Come interpretare i dati degli studi osservazionali

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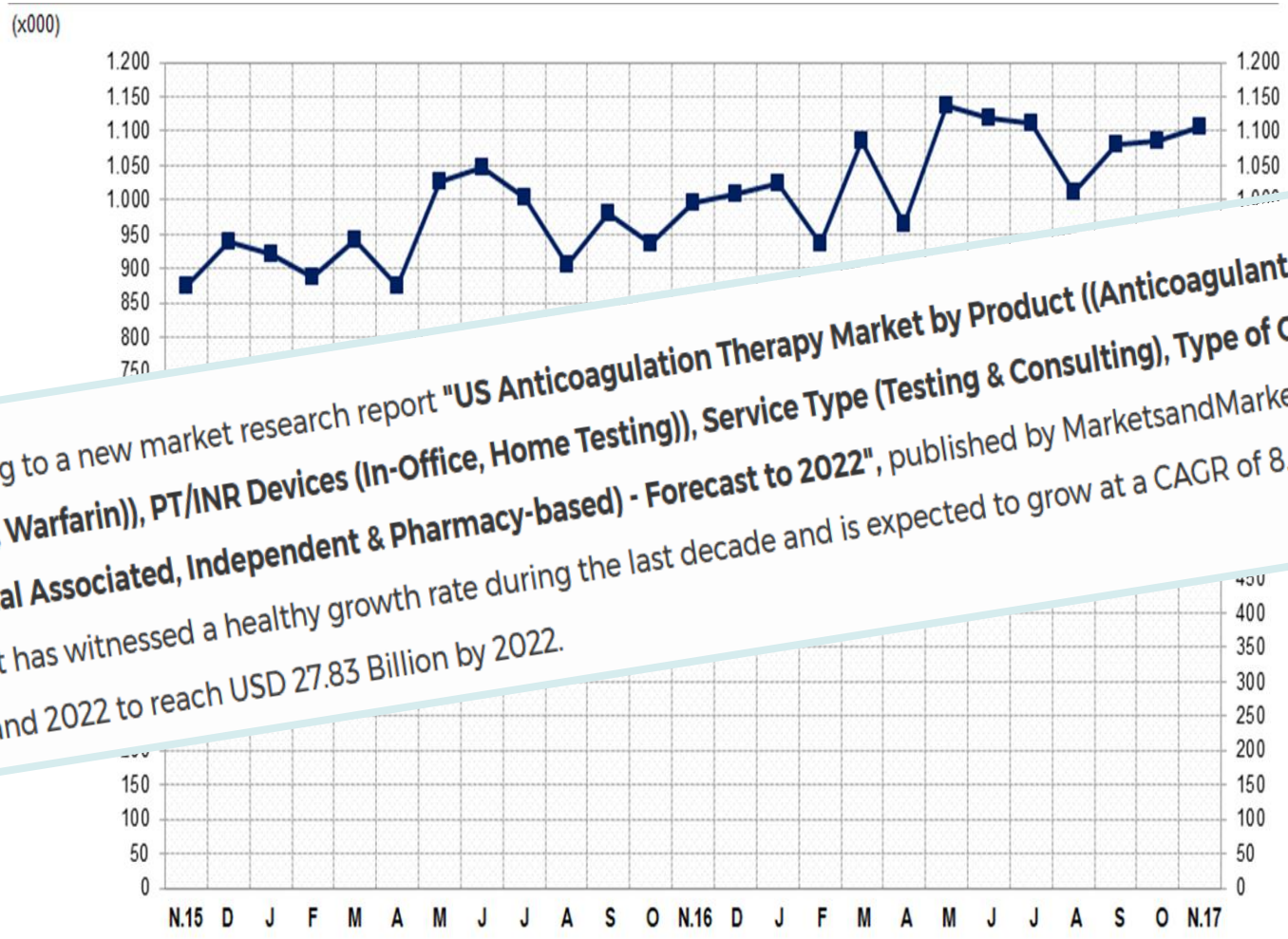
ITALY_ OA Unfactored Market: VKA vs NOA
Pack EQ (RETAIL, HOSPITAL & DPC – MONTHLY Data)
Novembre 2017

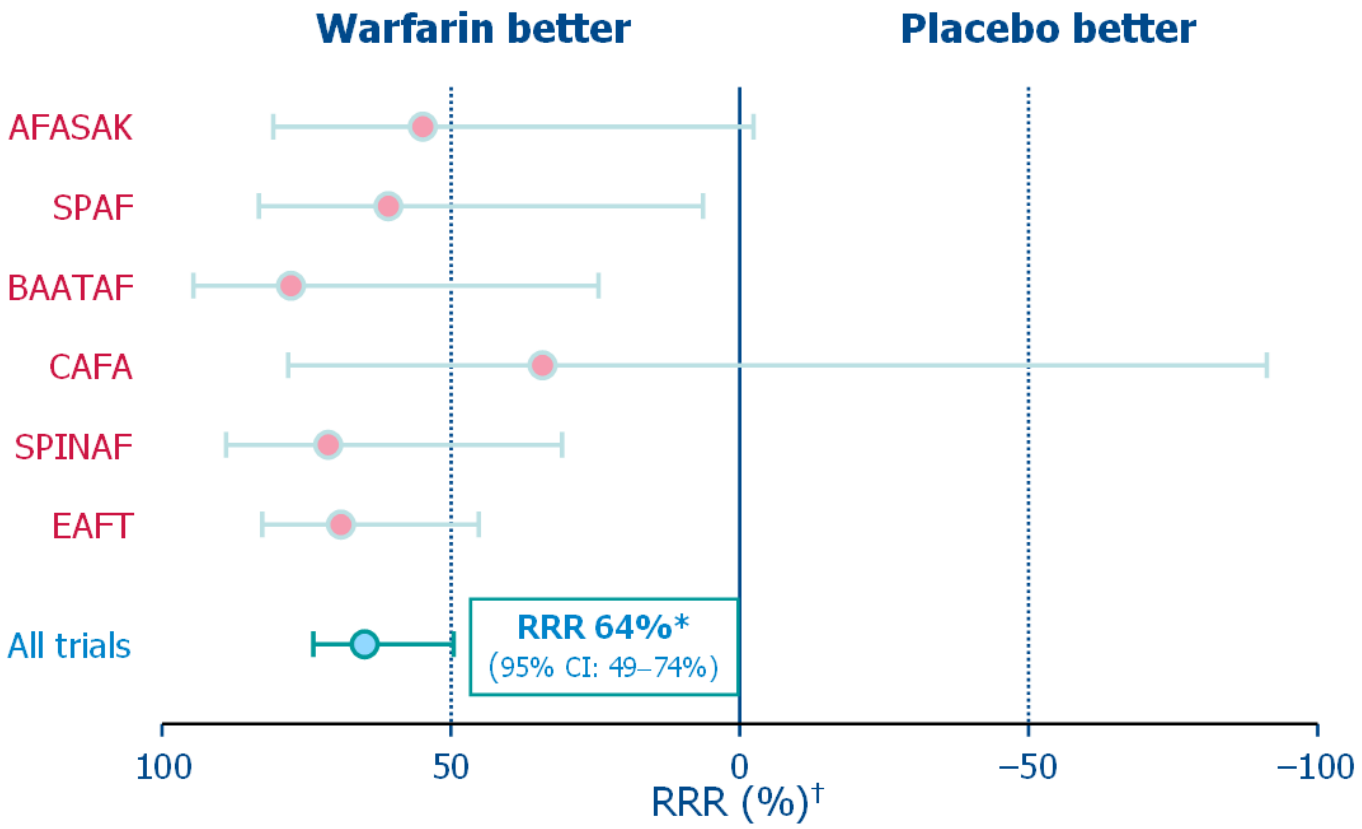


VKA	594	628	614	571	597	532	650	659	592	540	565	522	554	564	551	485	561	497	575	561	550	499	502	496	511
NOA	283	310	307	317	344	342	377	389	410	365	416	414	440	446	473	452	525	467	562	559	562	513	578	590	597
TOT OA	876	939	921	888	942	874	1.027	1.048	1.003	905	981	936	995	1.010	1.024	937	1.086	965	1.137	1.119	1.112	1.012	1.080	1.086	1.107
±% L.Y.	+12,2	+12,2	+4,2	+17,0	+8,2	+2,5	+15,5	+12,5	+3,4	+16,8	+9,2	+6,0	+13,5	+7,5	+11,2	+5,5	+15,4	+10,3	+10,7	+6,8	+10,8	+11,8	+10,1	+16,0	+11,3

According to a new market research report **"US Anticoagulation Therapy Market by Product ((Anticoagulants Drugs (NOACs, Warfarin)), PT/INR Devices (In-Office, Home Testing)), Service Type (Testing & Consulting), Type of Clinic (Hospital Associated, Independent & Pharmacy-based) - Forecast to 2022"**, published by MarketsandMarkets™, the market has witnessed a healthy growth rate during the last decade and is expected to grow at a CAGR of 8.5% between 2017 and 2022 to reach USD 27.83 Billion by 2022.

Source: IMS

WARFARIN AND STROKE RISK IN AF PATIENTS

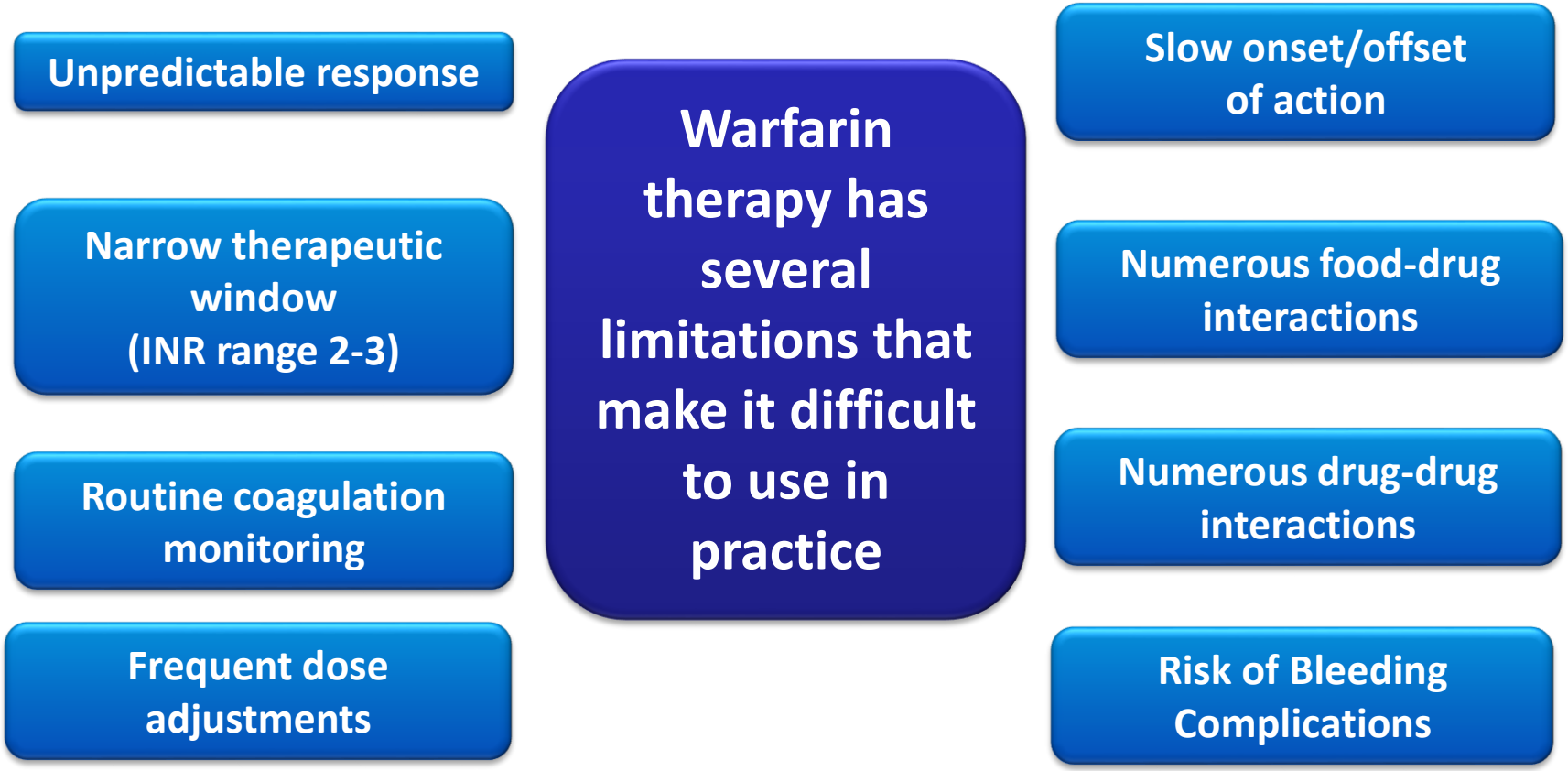


Hart RG et al. Ann Int Med 2007

RATES OF THROMBOEMBOLISM AND REDUCTION IN RISK DUE TO ANTICOAGULATION

INDICATION	RATE WITHOUT THERAPY	RISK REDUCTION WITH THERAPY
	percent	
Acute venous thrombo-embolism*		
Month 1	40	80
Months 2 and 3	10	80
Recurrent venous thrombo-embolism*†	15‡	80

