NOAC in the Real World

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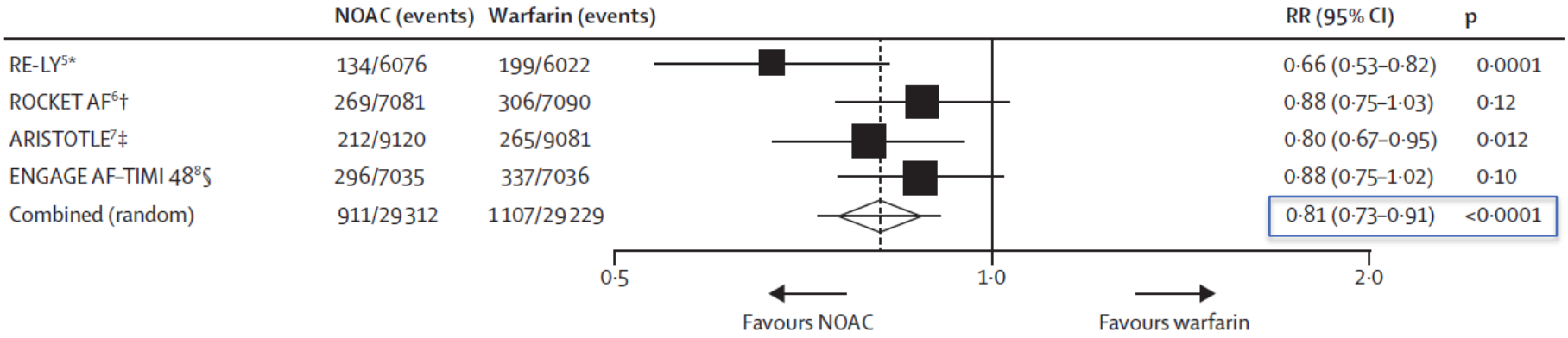
Conflitti di Interesse

Letture
Protocolli di Ricerca
Advisory Boards

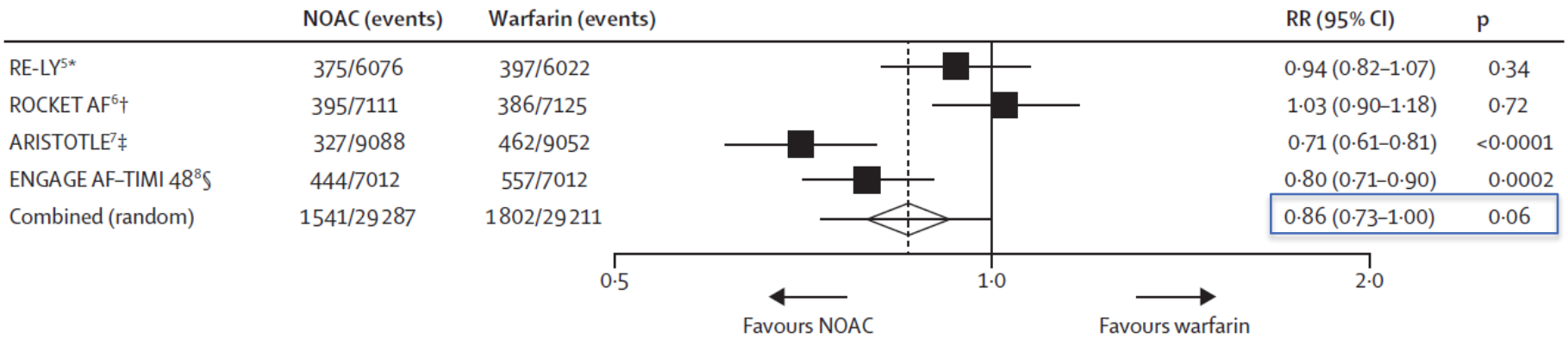
- Bayer
- BMS/Pfizer
- Boehringer
- Daiichi Sankyo
- Sanofi
- Alfa Wasserman
- IL

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



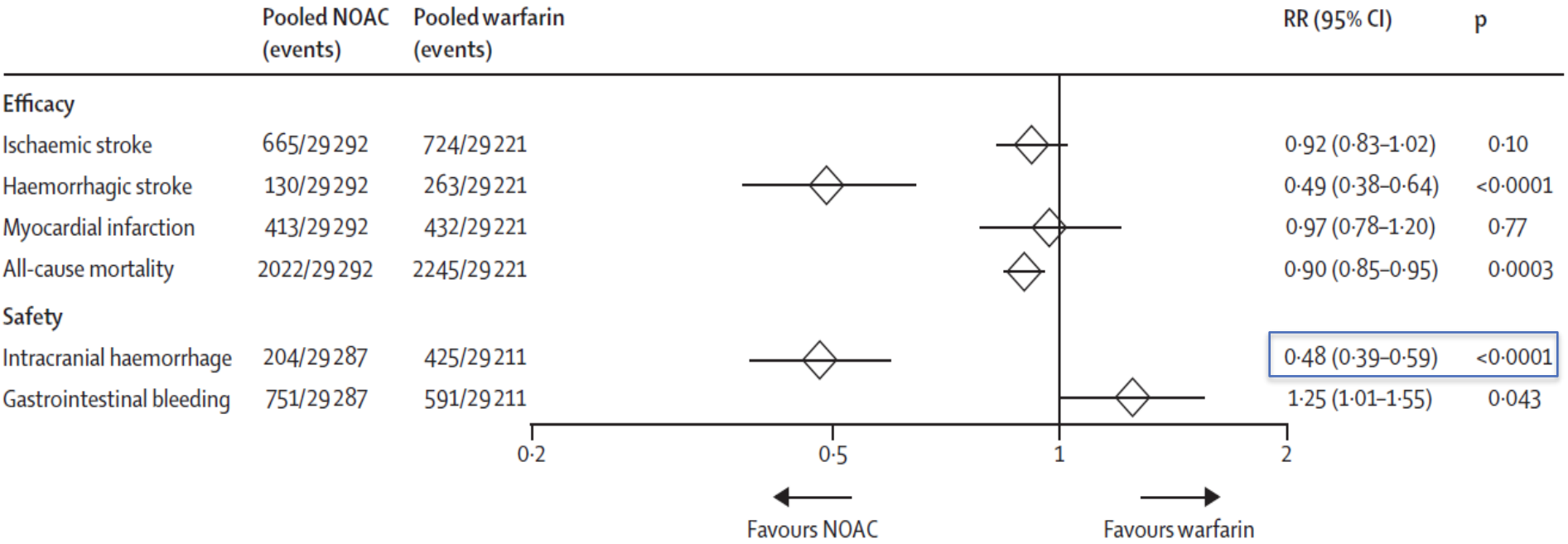
Major Bleeding



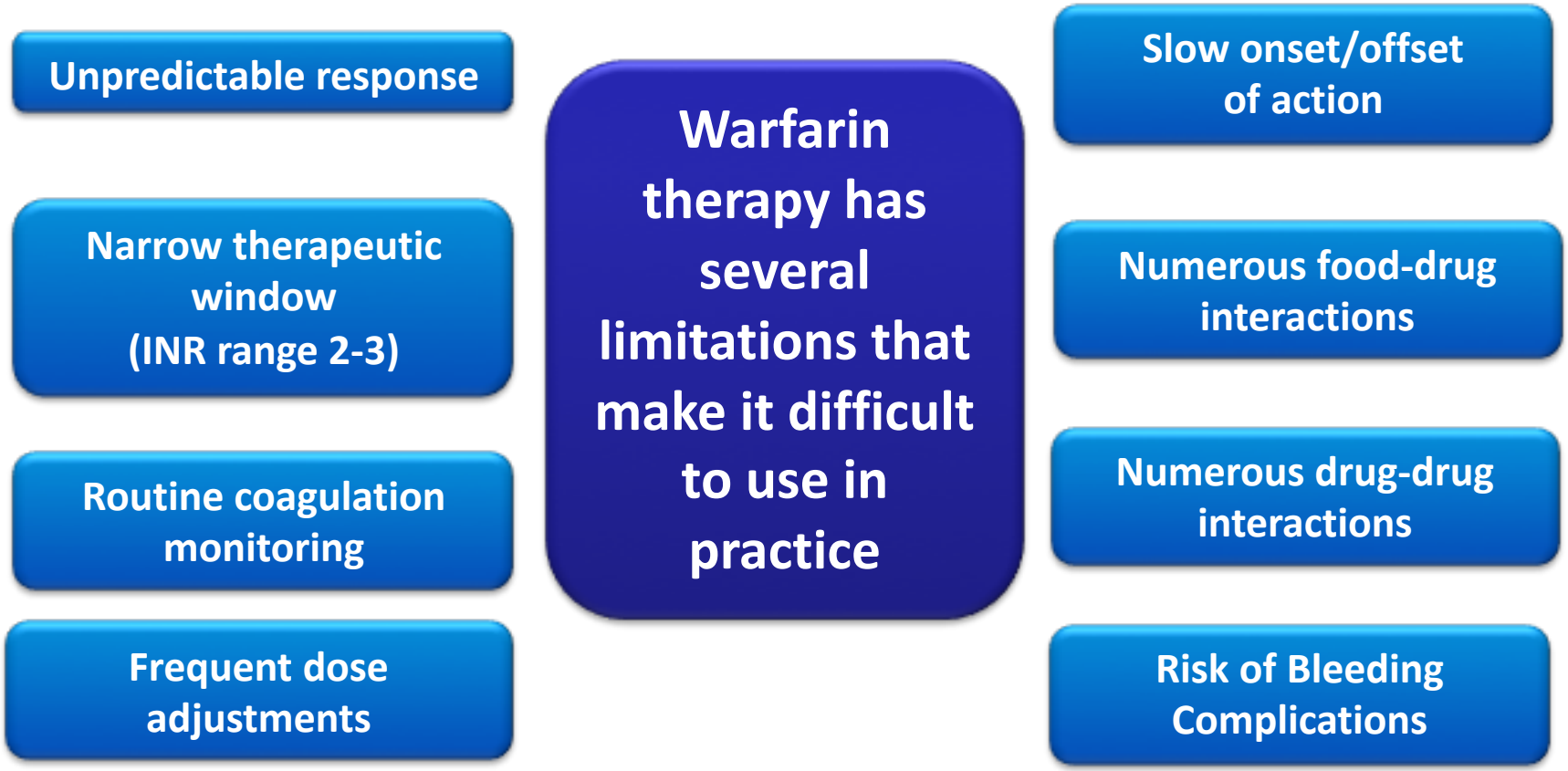
Ruff et al. Lancet 2013

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

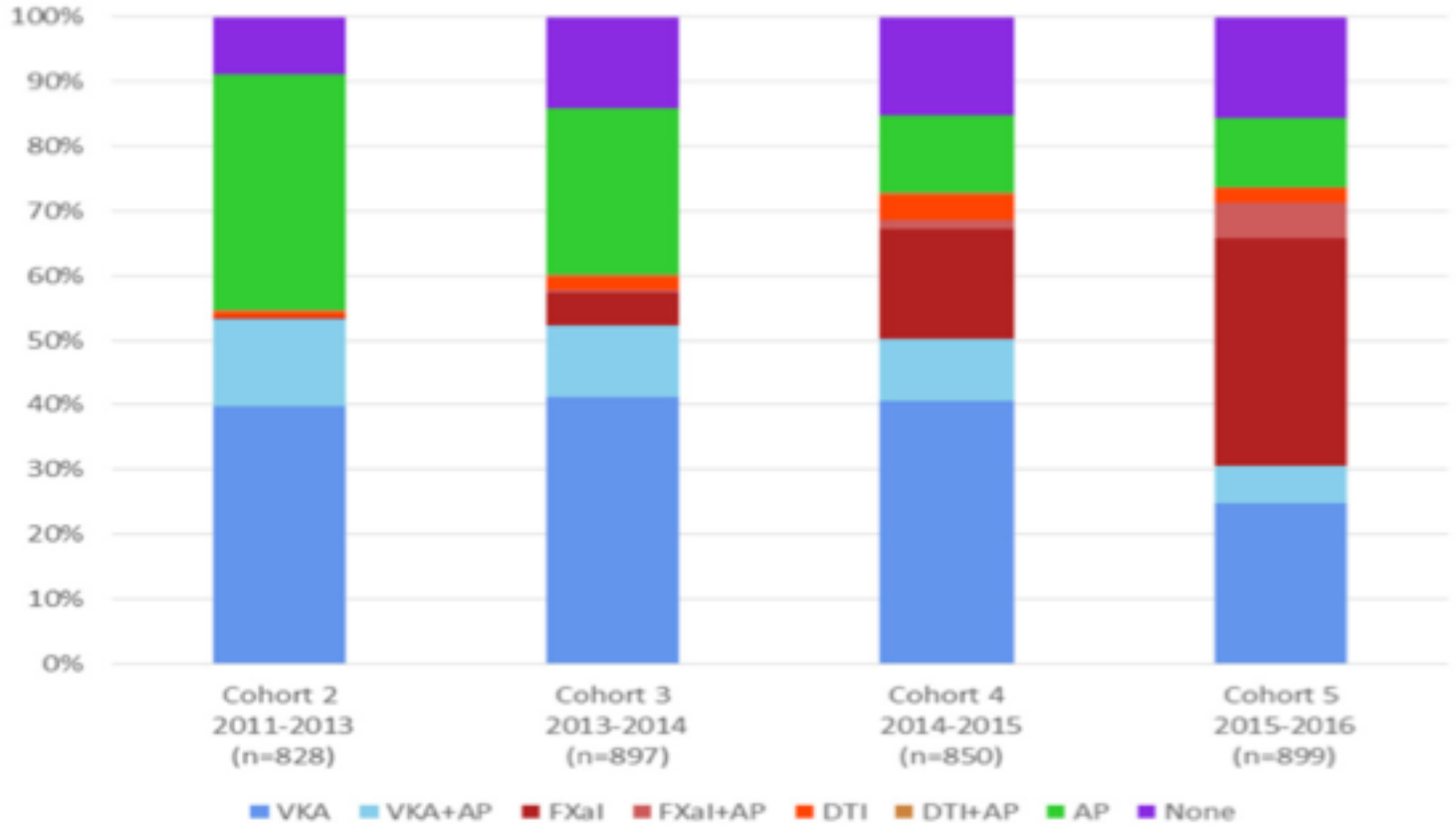


- Warfarin was #1 in 2003 and 2004 in the number of mentions of “deaths for drugs causing adverse effects in therapeutic use”
- Warfarin caused 6% of the 702,000 ADEs treated in the ED/year; 17% required hospitalization

