Direkte orale Antikoagulanzien (DOAK)

Michael Nagler, Prof. Dr. Dr. med.
Inselspital, Zentrum für Labormedizin

Behandlung mit Antikoagulanzien 1980

Vorteile von Vitamin K-Antagonisten wie Marcoumar

Fachinformation des Arzneimittel-Kompendium der Schweiz®

Marcoumar®

AMZV

Zusammensetzung

Wirkstoff: Phenprocoumonum.
Hilfsstoffe: Excipiens pro compresso.

Galenische Form und Wirkstoffmenge pro Einheit

Tabletten (Kreuzbruchrille) zu 3 mg.

Indikationen/Anwendungsmöglichkeiten

Thromboseprophylaxe, Thrombose, Embolie, Herzinfarkt.

CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Oral Anticoagulant Therapy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Walter Ageno, MD; Alexander S. Gallus, MBBS; Ann Wittkowsky, PharmD, FCCP; Mark Crowther, MD; Elaine M. Hylek, MD, MPH; and Gualtiero Palareti, MD

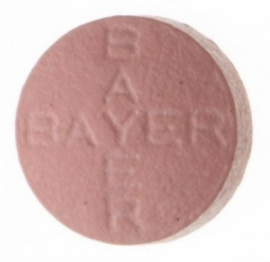
„Jahrzehntelange klinische Forschung und Millionen Menschen weltweit haben bestätigt dass Vitamin K Antagonisten in vielen Situationen hochgradig wirksam sind.“

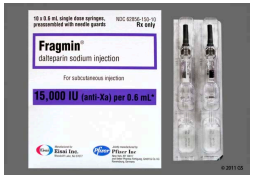
Indikationen/Anwendungsmöglichkeiten

Therapie und Prophylaxe thromboembolischer Krankheiten aller Ätiologien und Lokalisationen

Ageno W. CHEST 2012; 141(2)

Behandlung mit Antikoagulanzien 2021





Bevyxxa
betrixaban capsules

Lixiana

Vorteile direkter oraler Antikoagulanzien

Table 2. Advantages of New Oral Anticoagulants

Advantage	Clinical Implications
Rapid onset of action	No need for bridging
Predictable anticoagulant effect	No need for routine coagulation monitoring
Specific coagulation enzyme target	Low risk of off-target adverse effects
Low potential for food interactions	No dietary precautions
Low potential for drug interactions	Few drug restrictions

Circulation. 2010;121:1523-1532.

Wirksamkeit und Sicherheit von DOAK in Standardsituationen

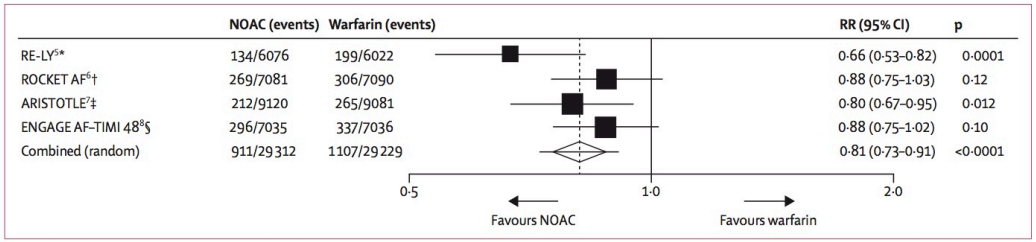


***Figure 1*: Stroke or systemic embolic events**

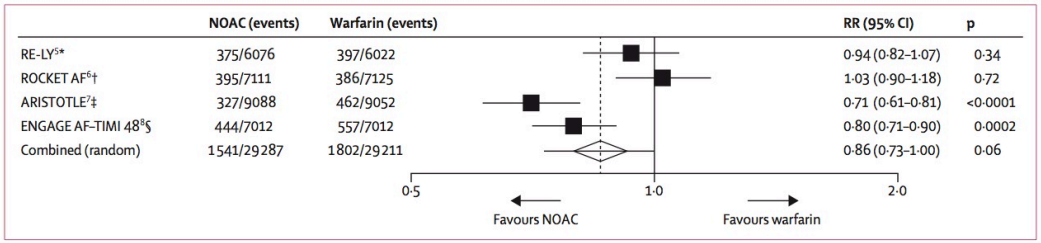


***Figure 3*: Major bleeding**

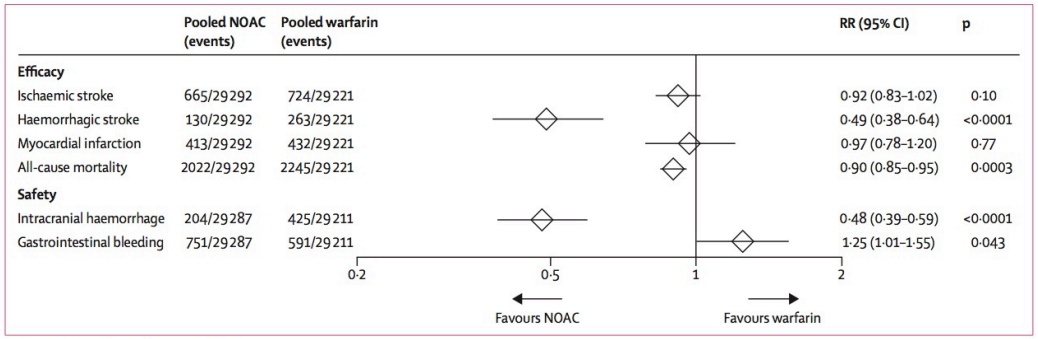


***Figure 2*: Secondary efficacy and safety outcomes**

Ruff et al. Lancet 2014; 383: 955–62

Wirksamkeit der DOAC in der klinischen Praxis

Table 6: Overview on the design, mean follow-up and outcomes of the presented analysis in comparison to ROCKET-AF and published "real-world" studies on the effectiveness and safety of NOAC therapy in AF.