Kearon et al. NEJM 1997

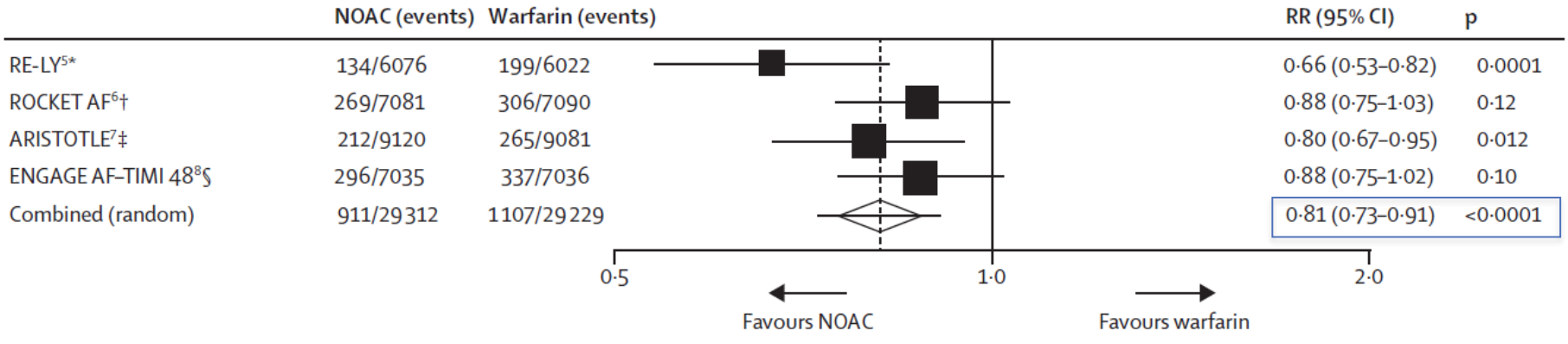


- Warfarin was #1 in 2003 and 2004 in the number of mentions of “deaths for drugs causing adverse effects in therapeutic use”
- Warfarin caused 6% of the 702,000 ADEs treated in the ED/year; 17% required hospitalization

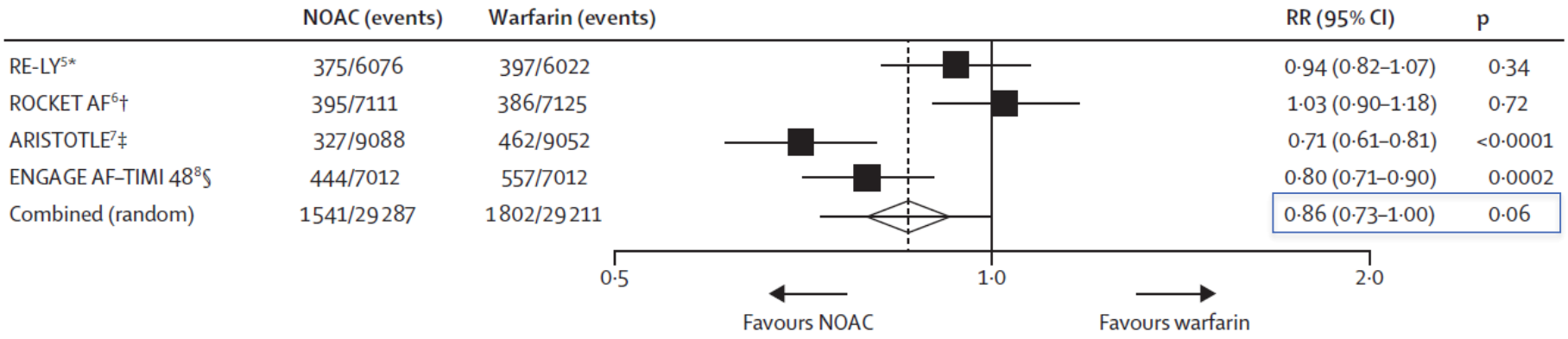
J Thromb Thrombolysis 2008

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

Stroke or SE



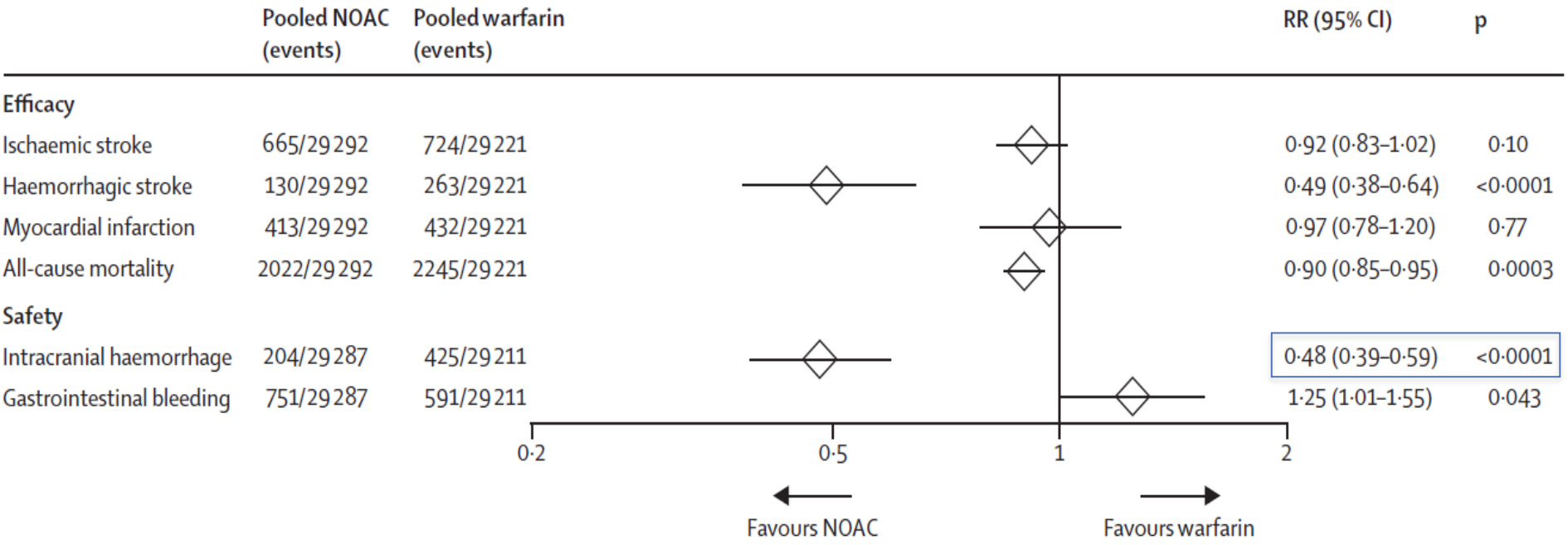
Major Bleeding



Ruff et al. Lancet 2013

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

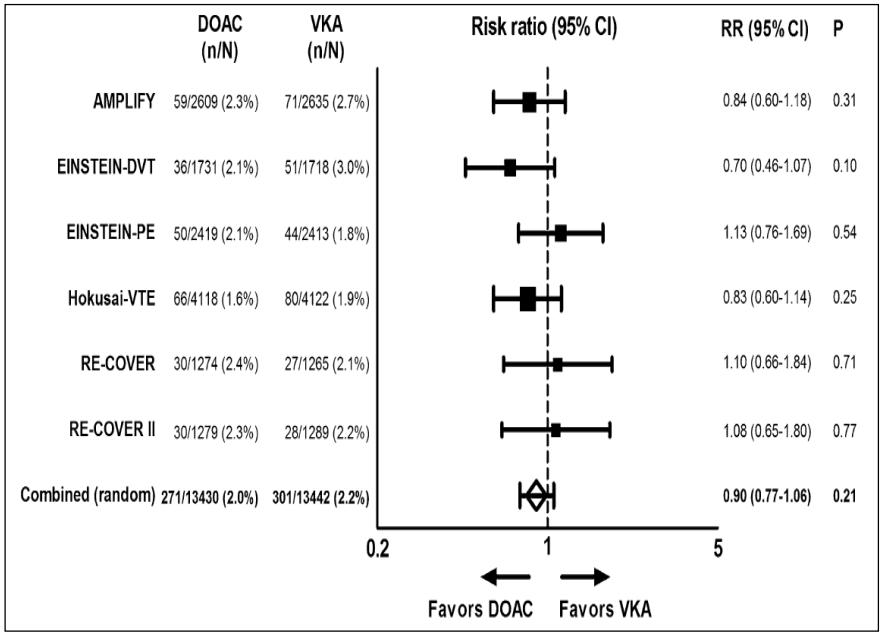
Other endpoints



Ruff et al. Lancet 2013

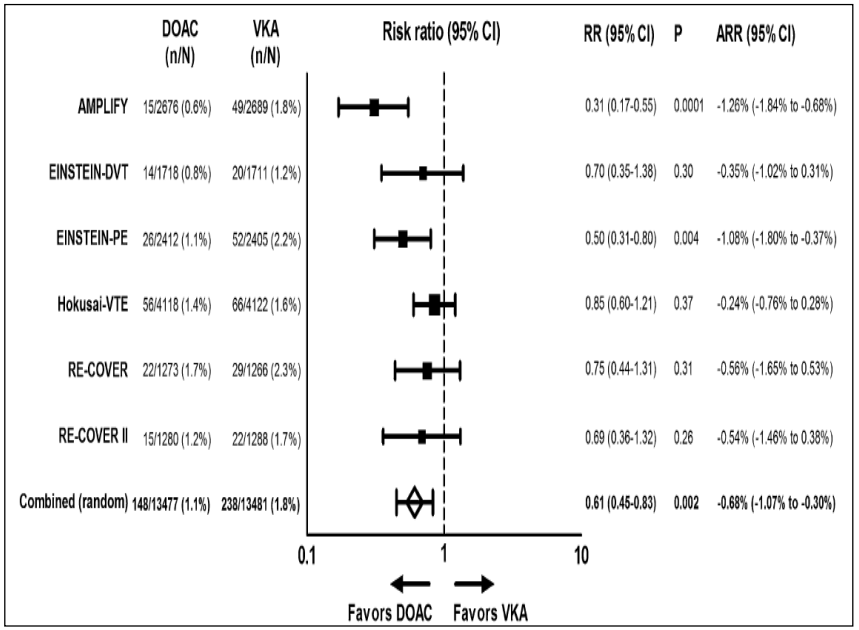
DOACs vs VKAs on VTE treatment

VTE recurrence



HR 0.90 (95%CI 0.77,1.06)

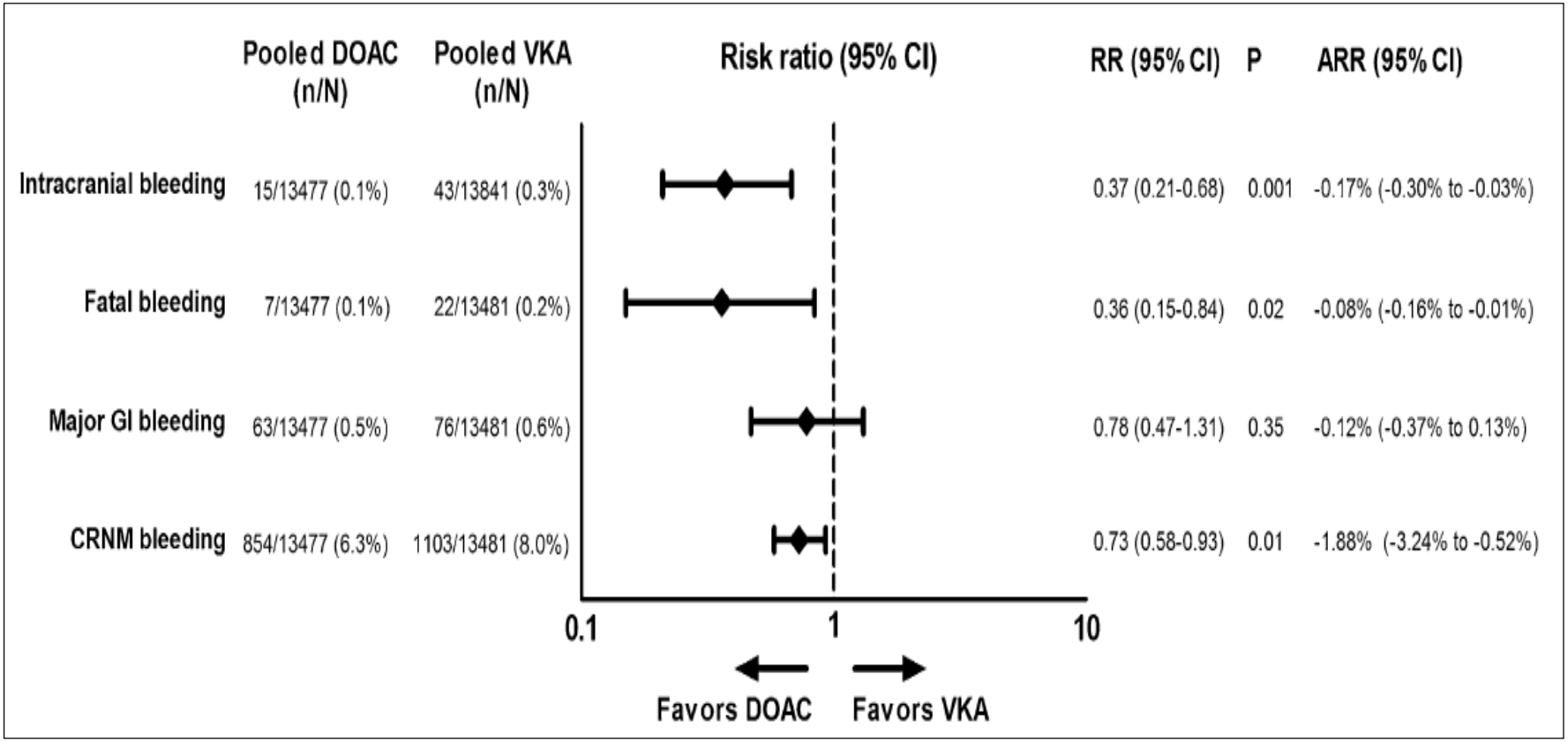
Major Bleeding



HR 0.61 (0.45,0.83)

