Hematuria – Others	46 (3.2) 17 (1.2) 8 (0.6) 8 (0.6) 13 (0.8)	40 (3.4) 16 (1.3) 7 (0.6) 6 (0.5) 13 (1.0)	4 (2.92) 1 (0.73) 1 (0.73) 1 (0.73) 1 (0.73)	0.999 0.999 0.566 0.513 0.593	2 (2.0) 0 0 1 (1.0) 1 (1.0)	0.767 0.517 0.999 0.309 0.999
No severe cognitive impairment, n (%)	33 (2.3)	24 (2.0)	8 (5.8)	**0.014**	1 (1.0)	0.715
Hepatic failure, n (%)	11 (0.8)	7 (0.6)	3 (2.2)	0.077	1 (1.0)	0.478
Biochemical parameters						
Hemoglobin (g/dl)	14.1 ± 1.7	14.1 ± 1.6	13.7 ± 1.8	**0.036**	13.7 ± 1.6	**0.033**
Creatinine clearance, ml/min (Cockroft–Gault) eFGR, ml/min/1.73m^2 (MDRD4) eFGR, ml/min/1.73m^2 (CKD-EPI)	76.0 ± 30.5 74.8 ± 21.5 69.6 ± 18.8	78.2 ± 31.1 76.7 ± 21.3 71.7 ± 18.2	67.5 ± 17.1 73.5 ± 19.8 66.9 ± 15.0	<0.001 0.023 <0.001	41.6 ± 7.7 54.3 ± 12.9 49.8 ± 11.8	<0.001 <0.001 <0.001

†Glomerular filtration rate <60 ml/min (investigator assessment).
‡Nonsteroidal anti-inflammatory drugs or antiplatelets at least once a week.
Bold terms indicate significant p-values.
AF: Atrial fibrillation; eFGR: Estimated glomerular filtration rate; INR: International normalized ratio.

Table 2. Factors associated with inadequate dosage†.

Independent variables	Bivariate analysis						Multivariate analysis					
	Dependent variable						Dependent variable					
	B	Standard error	p-value	OR	95% CI lower limit	95% CI upper limit	B	Standard error	p-value	OR	95% CI lower limit	95% CI upper limit
Age	0.09	0.01	**0.000**	1.10	1.08	1.12	0.09	0.01	**0.000**	1.09	1.07	1.11
Sex (women vs men)	0.35	0.14	**0.02**	1.41	1.07	1.87						
Prior major bleeding	-0.30	0.44	0.50	0.74	0.31	1.76						
Type 2 diabetes	-0.26	0.17	0.13	0.77	0.55	1.08						
Type of AF (permanent vs paroxysmal)	0.25	0.16	0.12	1.28	0.94	1.75						
Revascularization	0.17	0.14	0.23	1.19	0.90	1.57						
Aspirin	0.17	0.275	0.53	1.18	0.70	1.99						
Clopidogrel	0.38	0.44	0.38	1.46	0.62	3.44						
Renal insufficiency‡	1.07	0.17	**0.000**	2.92	2.11	4.04	0.69	0.18	**0.000**	2.00	1.41	2.84
Prior cerebrovascular disease	0.43	0.20	**0.03**	1.54	1.05	2.26						
Partial dependency	0.92	0.21	**0.000**	2.52	1.67	3.80						
Total dependency	2.05	0.56	0.000	7.77	2.66	22.65						

†Only those factors with a p-value < 0.150 in the bivariate analysis were included in the multivariate analysis.
‡Glomerular filtration rate <60 ml/min (Investigator assessment).
Bold terms indicate significant p-values.
AF: Atrial fibrillation; OR: Odds ratio.

of Type 2 diabetes, dependency and falls in the previous year were associated with overdosage. However, the only remaining independent factors were age (OR 1.13; 95% CI 1.10–1.16; p < 0.001) and absence of Type 2 diabetes (OR 0.47; 95% CI 0.26–0.85; p = 0.013).