J Thromb Thrombolysis 2008

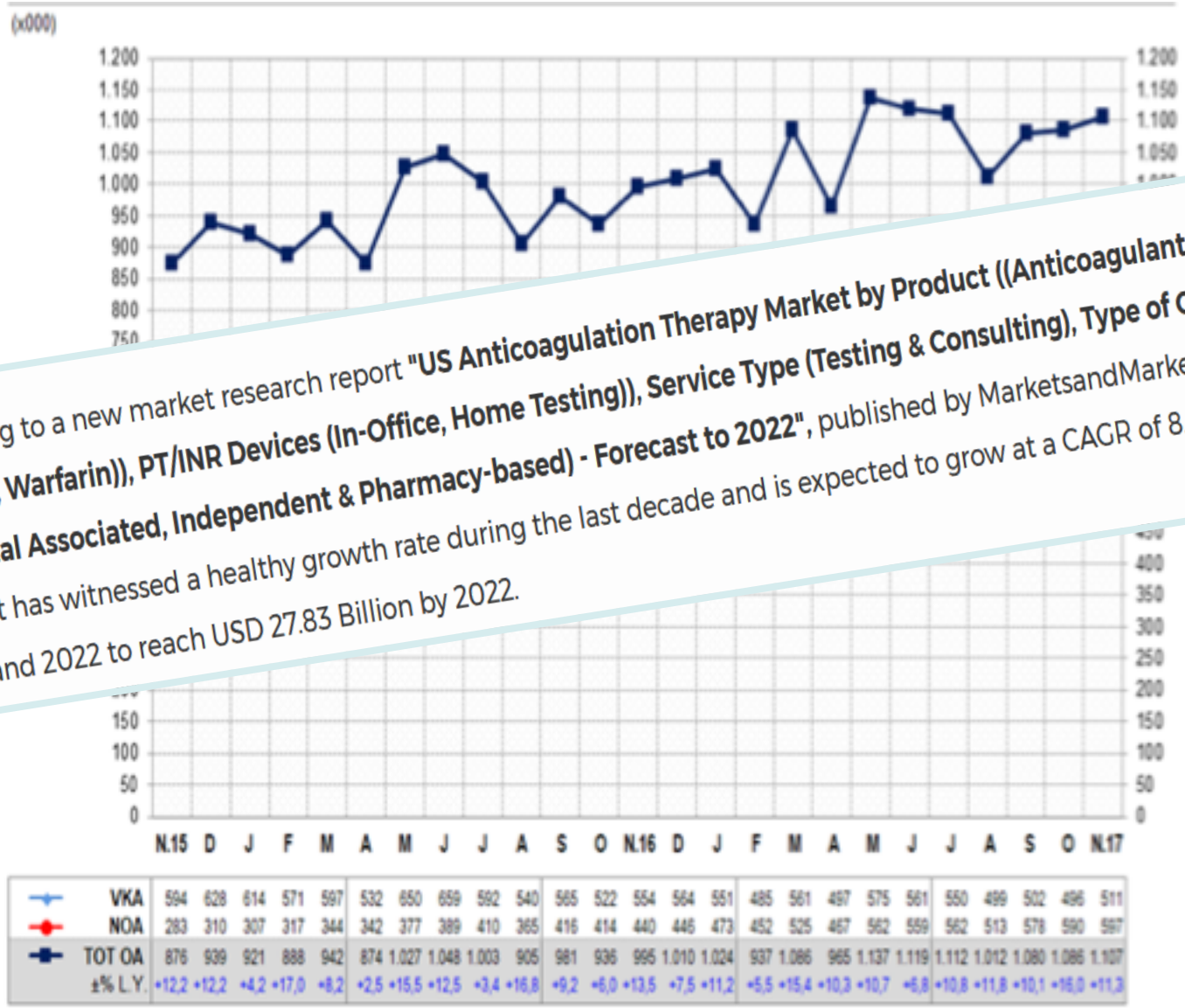
BMJ Open

Temporal trends in antithrombotic treatment of real-world UK patients with newly diagnosed atrial fibrillation



Apenteng et al. BMJ Open 2018

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



	N.15	D	J	F	M	A	M	J	J	A	S	O	N.16	D	J	F	M	A	M	J	J	A	S	O	N.17
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

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

Limitations of well conducted phase 3 RCTs

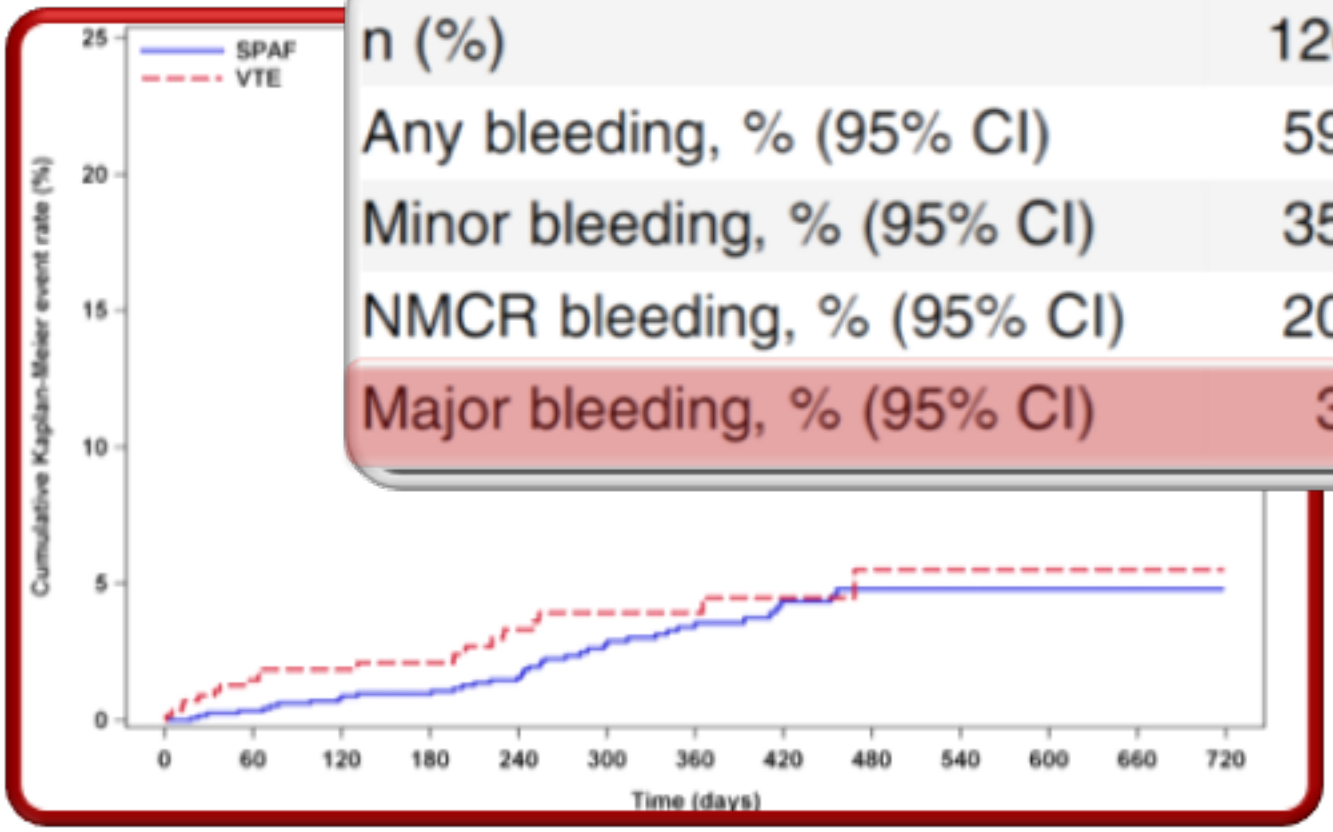
- Unintended adverse events (UAEs) are unlikely to be revealed during phase III trials because the usual sample sizes of such studies and even the entire new drug application may range from hundreds to only a few thousand patients.

- 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

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)



Beyer-Westerdorf et al. Blood 2014

Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation

- Observational cohort study
- US Medicare database
- Comparison of ischaemic stroke, ICH, major GI bleeding, acute MI, and mortality rates using insurance-claim and administrative data

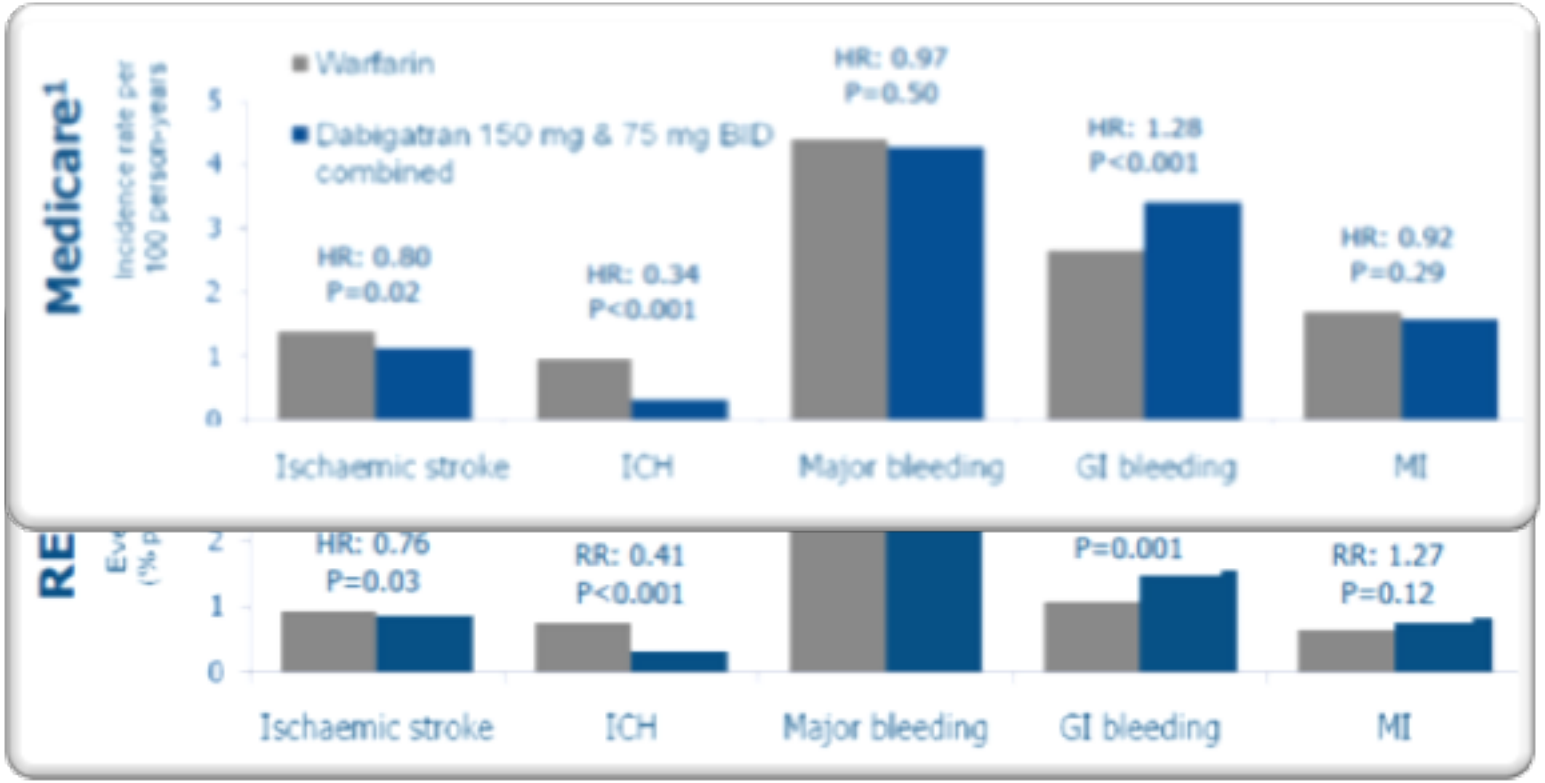
- 134 414 new users (OAC treatment-naïve) of dabigatran or warfarin
- All recently diagnosed with AF
- All aged ≥65 years