Van Es et al. Blood 2014

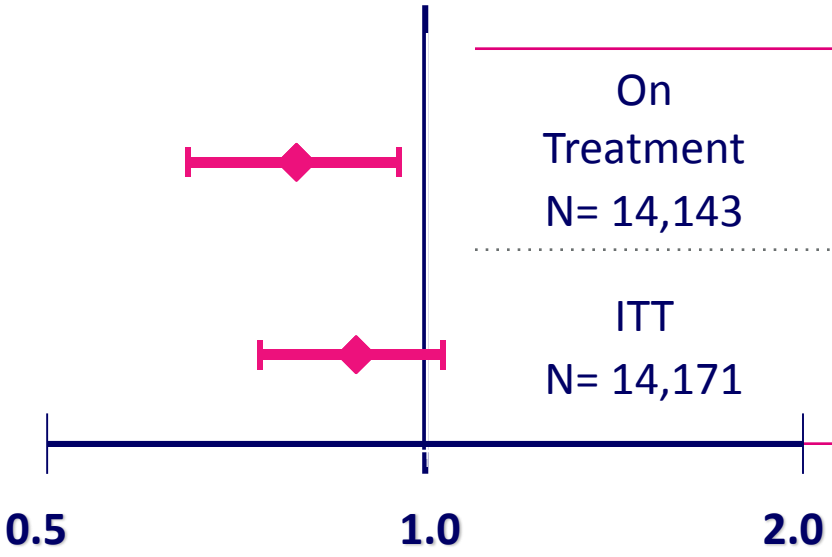
Other End Points



Van Es et al. Blood 2014

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Stroke and non-CNS Embolism



	Rivaroxaban Event Rate	Warfarin Event Rate	HR (95% CI)	P-value
On Treatment N= 14,143	1.70	2.15	0.79 (0.65,0.95)	0.015
ITT N= 14,171	2.12	2.42	0.88 (0.74,1.03)	0.117

Event Rates are per 100 patient-years
Based on Safety on Treatment or Intention-to-Treat

Patel M et al. NEJM 2011

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

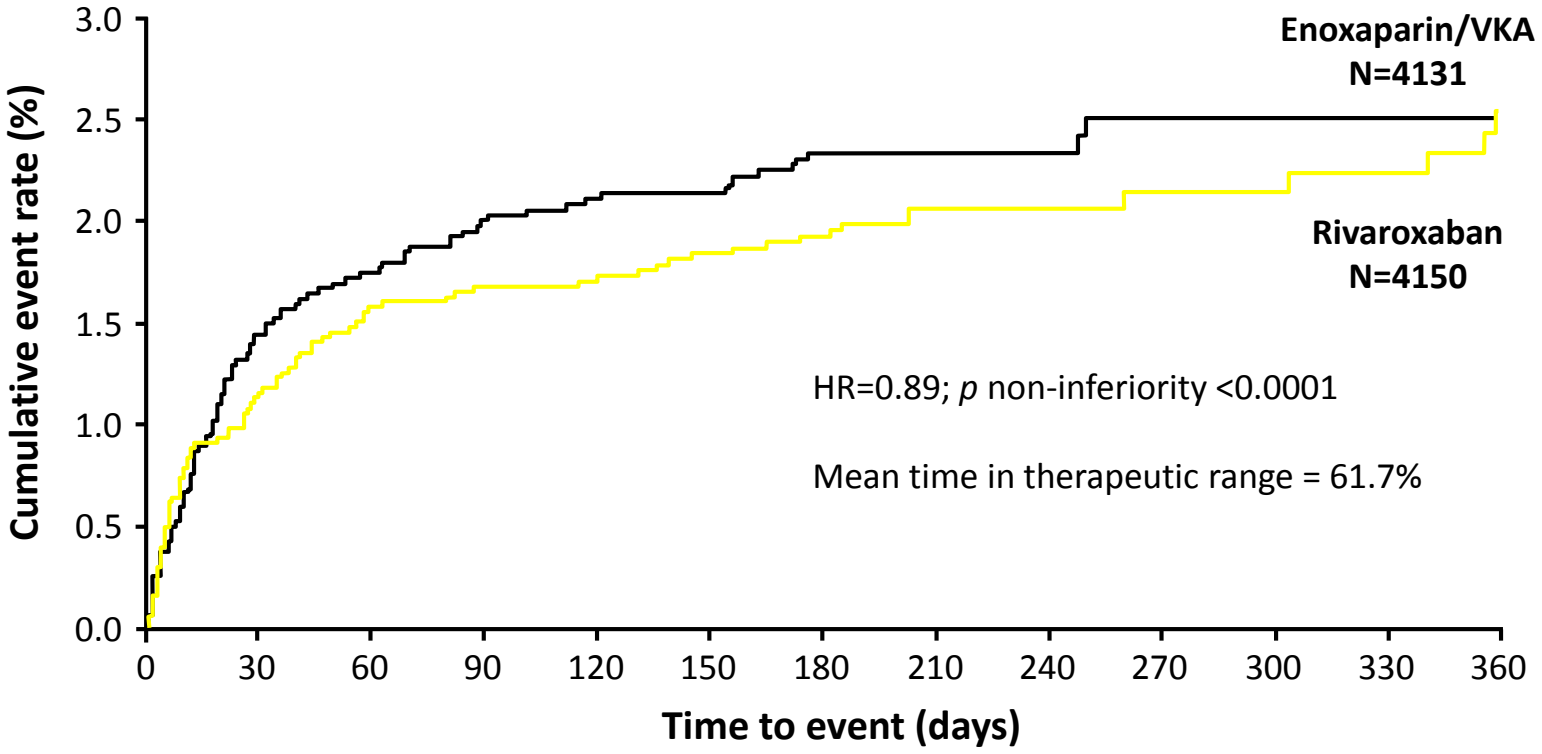
Primary Safety Outcomes

	Rivaroxaban	Warfarin		
	Event Rate	Event Rate	HR (95% CI)	p-value
Major and non-major Clinically Relevant	14.91	14.52	1.03 (0.96, 1.11)	0.442
Major	3.60	3.45	1.04 (0.90, 1.20)	0.576
Non-major Clinically Relevant	11.80	11.37	1.04 (0.96, 1.13)	0.345

Event Rates are per 100 patient-years
Based on Safety on Treatment Population

Patel M et al. NEJM 2011

EINSTEIN DVT and EINSTEIN PE pooled analysis: VTE recurrence

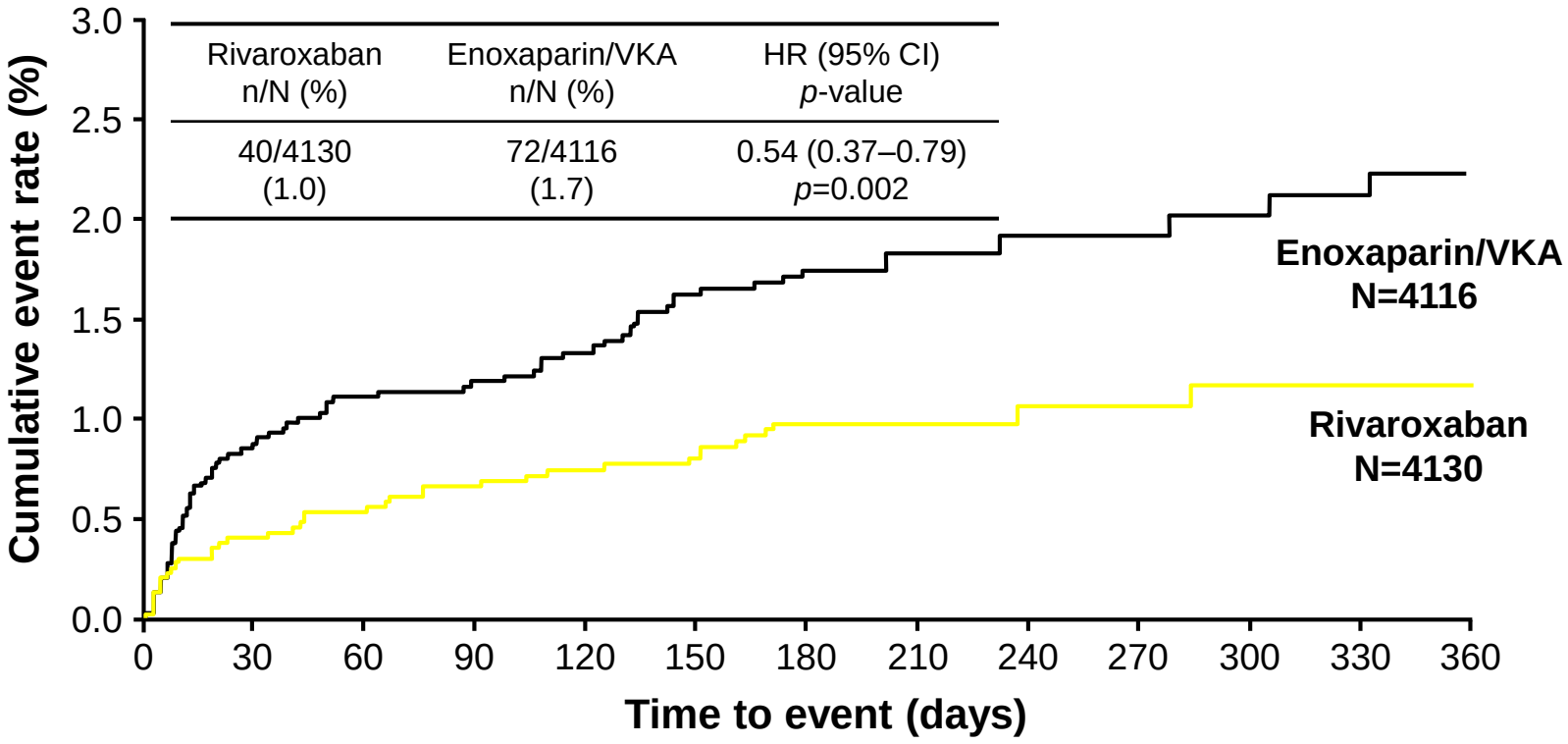


Number of patients at risk													
Rivaroxaban	4150	4018	3969	3924	3604	3579	3283	1237	1163	1148	1102	1034	938
Enoxaparin/VKA	4131	3932	3876	3826	3523	3504	3236	1215	1149	1109	1071	1019	939

ITT population

1. The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–510;
2. The EINSTEIN–PE Investigators. *N Engl J Med* 2012;366:1287–97

EINSTEIN DVT and EINSTEIN PE pooled analysis: major bleeding



Number of patients at risk													
Rivaroxaban	4130	3921	3862	3611	3479	3433	2074	1135	1095	1025	969	947	499
Enoxaparin/VKA	4116	3868	3784	3525	3394	3348	1835	1109	1065	990	950	916	409

Safety population

1. The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–510;
2. The EINSTEIN–PE Investigators. *N Engl J Med* 2012;366:1287–97

Differences Between Clinical Trials and Real-Life Settings

Clinical trial

- Strict inclusion and exclusion criteria
- Strict study protocol
- Objectively adjudicated event rates

Real life

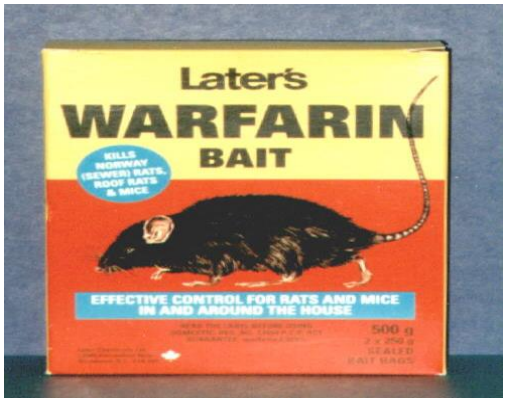
- Unselected patient population
- Dose recommendations only
- Over- and under-reporting of events

APPROVAL NUMBER: L.IT.MA.05.2017.2517

Limitations of well conducted phase 3 RCTs

- Unintended adverse events (UAEs) are unlikely to be revealed during phase III trials because the usual sample sizes of such studies and even the entire new drug application may range from hundreds to only a few thousand patients.