Clinical outcomes after 2 years of follow-up are presented in Table 4. Cumulative time was 2537.56 years. Annual rates for death, thromboembolic events (stroke, transient ischemic attack, systemic embolism or myocardial infarction), and major bleeding were 2.68, 0.71 and 0.95 events per 100 patient-years, respectively in total population. The equivalent values for underdosed and overdosed patients were 5.76, 0.89 and 1.33 events per 100 patient-years and 3.43, 1.14 and 2.29, respectively. There was a trend toward higher all-cause mortality among underdosed patients (unadjusted HR 2.51; 95% CI 1.36–4.63; adjusted HR 1.39; 95% CI 0.75–2.58; Supplementary Table 1). No significant differences were found in cardiovascular mortality among underdosed

Table 3. Factors associated with underdosage and overdosage†.

Independent variables	Factors associated with underdosage											
	Bivariate analysis						Multivariate analysis					
	Dependent variable						Dependent variable					
	B	Standard error	p-value	OR	95% CI lower limit	95% CI upper limit	B	Standard error	p-value	OR	95% CI lower limit	95% CI upper limit
Age	0.06	0.01	**0.000**	1.06	1.04	1.08	0.04	0.01	**0.000**	1.04	1.02	1.07
Sex (women vs men)	0.08	0.18	0.65	1.09	0.76	1.54						
Previous bleeding	-0.13	0.53	0.81	0.88	0.31	2.50						
Type 2 diabetes	0.10	0.20	0.62	1.11	0.75	1.64						
Type of AF (permanent vs paroxysmal)	0.41	0.20	**0.04**	1.51	1.02	2.24						
Revascularization	0.22	0.25	0.39	1.24	0.76	2.03						
Prior cardiac disease	0.27	0.18	0.14	1.31	0.92	1.87						
Antiplatelet therapy	0.14	0.31	0.64	1.16	0.63	2.11						
Prior cerebrovascular disease	0.44	0.24	0.07	1.56	0.97	2.49						
Dependency (dependency vs autonomous)	1.08	0.23	**0.000**	2.94	1.86	4.64	0.76	0.20	**0.000**	2.13	1.43	3.18
Anemia	0.64	0.27	**0.02**	1.89	1.11	3.20						
Falls in the last year	0.22	0.35	0.54	1.24	0.63	2.46						
Verapamil	-18.98	14210.36	0.99	0.000	0.000	.						
Dronedarone	0.072	0.62	0.91	1.07	0.32	3.60						
Amiodarone	-0.34	0.33	0.30	0.71	0.38	1.35						
	Factors associated with overdosage											
	Bivariate analysis						Multivariate analysis					
	Dependent variable						Dependent variable					
Age	0.13	0.02	**0.000**	1.13	1.10	1.17	0.12	0.02	**0.000**	1.13	1.10	1.16
Sex (women vs men)	0.63	0.21	**0.003**	1.87	1.24	2.83						
Previous bleeding	-0.52	0.73	0.47	0.59	0.14	2.48						
Type 2 diabetes	-0.80	0.30	**0.006**	0.45	0.25	0.80	-0.75	0.30	**0.013**	0.47	0.26	0.85
Type of AF (permanent vs paroxysmal)	-0.04	0.24	0.86	0.96	0.60	1.53						
Revascularization	-0.43	0.36	0.23	0.65	0.32	1.32						
Prior cardiac disease	0.003	0.21	0.99	1.003	0.67	1.51						
Antiplatelet therapy	0.09	0.36	0.82	1.09	0.53	2.22						
Prior cerebrovascular disease	0.32	0.29	0.27	1.37	0.78	2.40						
Dependency (dependency vs autonomous)	0.69	0.28	**0.015**	1.99	1.14	3.47						
Anemia	0.24	0.35	0.49	1.27	0.64	2.53						
Falls in the last year	0.72	0.34	**0.035**	2.05	1.05	4.01						
Verapamil	0.64	1.07	0.55	1.90	0.23	15.57						
Dronedarone	-0.02	0.74	0.97	0.98	0.23	4.17						
Amiodarone	0.16	0.32	0.63	1.17	0.62	2.19						