Study period

37500 person-year of follow-up

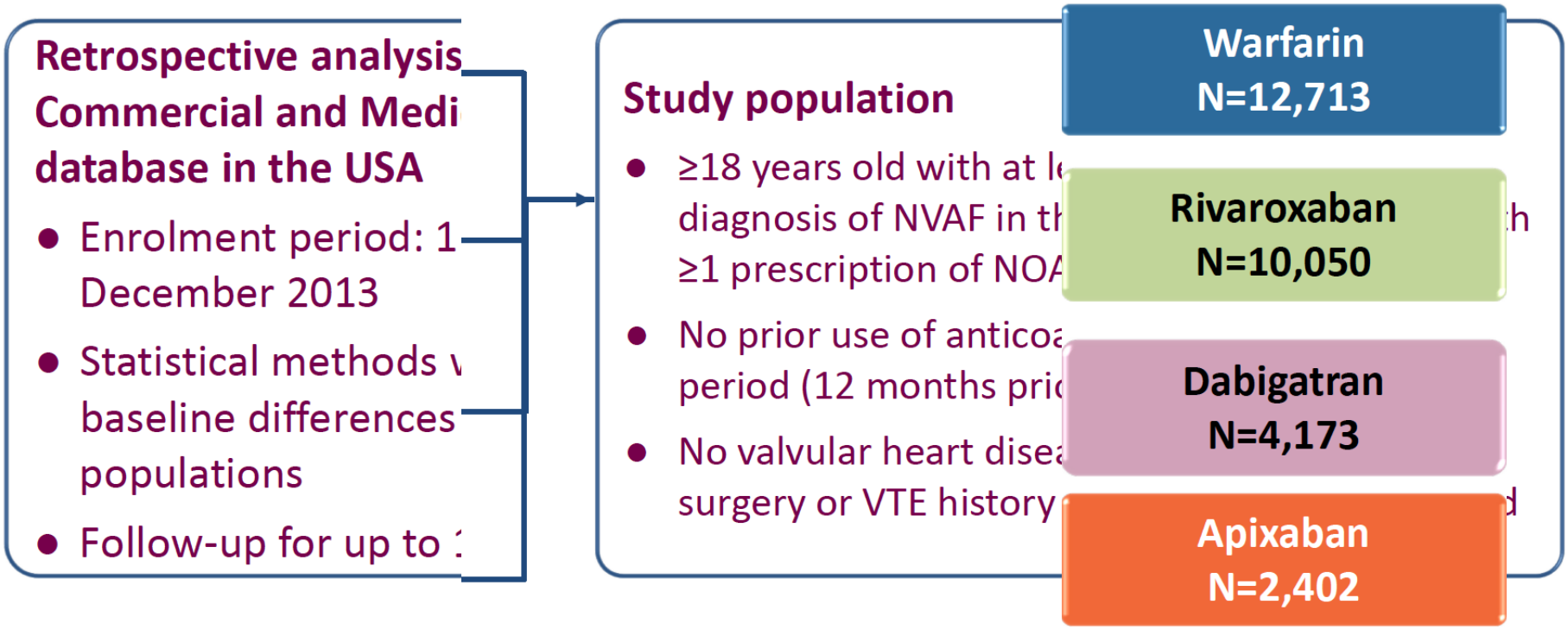
Graham DJ et al. Circulation 2015

Cardiovascular, Bleeding, and Mortality Risks in Elderly Medicare Patients Treated With Dabigatran or Warfarin for Nonvalvular Atrial Fibrillation



Graham DJ et al. Circulation 2015

US retrospective real-world database research (MarketScan® commercial & Medicare supplemental database)

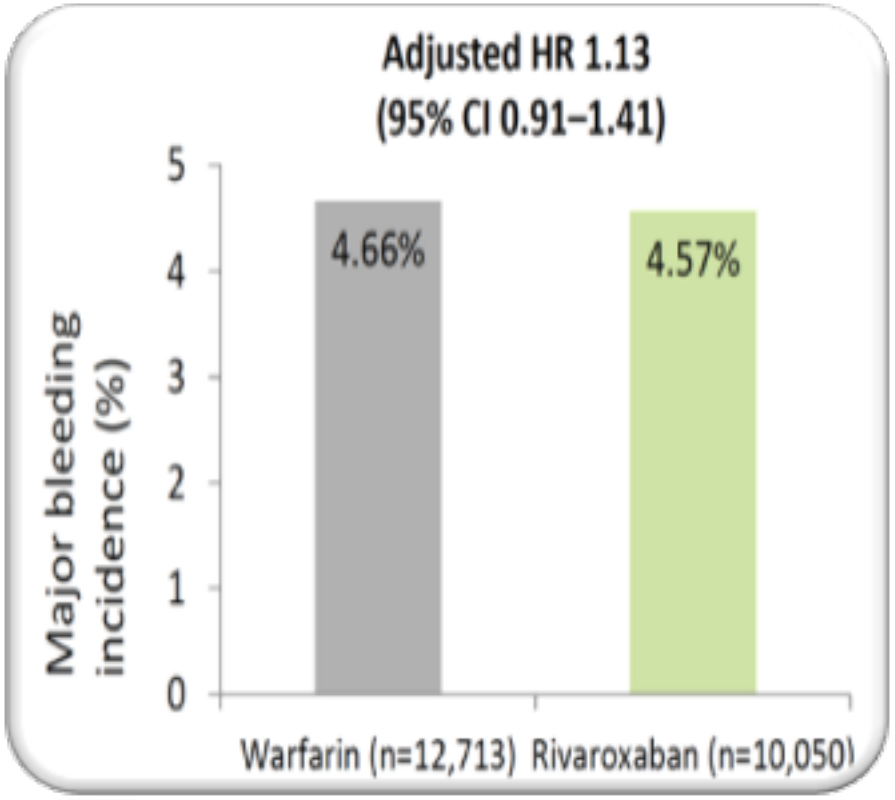


Lip GYH et al Int J Clin Pract 2016

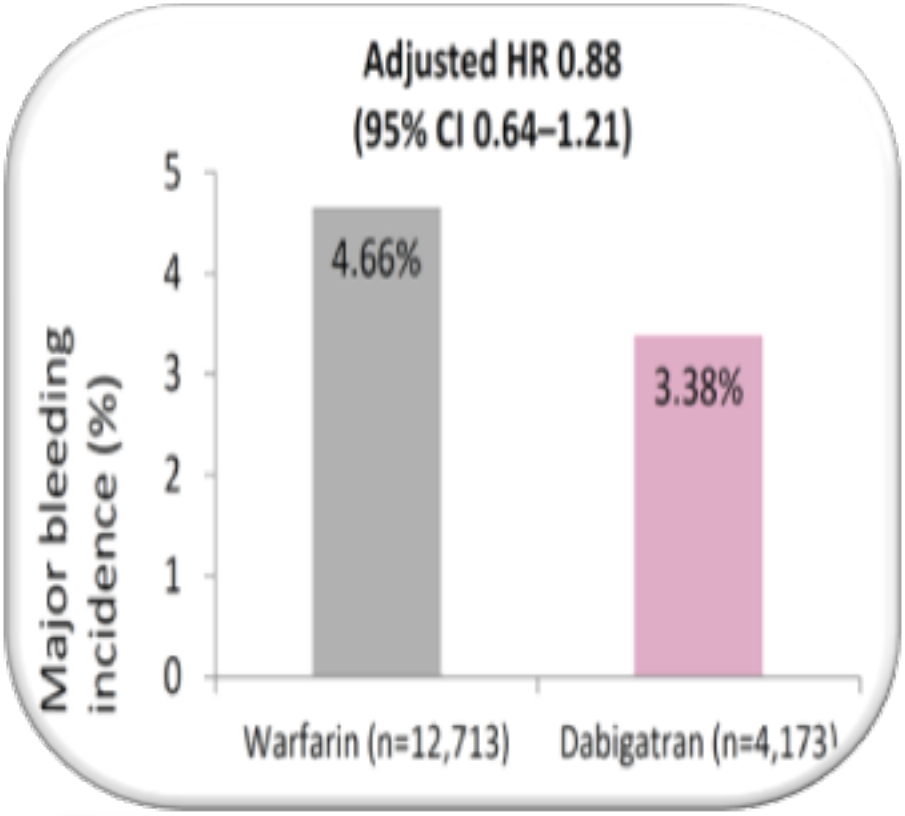
US retrospective real-world database research
(MarketScan® commercial & Medicare supplemental database)

Characteristic	Apixaban (N=2,402)	Dabigatran (N=4,173)	Rivaroxaban (N=10,050)	Warfarin (N=12,713)	p value*
Age, mean (SD)	69.34 (12.33)	66.83 (12.17)	67.33 (12.25)	72.53 (11.88)	<0.0001
$CHADS_2$ Score, mean (SD)	1.78 (1.21)	1.66 (1.19)	1.66 (1.20)	2.05 (1.26)	<0.0001
CHA_2DS_2-VASc Score, mean (SD)	2.83 (1.64)	2.58 (1.65)	2.62 (1.65)	3.22 (1.65)	<0.0001
Charlson Comorbidity Index (CCI),† mean (SD)	1.85 (1.98)	1.74 (1.97)	1.79 (2.04)	2.37 (2.33)	<0.0001

US retrospective real-world database research (MarketScan® commercial & Medicare supplemental database)



Of the 10,050 rivaroxaban patients, 80.3% received rivaroxaban 20 mg OD

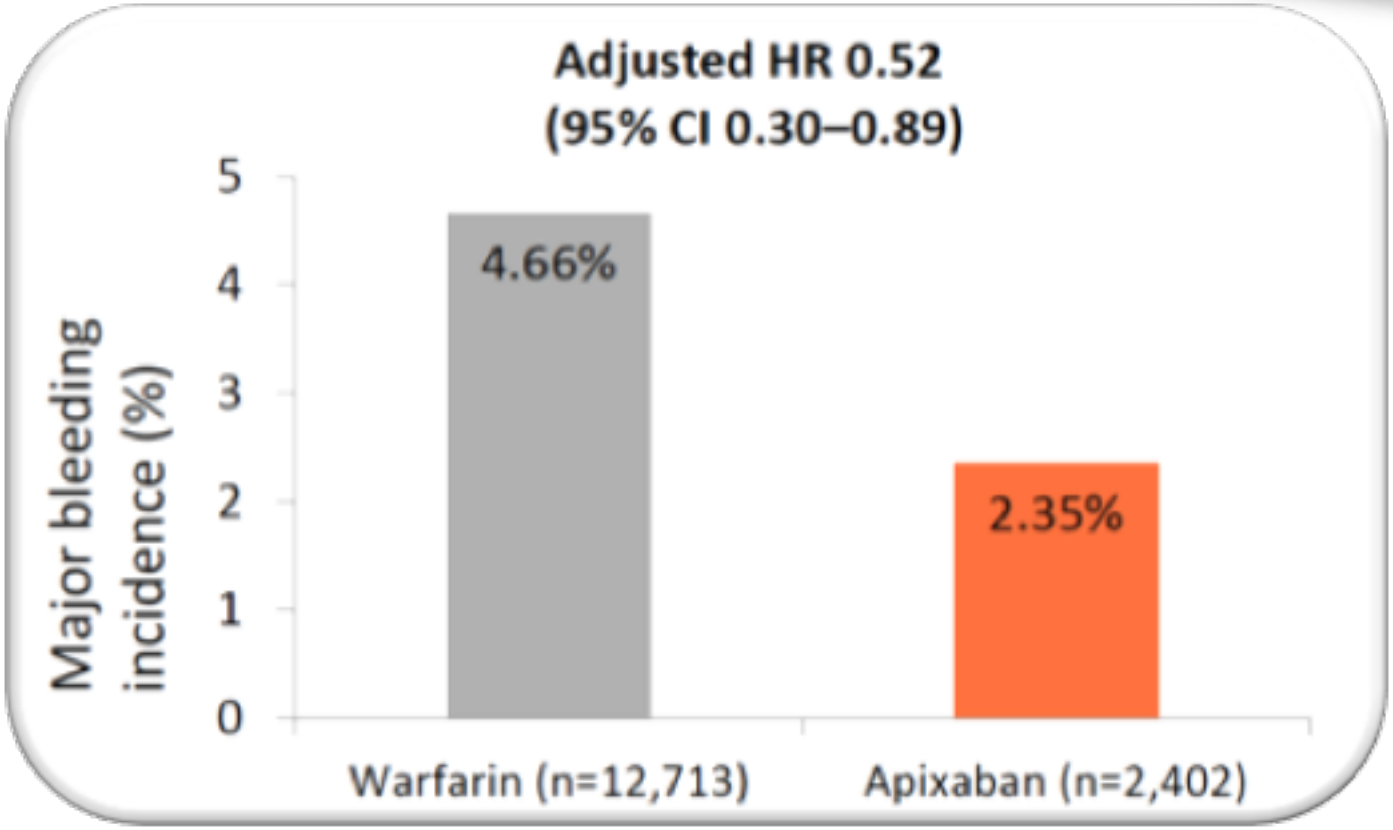


Of the 4,173 dabigatran patients, 90.3% received dabigatran 150 mg BD†

Lip GYH et al Int J Clin Pract 2016

US retrospective real-world database research (MarketScan® commercial & Medicare supplemental database)