- Phase III trials also are not useful for detecting UAEs that occur only after long-term therapy because of insufficient length of follow-up time

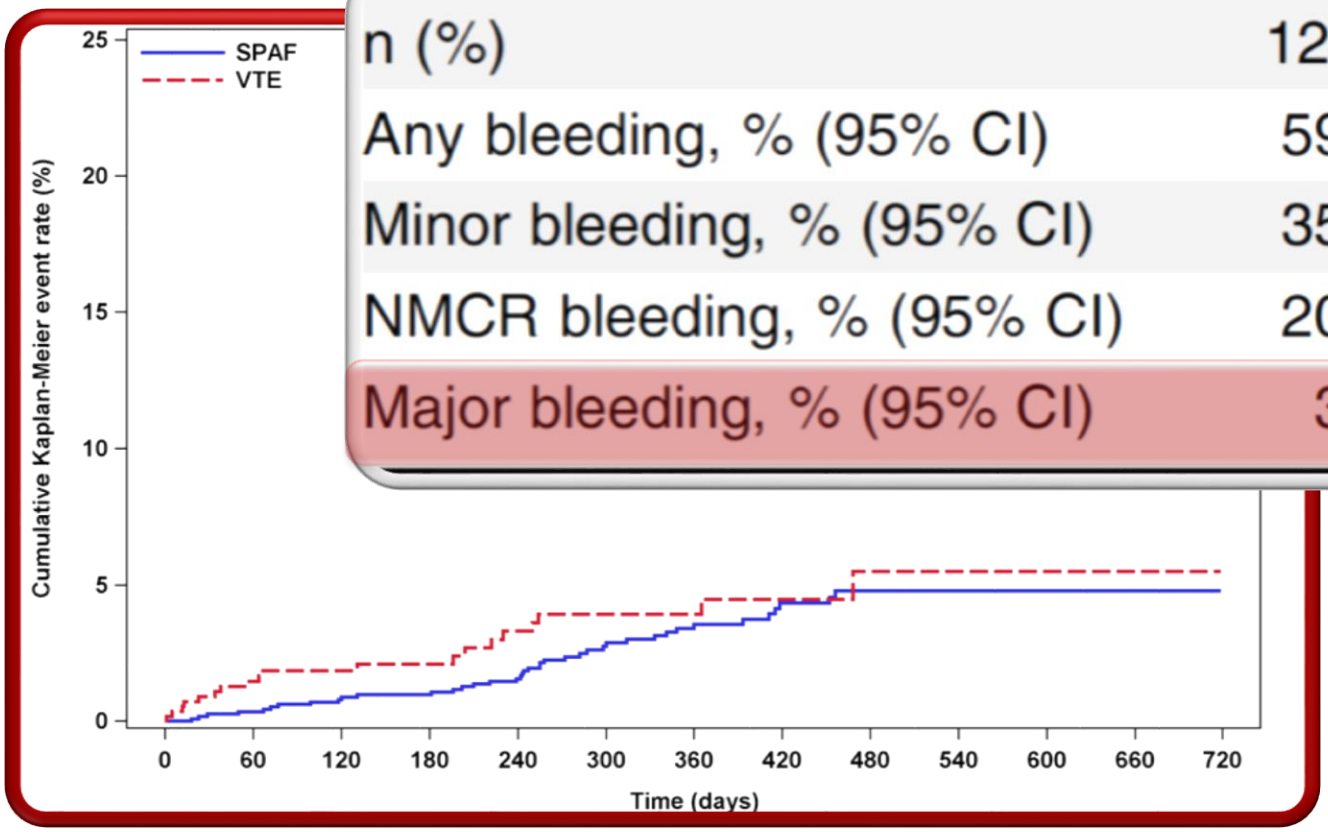

Later's
WARFARIN
BAIT
KILLS NORWAY (SEWER) RATS, ROOF RATS & MICE
EFFECTIVE CONTROL FOR RATS AND MICE IN AND AROUND THE HOUSE


ziguli vit
Compilation
Vitamine e Minerali
24g

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

Bleeding rates per 100 patient-years

n (%)	1200 (67.6)
Any bleeding, % (95% CI)	59.3 (54.4-64.6)
Minor bleeding, % (95% CI)	35.8 (32.2-39.7)
NMCR bleeding, % (95% CI)	20.7 (18.1-23.5)
Major bleeding, % (95% CI)	3.1 (2.2-4.3)



Bleeding

Beyer-Westerdorf J et al. Blood 2014

Quality and Outcomes

Characterizing Major Bleeding in Patients With Nonvalvular Atrial Fibrillation: A Pharmacovigilance Study of 27 467 Patients Taking Rivaroxaban

Major bleeding

MB, n = 478	No MB, n = 26 989

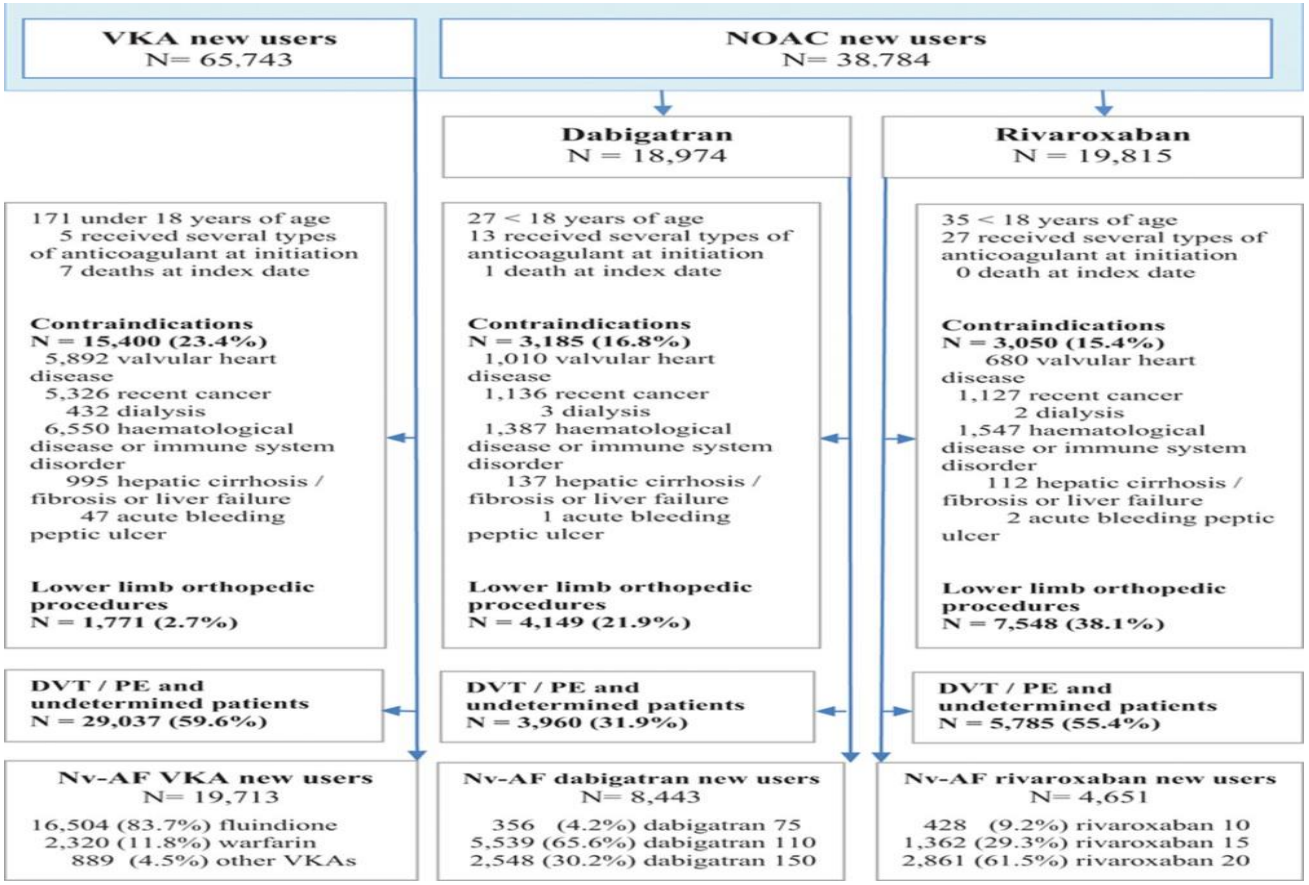
	MB Cases (N = 478)
MB cases with fatal outcome	14
Patients with multiple MB events	16
MB incidence rate per 100 person-years (95% CI)[b]	2.86 (2.61-3.13)

Case fatality rate: 3%

Tamayo D et al. Clin Cardiol 2015

Un farmaco è superiore all'altro? Dati dei registri

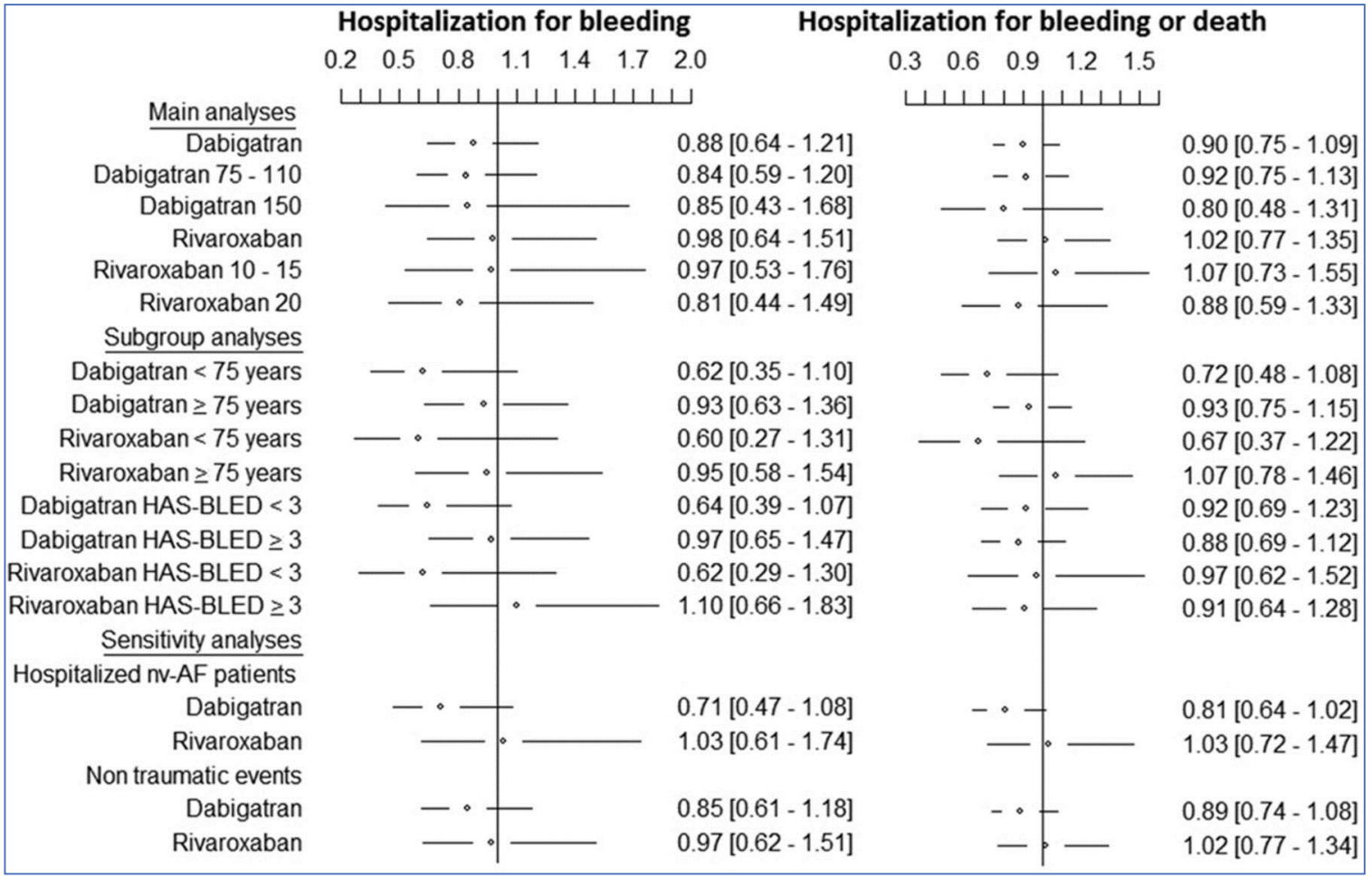
Rivaroxaban vs Dabigatran



Maura et al; Circulation 2015

French National Database

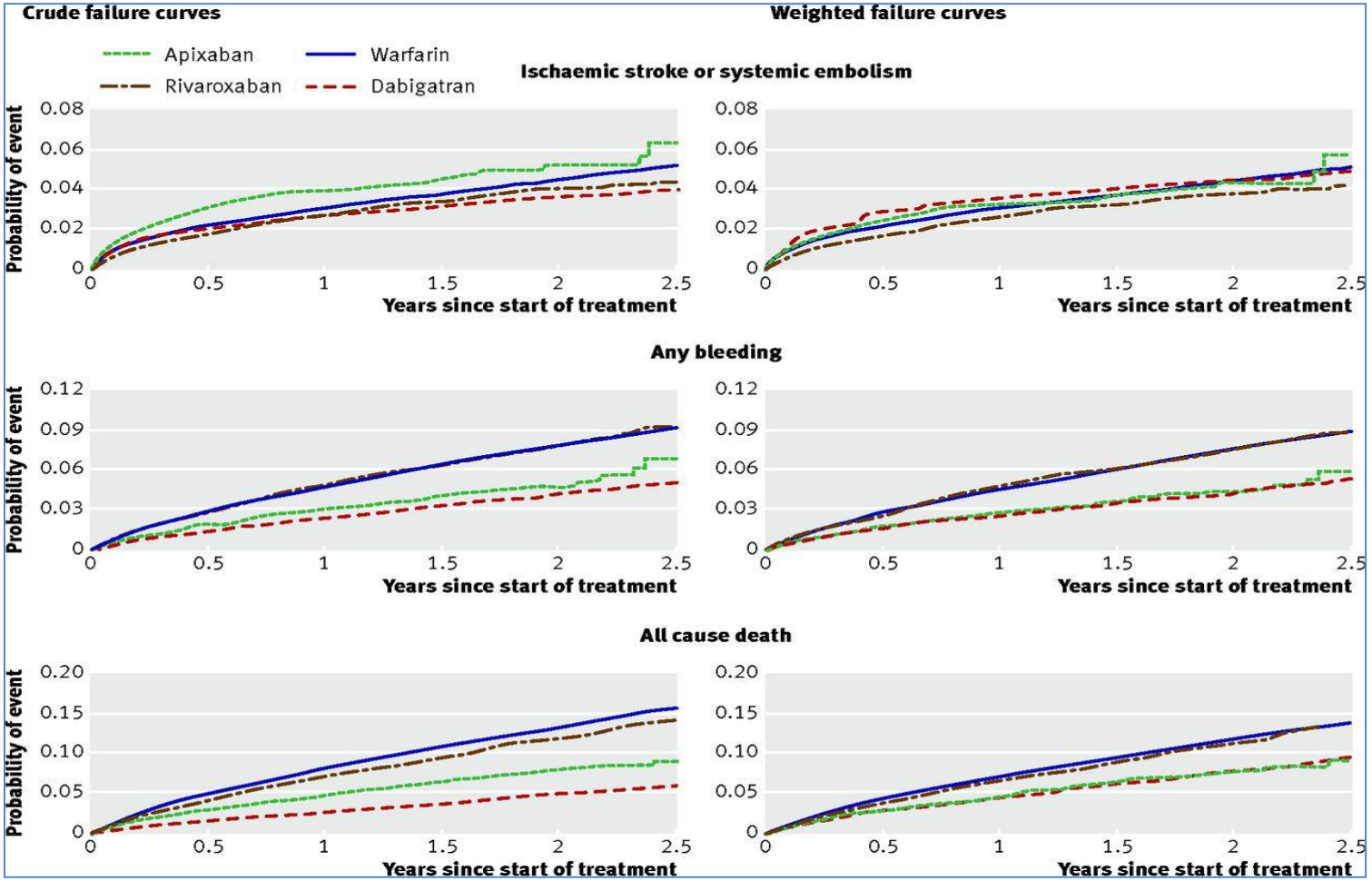
Hospitalization for MB (after PSM)