Study	Drug	Design and duration of follow-up	Mean $CHADS_2$ score	Effectiveness outcome (stroke/SE ± TIA)	Major bleeding
Dresden NOAC (present data)	*rivaroxaban*	*Prospective cohort study; 796 days*	*2.4*	*2.0/100py (ITT) 1.7/100py (OT)*	*3.0/100py*
ROCKET-AF (6)	rivaroxaban	RCT; 707 days	3.5	2.1/100py (ITT) 1.7/100py (PP)	3.6/100py
XANTUS (19)	rivaroxaban	Prospective cohort study; 329 days	2.0	1.8/100py	2.1/100py
Laliberté (17)	rivaroxaban	Retrospective database analysis; 83 days	2.0	4.6/100py	3.3/100py
Maura (24)	rivaroxaban	Retrospective database analysis; 80 days	UNK	1.4/100py (stroke/SE)	3.7/100py
Maura (24)	dabigatran	Retrospective database analysis; 87 days	UNK	2.0/100py (stroke/SE)	3.3/100py
Dresden NOAC (11)	dabigatran	Prospective cohort study; 671 days	2.5	2.9/100py (ITT) 1.9/100py (OT)	2.3/100py
Villines (22)	dabigatran	Retrospective database analysis; 297 days	2.3	0.9/100py (stroke) 0.5/100py (TIA)	3.1/100py
Seeger (20)	dabigatran	Retrospective database analysis;5 months	1.8	0.8/100py (stroke) 0.2/100py (TIA)	4.4/100py
Lauffenburger (34)	dabigatran	Retrospective database analysis; 358 days	UNK	1.7/100py (stroke) 0.9/100py (TIA)	3.2/100py
Graham (15)	dabigatran	Retrospective database analysis, UNK	UNK	1.1/100py	4.3/100py
Larsen (35)	dabigatran	Retrospective database analysis; 13.2 months	0.9–2.1	UNK	2.1–3.7/100py
Sorensen (16)	dabigatran	Retrospective database analysis; 129 days	1.0–1.8	2.6–3.7/100py	3.7–11.0/100py

SE, systemic embolism; TIA, transitory ischaemic attack; py, patient-years; UNK, unknown.

THROMBOSIS AND HEMOSTASIS

Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry

Jan Beyer-Westendorf,[1] Kati Förster,[1] Sven Pannach,[2] Franziska Ebertz,[1] Vera Gelbricht,[1] Christoph Thieme,[1] Franziska Michalski,[1] Christina Köhler,[1] Sebastian Werth,[1] Kurtulus Sahin,[3] Luise Tittl,[1] Ulrike Hänsel,[1] and Norbert Weiss[1]

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Coagulation and Fibrinolysis

OPEN ACCESS

Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in "real-world" clinical practice

A propensity-matched analysis of 76,940 patients

Xiaoyan Li[1]; Steve Deitelzweig[2]; Allison Keshishian[3]; Melissa Hamilton[1]; Ruslan Horblyuk[4]; Kiran Gupta[1]; Xuemei Luo[5]; Jack Mardekian[4]; Keith Friend[1]; Anagha Nadkarni[1]; Xianying Pan[6]; Gregory Y. H. Lip[7,8]

[1]Bristol-Myers Squibb Company, Lawrenceville, New Jersey, USA; [2]Ochsner Clinic Foundation, Department of Hospital Medicine, New Orleans, Louisianna, USA and The University of Queensland School of Medicine, Ochsner Clinical School, New Orleans, Louisianna, USA; [3]STATinMED Research, Ann Arbor, Michigan, USA; [4]Pfizer, Inc., New York, New York, USA; [5]Pfizer, Inc., Groton, Conneticut, USA; [6]Bristol-Myers Squibb Company, Wallingford, Conneticut, USA; [7]Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK; [8]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Thromb Haemost 2016; 115: 939–949; Blood. 2014;124(6):955-962; Thromb Haemost 2017; 117: 1072–1082

