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CardioLUCCA 2019

Cuore d'Autore

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Dai Trial di Fase 3 al Real World: i DOACs Confermano il Profilo di Sicurezza ed Efficacia

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NOACs are Associated with Improved Outcomes for Patients with AF Compared with Warfarin

	Dabigatran (RE-LY[1,2,7]) 150 mg BID	Dabigatran (RE-LY[1,2,7]) 110 mg BID	Apixaban (ARISTOTLE[3,4]) 5/2.5 mg BID	Rivaroxaban (ROCKET AF[5]) 20/15 mg OD	Edoxaban (ENGAGE AF-TIMI 48[6]) 60/30 mg OD
Stroke/SE	↓ 35%	Similar	↓ 21%	Similar	Similar
Ischemic stroke	↓ 24%	Similar	Similar	Similar	Similar
Hemorrhagic stroke	↓ 74%	↓ 69%	↓ 49%	↓ 41%	↓ 46%
CV mortality	↓ 15%	Similar	Similar	Similar	↓ 14%
Major bleeding	Similar	↓ 20%	↓ 31%	Similar	↓ 20%

1. Connolly et al. N Engl J Med 2014; 2. Connolly et al. N Engl J Med 2010; 3. Granger et al. N Engl J Med 2011; 4. Lopes et al. Lancet 2012; 5. Patel et al. N Engl J Med 2011; 6. Giugliano et al. N Engl J Med 2013; 7. Pradaxa SPC, 2018

Real-world Evidence Can Add to Data from RCTs

Randomized control trials (RCT)

Post approval, use in clinical practice provides an opportunity to study:

Tightly controlled patient population

Broader patient populations

Alternative comparators

Different outcomes

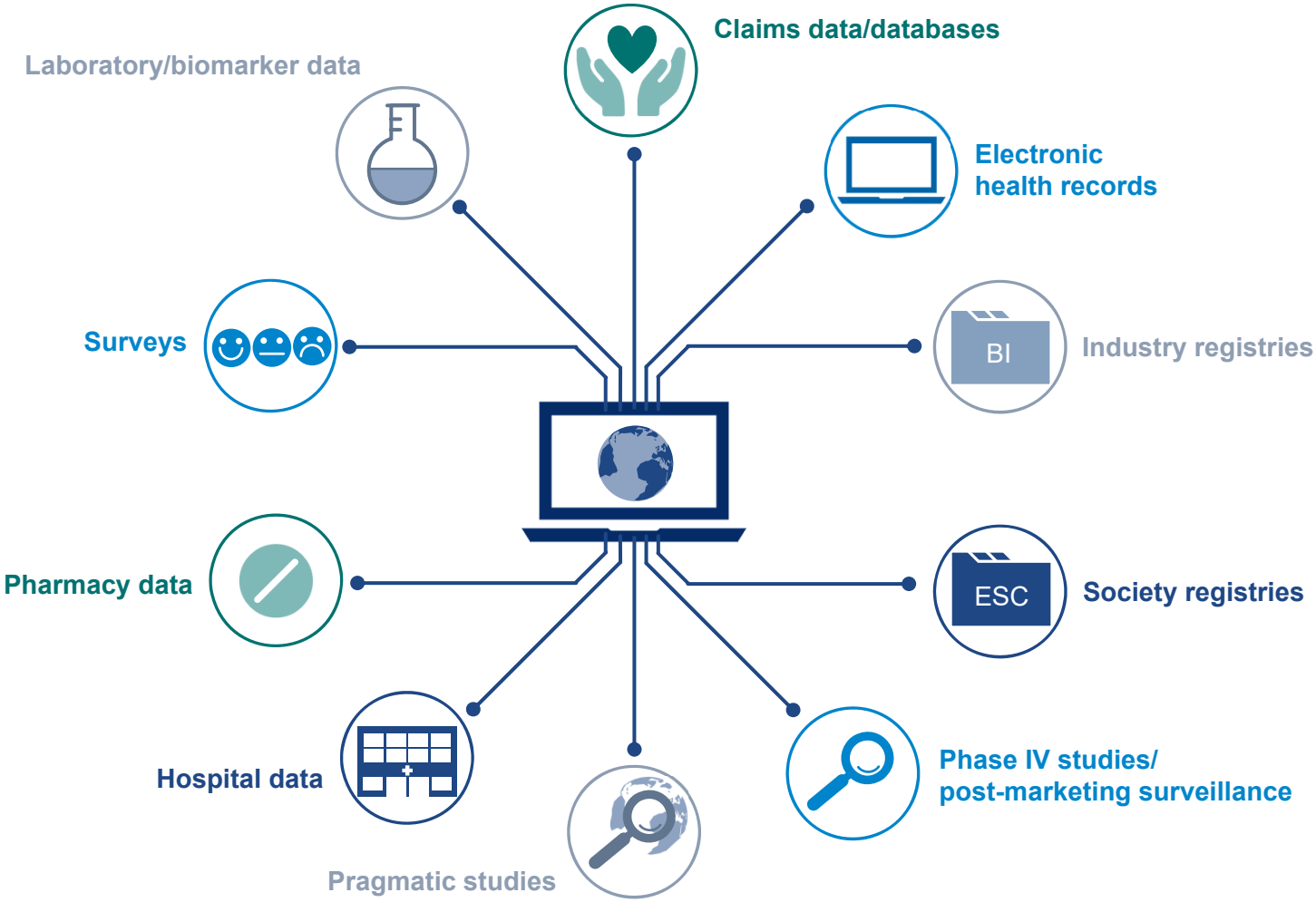
Different settings

Real-world evidence can:

- confirm whether the **results of an RCT are observed in everyday clinical practice**
- inform on **safety, effectiveness, and healthcare resource utilization** in routine care (which cannot usually be addressed by RCTs)
- support **reimbursement, regulatory, and clinical decision-making**

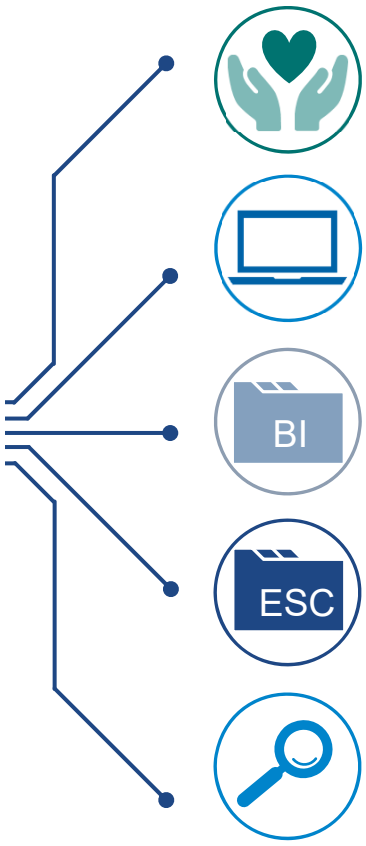
Sherman et al. N Engl J Med 2016;
Nallamothu et al. Circulation 2008

Real-world Data
Can Come from a Variety of Sources



Sherman et al. N Engl J Med 2016

What are the Important Sources of Real-world Data?



Source	Design	Enrolment	Outcomes
Claims data/ databases	Retrospective	All relevant patients	Data linking
Electronic health records	Retrospective	All relevant patients	Data linking
Industry registries	Prospective	Informed consent	Investigator reported
Society registries	Retrospective	Informed consent	Investigator reported
Phase IV studies/ post-marketing surveillance	Prospective	Informed consent	Adjudicated

Retrospective and prospective real-world study designs can both provide important data to add to results from RCTs

Minimizing the *Ground Noise* of Real World Evidence
What is Important for YOU?

1. **Number of patients enrolled**
2. **Data source** (Independent vs industry funded)
3. **Endpoints** (blinded adjudication, admin charts)
4. **Statistical analysis** (propensity score methods)

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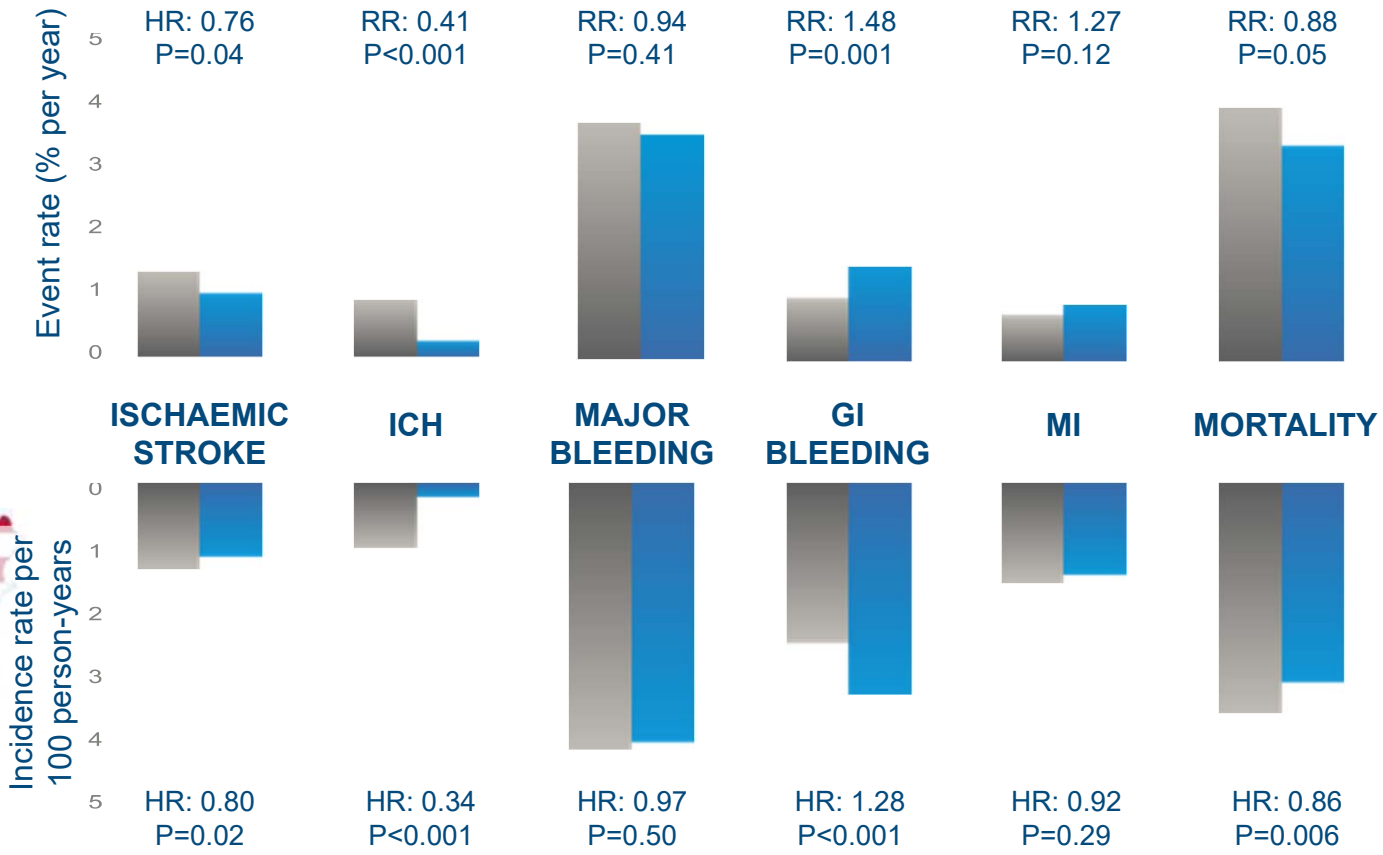
5. **All of the above** (look to the type of publication.. and journal)