†Only those factors with a p-value <0.150 in the bivariate analysis were included in the multivariate analysis.
Bold terms indicate significant p-values.
AF: Atrial fibrillation; OR: Odds ratio.

patients (0.44 vs 0.75 events per 100 patient-years; p = 0.99). More bleedings were recorded in overdosed patients, although the difference was not significant (2.29 vs 0.80 events per 100 patient-years; p = 0.14; Table 4).

Discussion

The main findings of this study are as follows: approximately 17% of patients treated with rivaroxaban for NVAF received off-label doses, more commonly the lower dose; advanced age and high dependency explained most of

Table 4. Clinical outcomes at 2-year follow-up.

Events	Total population (n = 1421)		Proper dose (n = 1183)		Underdosage (n = 138)		p-value (underdosed vs proper dose)	Overdosage (n = 100)		p-value (overdosed vs proper dose)
	n of events	Annual rate of events† (cumulative time = 2537.56 years)	n of events	Annual rate of events† (cumulative time = 2136.99 years)	n of events	Annual rate of events† (cumulative time = 225.59 years)		n of events	Annual rate of events† (cumulative time = 174.98 years)	
Death	68	2.68	49	2.29	13	5.76	**0.01**	6	3.43	0.47
– CV death	18	0.71	16	0.75	1	0.44	0.99	1	0.57	0.99
– Heart failure death	11	0.43	9	0.42	1	0.44	0.99	1	0.57	0.99
Thromboembolic events‡	18	0.71	14	0.66	2	0.89	0.92	2	1.14	0.69
– Ischemic stroke + SE + TIA	13	0.51	10	0.47	1	0.44	0.99	2	1.14	0.46
– Ischemic stroke	10	0.39	7	0.33	1	0.44	0.99	2	1.14	0.29
– Myocardial infarction	5	0.20	4	0.19	1	0.44	0.79	0	0.00	0.99
Major bleeding	24	0.95	17	0.80	3	1.33	0.60	4	2.29	0.14
– Fatal bleeding	2	0.08	1	0.05	1	0.44	0.36	0	0	0.99
– Intracranial bleeding	7	0.28	6	0.28	0	0	0.99	1	0.57	0.85

†Events per 100 patient-years.
‡Thromboembolic events: ischemic stroke + transient ischemic attack + systemic embolism + myocardial infarction.
CV: Cardiovascular; SE: Systemic embolism; TIA: Transient ischemic attack.

the underdosing prescriptions; after a 2-year follow-up period, rates of thromboembolic or bleeding complications were lower than expected based on data from other prospective real-world registries.

The ROCKET-AF trial, which was performed in a population with a high thromboembolic risk, showed that rivaroxaban was at least as effective as warfarin for the prevention of stroke or systemic embolism with the same risk of major bleeding, but with a lower risk of fatal and intracranial bleeding [17]. Compared with the rivaroxaban arm of the ROCKET-AF trial, both the number of comorbidities and the thromboembolic risk were lower ($CHADS_2$ score 3.5 vs 2.0), even though the patients in our study were slightly older [17]. The XANTUS study was the first real-world, prospective and observational study of patients treated with rivaroxaban for prevention of stroke in AF, with a thromboembolic risk that was similar to that reported in our study [18]. Other studies of NVAF patients treated with rivaroxaban in Spain have revealed a similar clinical profile [19–22]. Therefore, these data suggest that the EMIR population is highly representative.