	Rivaroxaban *Xarelto®*	**Apixaban** *Eliquis®*	**Edoxaban** *Lixiana®*	**Dabigatran** *Pradaxa®*
Orthopädische Chirurgie	Zugelassen	Zugelassen	Phase III	Phase III
Vorhofflimmern	Zugelassen	Zugelassen	Zugelassen	Zugelassen
Behandlung von venösen Thrombosen *TVT, Lungenembolie*	Zugelassen	Zugelassen	Zugelassen	Zugelassen
Sekundärprophylaxe von venösen Thrombosen	Zugelassen	Zugelassen	Zugelassen	Zugelassen
Mechanische Herzklappen	Nicht untersucht	Nicht untersucht	Nicht untersucht	Keine Vorteile
Koronare Herzerkrankung *Herzinfarkt*	Zugelassen/ mixed results	Nicht untersucht	Nicht untersucht	Nicht untersucht
Zerebrovaskuläre Erkrankung *Schlaganfall*	Keine Vorteile	Nicht untersucht	Nicht untersucht	Nicht untersucht
Hospitalisierte, medizinisch kranke Patienten	Keine Vorteile	Keine Vorteile	Nicht untersucht	Nicht untersucht
Niereninsuffizienz	Dosisreduktion	Dosisreduktion	Dosisreduktion	Nicht empfohlen
Leberfunktionsstörung	Vorsicht	Vorsicht	Vorsicht	Vorsicht
Übergewichtige Patienten	Zugelassen	Zugelassen	Zugelassen	Zugelassen
Ältere Patienten	Zugelassen	Dosisreduktion	Zugelassen	Dosisreduktion
Thrombozytenfunktionshemmer *Aspirin®, Plavix® u.ä.*	Vorsicht	Vorsicht	Vorsicht	Vorsicht
Krebserkrankungen	Zugelassen	Zugelassen	Zugelassen	Nicht untersucht
Antiphospholipid-Antikörpersyndrom	Nicht empfohlen	Nicht untersucht	Nicht untersucht	Nicht untersucht
Schwangerschaft/ Stillzeit	Verboten	Verboten	Verboten	Verboten

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Rivaroxaban in patients with mechanical heart valves: A pilot study

Eva Roost[a,1], Alberto Weber[a,1], Lorenzo Alberio[b,c,*], Lars Englberger[a], David Reineke[a], Dorothée Keller[a], Michael Nagler[d,**,2], Thierry Carrel[a,2]

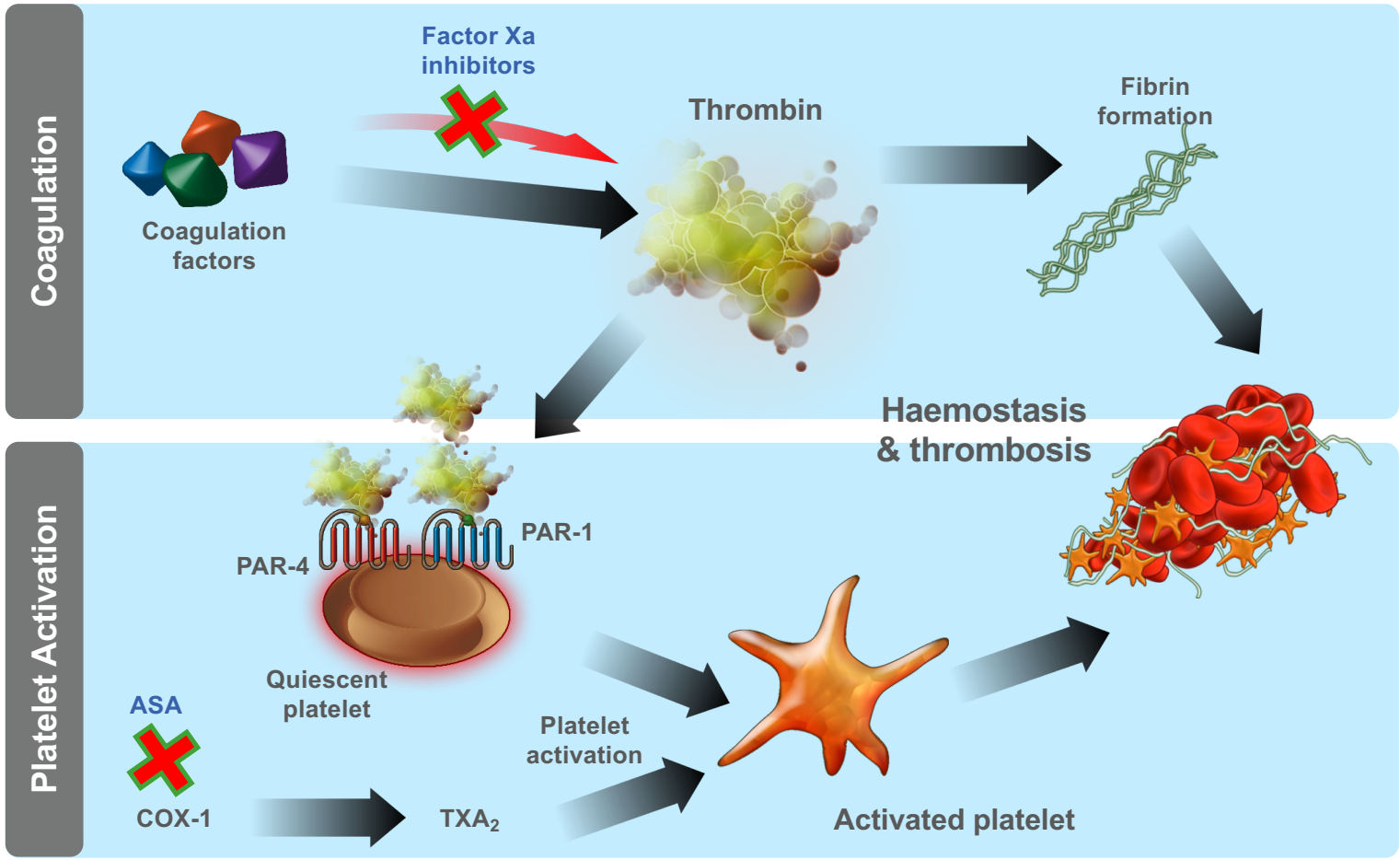
[a] Department of Cardiothoracic Surgery, Inselspital, Bern University Hospital, University of Bern, CH-3010 Bern, Switzerland
[b] Division of Haematology and Central Haematology Laboratory, Lausanne University Hospital (CHUV), Lausanne, Switzerland
[c] Faculty of Biology and Medicine, University of Lausanne (UNIL), Lausanne, Switzerland
[d] University Institute of Clinical Chemistry, Inselspital, Bern University Hospital, University of Bern, CH-3010 Berne, Switzerland