Maura et al; Circulation 2015

Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study

Torben Bjerregaard Larsen,[1,2] Flemming Skjøth,[2,3] Peter Brønnum Nielsen,[2] Jette Nordstrøm Kjældgaard,[2] Gregory Y H Lip[2,4]

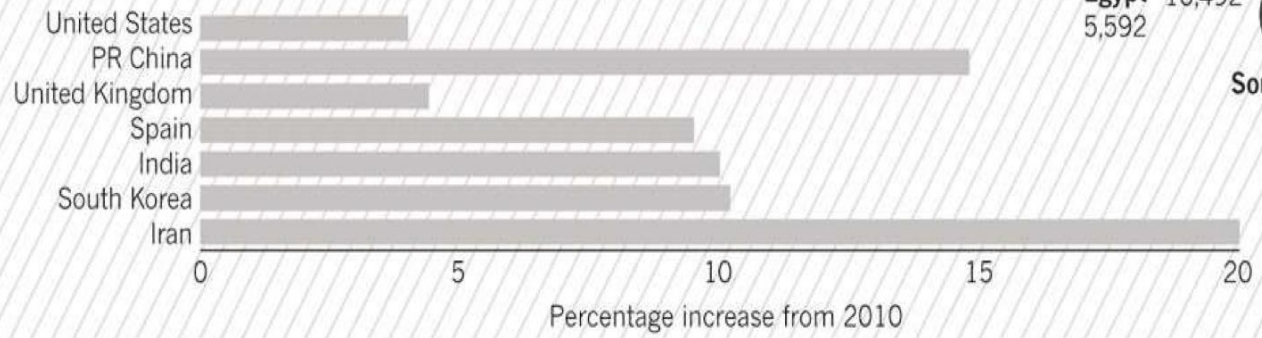


BMJ 2016

SCIENTIFIC PAPER TRAIL

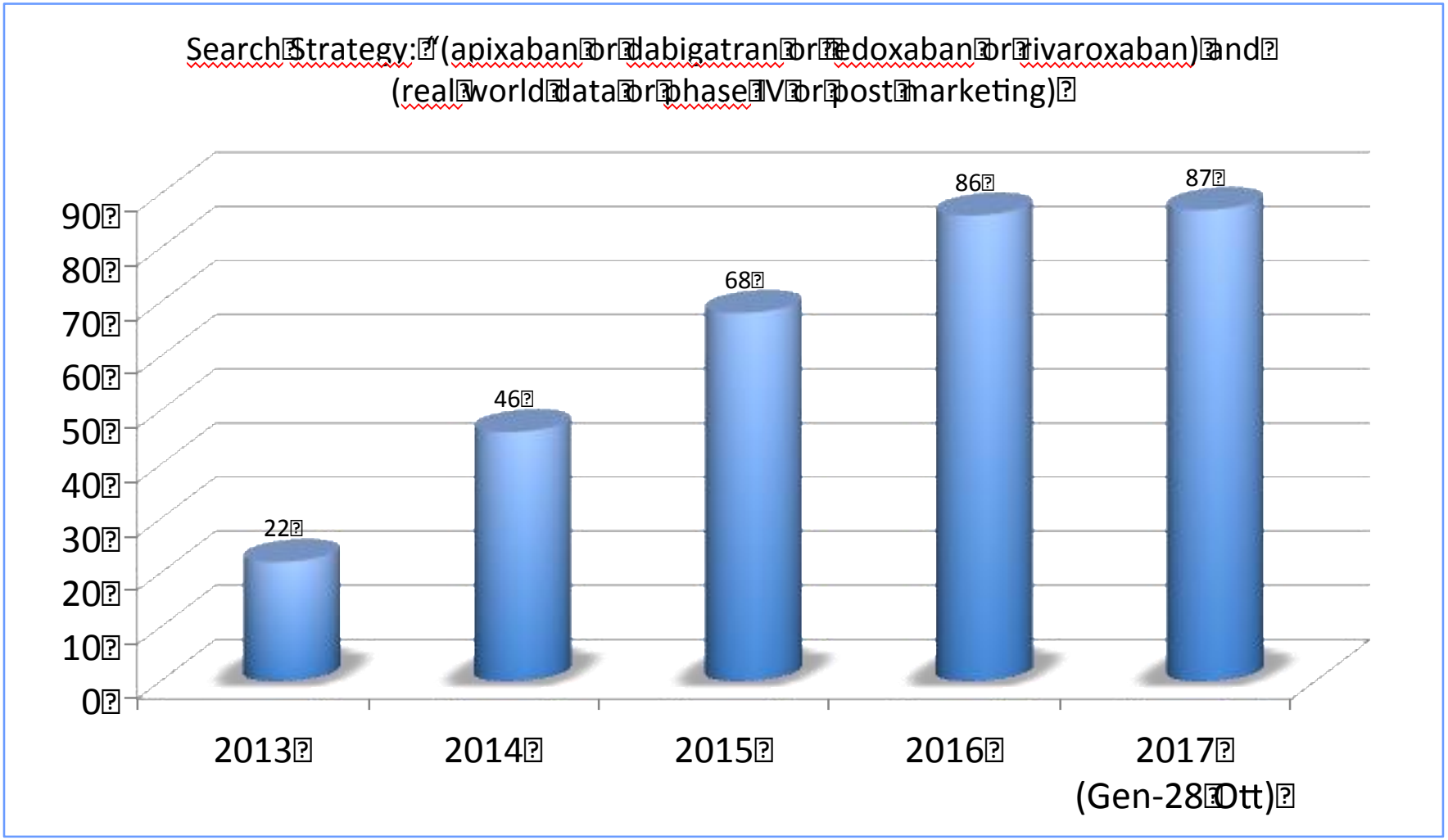
The top 40 countries by number of research papers published this year*.

Ireland 6,429
Sweden 18,645
Norway 9,207
Finland 9,207
Denmark 11,787
United Kingdom 90,018
Canada 49,947
Netherlands 29,296
Russia 22,296
Poland 17,186
Belgium 16,111
Germany 82,550
United States 310,206
France 57,751
Czech Republic 8,163
Switzerland 21,372
Austria 11,011
Romania 5,240
PR China 142,645
South Korea 39,285
Japan 68,308
India 39,640
Taiwan 24,255
Thailand 5,190
Singapore 8,768
Malaysia 6,565
Mexico 8,626
Brazil 27,808
Spain 43,300
Italy 47,403
Turkey 19,753
Iran 17,598
Israel 10,492
Egypt 5,592
Argentina 6,766
Portugal 9,034
Greece 9,451
South Africa 6,988
Australia 38,607
New Zealand 6,805



*Figures estimated from data for January–October

Pubblicazioni “Real World”



Tempo Medio per leggere un articolo scientifico

Minuti

THE
LITERATURE
OF
MEDICINE

How to Keep Up with the Medical Literature: V. Access by Personal Computer to the Medical Literature

R. BRIAN HAYNES, M.D., Ph.D.; K. ANN McKIBBON, M.L.S.; DOROTHY FITZGERALD, M.L.S.; GORDON H. GUYATT, M.D., M.Sc.; CYNTHIA J. WALKER, M.L.S.; and DAVID L. SACKETT, M.D., M.Sc.Epid.; Hamilton, Ontario, Canada

Access to the medical literature through personal computers is now readily available and can greatly reduce logistical barriers to using recently published journal articles to support clinical decisions. In this article, we describe many of the options available to clinicians who wish to do their own computer searching of MEDLINE, the largest of the electronic services for the biomedical literature. The "bare bones" computer equipment needed includes a terminal or personal computer, a modem and telephone line, and a printer. Access to MEDLINE is then gained through subscribing to any of a burgeoning number of database vendors. A comparison of 17 permutations and combinations of software and vendors shows that the software and vendors vary substantially in efficiency, cost, and ease of use. Direct subscription to MEDLINE is least expensive, PaperChase is the simplest service to use, and Colleague and Medis provide both MEDLINE access plus full-text journals online. Basic search techniques are illustrated for three clinical problems.

IN PREVIOUS ARTICLES in this series, we have discussed critical appraisal of published medical literature (1), methods for regular surveillance of the literature (2), and ways to search the literature to find the best published evidence concerning specific clinical problems (3). In this article, we describe how to gain fingertip access to the medical literature through a personal computer. Let's start with a clinical example.

Your patient, a 23-year-old college student with insulin-dependent diabetes, is developing early signs of retinopathy. She asks whether further retinopathy could be prevented if she were to keep her blood sugar levels under very tight control with an insulin pump. Although you know that insulin pumps can achieve close to normal blood sugar levels, you cannot recall having read anything definitive about their value in slowing or reversing retinopathy.

You excuse yourself from the patient and step into the room that contains your office computer. You interrupt its billing routine and type in four letters that stand for the computer program that connects you with the National Library of Medicine's (NLM) current MEDLINE file (see the Appendix for addresses and telephone numbers for all computer information services mentioned in this article). The system gives you a polite computer welcome, and then you type in the terms *diabetic retinopathy and insulin infusion systems*. MEDLINE replies that 38 articles are classified with both these descriptors. You then type in *1 and random allocation* (the *1* stands for the first search statement you typed in). MEDLINE replies that just 4 articles meet all three criteria you have indicated (4-7). You ask for a printout of the titles, authors, and abstracts of these articles. The online search time for the session was less than 2 minutes, and the search charge was just $0.93.

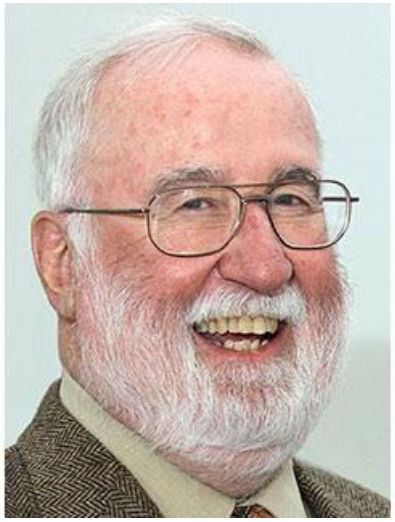
One of the articles (6) that MEDLINE selected is in a recent issue of *The New England Journal of Medicine*, so you direct your computer to contact the Colleague full-text service of BRS/Saunders and ask for a printout of the complete article. You scan the abstracts of the articles retrieved from the first search and then the methods section of the full-text article as your high-speed printer churns it out. One article reports a trial that is in progress (5), and the others provide the results of controlled trials. The findings of these studies are in accordance. They report greater deterioration in retinal structure in patients treated with infusion pumps, though the studies are small and none reports on major outcomes such as blindness. Thus, although the findings are not definitive, these initial studies give rise to caution.

You return to the patient, whose mild annoyance at having been kept waiting for 10 minutes turns to amazed admiration when you hand her a copy of the abstracts and indicate that you do not feel pump therapy has yet shown that it can be helpful in controlling diabetic retinopathy. You inform her that her retinopathy is mild as far as you can discern and that you are referring her to an ophthalmologist for further assessment. You reassure her that there are well-established and effective treatments for retinopathy and that the ophthalmologist will arrange for these should they be required.

Romancing the Literature Electronically

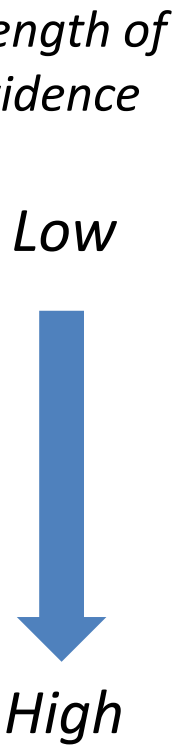
If you think that the clinical scenario just described is far-fetched, then you have not been keeping track of recent developments in user-friendly electronic access to medical information. It is now possible and reasonably straightforward for clinicians (called "end-users" in computer-speak) to retrieve highly pertinent information from huge literature databases in order to support clinical decisions that must be made immediately (that is, in "real time" in computer jargon). For example, two surgeons recently reported consulting the medical literature on line in the midst of an operation (8). One of the surgeons was doing an exploratory laparotomy on a patient with an undiagnosed abdominal mass that proved, on frozen section, to be sclerosing mesenteritis. Not being conversant with this condition, he notified his partner who

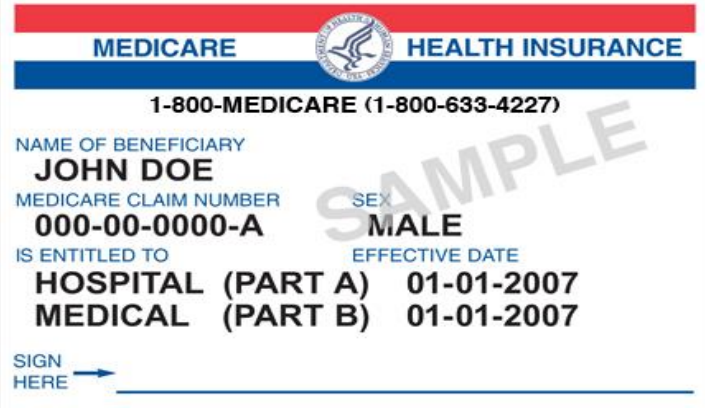
▶ From the Program for Educational Development, Departments of Clinical Epidemiology and Biostatistics and of Medicine, and the Health Sciences Library, McMaster University Faculty of Health Sciences; Hamilton, Ontario, Canada.