In the EMIR study, the proportion of patients taking 20 and 15 mg of rivaroxaban (77 and 23%, respectively) was similar to that of the ROCKET-AF trial (20 mg dose: 79.3%) and the XANTUS real-world study (79 and 21%, respectively) [17,18]. We found that approximately 83% of patients were taking the correct dose of rivaroxaban according to approved recommendations, 10% of patients were underdosed and 7% were overdosed. Remarkably, during the study, the proportion of overdosed patients decreased to only 3%. As a result, our data showed that in most cases, rivaroxaban is adequately prescribed in clinical practice, and that only a small proportion of patients are underdosed. However, there were relevant differences in the numbers according to the method used to estimate renal function and this could have an impact on the appropriateness of dosage in clinical practice.

Various studies have analyzed the frequency of inappropriate dosing of rivaroxaban. In the XANTUS study, 15% of patients with a creatinine clearance ≥50 ml/min received rivaroxaban 15 mg, whereas 36% of patients with a creatinine clearance <50 ml/min received rivaroxaban 20 mg [18]. In a preplanned pooled analysis of the XANTUS, XANAP (Asia) and XANTUS-EL (Latin America and EMEA Region) registries, 18.3% of patients with a creatinine clearance ≥50 ml/min received rivaroxaban 15 mg [23].

Although other authors have found that a higher risk of bleeding may be associated with the use of low doses of DOACs [9], in our study, advanced age and dependency, but not bleeding risk, were associated with underdosage. In fact, we found thromboembolic and bleeding risk to be similar in underdosed and overdosed patients. Many authors report that underdosage is more common in elderly patients, particularly in those with creatinine clearance consistent with the dose reduction criteria [7,24,25]. Of note, some studies, but not all, have shown that dependency and frailty, that are commonly observed in elderly patients, may be associated with underdosage [26,27]. However, dosage of DOACs should be performed according to the summary of product characteristics [2]. This is very

relevant, since some studies have shown that inadequate prescription may be associated with worse outcomes and that this is more evident when adjustment of the DOACs prescribed is more complex [10–12,15,26,28,29]. Thus, recent data from the GARFIELD-AF registry have shown a higher risk of all-cause mortality – mainly cardiovascular – for underdosing [29]. We recorded numerically higher rates of death and thromboembolic and bleeding outcomes in underdosed patients, although these numbers did not reach statistical significance, likely due to the low number of events during follow-up. On the other hand, frailty is frequent in patients with AF and is associated with adverse clinical outcomes, partially due to lower rates of adequate anticoagulation in this population [30,31]. As a result, the dosage of rivaroxaban should also be based on renal function in this population.

Although less common, overdosage is also recorded with rivaroxaban. In our study, the proportion of overdosed patients decreased from 7 to 3% over time. Due to pharmacovigilance safety reasons, the investigators were advised in case of inappropriate dosage according to the summary of product characteristics (Cockcroft–Gault creatinine clearance). Then, the investigators could modify the dosage according to their clinical criteria, but this only occurred in case of overdosing during the second year of follow-up. While study results vary, most are similar to those we report [19,21,32–34]. Of note, after 2 years of treatment with rivaroxaban, renal function remained stable. Compared with patients prescribed warfarin, patients treated with DOACs may experience a less pronounced decline in renal function [35], thus indicating an added value in the management of patients with NVAF compared with VKAs [36].

After 2 years of follow-up, rates for death, thromboembolic events and major bleeding were 2.68, 0.71 and 0.95 events per 100 patient-years, respectively. The equivalent values were 1.9, 1.7 and 3.6 per 100 patient-years, respectively, in the ROCKET-AF trial (rivaroxaban-arm) and 1.9, 1.8 and 2.1 per 100 patient-years, respectively in the XANTUS study [17,18]. Therefore, in clinical practice, thromboembolic and bleeding events are less frequent than in the pivotal clinical trial, likely because of differences in the patients' clinical profile. Of note, bleeding outcomes occur more frequently during the first weeks after initiating treatment, and in the EMIR study, patients were on continuous rivaroxaban therapy, thus potentially leading these events to be underrepresented.