Table 1
Patient characteristics.

Patient	Age (years)	Sex	BMI (kg/m^2)	Indication for AVR	Extend of heart failure	Type of intervention	Type of valve[a] (mm)	Concomitant disorders
1	47	Male	28	Aortic valve stenosis	NYHA I	Isolated AVR	20	None
2	60	Male	35	Aortic valve stenosis	NYHA II	Isolated AVR	24	None
3	51	Male	31	Aortic valve stenosis	NYHA II	Isolated AVR	22	None
4	50	Male	25	Aortic stenosis and regurgitation; aortic root aneurysm	NYHA I	Root replacement	25	None
5	49	Male	26	Aortic valve stenosis	NYHA II	Isolated AVR	22	None
6	48	Male	24	Aortic valve stenosis	NYHA II	Isolated AVR	22	None
7	39	Male	29	Aortic valve insufficiency	NYHA II	Isolated AVR	24	None
8	48	Male	30	Aortic root aneurysm	NYHA I	Root replacement	23	Dyslipidemia
9	44	Female	24	Aortic stenosis and regurgitation	NYHA I	AVR, replacement of ascending aorta and aortic arch	22	None
10	48	Male	26	Aortic root aneurysm	NYHA I	Root replacement	25	History of thyroid cancer

Abbreviations: AVR, aortic valve replacement. BMI, body mass index; NYHA, New York Heart Association Functional Classification.
[a] Medtronic open Pivot©.

Die duale Thrombozytenaggregationshemmung bietet theoretische Vorteile



Eur Heart J 2010;31:17–28

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Controlled Trial of Rivaroxaban after Transcatheter Aortic-Valve Replacement

G.D. Dangas, J.G.P. Tijssen, J. Wöhrle, L. Søndergaard, M. Gilard, H. Möllmann, R.R. Makkar, H.C. Herrmann, G. Giustino, S. Baldus, O. De Backer, A.H.C. Guimarães, L. Gullestad, A. Kini, D. von Lewinski, M. Mack, R. Moreno, U. Schäfer, J. Seeger, D. Tchétché, K. Thomitzek, M. Valgimigli, P. Vranckx, R.C. Welsh, P. Wildgoose, A.A. Volkl, A. Zazula, R.G.M. van Amsterdam, R. Mehran, and S. Windecker, for the GALILEO Investigators*

CONCLUSIONS

In patients without an established indication for oral anticoagulation after successful TAVR, a treatment strategy including rivaroxaban at a dose of 10 mg daily was associated with a higher risk of death or thromboembolic complications and a higher risk of bleeding than an antiplatelet-based strategy. (Funded by Bayer and Janssen Pharmaceuticals; GALILEO ClinicalTrials.gov number, NCT02556203.)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 5, 2012 VOL. 366 NO. 1

Rivaroxaban in Patients with a Recent Acute Coronary Syndrome

METHODS

In this double-blind, placebo-controlled trial, we randomly assigned 15,526 patients with a recent acute coronary syndrome to receive twice-daily doses of either 2.5 mg or 5 mg of rivaroxaban or placebo for a mean of 13 months and up to 31 months. The primary efficacy end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke.