Independent FDA Study Mirrors the Favourable Benefit–Risk Profile of Dabigatran from RE-LY

N=134,414



In the USA, the licensed doses for Pradaxa® are: Pradaxa® 150 mg BID and Pradaxa® 75 mg BID for the prevention of stroke and systemic embolism in adult patients with NVAF

1. Graham et al. Circulation 2015;
2. Connolly et al. N Engl J Med 2009;
3. Connolly et al. N Engl J Med 2010;
4. Pradaxa®: EU SPC, 2015;
5. Connolly et al. N Engl J Med 2014

GI Bleeding in the FDA Study of Medicare Patients

Age group (n)	Men HR (95% CI)	Women HR (95% CI)
65-74 (55.761)	0.83 (0.60-1.14)	0.99 (0.72-1.37)
75-84 (57.345)	1.02 (0.79-1.31)	1.50 (1.20-1.88)
≥85 (21.308)	1.55 (1.04-2.32)	2.18 (1.61-2.97)

The vast majority of Medicare patients (≈ 84%) received the 150 mg BID dose of Dabigatran

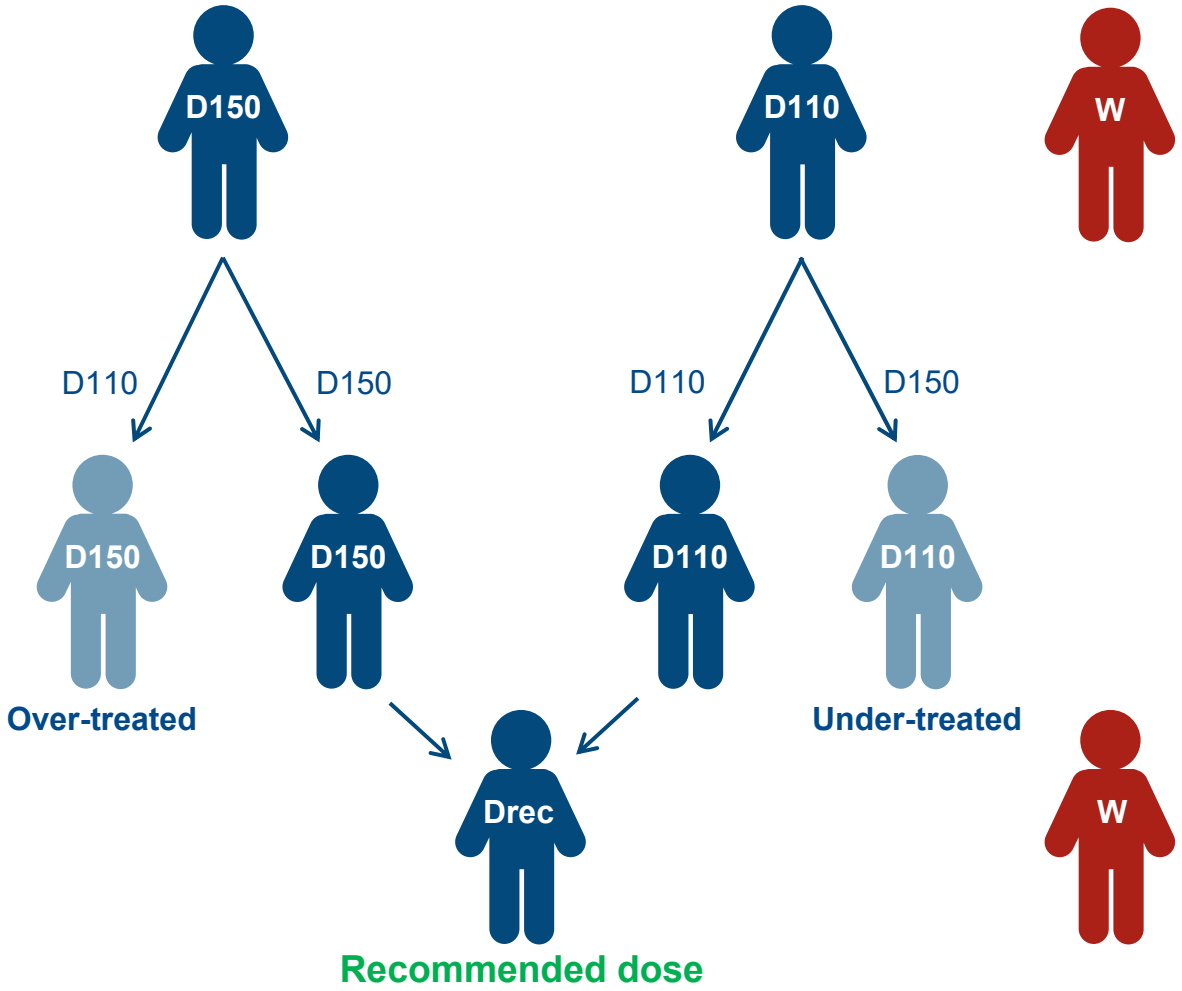
Graham DJ et al. Circulation 2015;131:157