In addition, real-life studies have shown lower rates of thromboembolic complications of rivaroxaban compared with warfarin [14,37]. These data strongly suggest that rivaroxaban can be safely used in clinical practice.

Study limitations

Our study is subject to a series of limitations. First, as this was an observational study, no control group was available, and only indirect comparisons could be made with data from other studies. Second, although rivaroxaban was prescribed appropriately in most patients, a limited number of patients were underdosed or overdosed and this reduced the power of the study to detect differences. However, the meticulousness of the data recorded and the consistency of the results with available evidence reduce this potential bias. Third, medication adherence was not assessed and this could have an impact on the results. However, the number of events was low, suggesting that rivaroxaban persistence was high. Finally, as follow-up was limited to 2 years, it is uncertain whether thromboembolic or bleeding events could vary beyond this period.

Conclusion

Our study confirms that dosing of rivaroxaban for prevention of thromboembolic events in patients with NVAF is appropriate in most patients in current clinical practice in Spain. Older age and renal insufficiency are the main predictors of inadequate prescription. After a 2-year follow-up period, rates of death and thromboembolic and major bleeding events are low. There was a trend toward a higher risk of death among underdosed patients. As a result, adequate prescription of rivaroxaban according to renal function should be strongly encouraged.

Summary points

- Published data suggest that the effectiveness and safety of direct oral anticoagulants in clinical practice may differ from their respective pivotal clinical trials.
- This could be associated, at least in part, with inappropriate dosage of direct oral anticoagulants, which could in turn lead to more frequent thromboembolic or bleeding events.
- In Spain, patients taking rivaroxaban are old and have a high thromboembolic risk.
- Dosage of rivaroxaban is properly performed in most patients in Spain.
- Older age and renal insufficiency are the main predictors of inadequate prescription.
- After 2 years of treatment, rates of death, thromboembolic events, major bleeding, and fatal bleeding are low.
- There is a trend toward a higher death risk among underdosed patients.
- There is a trend toward a higher bleeding risk among overdosed patients.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2020-0286

Financial & competing interests disclosure

M Sanmartín Fernandez has received speaker and advisory fees from the following companies in the past 3 years: Bayer, Boehringer-Ingelheim, BMS and Pfizer. F Marín has received consultancy/lecturing fees from Bayer, Boehringer Ingelheim, Pfizer, Bristol Myers Squibb and Daiichi Sankyo. C Rafols is an employee of the Medical Department, Bayer Hispania SL. Bayer Hispania SL is the sponsor of the EMIR study. F Arribas has received consultancy/lecture fees and research funding from Daiichi Sankyo, Pulse Dynamics, Medtronic, Boston Scientific, Bayer, Bristol Myers Squibb, Arrhythmia Network Technology SL/BAROSTIM, Abbott, Novartis, Janssen-Cilag, Biosensors, Edwards Lifesciences. He has also received financial compensation from Bayer for participating in the EMIR registry. V Barrios has received consultancy/lecture fees from Bayer, BMS/Pfizer, Boehringer Ingelheim and Daiichi Sankyo. He has also received financial compensation from Bayer for participating in the EMIR registry. J Cosín-Sales has received financial compensation from Bayer for participating in the EMIR registry. M Anguita Sánchez has received financial compensation from Bayer for participating in the EMIR registry. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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The Supplementary Material details the names of the EMIR Study Investigators.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical conduct of research

The study was approved by each participating Institutional Review Board. All patients gave their written consent prior to enrollment.

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Bristol Myers Squibb
Hummeltoftevej 49
2830 Virum
Danmark
Tlf: 45930506
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Til Medicintilskudsnævnet

Hermed synspunkter som er relevante for Medicintilskudsnævnets arbejde angående den planlagte revurdering af tilskudsstatus for antitrombotisk medicin i ATC-gruppe B01.