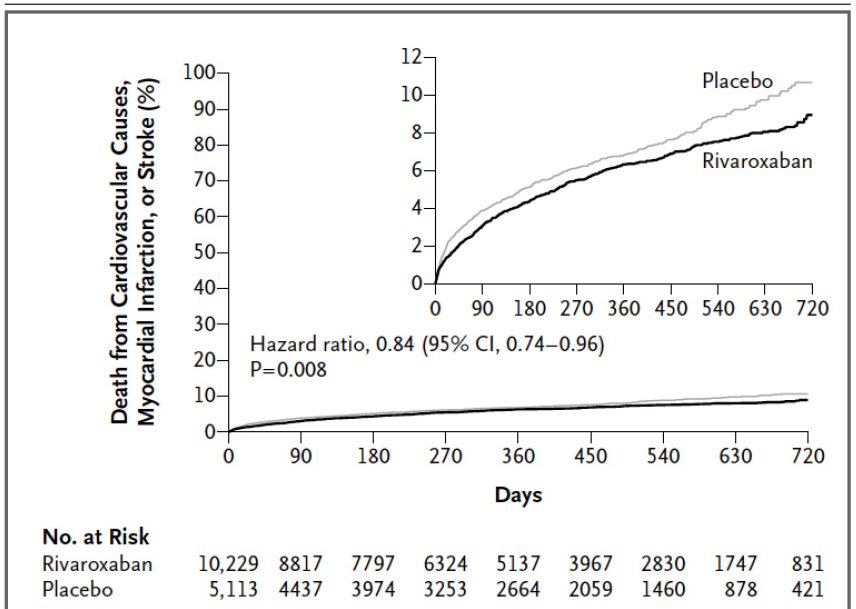


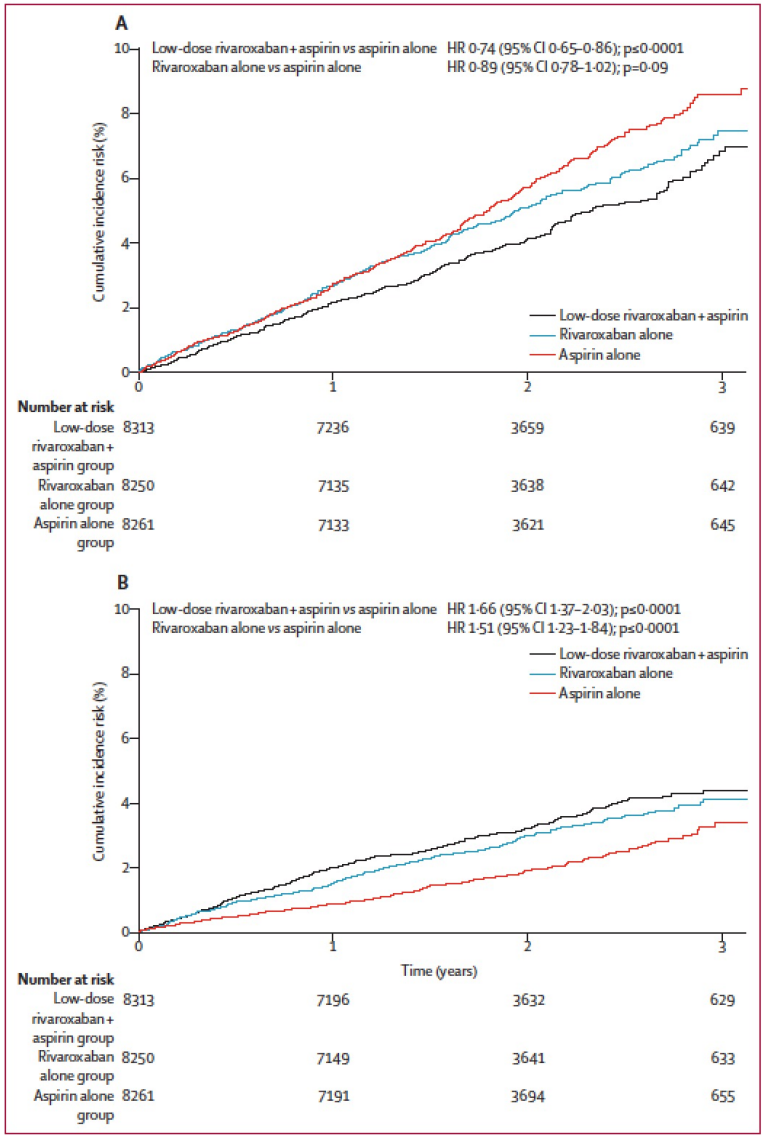
Figure 1. Cumulative Incidence of the Primary Efficacy End Point.

The primary efficacy end point consists of death from cardiovascular causes, myocardial infarction, or stroke. According to these results, the composite end point would be prevented in 1 patient if 56 patients were treated for 2 years with rivaroxaban. The P value is for the modified intention-to-treat analyses. P=0.002 for the intention-to-treat analysis.

High risk of major bleeding (HR 4.0)

Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial

Methods In this multicentre, double-blind, randomised, placebo-controlled, outpatient trial, patients with stable coronary artery disease or peripheral artery disease were recruited at 602 hospitals, clinics, or community centres in 33 countries. This paper reports on patients with coronary artery disease. Eligible patients with coronary artery disease had to have had a myocardial infarction in the past 20 years, multi-vessel coronary artery disease, history of stable or unstable angina, previous multi-vessel percutaneous coronary intervention, or previous multi-vessel coronary artery bypass graft surgery. After a 30-day run in period, patients were randomly assigned (1:1:1) to receive rivaroxaban (2·5 mg orally twice a day) plus aspirin (100 mg once a day), rivaroxaban alone (5 mg orally twice a day), or aspirin alone (100 mg orally once a day). Randomisation was computer generated. Each treatment group was double dummy, and the patients, investigators, and central study staff were masked to treatment allocation. The primary outcome of the COMPASS trial was the occurrence of myocardial infarction, stroke, or cardiovascular death. This trial is registered with ClinicalTrials.gov, number NCT01776424, and is closed to new participants.