Real-World Evidence

- Real-world evidence is a broad term for many different study designs, including, in order of strength of evidence:
  - Retrospective clinical studies (including case/case series studies)
  - Claims database analyses
  - Prospective registries
  - Phase IV non-interventional studies





Medicare

Medicare is a federally funded program that provides health insurance for the elderly, patients with end-stage renal disease, and some disabled persons. Among those age 65 years or older, 97% receive Medicare. Almost all Medicare beneficiaries have Part A coverage that includes hospital, skilled-nursing facility, hospice, and some home health care. In addition, 96% of elderly Part A beneficiaries choose to pay a monthly premium to enroll in Part B, which covers physician and outpatient services as well as durable medical equipment. It includes a number of files that have specific billing information within them. Each carrier claim is composed of Current Procedural Terminology codes and an International Classification of Diseases, Ninth Revision (ICD-9), diagnosis code to describe the nature of the billed service. In addition, each bill has the dates of service, reimbursement amount, encrypted provider numbers, and beneficiary demographic data.

Primer on Statistical Interpretation or Methods

1.	Explicitly describe the matching method used.
2.	Explicitly compare and report the balance in baseline characteristics between treated and untreated subjects. Do not use statistical tests of hypothesis.
3.	Use statistical methods that account for the lack of independence induced by matching on the propensity score when estimating the statistical significance of the effect of treatment on outcomes.

Austin et al; Circ Card out 2008

STATISTICS IN MEDICINE
Statist. Med. 2008; **27**:2037–2049
Published online 23 November 2007 in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/sim.3150

A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003

Peter C. Austin[1, 2, 3, *, †]

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[2]*Department of Public Health Sciences, University of Toronto, Toronto, Ont., Canada*
[3]*Department of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ont., Canada*

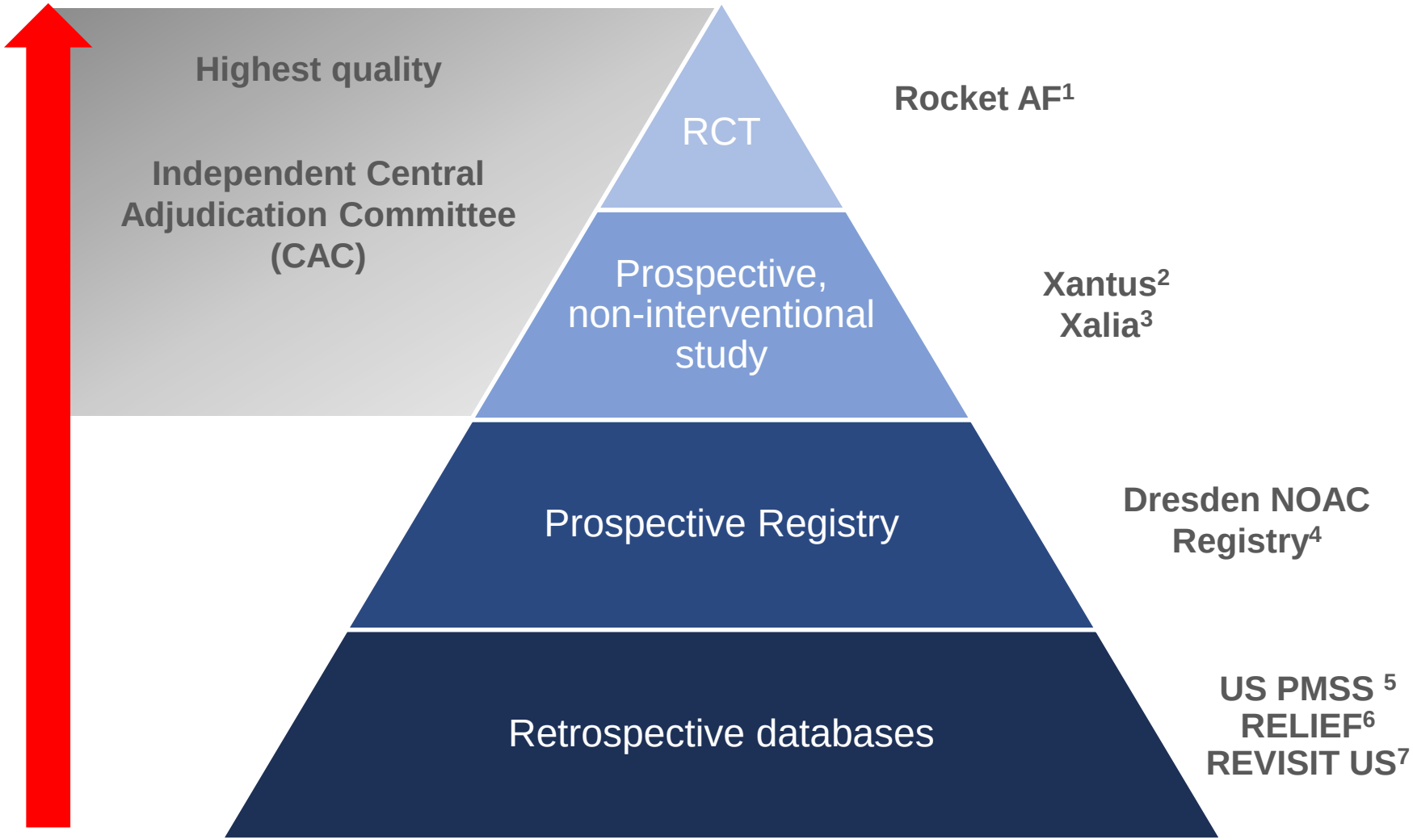
SUMMARY

Propensity-score [illegible] selection bias in the estimation of treatment effects with observational data. [illegible] methods include covariate adjustment using the propensity score, stratification on the propensity score, and propensity-score matching. Empirical and theoretical research has demonstrated that matching on the propensity score eliminates a greater proportion of baseline differences between treated and untreated subjects than does stratification on the propensity score. However, the analysis of propensity-score-matched samples requires statistical methods appropriate for matched-pairs data. We critically evaluated 47 articles that were published between 1996 and 2003 in the medical literature and that employed propensity-score matching. We found that only two of the articles reported the balance of baseline characteristics between treated and untreated subjects in the matched sample and used correct statistical methods to assess the degree of imbalance. Thirteen (28 per cent) of the articles explicitly used statistical methods appropriate for the analysis of matched data when estimating the treatment effect and its statistical significance. Common errors included using the log-rank test to compare Kaplan–Meier survival curves in the matched sample, using Cox regression, logistic regression, chi-squared tests, *t*-tests, and Wilcoxon rank sum tests in the matched sample, thereby failing to account for the matched nature of the data. We provide guidelines for the analysis and reporting of studies that employ propensity-score matching. Copyright © 2007 John Wiley & Sons, Ltd.

UNMEASURED VARIABLES???

KEY WORDS: propensity score; observational studies; matching; systematic review

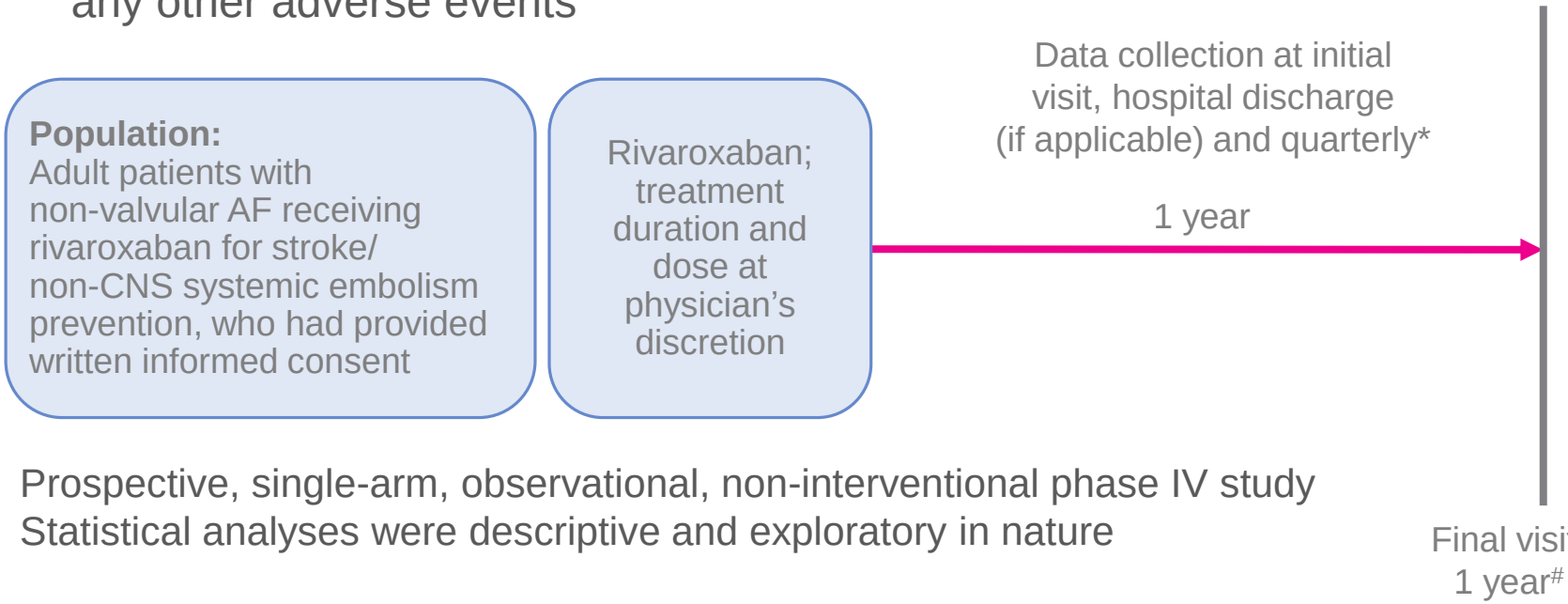
Rivaroxaban Provides a Consistent and Unique Dataset Covering the Full Patient-Risk Spectrum



1) Patel MR *et al*, *N Engl J Med* 2011;365:883–891 2) Camm AJ et al. Eur Heart J 2016;37:1145-53 3) Ageno W *et al, Lancet Haematol* 2016;3(1):e12–e21 4) Hecker J *et al*, *Thromb Haemost* 2016;115:939-49 5) Tamayo S et al, *Clin Cardiol* 2015;38:63–68 6) Coleman CI et al. *Int J Cardiol* 2016;203:882-4 7)Coleman CI et al, Curr Med Res Opin 2016;Sep 20:1-7

XANTUS: Study Objective and Design

- To collect real-life data on adverse events in patients with non-valvular AF treated with rivaroxaban to determine the safety profile of rivaroxaban across the broad range of patient risk profiles encountered in routine clinical practice
  - Primary outcomes: major bleeding (ISTH definition), all-cause mortality, any other adverse events



Prospective, single-arm, observational, non-interventional phase IV study
Statistical analyses were descriptive and exploratory in nature

*Exact referral dates for follow-up visits not defined (every 3 months recommended); #for rivaroxaban discontinuation ≤1 year, observation period ends 30 days after last dose. Observational design means no interference with clinical practice was allowed

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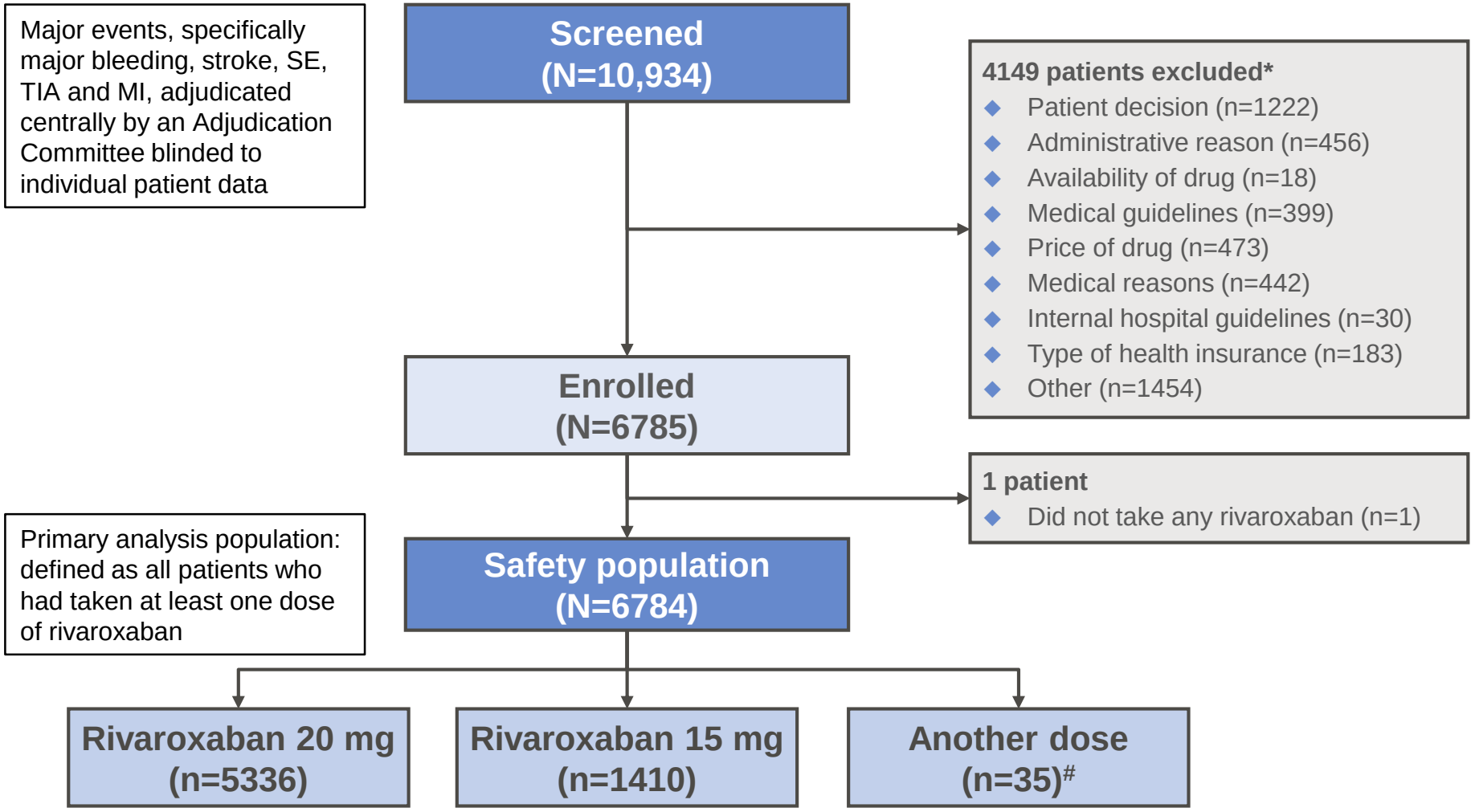
XANTUS: Patient Disposition