Det nuværende udgangspunkt for ATC-gruppe B01 omfatter over 500.000 patienter i Danmark og en lang række sygdomsområder og behandlinger.[1] Vi anser den fulde ATC-gruppe (B01) som en yderst omfattende revurdering og urealistisk at opnå inden for en rimelig tidsramme.

Det anbefales derfor at ekskludere følgende ATC-grupper i revurderingen: B01AA, B01AE og B01AF, da snarlige patentudløb markant vil forandre priserne på en række af disse, i øvrigt rationelt anvendte, lægemidler. En revurdering af tilskuddet til disse lægemidler vil måske isoleret set kunne sikre lavere udgifter til medicin på kort sigt, men der må forventes omkostninger til håndtering af utilsigtede hændelser, bivirkninger, samt behovet for opfølgning og dosisjustering.

Synspunkterne nedenfor opfordrer til at Medicintilskudsnævnet indstiller til Lægemiddelstyrelsen at ekskludere ATC gruppe: B01AA, B01AE og B01AF i revurdering af tilskudsstatus for antitrombotisk medicin i ATC-gruppe B01.

1. Det kan potentielt have konsekvenser for gennemførslen af det danske studie: DANNOAC, som af studie-gruppen er beskrevet på følgende måde: *Målet med undersøgelsen er, ved at sammenligne bl.a. effekten af de fire NOAK-lægemidler og de bivirkninger, der kan optræde, at få kortlagt den helt optimale behandling til at forebygge blodpropper, redde flest liv og giver færrest bivirkninger – til gavn for patienter i fremtiden.*[2]
   Revurdering kan potentielt bremse det første klyngerandomiserede studie i Europa og dermed førende dansk forskning – en revurdering kan muligvis føre til en anbefaling om at afslutte studiet før tid, hvorfor flere års forberedelse og forskning vil gå tabt. Ønskes mere information kan det anbefales at kontakte studiegruppen bag DANNOAC.

2. I flere behandlingsvejledninger fra Dansk Kardiologisk Selskab fremgår det, at der er forskel på de enkelte blodfortyndende præparater og fx: *I forhold til valget mellem de enkelte NOAK-præparater kan følgende parametre overvejes:*
   - *graden af renal udskillelse (dabigatran > rivaroxaban = edoxaban > apixaban)*
   - *en- eller togangsdosering*
   - *evidensniveau for de enkelte NOAK-præparater i forhold til patientens karakteristika (f.eks. alder, vægt, nyrefunktion, komorbiditet)*
   - *bivirkningsprofil, herunder risikoen for gastrointestinal og urogenital blødning*[3]

   Det er essentielt at klinikere har forskellige blodfortyndende præparater til rådighed, for at kunne vælge den rigtige behandling til den rigtige patientprofil.

[1] Medstat.dk
[2] https://dannoac.dk/
[3] https://www.cardio.dk/ak#144-peroral-akbehandling - Kapital 14.4.1 - Overvejelser i forbindelse med valg af peroral AK-behandling

3. Blodfortyndende medicin er af Styrelsen for Patientsikkerhed karakteriseret som risikosituationslægemidler, hvoraf det fremgår at ændringer i behandlingen er en situation der kræver særlig opmærksomhed[4], og det fremgår herefter at der er findes:
    - Forholdsregler ved brug af blodfortyndende medicin[5]
    - Detaljeret huskeliste til at undgå utilsigtede hændelser, som blandt andet indebærer dobbeltkontroller af beregnet dosis og ordinationsform, samt særlig opmærksomhed omkring blodprøver i forbindelse med kontrol.[6]

    En revurdering kan potentielt betyde et skift af behandling, hvilket forventeligt vil øge antallet af utilsigtede hændelser for en ikke uvæsentlig del af de i forvejen velbehandlede patienter. Der er i dag over 100.000 danske patienter i aktiv blodfortyndende behandling (B01AA, B01AE og B01AF).[7] Det vil betyde en signifikant øget arbejdsbyrde hos de danske sundhedspersoner og udgøre et pres på det danske sundhedsvæsen, som dets nuværende forfatning ikke er i stand til at imødekomme.