‘EU label’ Analysis: Outcomes when Dabigatran was Used According to EU Label

Full RE-LY population

Post hoc analysis of patients’ baseline characteristics

Post hoc pooled analysis
‘EU label-simulated dabigatran’ vs warfarin

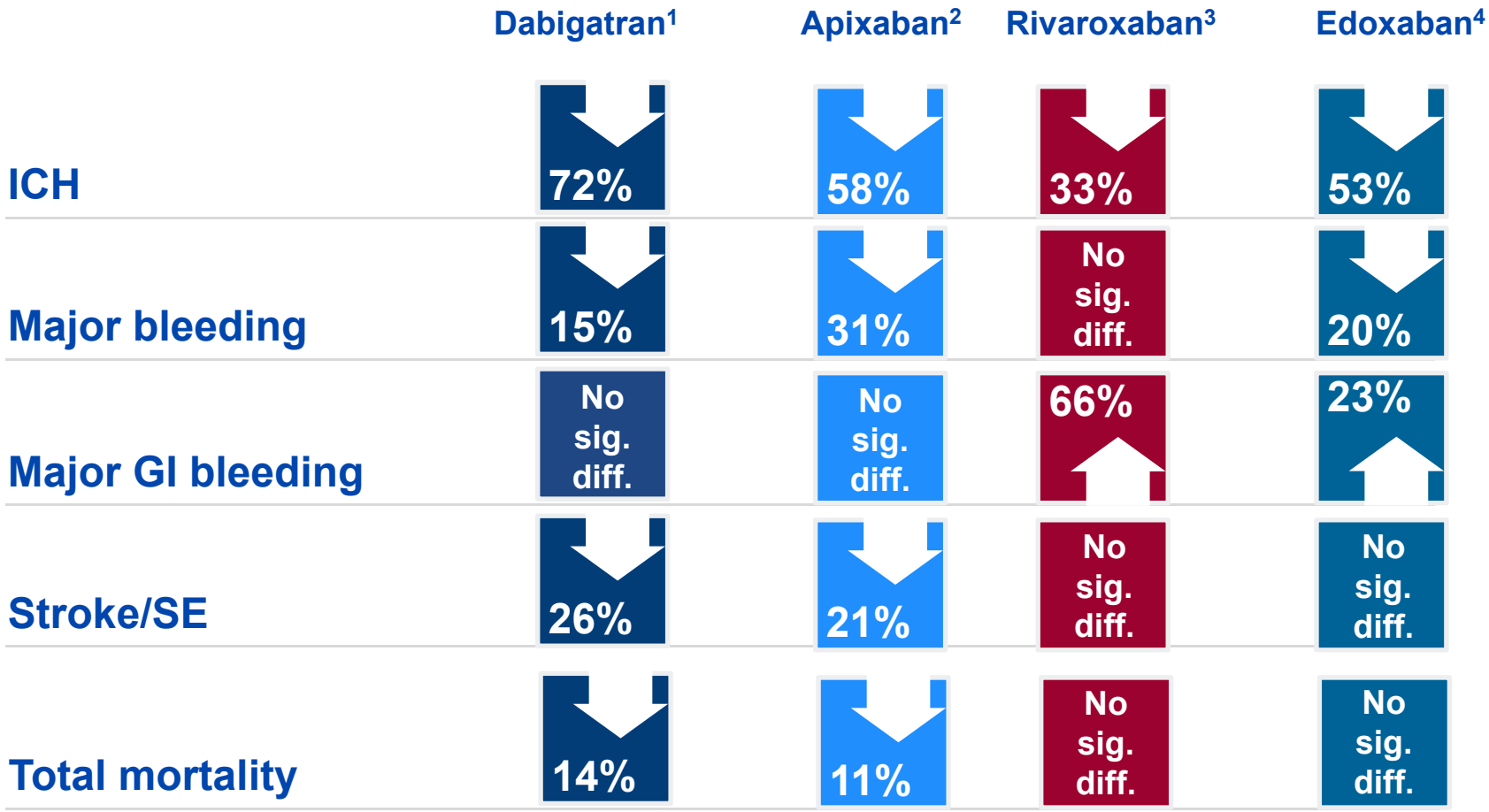


*D110 recommended for ≥80 years *OR* HAS-BLED ≥3 *OR* verapamil; D150 recommended for <80 years *AND* HAS-BLED <3

Lip GY et al. Thromb Haemost 2014;111:933–42

Are all NOACs the Same?