Of the 2,402 apixaban patients, 85.6% received apixaban 5 mg BD

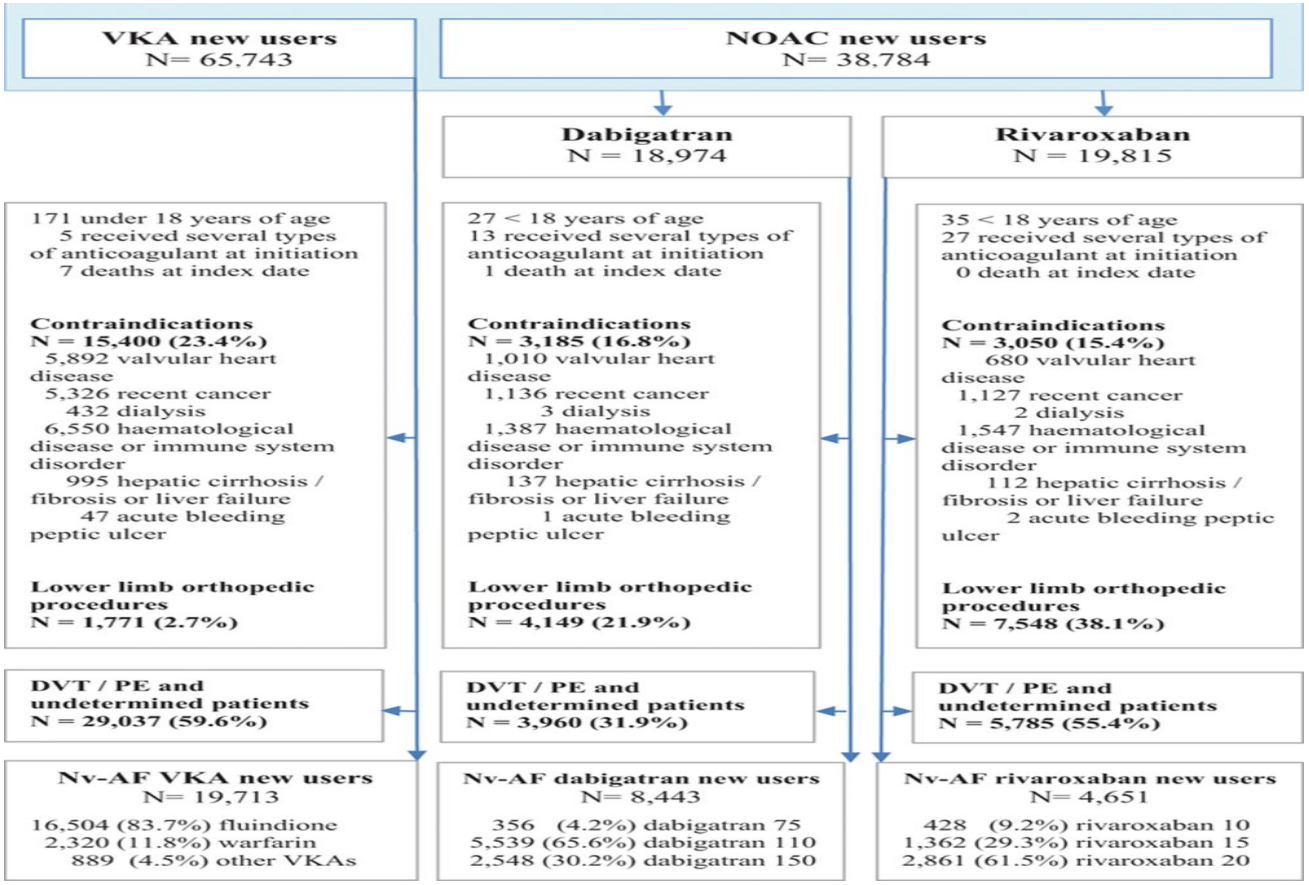


Lip GYH et al Int J Clin Pract 2016

Un farmaco è superiore all'altro?

Dati dei registri

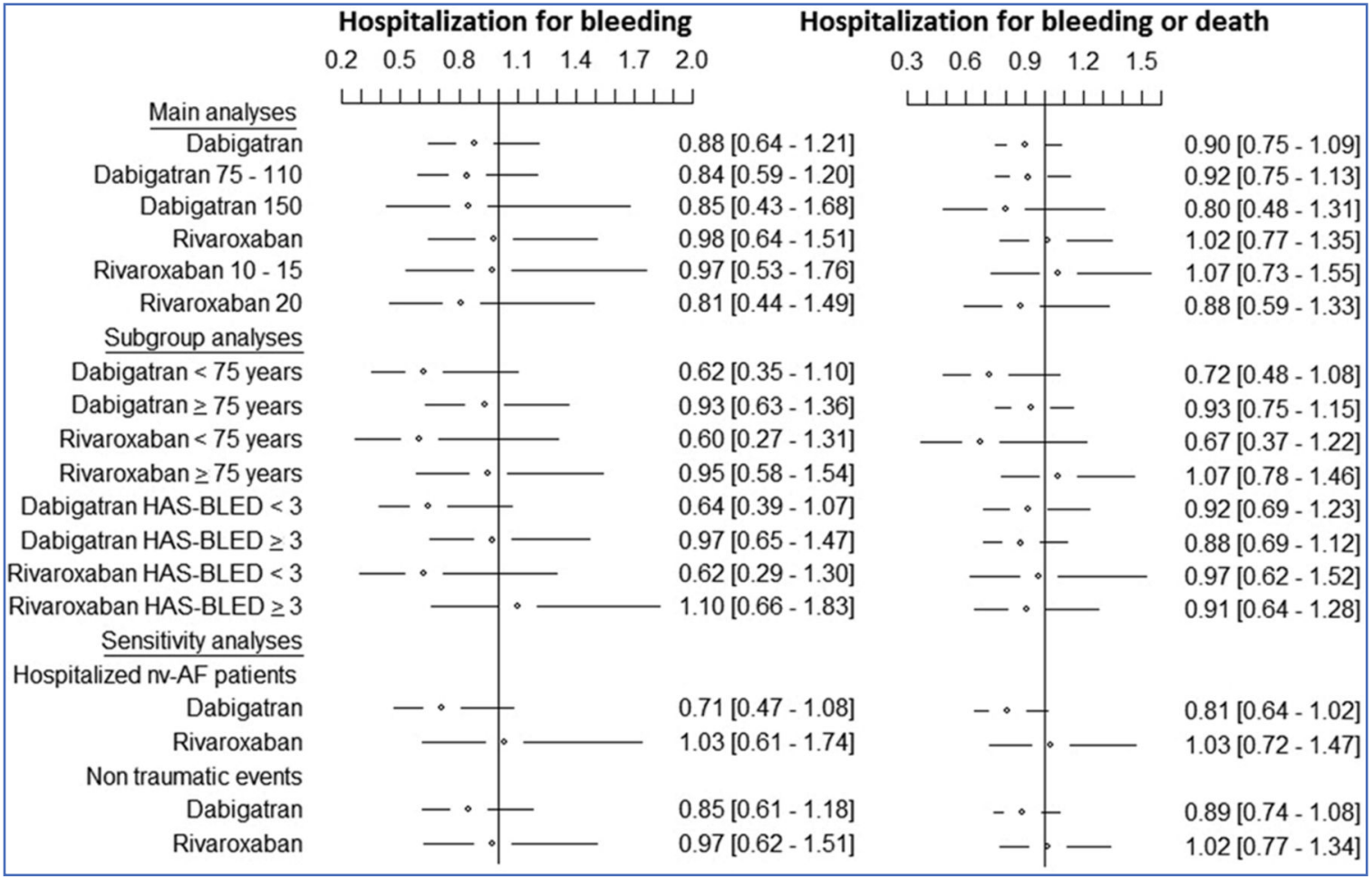
Rivaroxaban vs Dabigatran



Maura et al; Circulation 2015

French National Database

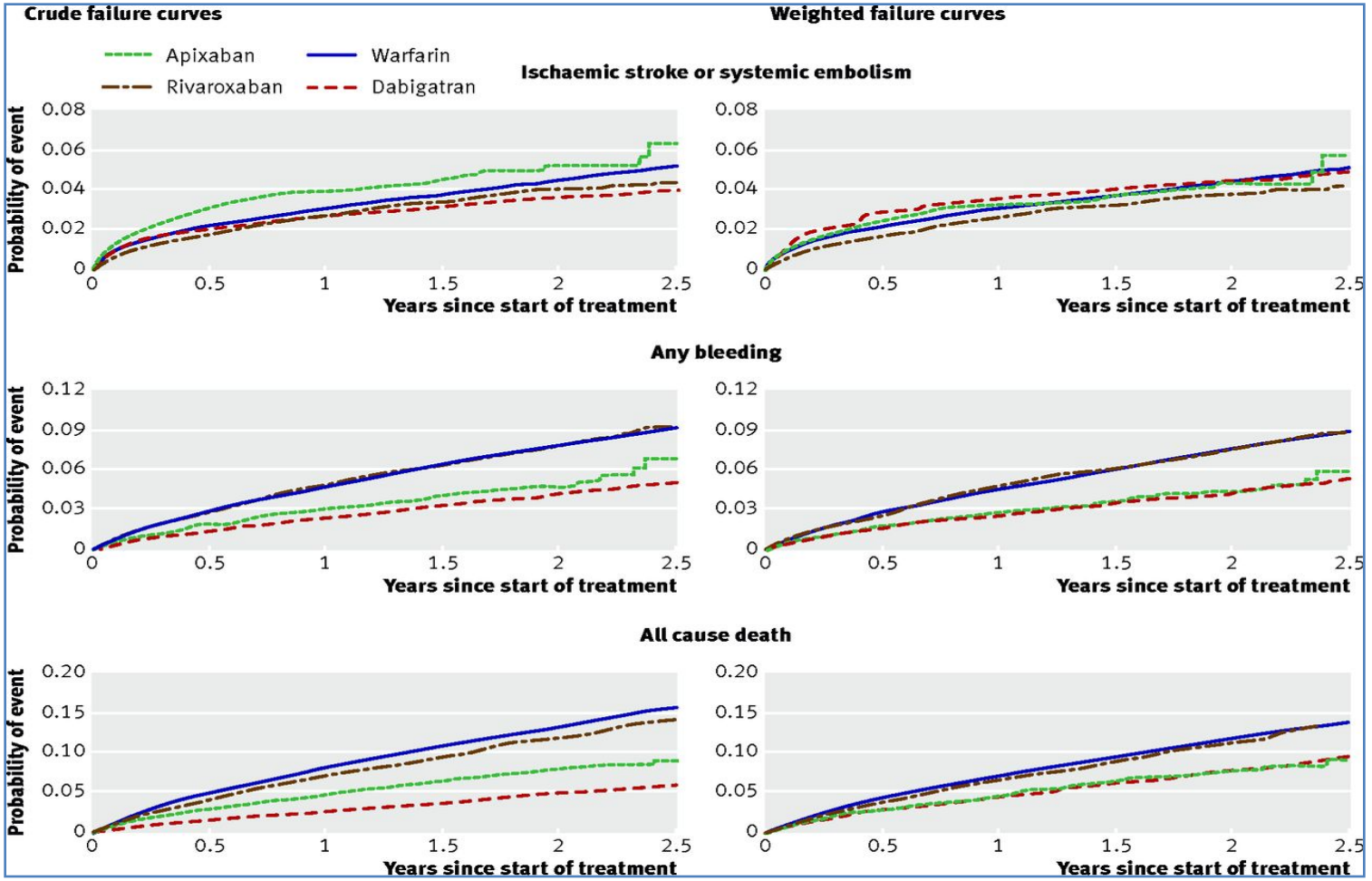
Hospitalization for MB (after PSM)



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

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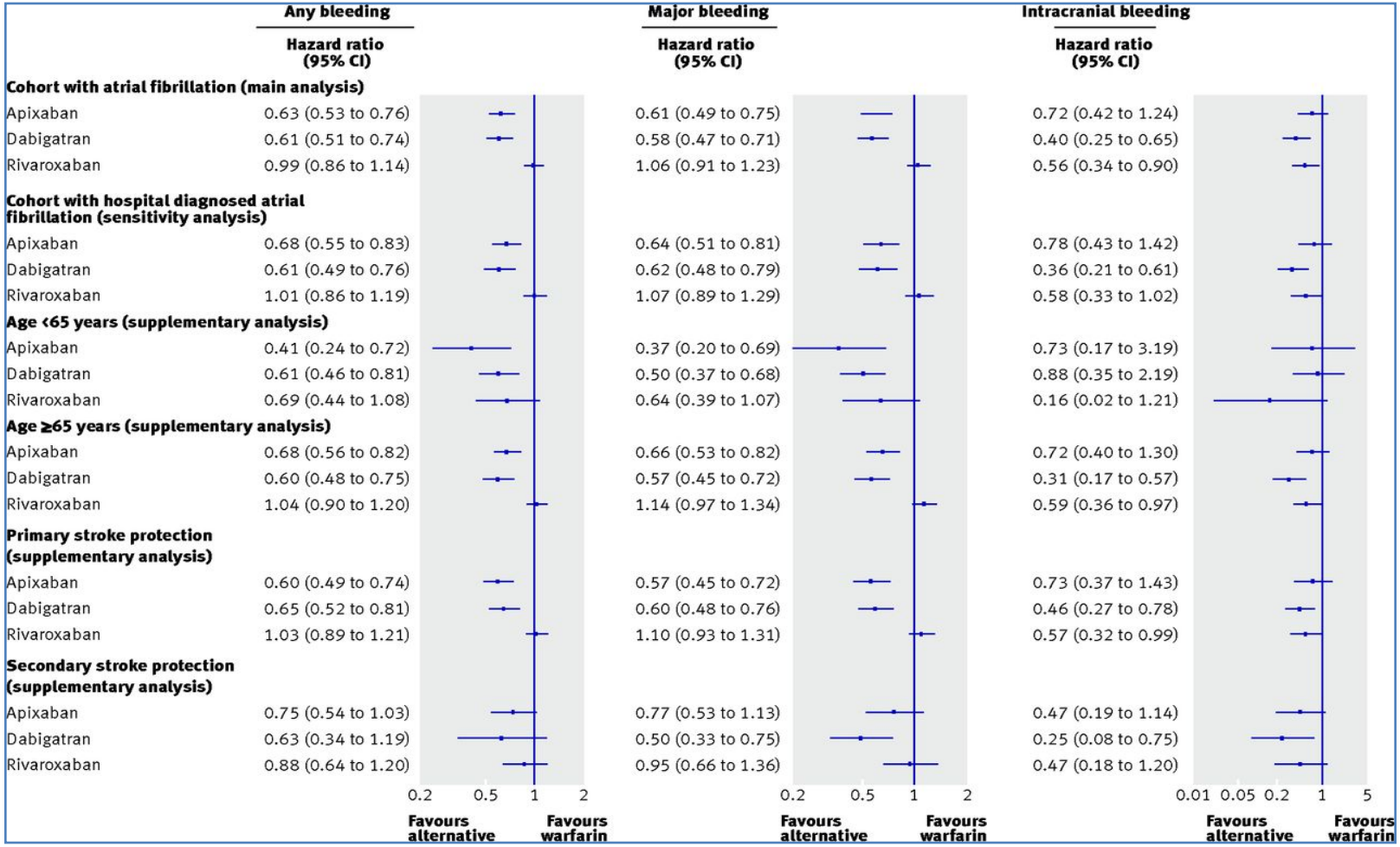