Vi opfordrer til at Medicintilskudsnævnet indstiller til Lægemiddelstyrelsen, at ekskludere ATC gruppe: B01AA, B01AE og B01AF i revurdering af tilskudsstatus for antitrombotisk medicin i ATC-gruppe B01 på baggrund af synspunkterne ovenfor.

Med venlig hilsen

Anders Thelborg
General Manager Denmark
Tlf: 30655570
E-mail: Anders.thelborg@bms.com

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[4] https://stps.dk/sundhedsfaglig/viola-viden-og-aering/risikoomraader/risikosituationslaegemidler/risikosituationer
[5] https://stps.dk/Media/638272658678521125/Risikosituationsl%c3%a6gemidler%20En%20guide%20til%20sikker%20medicinha%c2%b0ndtering_Nov_2021.pdf
[6] https://stps.dk/Media/638267293605502531/Huskeliste_Syv%20situationer%20som%20kr%c3%a6ver%20din%20s%c3%a6rlige%20opm%c3%a6rksomhed_2018.pdf
[7] Medstat.dk

Medicinrådet

Lægemiddelstyrelsens Medicintilskudsnævn
Axel Heides Gade 1
2100 København Ø

25. marts 2024

Medicinrådet
Dampfærgevej 21-23, 3. sal
2100 København Ø

+45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk

Synspunkter angående Medicintilskudsnævnets revurdering af tilskudsstatus for antitrombotisk medicin i ATC-gruppe B01

I forbindelse med Medicintilskudsnævnets revurdering af tilskudsstatus for antitrombotisk medicin, vil vi gerne orientere om status for Medicinrådets behandlingsvejledninger og lægemiddelrekommandationer på området.

Medicinrådets forgænger, Rådet for Anvendelse af Dyr Sygehusmedicin (RADS), har udarbejdet flere baggrundsnotater og vejledninger for antikogulansbehandling. Medicinrådet opdaterer ikke længere lægemiddelrekommandationer på baggrund af disse vejledninger, som er fra 2016 eller ældre. På Medicinrådets hjemmeside findes en behandlingsvejledning for behandling og sekundær profylakse efter venøs tromboemboli (VTE). Den er færdiggjort efter RADS-metoder i 2017 og bliver ikke længere opdateret. Vi forventer den snart placeres i et arkiv på vores hjemmeside, da den ikke længere er fagligt relevant.

Et enkelt klinisk spørgsmål i behandlingsvejledningen for VTE, nemlig angående behandling af kræftpatienter, er blevet opdateret efter Medicinrådets metoder i 2022. Evidensgennemgangen findes på Medicinrådets hjemmeside under ”Behandling af venøse tromboembolier hos kræftpatienter”. På nuværende tidspunkt er der ikke udarbejdet en lægemiddelrekommandation. Vi gør opmærksom på, at lægemidlerne i kategorierne ”anvend” og ”overvej” (direkte faktor Xa hæmmere og lavmolekylære hepariner) udleveres vederlagsfrit til kræftpatienter (liste med virkning fra 2. maj 2023).

Derudover har Medicinrådet ikke aktuelle planer om at udarbejde behandlingsvejledninger for lægemidler i ATC-gruppe B01. Vi mener, der er mange væsentlige problemstillinger forbundet med antikoagulansbehandling i dansk klinisk praksis, heriblandt både risiko for over- og underbehandling og suboptimal behandling. Udover jeres revurdering af tilskudsstatus kan relevante løsninger bedst findes hos interessenter som ”Vælg klogt”, seponeringslisten og faglige selskaber.

Med venlig hilsen
Birgitte Klindt Poulsen og Jørgen Schøler Kristensen
Medicinrådets formandskab