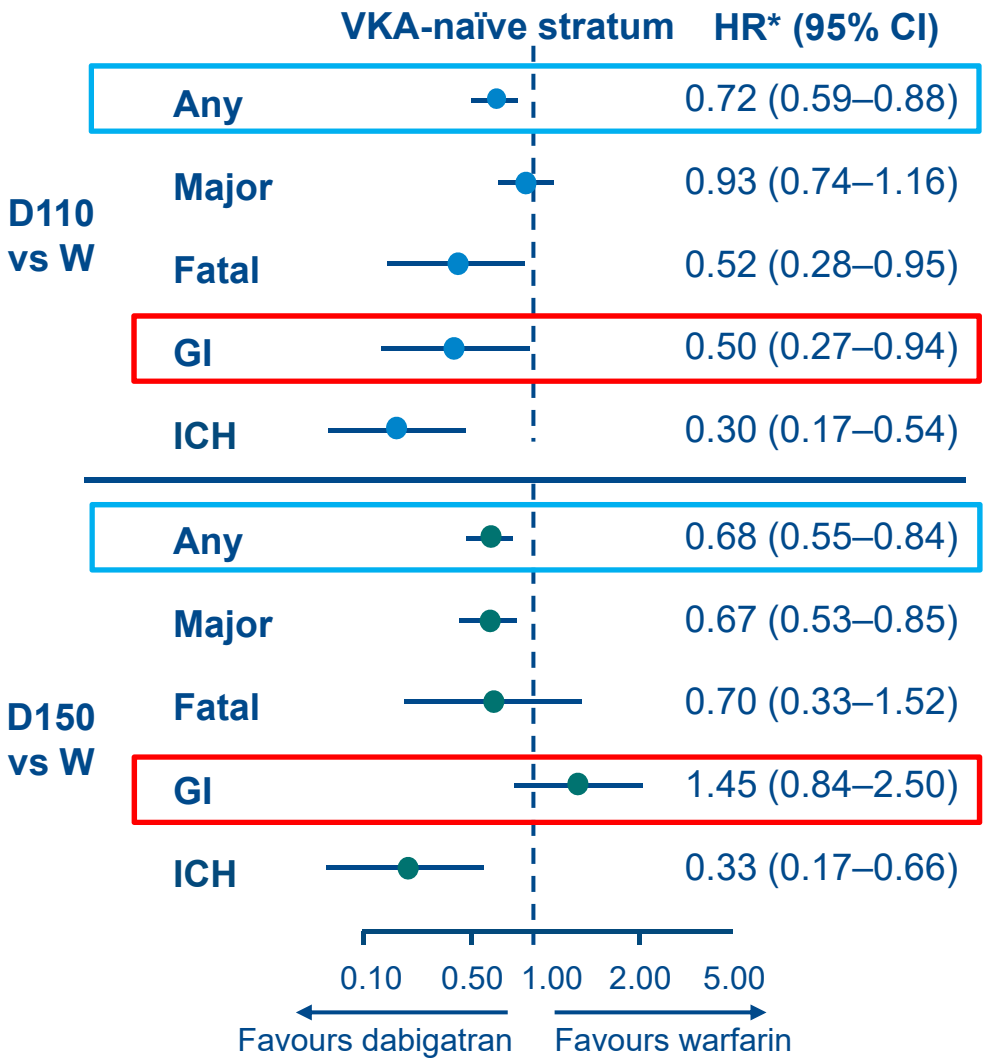
Risk reductions vs warfarin



1. Lip GY et al. Thromb Haemost 2014; 2. Granger CB et al. NEJM 2011; 3. Patel MR et al. NEJM 2011; 4. Giugliano RP et al. NEJM 2013

Favourable Benefit–Risk Profile of Dabigatran in Real-World: Independent Danish Registry

11 315 first-time dabigatran users (7063 VKA-naïve) vs **22 630** matched warfarin users



*Adjusted HR: age, components of CHA_2DS_2-VASc, HAS-BLED, months since August 2011, time since initiation of VKA therapy

Larsen TB et al. Am J Med 2014;127:650

Real-world Analyses: Dabigatran vs VKAs

17 analyses from >**550 000 patients** investigating dabigatran vs VKAs for risk of **major bleeding**