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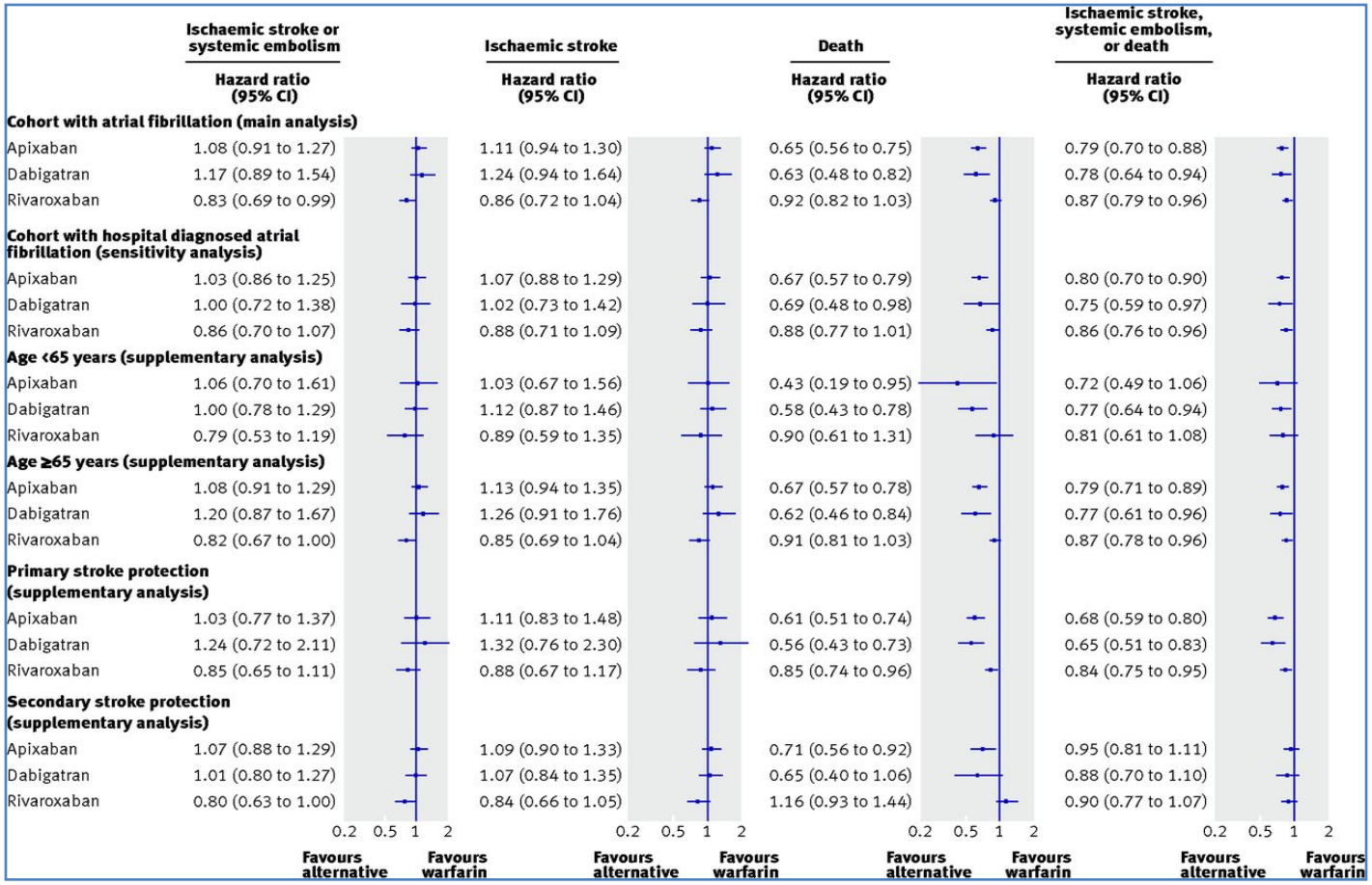
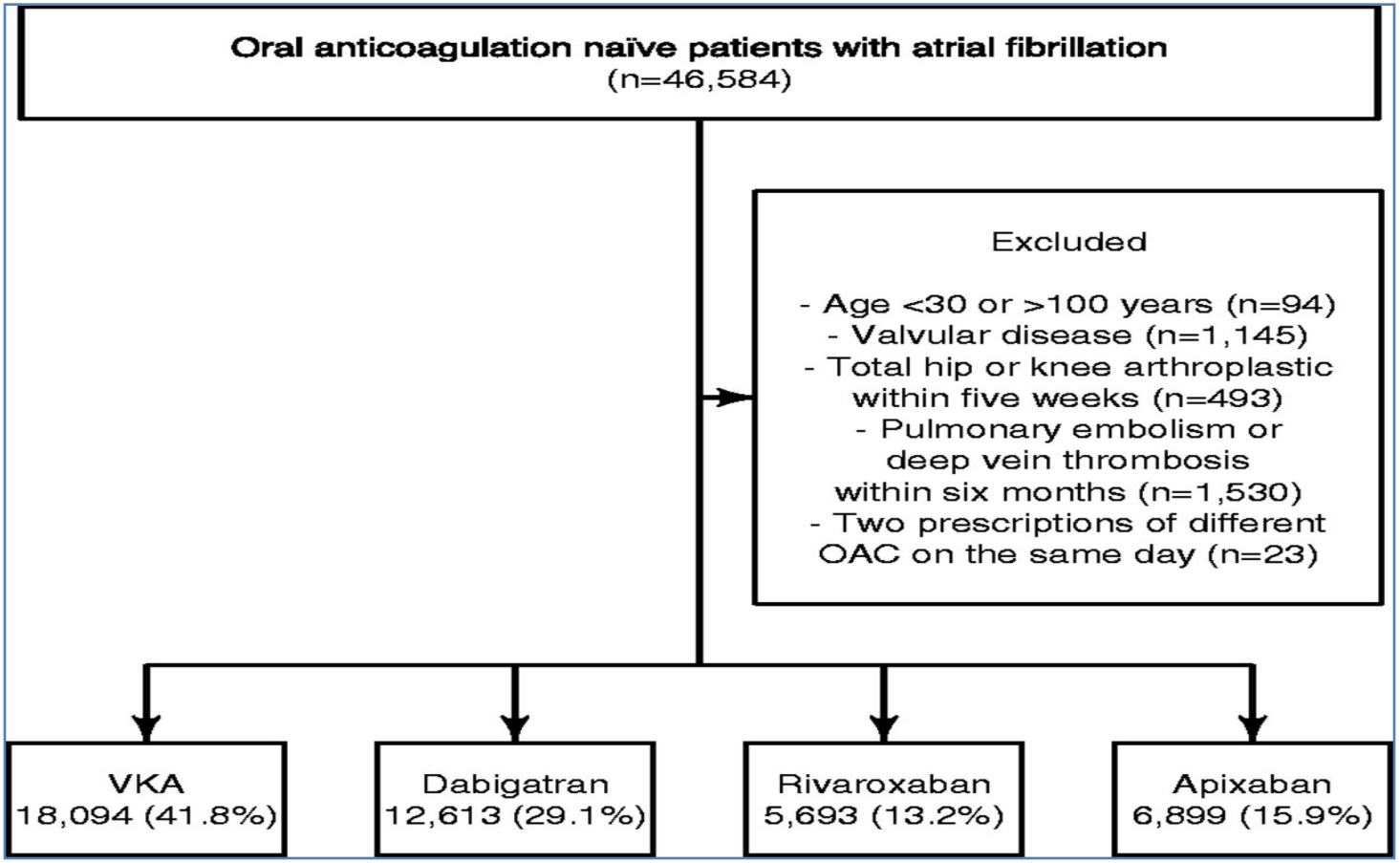


BMJ 2016

Ischemic and Haemorrhagic Stroke

Danish Database



Staerk et al; EHJ 2016

Ischemic and Haemorrhagic Stroke

Danish Database

	VKA	Dabigatran	Rivaroxaban	Apixaban	*P*-value
n (%)	18 094 (41.8)	12 613 (29.1)	5693 (13.2)	6899 (15.9)	
Males (%)	10 265 (56.7)	6938 (55.0)	2838 (49.9)	3439 (49.8)	<0.001
Age [median (IQR)]	73 (65–80)	71 (65–80)	74 (67–83)	76 (68–84)	<0.001
Age groups (%)					<0.001
<65	4005 (22.1)	3053 (24.2)	979 (17.2)	1051 (15.2)	
65–74	6028 (33.3)	4467 (35.4)	1885 (33.1)	2146 (31.1)	
75–84	5671 (31.3)	3507 (27.8)	1656 (29.1)	2156 (31.3)	
≥85	2390 (13.2)	1586 (12.6)	1173 (20.6)	1546 (22.4)	
$CHADS_2$ [mean (SD)]	1.54 (1.24)	1.40 (1.19)	1.57 (1.25)	1.66 (1.26)	<0.001
CHA_2DS_2-VASc [mean (SD)]	2.89 (1.64)	2.70 (1.58)	2.99 (1.60)	3.11 (1.60)	<0.001
HAS-BLED [mean (SD)]	2.16 (1.22)	2.00 (1.16)	2.14 (1.15)	2.20 (1.19)	<0.001

Staerk et al; EHJ 2016

Ischemic and Haemorrhagic Stroke

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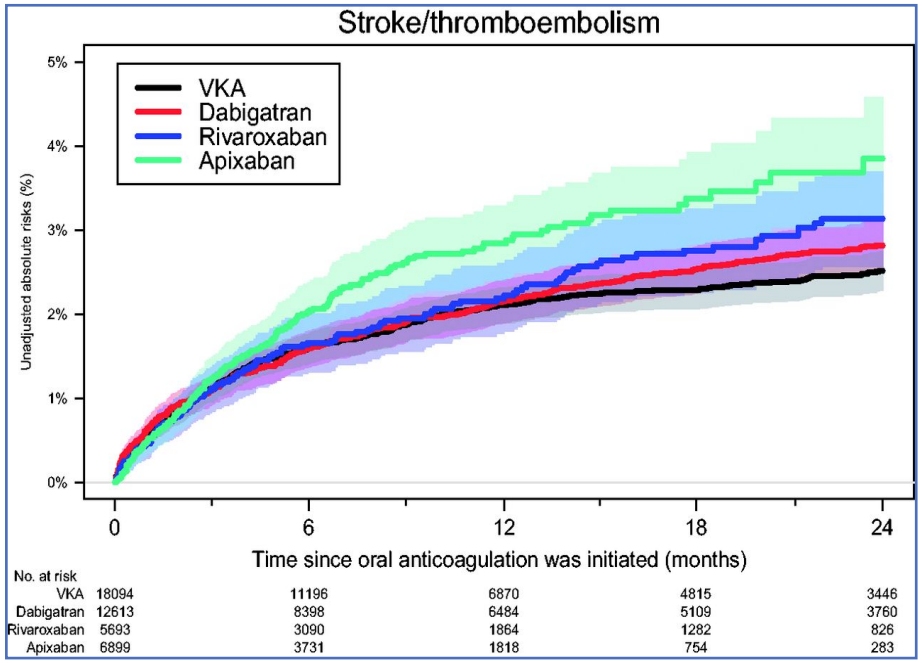

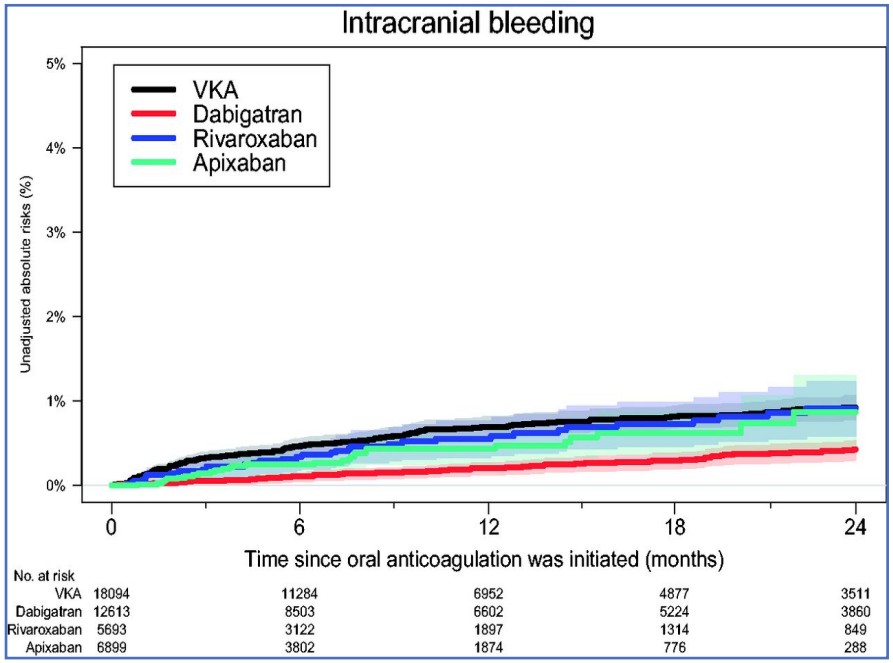

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Ischemic and Haemorrhagic Stroke