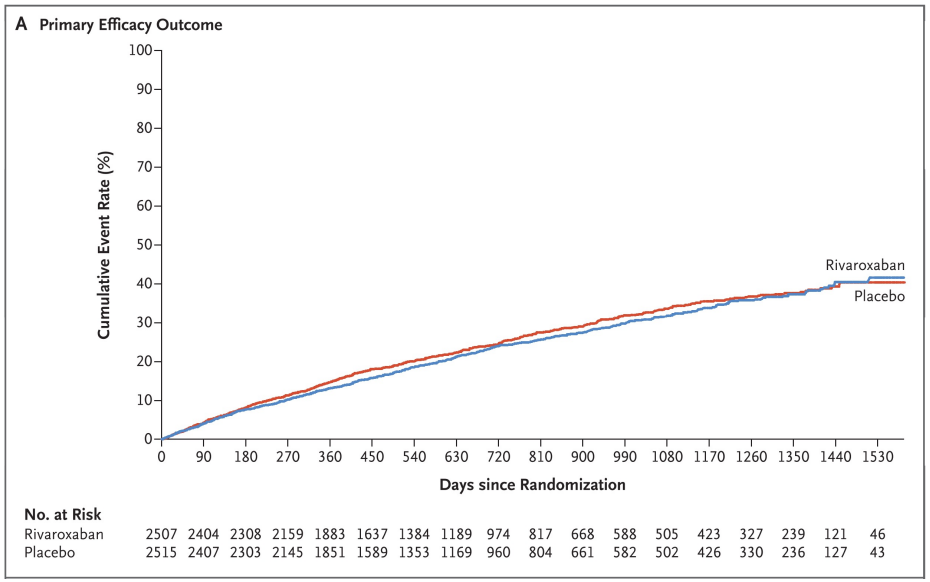
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease

METHODS

In this double-blind, randomized trial, 5022 patients who had chronic heart failure, a left ventricular ejection fraction of 40% or less, coronary artery disease, and elevated plasma concentrations of natriuretic peptides and who did not have atrial fibrillation were randomly assigned to receive rivaroxaban at a dose of 2.5 mg twice daily or placebo in addition to standard care after treatment for an episode of worsening heart failure. The primary efficacy outcome was the composite of death from any cause, myocardial infarction, or stroke. The principal safety outcome was fatal bleeding or bleeding into a critical space with a potential for causing permanent disability.



While taking the trial regimen, patients assigned to rivaroxaban had a higher risk of ISTH-defined major bleeding than those assigned to placebo (3.3% vs. 2.0%; hazard ratio, 1.68; 95% CI, 1.18 to 2.39). This result was mainly driven by the

Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial

Methods In this double-blind, multicentre, randomised trial (GEMINI-ACS-1) done at 371 clinical centres in 21 countries, eligible patients were older than 18 years with unstable angina, non-ST segment elevation myocardial infarction (NSTEMI) or ST segment elevation myocardial infarction (STEMI), with positive cardiac biomarkers and either ischaemic electrocardiographic changes or an atherosclerotic culprit lesion identified during angiography. Participants were randomly assigned (1:1) within 10 days after admission for the index acute coronary syndromes event to either aspirin or rivaroxaban based on a computer-generated randomisation schedule. Randomisation was balanced by using randomly permuted blocks with size of four and was stratified based on the background P2Y12 inhibitor (clopidogrel or ticagrelor) intended to be used at the time of randomisation. Investigators and patients were masked to treatment assignment. Patients received a minimum of 180 days of double-blind treatment with rivaroxaban 2·5 mg twice daily or aspirin 100 mg daily. The choice of clopidogrel or ticagrelor during trial conduct was not randomised and was based on investigator preference. The primary endpoint was thrombolysis in myocardial infarction (TIMI) clinically significant bleeding not related to coronary artery bypass grafting (CABG; major, minor, or requiring medical attention) up to day 390. Primary analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT02293395.

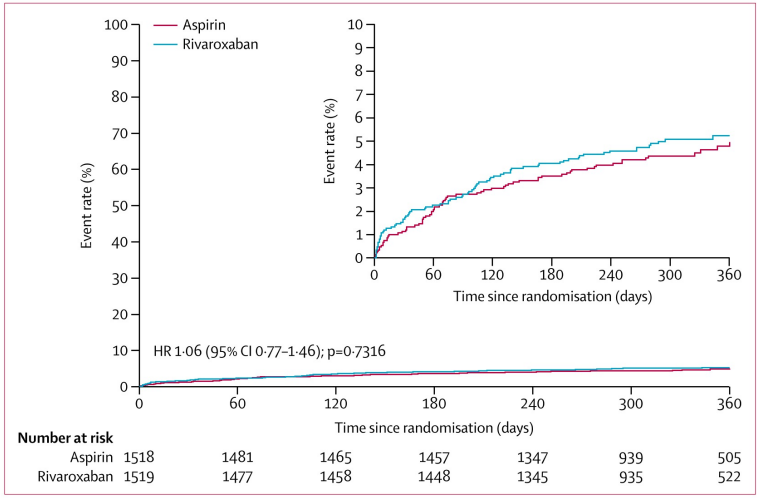


Figure 4: **Cardiovascular death, myocardian infarction, stroke, or definite stent thrombosis between treatment groups**