*Reasons for not continuing in the study included, but were not limited to, patient decision, administrative or medical reasons. Some patients could have more than one reason for exclusion; #other dose includes any initial daily rivaroxaban dose besides 15/20 mg od (excluding missing information, n=3)

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Baseline Demographics and Clinical Characteristics

	Rivaroxaban (N=6784)
Age (years)	
Mean±SD	71.5±10.0
Age <65, n (%)	1478 (21.8)
Age ≥65–≤75, n (%)	2782 (41.0)
Age >75, n (%)	2524 (37.2)
Gender (male), n (%)	4016 (59.2)
Weight (kg), mean±SD	83.0±17.3
BMI (kg/m^2), mean±SD	28.3±5.0
$CHADS_2$ score, mean±SD	2.0±1.3
CHA_2DS_2-VASc score, mean±SD	3.4±1.7
AF, n (%)	
First diagnosed	1253 (18.5)
Paroxysmal	2757 (40.6)
Persistent	923 (13.6)
Permanent	1835 (27.0)
Missing	16 (0.2)

	Rivaroxaban (N=6784)
VKA experienced	3089 (45.5)
VKA naïve	3695 (54.5)
Creatinine clearance, n (%)	
<15 ml/min	20 (0.3)
≥15–<30 ml/min	75 (1.1)
≥30–<50 ml/min	545 (8.0)
≥50–≤80 ml/min	2354 (34.7)
>80 ml/min	1458 (21.5)
Missing	2332 (34.4)
Co-morbidities, n (%)	
Hypertension	5065 (74.7)
Diabetes mellitus	1333 (19.6)
Prior stroke/non-CNS SE/TIA	1291 (19.0)
Congestive HF	1265 (18.6)
Prior MI	688 (10.1)
Hospitalization at baseline, n (%)	1226 (18.1)

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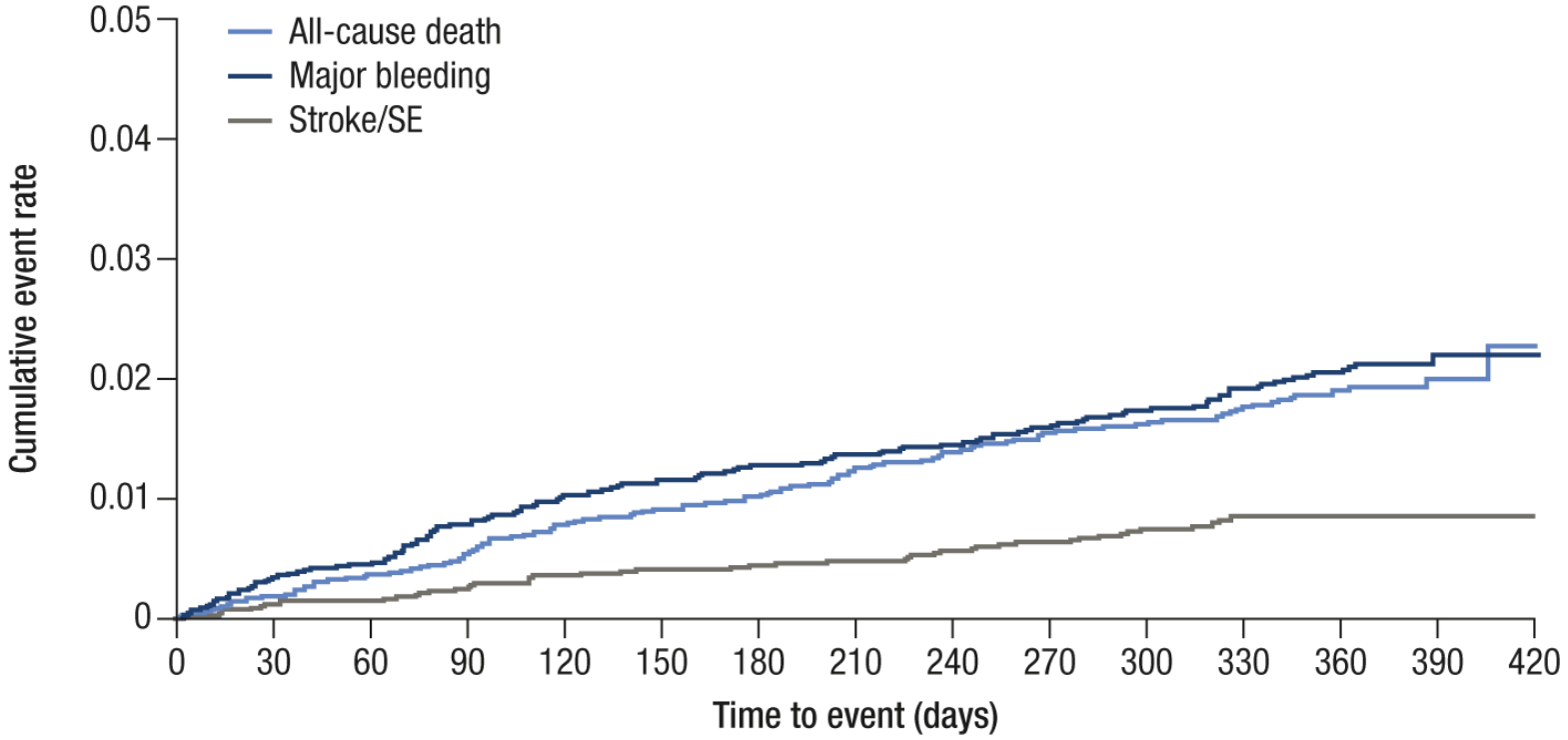
Cumulative Rates (Kaplan–Meier) for Treatment-Emergent Primary Outcomes



Patients at risk:

All-cause death	6784	6530	6349	6211	6054	5938	5853	5754	5679	5597	5512	5295	4307	1153	514
Major bleeding	6784	6522	6340	6197	6033	5909	5824	5726	5649	5559	5471	5256	4273	1144	513
Stroke/SE	6784	6532	6353	6216	6053	5933	5848	5752	5674	5587	5499	5282	4296	1149	513

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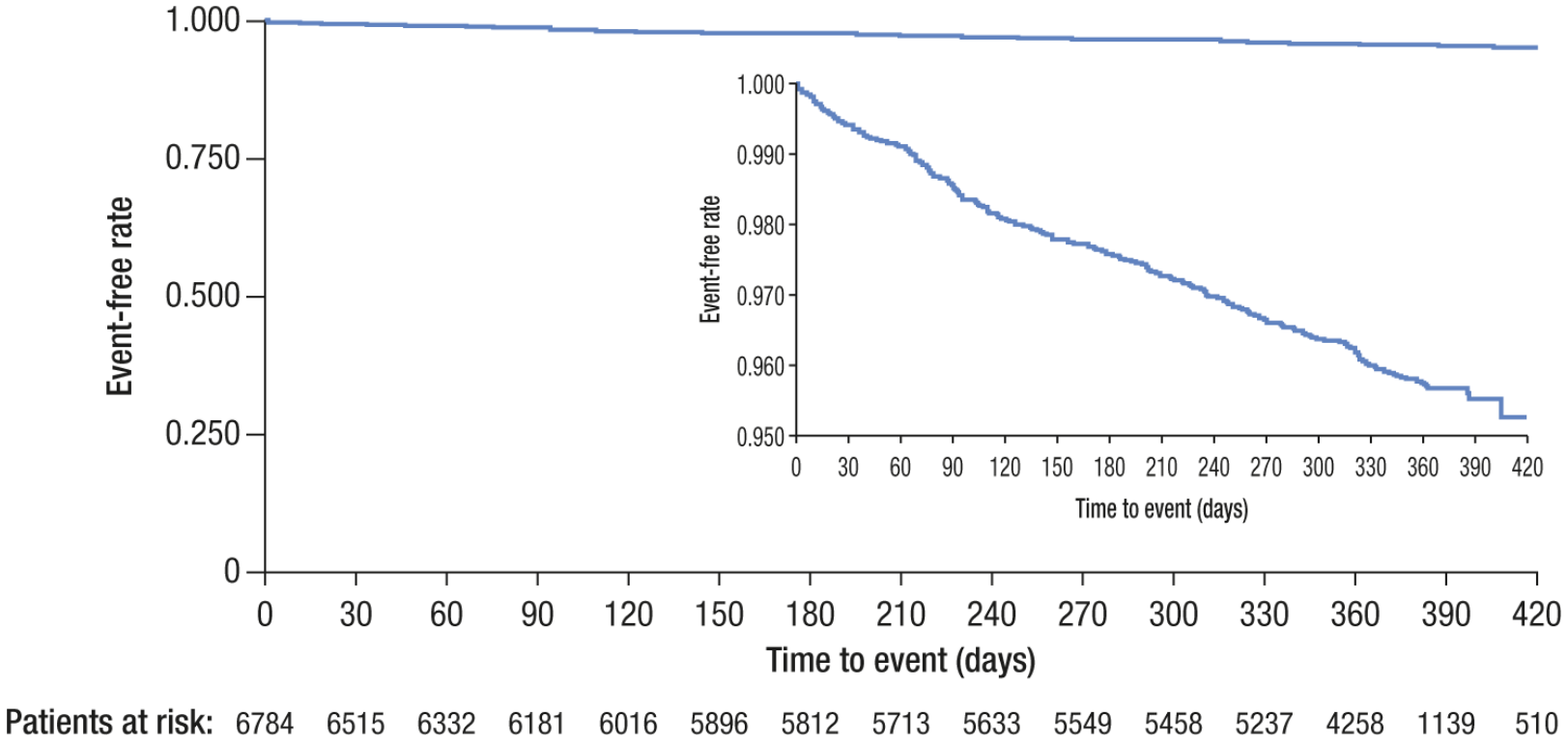
Event-Free Rate (Kaplan–Meier) for Treatment-Emergent Primary Outcomes

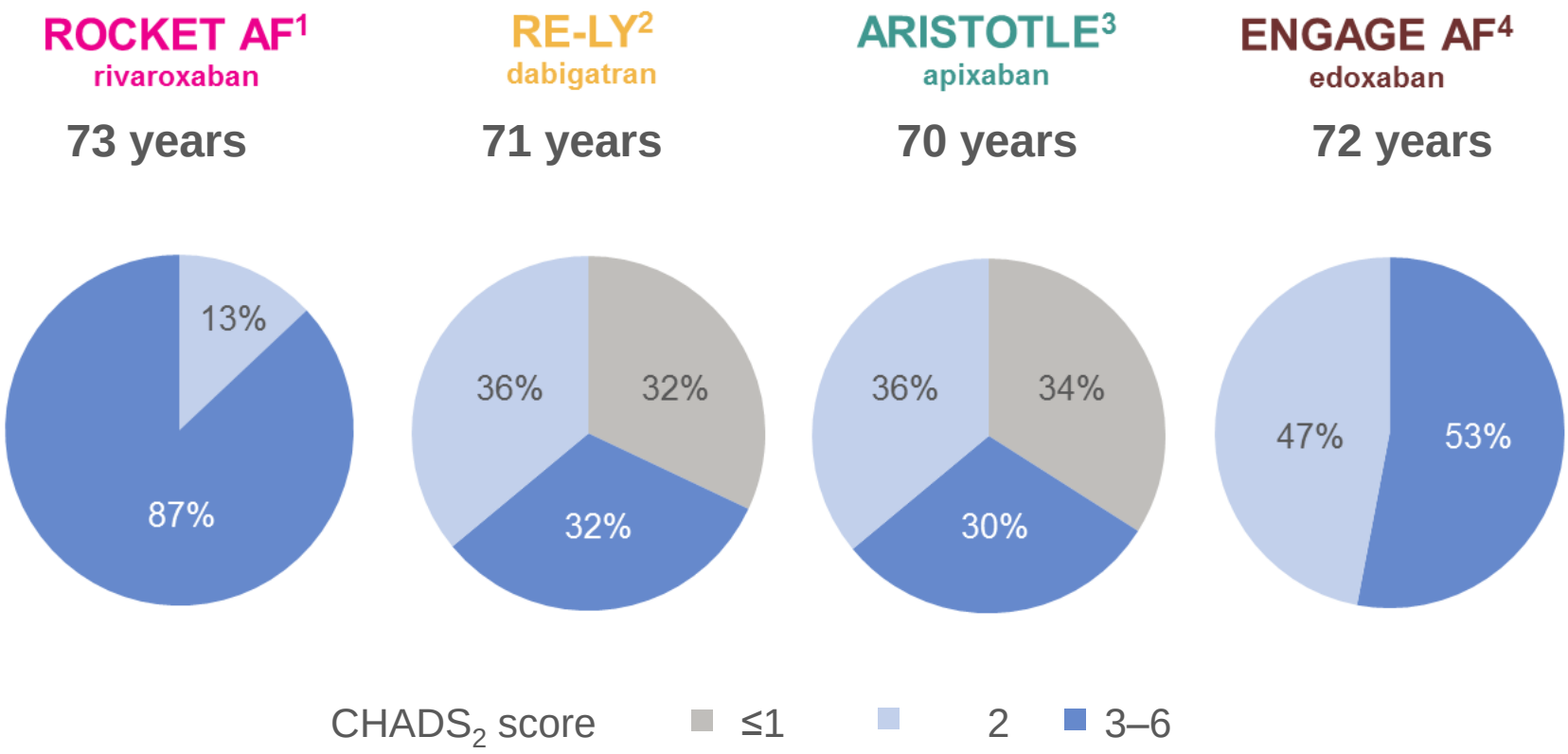
- In total, 6522 (96.1%) patients did not experience any of the outcomes of treatment-emergent all-cause death, major bleeding or stroke/SE