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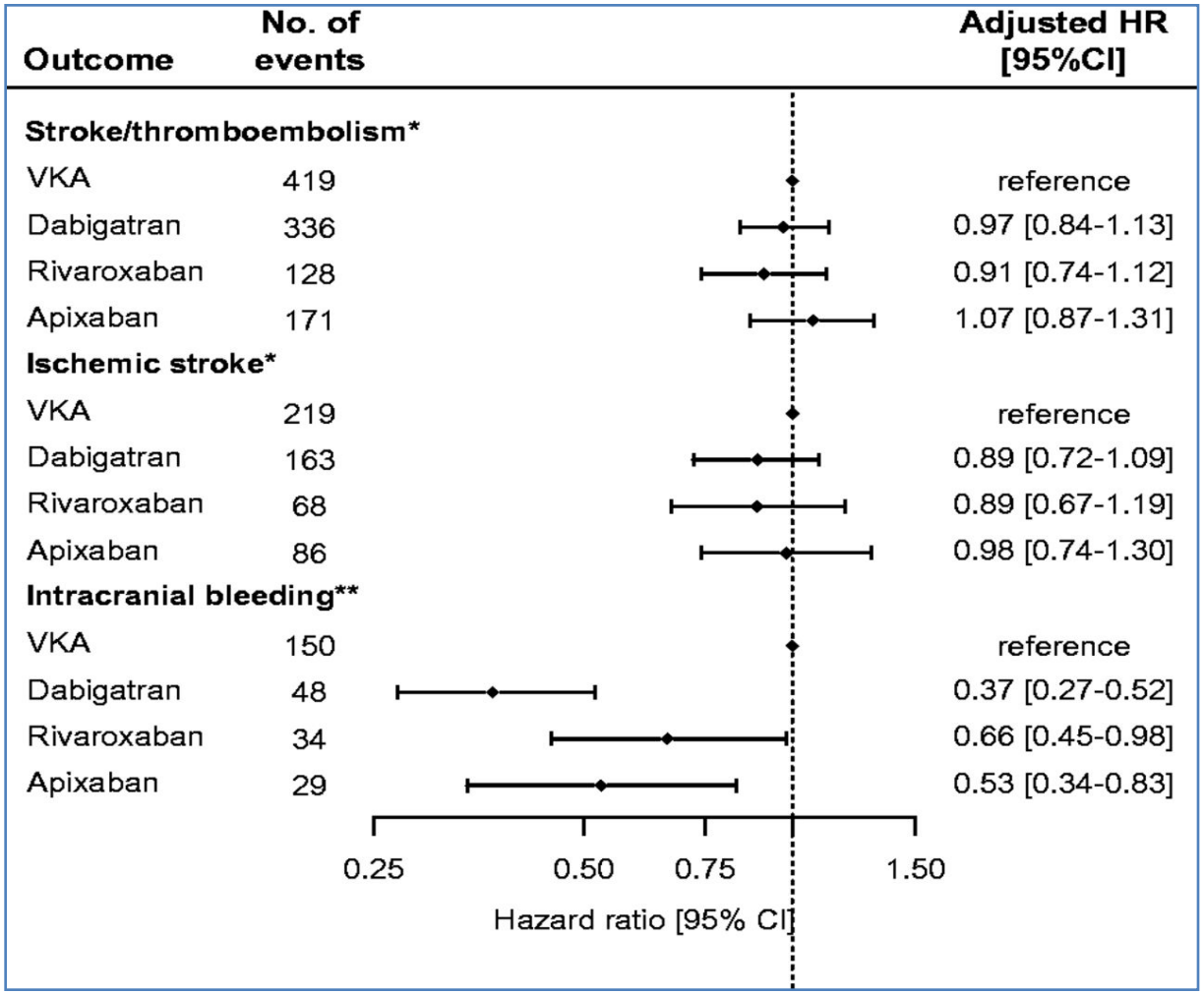
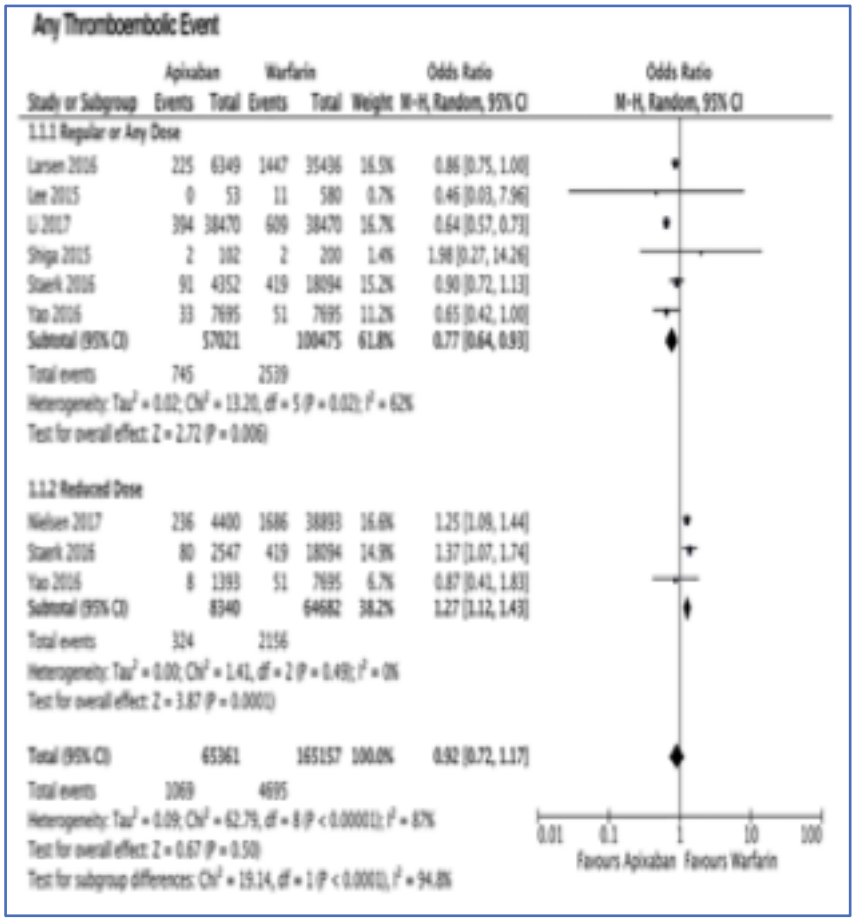
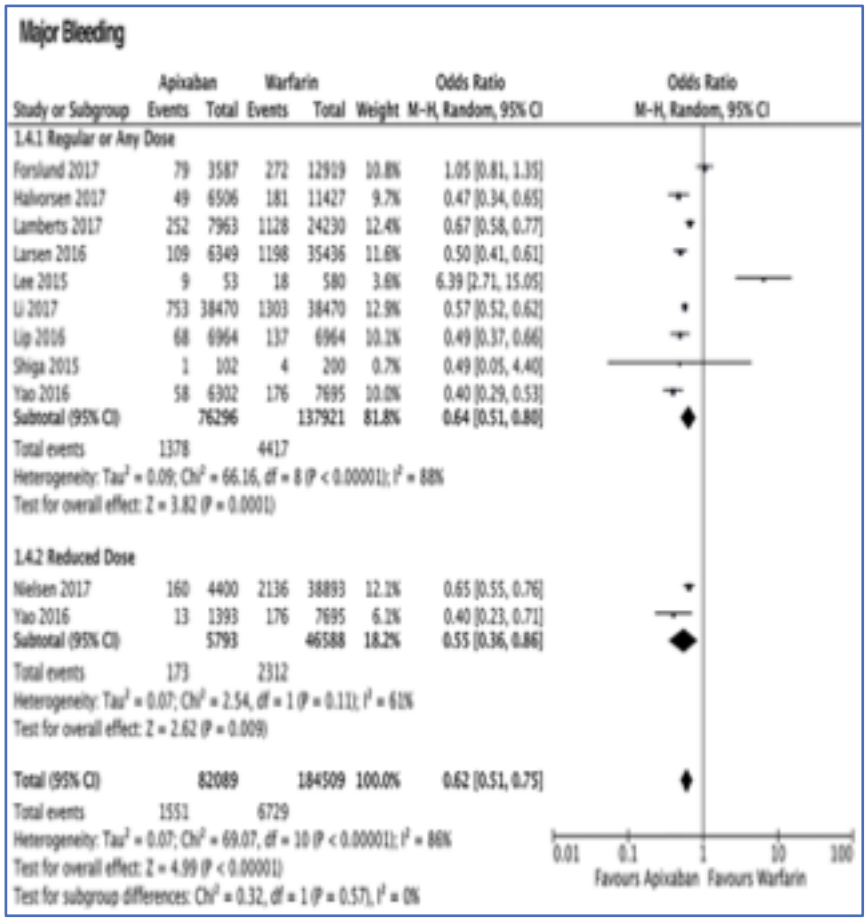


Staerk et al; EHJ 2016

Real-World Use of Apixaban for Stroke Prevention in Atrial Fibrillation

A Systematic Review and Meta-Analysis





Proietti et al; Stroke 2018

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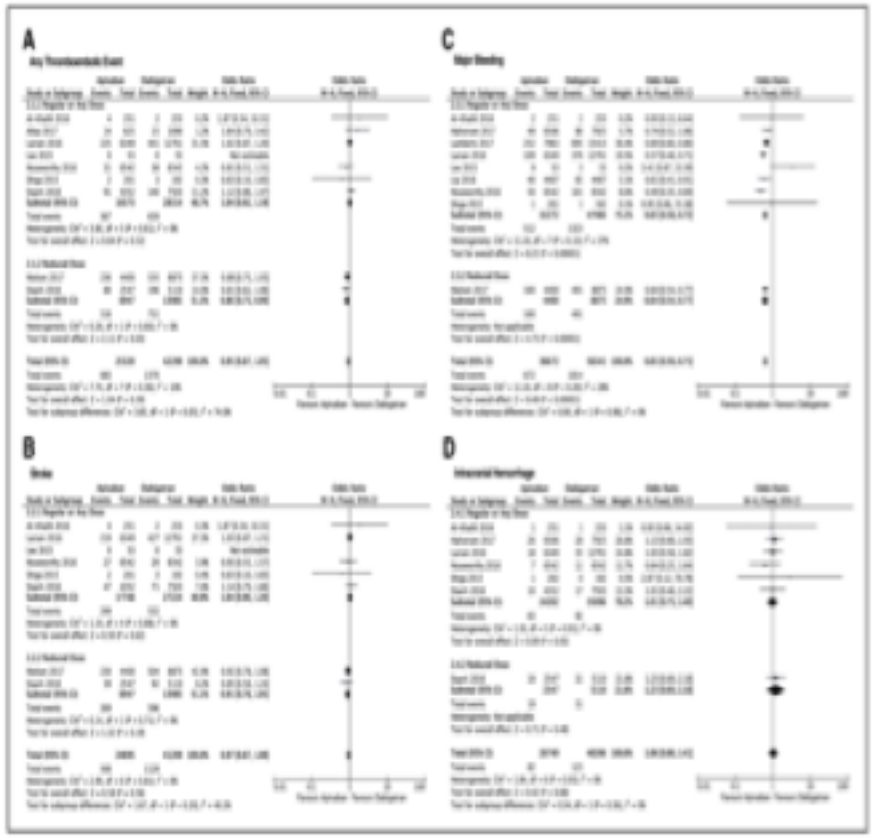
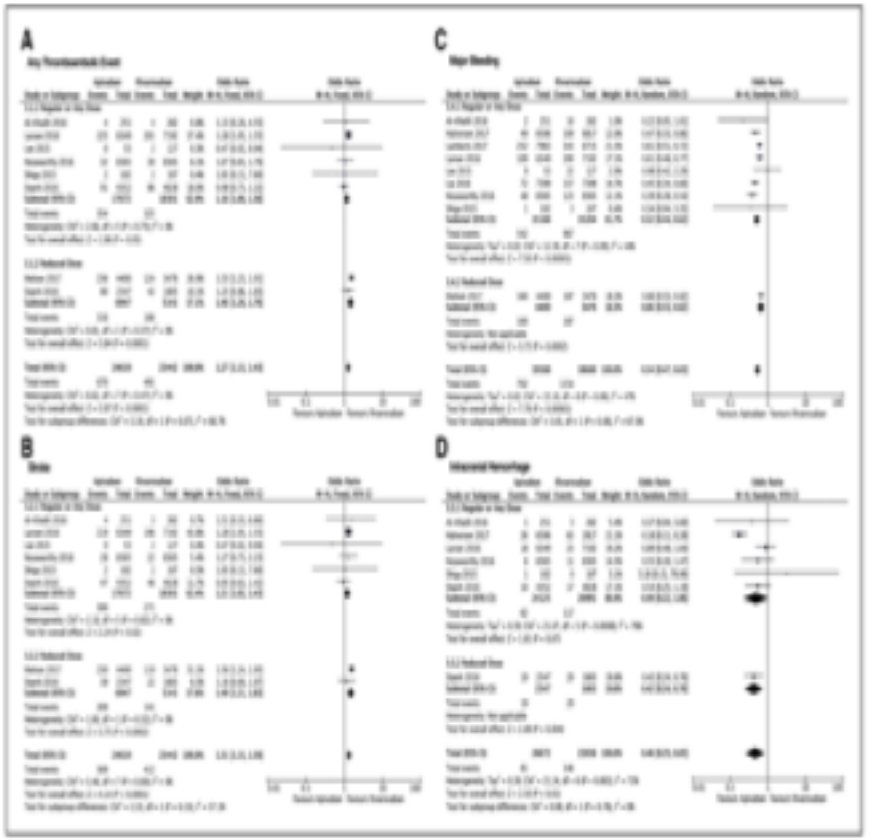




Proietti et al; Stroke 2018

Ragione/i per questi differenti risultati?