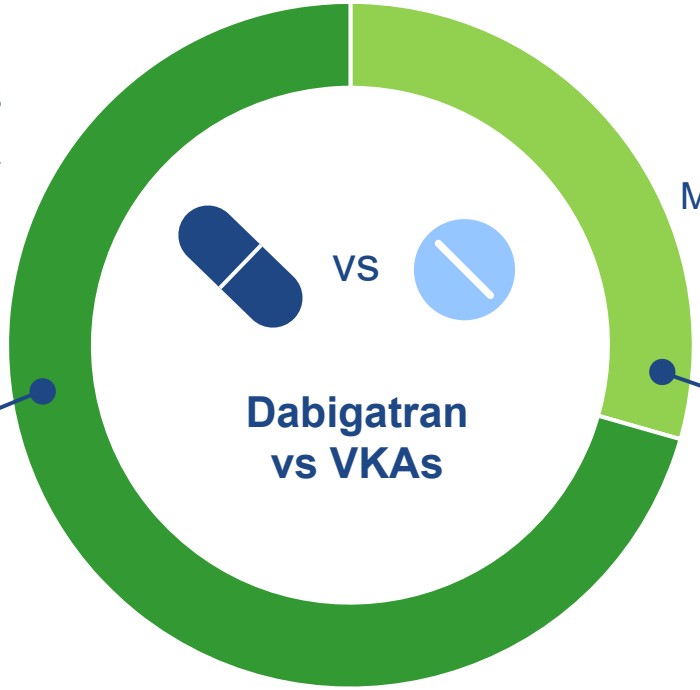
Major bleeding for dabigatran was

significantly reduced

vs VKAs in

71%

of analyses



Major bleeding for dabigatran was

similar

to VKAs in

29%

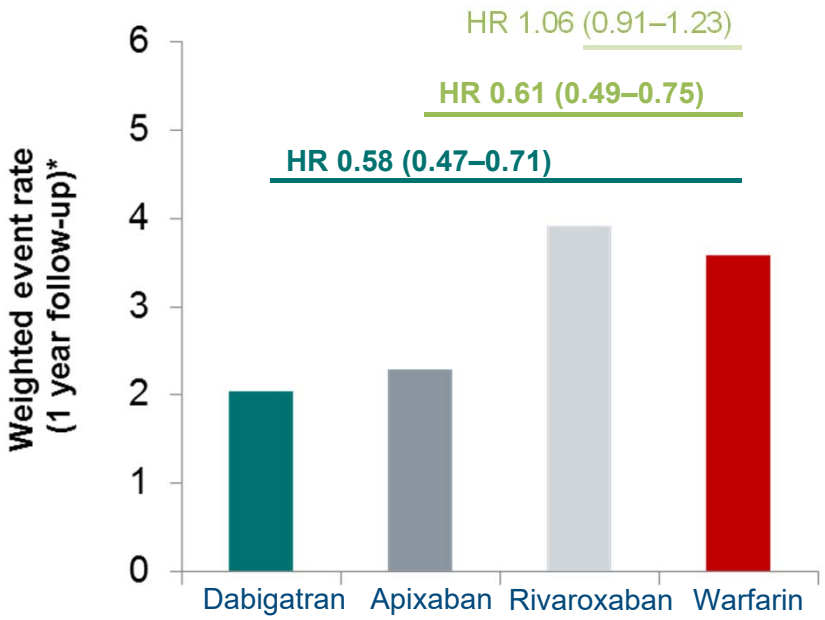
of analyses

Adeboyeje G et al. J Manag Care Spec Pharm 2017;23:968–78; Amin A et al. Curr Med Res Opin 2017;33:1595–604; Chan YH et al. Stroke 2016;47:441–9 Chan YH et al. J Am Coll Cardiol 2016;68:1389–401; Cottin Y et al. Poster presented at ESC 2017. Abstract P4021; Graham DJ et al. Circulation 2015;131:157–64; Halvorsen S et al. Eur Heart J CVP 2017;3:28–36; Hernandez I et al. Am J Cardiol 2017;120:1813–9 Hohnloser SH et al. Clin Res Cardiol 2017;106:618–28; Larsen TB et al. Am J Med 2014;127:650–6; Larsen TB et al. BMJ 2016;353:i3189 Lip GYH et al. JAMA Cardiol 2017;2:872–81; Lip GYH et al. Thromb Haemost 2016;116:975–86; Nielsen PB et al. BMJ 2017;356:j510 Seeger JD et al. Thromb Haemost 2015;114:1277–89; Villines TC et al. Thromb Haemost 2015;114:1290–8 ;Yao X et al. J Am Heart Assoc 2016;5:e003725