Camm AJ et al. Eur Heart J 2016;37:1145-53

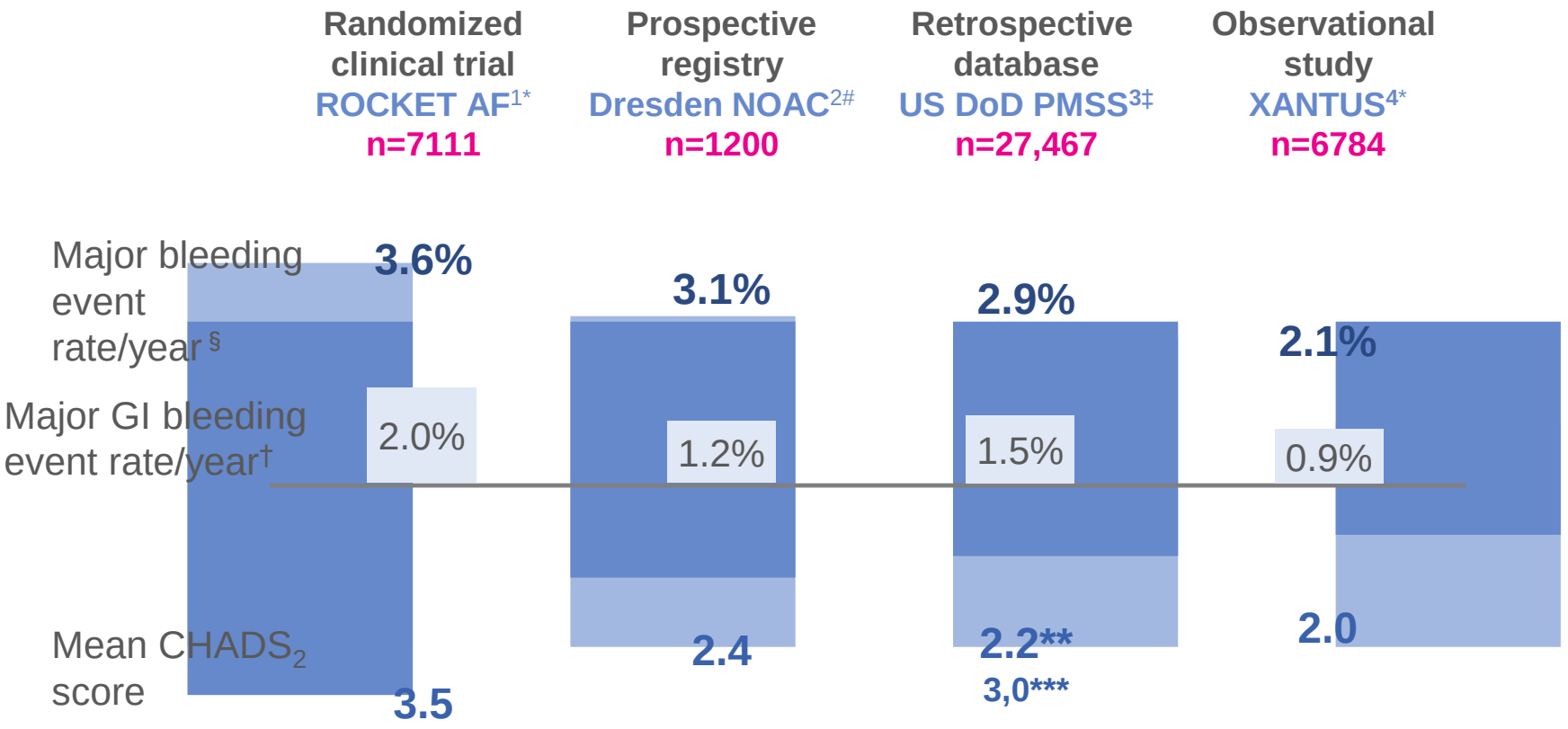
AF Patients in ROCKET AF Had a Higher Risk of Stroke than Patients in Other Phase III Trials

$CHADS_2$ score and age patient distribution



1. Patel MR et al. N Engl J Med. 2011;365(10):883-891; 2. Connolly SJ et al. N Engl J Med. 2009;361(12):1139-1151;
3. Granger CB et al. N Engl J Med. 2011;365(11):981-992; 4. Giugliano RP et al. N Engl J Med. 2013;369(22):2093-2104

Safety Profile of Rivaroxaban Confirmed Through Real-World Evidence Regardless of Data Source[6]



** Referred to patient population with no major bleeding cohort (representative of > 98% of the patient population)
*** Referred to pts with major bleeding (Beyer-Westendorf et Al. Thromb and Haemost Suppl 2/2016)

*Major bleeding definition according to ISTH; #modified ISTH definition (additionally included surgical revision from bleeding);
‡major bleeding defined by the Cunningham algorithm[5];
§ Warfarin MB 3,4% †Warfarin MB-GI 1,24

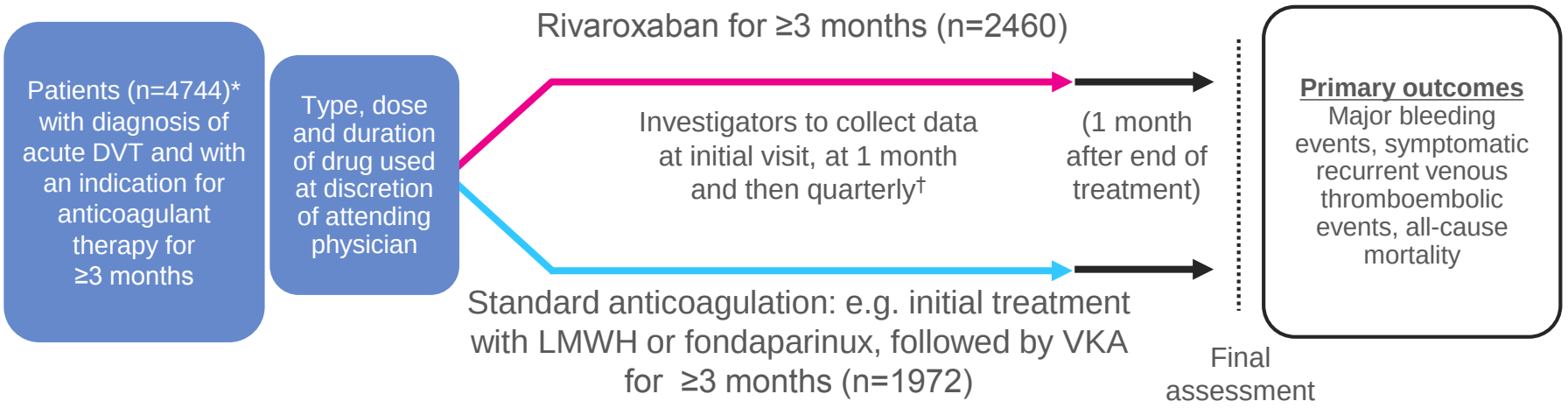
1. Patel MR *et al*, *N Engl J Med* 2011;365:883–891; 2. Hecker J *et al*, *Thromb Haemost* 2016 Jan 21;115(5)];
3. Tamayo S *et al*, *Clin Cardiol* 2015;38:63–68; 4 ; Camm AJ et al, Eur Heart J 2016;37(4):1145-53
5. Cunningham A *et al*, *Pharmacoepidemiol Drug Saf* 2011;20:560–566
6. Modified from Beyer-Westendorf J et al Thromb Hemost 2016:116:S13-S23

Results are not intended for direct comparison

XALIA: Study Design

Prospective, non-interventional cohort field study

Objective: To collect real-life data on adverse events (AEs), bleeding, thromboembolic events and mortality in patients diagnosed with acute DVT treated with rivaroxaban or SOC



Study start date: June 2012
Estimated study completion date: June 2015

*Includes 312 early switchers, defined as patients who received parenteral anticoagulation and/or VKA for >2–14 days before being switched to rivaroxaban; †protocol does not define exact referral dates for follow-up visits;

Ageno W *et al, Lancet Haematol* 2016;3(1):e12–e21

XALIA: Baseline Demographics and Clinical Characteristics (1)

	Rivaroxaban (n=2619)	Standard anticoagulation (n=2149)
Age, years, mean (SD)	57.3 (16.7)	63.0 (16.9)
<60 years, n (%)	1366 (52.2)	824 (38.8)
≥60 years, n (%)	1253 (47.8)	1325 (61.7)
Male sex, n (%)	1428 (54.5)	1116 (51.9)
Weight, kg, mean (SD)	82.4 (18.0)	80.6 (18.0)
Index diagnosis, n (%)		
DVT without PE	2399 (91.6)	1894 (88.1)
DVT with PE	220 (8.4)	255 (11.9)
Active Cancer, n (%)	146 (5.6)	411 (19.1)

Ageno W *et al, Lancet Haematol* 2016;3(1):e12–e21

Treatment-Emergent Clinical Outcomes (Propensity-Score Adjusted Comparison)

	Rivaroxaban (n=2505) n (%)	Standard anticoagulation (n=2010) n (%)	Hazard ratio (95% CI)	*p*-value
Major bleeding	19 (0.8)	43 (2.1)	0.77 (0.40–1.50)	0.44
Recurrent VTE	36 (1.4)	47 (2.3)	0.91 (0.54–1.54)	0.72
All-cause mortality	11 (0.4)	69 (3.4)	0.51 (0.24–1.07)	0.07

Ageno W *et al, Lancet Haematol* 2016;3(1):e12–e21

Summary of Product Characteristics

In confirmation of the weight of phase IV results, the summary of product characteristics has been recently updated:

In addition to the phase III ROCKET AF study, a prospective, single-arm, post-authorization, non-interventional, open-label cohort study (XANTUS) with central outcome adjudication including thromboembolic events and major bleeding has been conducted. 6,785 patients with non-valvular atrial fibrillation were enrolled for prevention of stroke and non-central nervous system (CNS) systemic embolism in clinical practice. The mean $CHADS_2$ and HAS-BLED scores were both 2.0 in XANTUS, compared to a mean $CHADS_2$ and HAS-BLED score of 3.5 and 2.8 in ROCKET AF, respectively. Major bleeding occurred in 2.1 per 100 patient years. Fatal haemorrhage was reported in 0.2 per 100 patient years and intracranial haemorrhage in 0.4 per 100 patient years. Stroke or non-CNS systemic embolism was recorded in 0.8 per 100 patient years.
These observations in clinical practice are consistent with the established safety profile in this indication.

Oltre al programma di fase III EINSTEIN, è stato condotto uno studio (XALIA) di coorte prospettico, non interventistico ed in aperto, con obiettivo principale la valutazione comprendente TEV recidivanti, sanguinamenti maggiori e morte. Sono stati arruolati 5.142 pazienti con TVP acuta per indagare la sicurezza a lungo termine di rivaroxaban rispetto alla terapia anticoagulante "standard of care" nella pratica clinica. I rapporti di sanguinamenti maggiori, recidive di TVE e morti per qualsiasi causa sono stati per rivaroxaban rispettivamente lo 0,7%, 1,4% e 0,5%. I pazienti presentavano al basale delle differenze tra cui l'età, la presenza/assenza di cancro e la compromissione della funzionalità renale. L'analisi statistica pre-specificata e stratificata tramite il propensity-score, è stata utilizzata al fine di ridurre le differenze al basale, sebbene dei fattori confondenti potrebbero, nonostante tutto, influenzare il risultato. Gli hazard ratios corretti per sanguinamenti maggiori, recidive di TVE e morti per qualsiasi causa erano rispettivamente lo 0,77 (95% CI 0,40 – 1,50), 0,91 (95% CI 0,54 – 1,54) e 0,51 (95% CI 0,24 – 1,07).
Questi risultati in pazienti osservati nella pratica clinica sono coerenti con il profilo di sicurezza definito per questa indicazione.

Rivaroxaban. Summary of product characteristics

Take home messages

- Gli studi di Fase III (RCT) sono importanti per stabilire l'efficacia e la sicurezza di un nuovo trattamento rispetto al gold standard (ma rappresenta la popolazione generale?)

- Gli studi "Real-life" e I registri ci danno informazioni sull'efficacia e la sicurezza di un trattamento in condizioni più aderenti alla realtà clinica di tutti i giorni.

- Attenzione alla qualità degli studi considerati e ai confronti tra diversi trattamenti negli studi osservazionali (differenti caratteristiche di base misurate e non misurate).

- Negli studi di più alta qualità rivaroxaban conferma l'efficacia e la sicurezza dei trials di fase III