a. Differenze nell'analisi

b. Differenze nelle popolazioni

c. Caso

d. Altro

SCIENTIFIC PAPER TRAIL

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

Canada 49,947

United States 310,206

Mexico 8,626

Brazil 27,808

Argentina 6,766

Ireland 6,429

Sweden 18,645

Norway 9,207
Finland 9,207
Denmark 11,787

United Kingdom 90,018

Netherlands 29,296

Belgium 16,111

Germany 82,550

Russia 22,296

Poland 17,186

France 57,751

Czech Republic 8,163
Switzerland 21,372
Austria 11,011
Romania 5,240

Spain 43,300

Italy 47,403

Portugal 9,034

Greece 9,451

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

Turkey 19,753

Iran 17,598

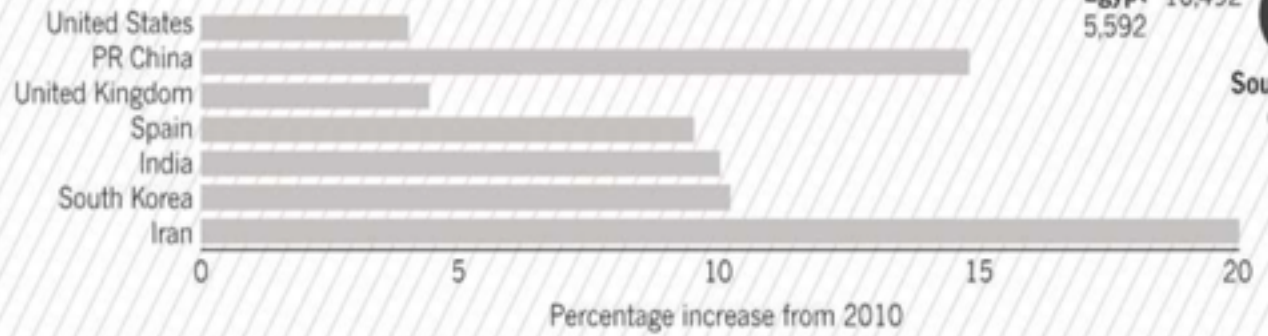
Israel 10,492

Egypt 5,592

South Africa 6,988

Australia 38,607

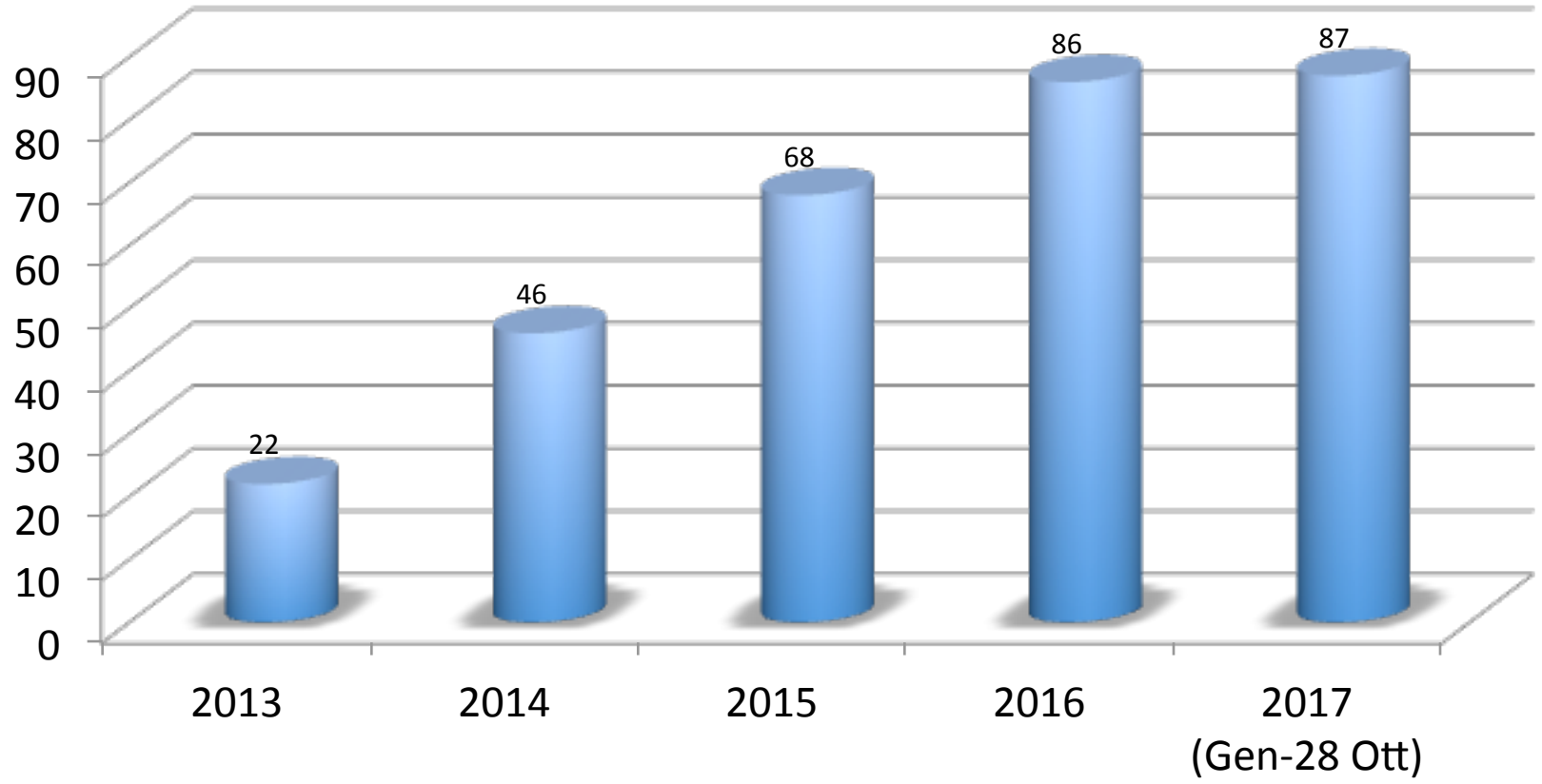
New Zealand 6,805



*Figures estimated from data for January–October

Pubblicazioni “Real World”

Search Strategy: “(apixaban or dabigatran or edoxaban or rivaroxaban) and (real world data or phase IV or post marketing)



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.

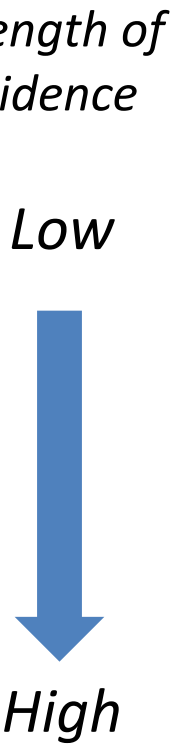
Romancing the Literature Electronically

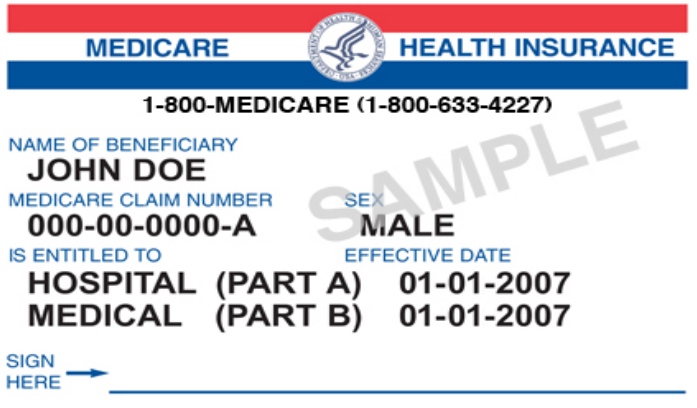
If you think that the clinical scenario just described is far-fetched, then you have not been keeping track of recent developments in user-friendly electronic access to medical information. It is now possible and reasonably straightforward for clinicians (called "end-users" in computer-speak) to retrieve 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

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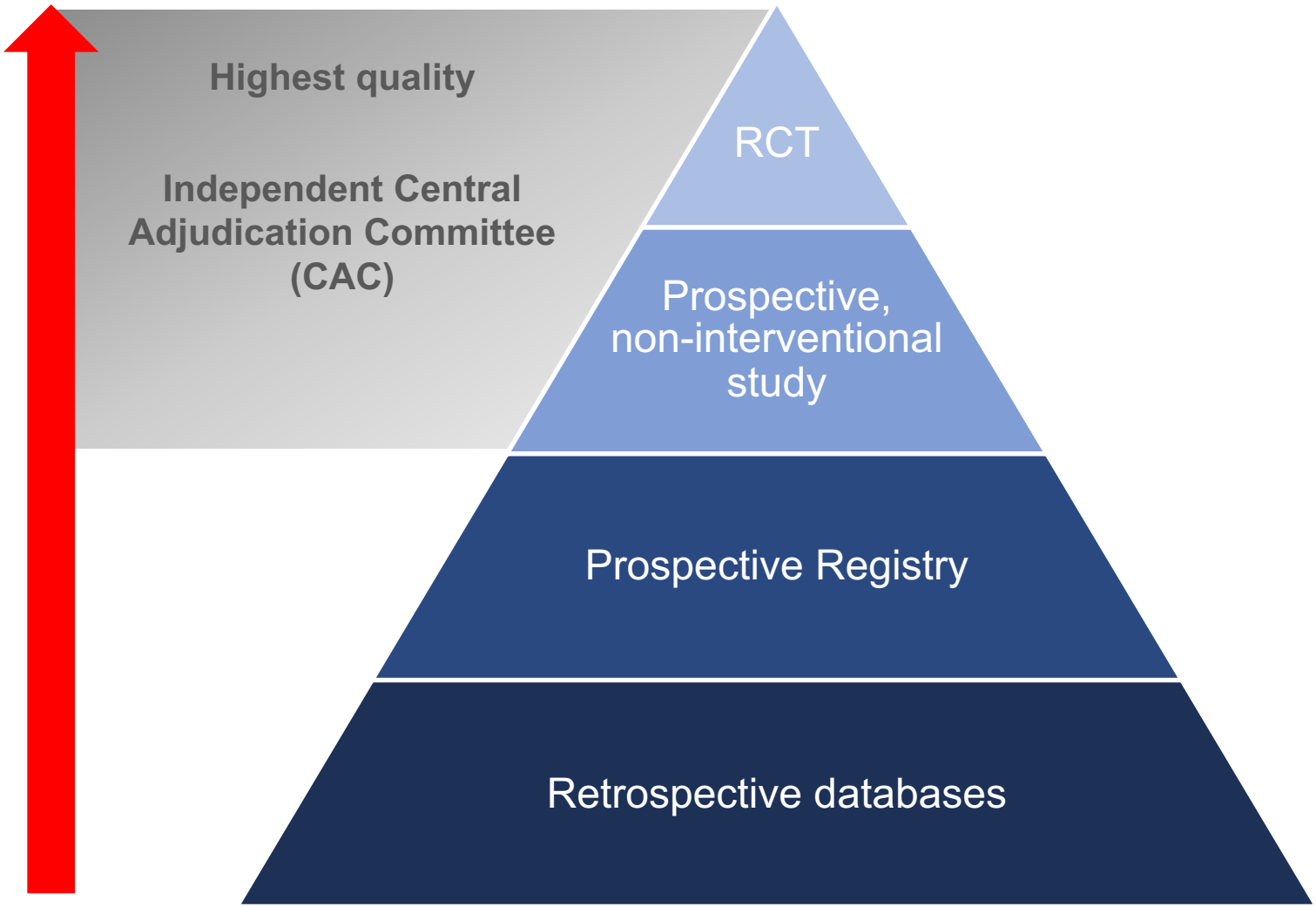
SUMMARY

Propensity-score [illegible] estimation of treatment effects using observational data. Two popular propensity-score 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.

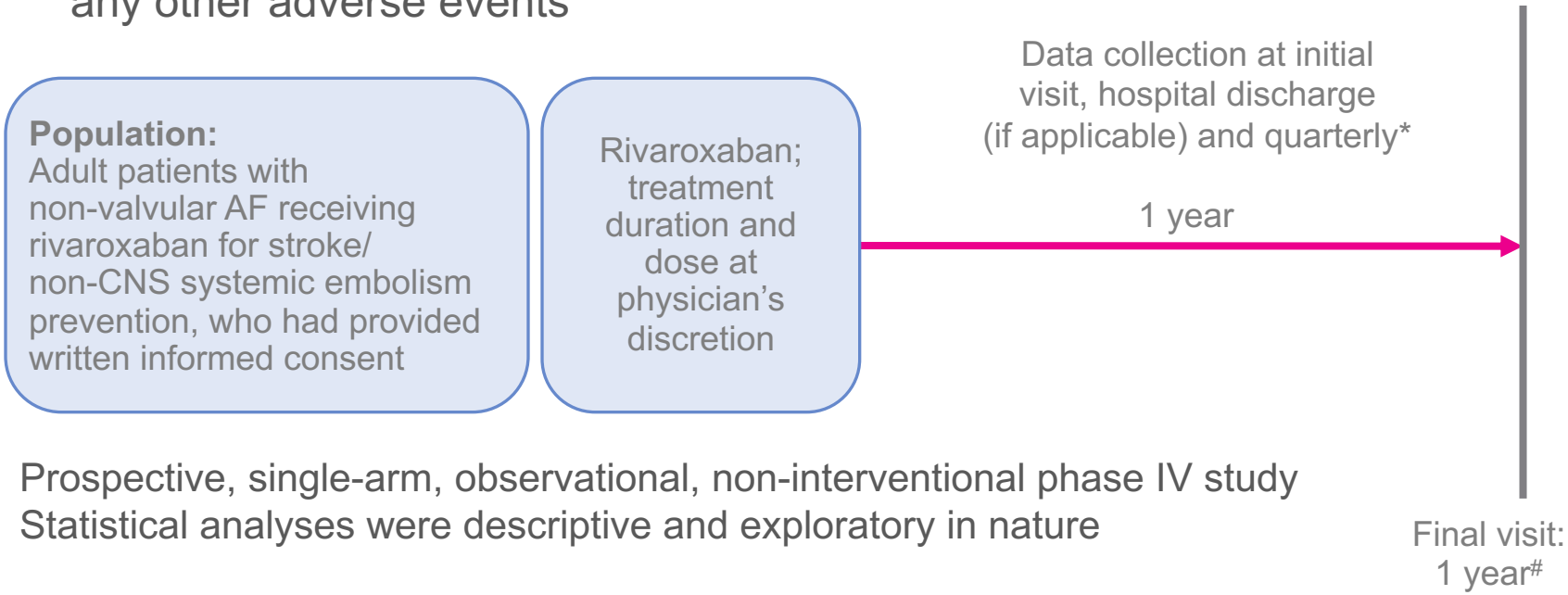
UNMEASURED VARIABLES???