Risk of any Major Bleeding or Death with High-Dose NOAC vs Warfarin

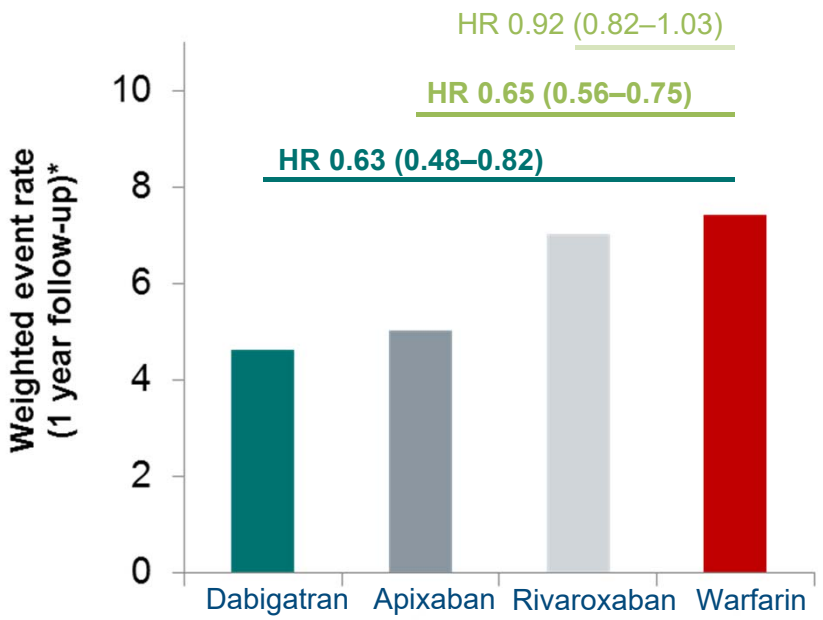
Major bleeding

Adjusted HR (95% CI) vs warfarin



All-cause mortality

Adjusted HR (95% CI) vs warfarin



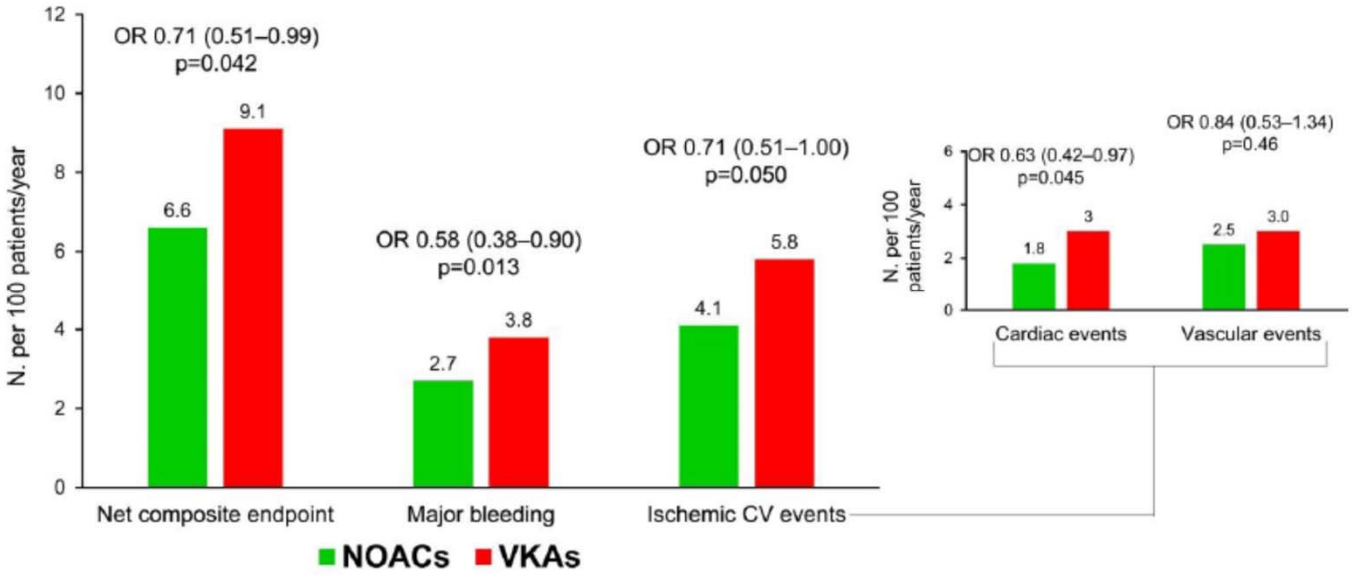
N=61,348

12 701 dabigatran; 6349 apixaban; 7192 rivaroxaban; 35 436 warfarin

Larsen TB, et al. BMJ 2016;353:i3189.

NOAC *vs* VKAs in Elderly Patients with AF

3,825 elderly patients were pooled
from the PREFER in AF and PREFER in AF PROLONGATION registries