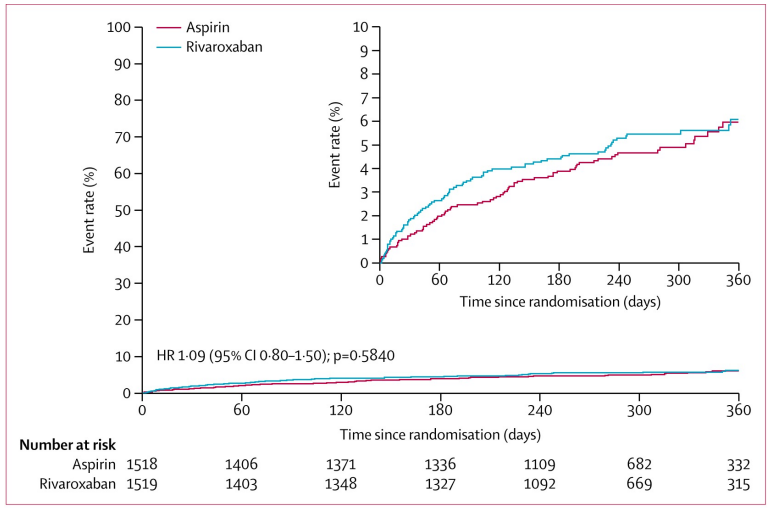


Figure 2: **TIMI non-CABG clinically significant bleeding between treatment groups**
TIMI=thrombolysis in myocardial infarction. CABG=coronary artery bypass graft. HR=hazard ratio.

Table 6: Pros and cons of different options for antithrombotic drug combinations after an ACS.

	Pros	Cons
aspirin	lowest rates of bleeding (as for clopidogrel alone)	inferior in efficacy to combination treatment with a P2Y12 inhibitor in preventing recurrent events; not sufficient to avert stent thrombosis; gastro-intestinal side effects
clopidogrel	lowest rates of bleeding (as for aspirin alone)	inferior in efficacy to combination treatment with aspirin; not sufficient alone to avert stent thrombosis
aspirin + clopidogrel	lower rate of bleeding compared to other drug combination treatments; use extensible in some patients beyond one year, when deemed appropriate	inferior in efficacy to combination treatment with aspirin and a newer P2Y12 inhibitor (prasugrel or ticagrelor) or to the addition of rivaroxaban or voraxapar; not sufficient alone to avert stent thrombosis
aspirin + prasugrel	possibly best efficacy in STEMI and in diabetic patients	more bleeding compared with aspirin + clopidogrel; not to be used in patients not being treated with PCI; not to be used in patients with previous stroke; to be used with caution in patients with low body weight (<60 kg); restricted to clopidogrel-naïve patients; not to be given as pre-treatment before knowing coronary anatomy in NSTE-ACS patients; no favourable data beyond one year of treatment
aspirin + ticagrelor	usable in a broad range of ACS patients; pretreatment in patients with NSTE-ACS possible; proven to reduce cardiovascular and total mortality up to 1 year; favourable data for prolonged treatment for years after an ACS in selected patients	more bleeding compared with aspirin + clopidogrel; not to be used in patients with previous haemorrhagic stroke; possible interaction with high-dose aspirin; to be used with caution in those with sinoatrial disease who do not have a pacemaker or with history of asthma/chronic obstructive pulmonary disease
aspirin + clopidogrel + rivaroxaban	largest reduction in cardiovascular and total mortality so far reported post-ACS; treatment proven effective up to 2 years after an ACS	increased rates of major (non-fatal) bleeding, including intracranial haemorrhage, compared with aspirin + clopidogrel; to be restricted to patients without history of previous stroke
aspirin + clopidogrel + vorapaxar	effective also in patients with peripheral arterial disease, with a long follow-up (30 months median)	not to be used in patients with previous stroke or TIA; long half-life, without antidotes. No significant reduction in mortality

Abbreviations: ACS, acute coronary syndrome(s); NSTE, non-ST elevation; STEMI, ST-elevation myocardial infarction; TIA, transient ischaemic attack.

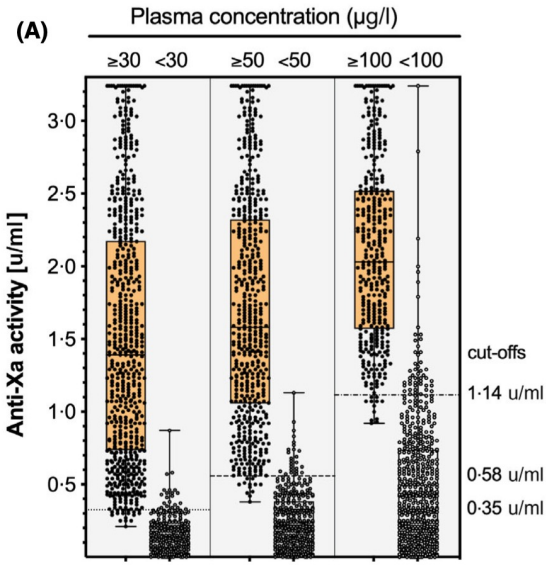
bjh research paper

A universal anti-Xa assay for rivaroxaban, apixaban, and edoxaban measurements: method validation, diagnostic accuracy and external validation