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


Highest quality
Independent Central Adjudication Committee (CAC)
RCT
Prospective, non-interventional study
Prospective Registry
Retrospective databases

XANTUS Registry

- 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

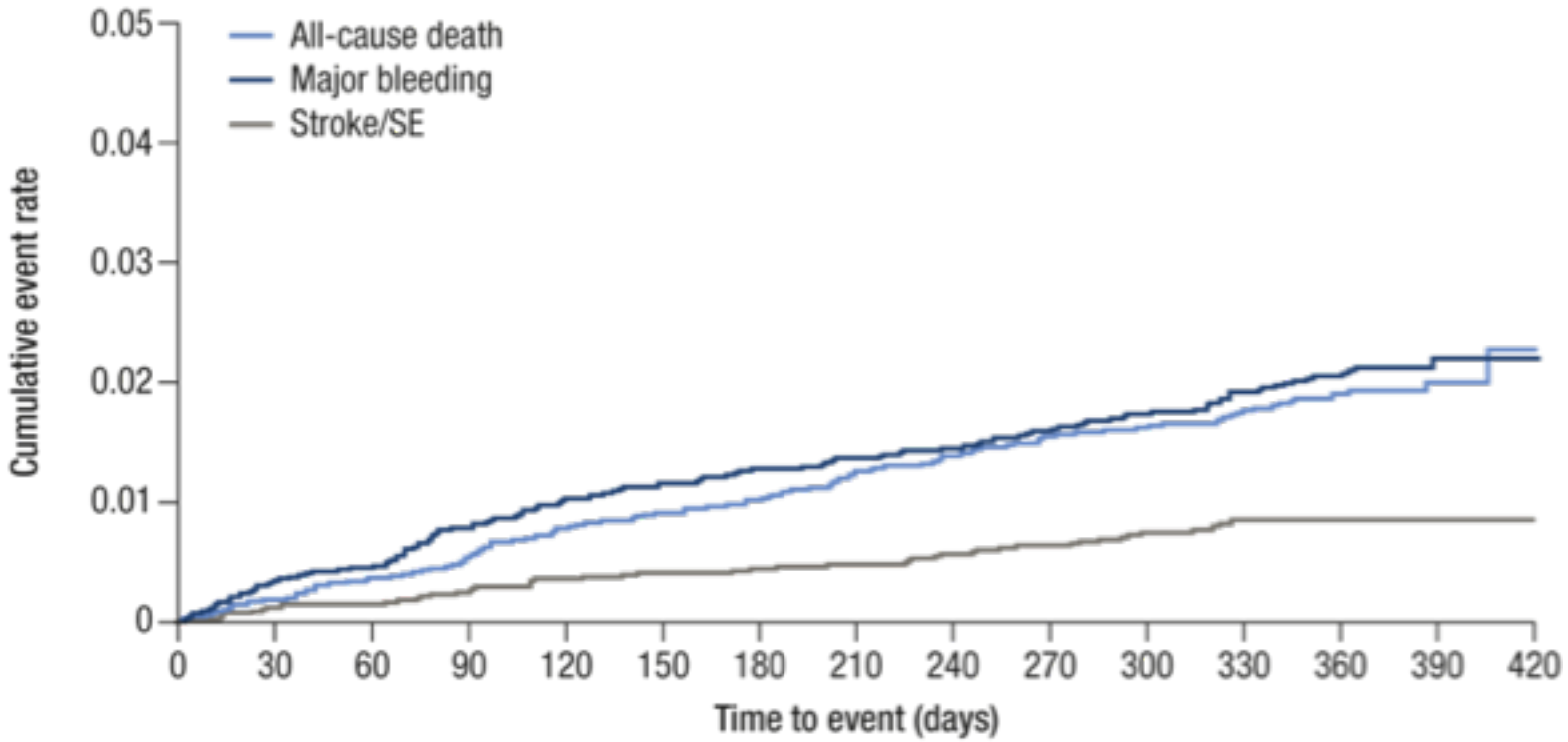


Prospective, single-arm, observational, non-interventional phase IV study
Statistical analyses were descriptive and exploratory in nature

*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

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

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



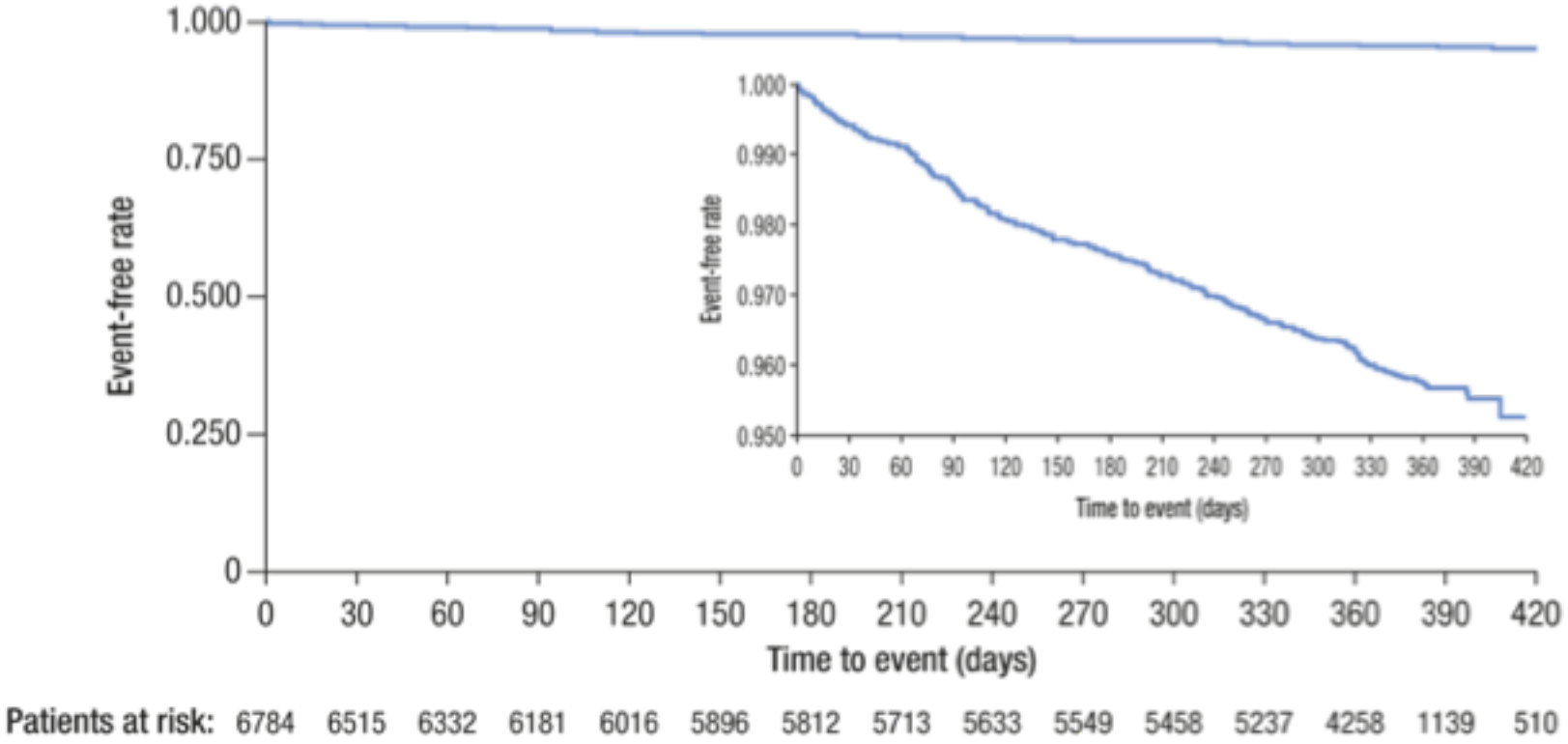
Patients at risk:

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

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

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



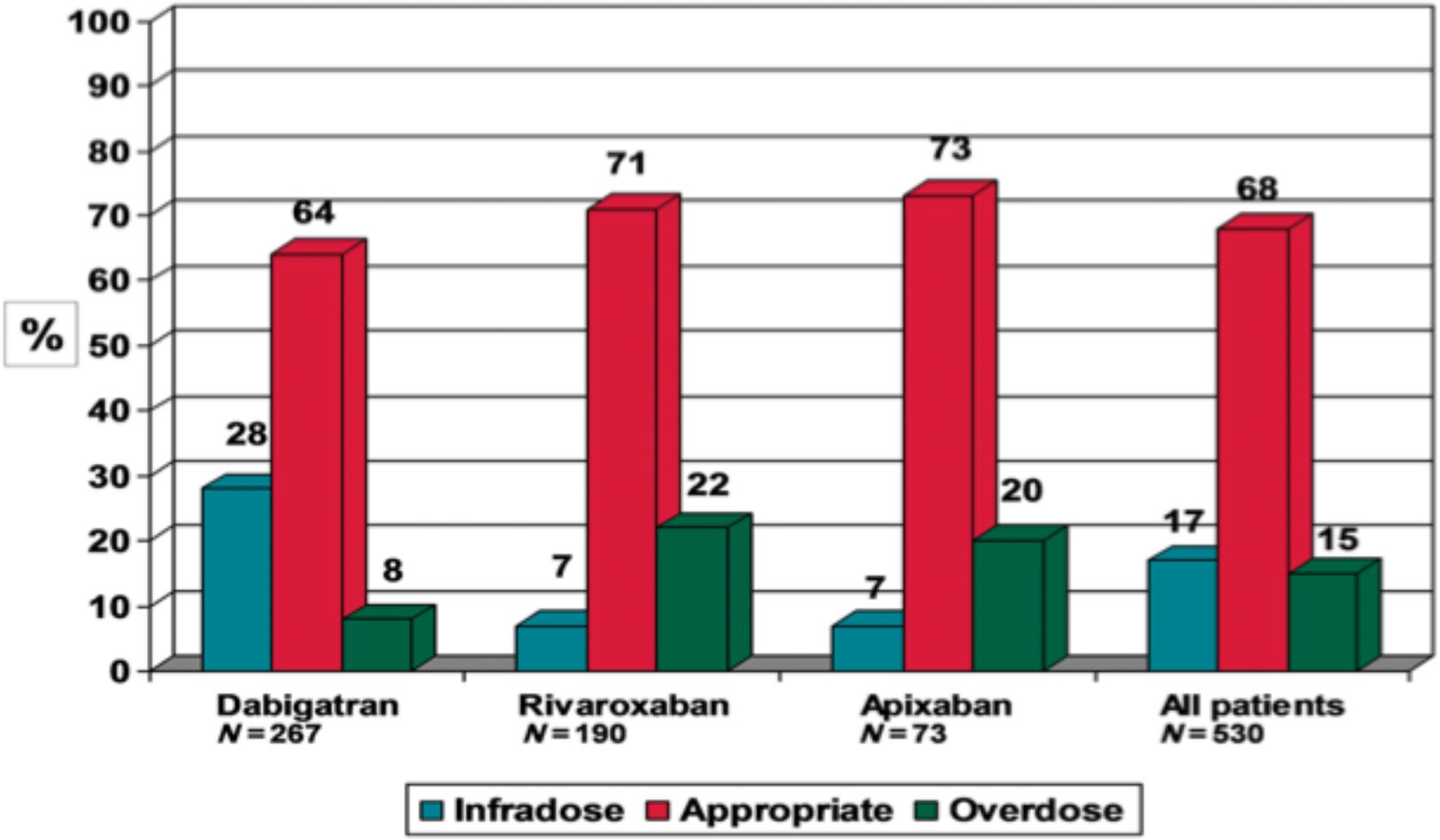
Camm et al. Eur Heart J 2016

ETNA-AF Registry

	ETNA-AF EU w/o Italy [9.962]	ITALY [3.512]
Gender: - male - female	 57.9% 42.1%	 53.6% 46.4%
Age [yrs] Mean (SD)	73.1 (9.50)	75.0 (9.43)
Weight [kg] Mean (SD)	82.8 (17.75)	76.2 (15.31)
BMI [kg/m^2] Mean (SD)	28.5 (5.27)	27.1 (4.71)

	ENGAGE AF
Age (mean) [IQR]	72 (64-78)

Inappropriate doses of direct oral anticoagulants in real-world clinical practice



Ruiz Ortiz et al. Europace 2018

Inappropriate doses of direct oral anticoagulants in real-world clinical practice

Variable	Odds ratio	95% confidence interval	*P*-value
Factors associated with inappropriately low dose of direct anticoagulants			
Age	0.97	0.94–1.00	0.022
$CHADS_2$ score	0.73	0.58–0.92	0.008
Body mass index	1.07	1.02–1.13	0.008
Direct anticoagulant			
Dabigatran	1 (reference)		
Apixaban	0.19	0.07–0.50	0.001
Rivaroxaban	0.20	0.10–0.37	<0.001
Factors associated with inappropriately high dose of direct anticoagulants			
Charlson comorbidity index	0.62	0.45–0.85	0.003
CHA_2DS_2-VASc score	1.68	1.36–2.08	<0.001
Hypertrophic cardiomyopathy	5.82	1.36–24.97	0.018
Aortic valvular disease	4.40	1.37–14.14	0.013
Aldosterone antagonists	2.41	1.10–5.28	0.028
Angiotensin receptor blockers	0.52	0.29–0.91	0.022
Antiplatelet agents	3.49	1.73–7.06	<0.001
Direct anticoagulant			
Dabigatran	1 (reference)		
Apixaban	3.10	1.42–6.78	0.005
Rivaroxaban	2.91	1.58–5.37	0.001

Ruiz Ortiz et al. Europace 2018

Take home messages

- ✓ Beneficio Clinico netto dei DOACs vs AVK nei trials randomizzati e controllati
- ✓ Safety confermata anche nel mondo reale
- ✓ Attenzione alla qualità degli studi! (utilità dei confronti?)
- ✓ Attenzione alle dosi!