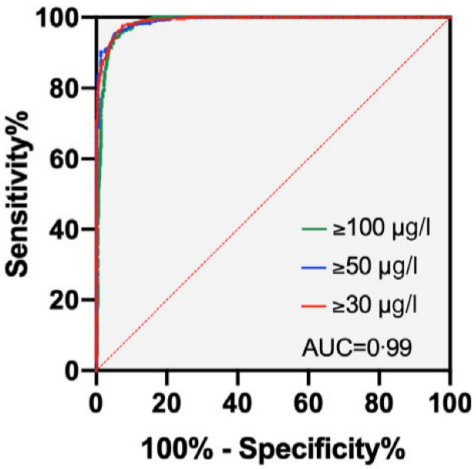
Guido Willekens,[1,2,*] Jan-Dirk Studt,[3,*] Adriana Mendez,[4] Lorenzo Alberio,[5] Pierre Fontana,[6] Walter A. Wuillemin,[7] Adrian Schmidt,[8] Lukas Graf,[9] Bernhard Gerber,[10] Cedric Bovet,[2] Thomas C. Sauter[11] and Michael Nagler[2,12]

Summary

A universal anti-Xa assay for the determination of rivaroxaban, apixaban and edoxaban drug concentrations would simplify laboratory procedures and facilitate widespread implementation. Following two pilot studies analysing spiked samples and material from 698 patients, we conducted a prospective multicentre cross-sectional study, including 867 patients treated



(B)



frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 01 October 2021
doi: 10.3389/fcvm.2021.749342

Long-Term Survival After Venous Thromboembolism: A Prospective Cohort Study

*Henning Nilius[1,2], Tamara Mertins[1], Robin Boss[1], Matthias Knuchel[1], Eva Blozik[3], Johanna Anna Kremer Hovinga[4], Sabine Eichinger[5] and Michael Nagler[1,4]**

[1] University Institute of Clinical Chemistry, Inselspital University Hospital, University of Bern, Bern, Switzerland, [2] Department of Epidemiology, Maastricht University, Maastricht, Netherlands, [3] Department of Health Sciences, Helsana Group, Zuerich, Switzerland, [4] Department of Hematology and Central Hematology Laboratory, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland, [5] Department of Medicine 1, Medical University of Vienna, Vienna, Austria

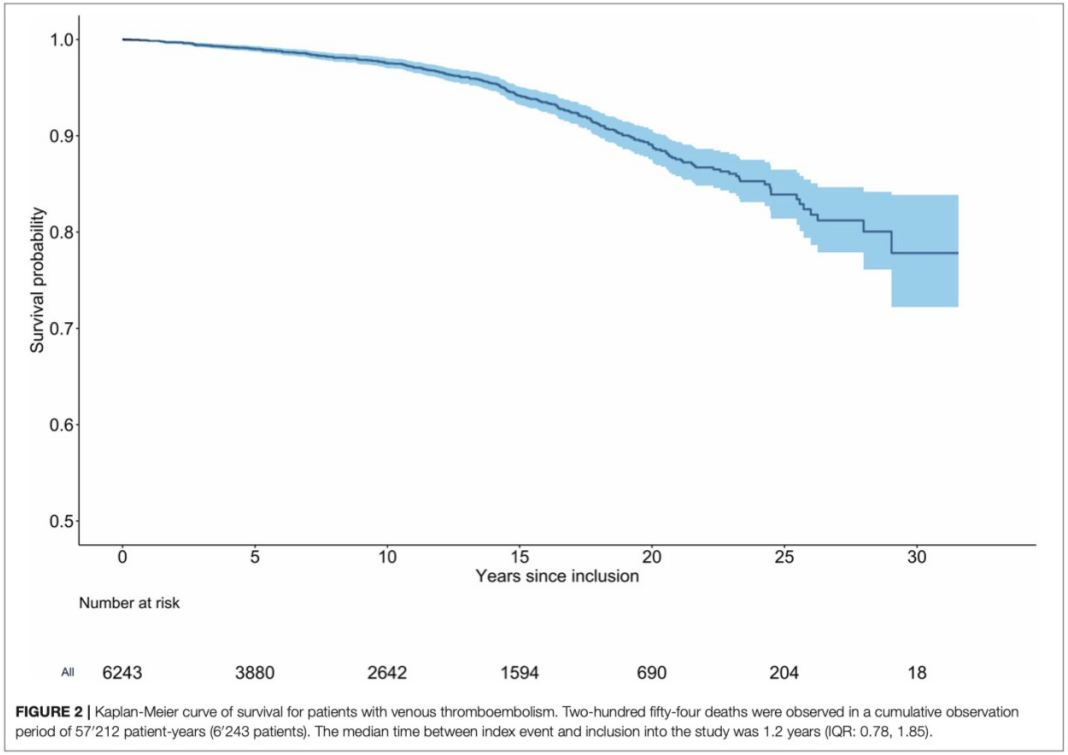


FIGURE 2 | Kaplan-Meier curve of survival for patients with venous thromboembolism. Two-hundred fifty-four deaths were observed in a cumulative observation period of 57′212 patient-years (6′243 patients). The median time between index event and inclusion into the study was 1.2 years (IQR: 0.78, 1.85).

Vielen Dank für Ihre Aufmerksamkeit

Michael Nagler, Prof. Dr. Dr. med.
Inselspital, Zentrum für Labormedizin