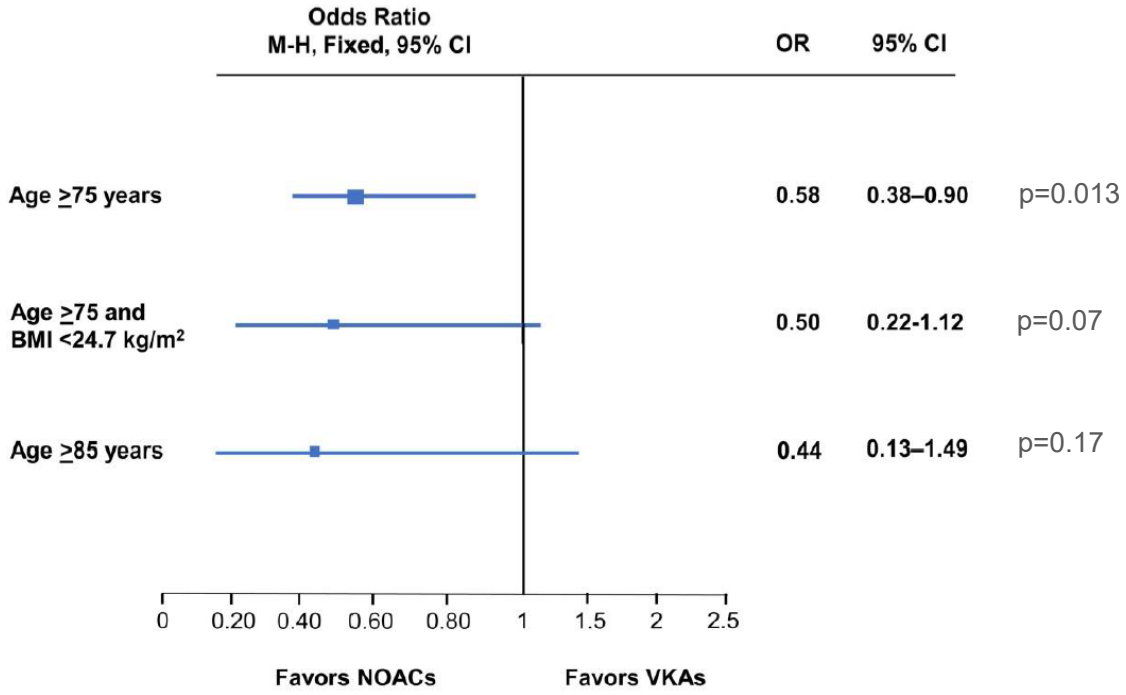


NOAC use was associated with a 42% lower incidence of major bleeding, mainly non-gastro-intestinal
(adjusted OR 0.78, CI 0.50-1.21; p=0.26)
There were nominally fewer ischemic CV events especially cardiac events, without difference in vascular complications

Patti G et al. Am J Med 2019

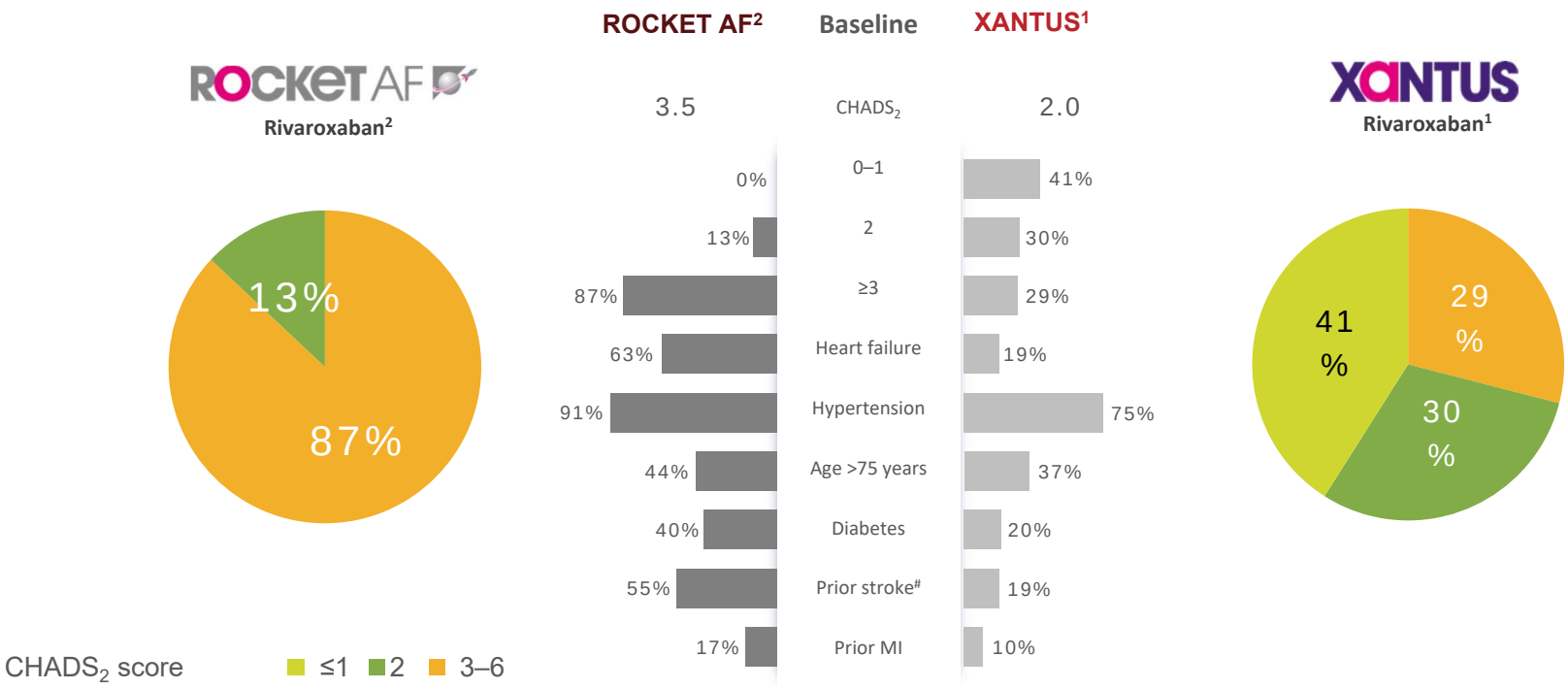
The clinical benefit of NOACs manteined in Elderly patients with low BMI and in Very Elderly patients

Adjusted odds ratios (OR) for major bleeding with NOACs versus VKAs in elderly patients (aged ≥75 years), elderly patients with BMI <24.7 kg/m2 and very elderly patients (aged ≥85 years)



Patti G et al. Am J Med 2019

Comparison of Main Outcomes: XANTUS versus ROCKET AF



1. Patel MR et al, N Engl J Med 2011;365:883;
2. Camm AJ et al, Eur Heart J 2016;37:1145

Comparison of Main Outcomes: XANTUS versus ROCKET AF

1. Patel MR et al, N Engl J Med 2011;365:883;
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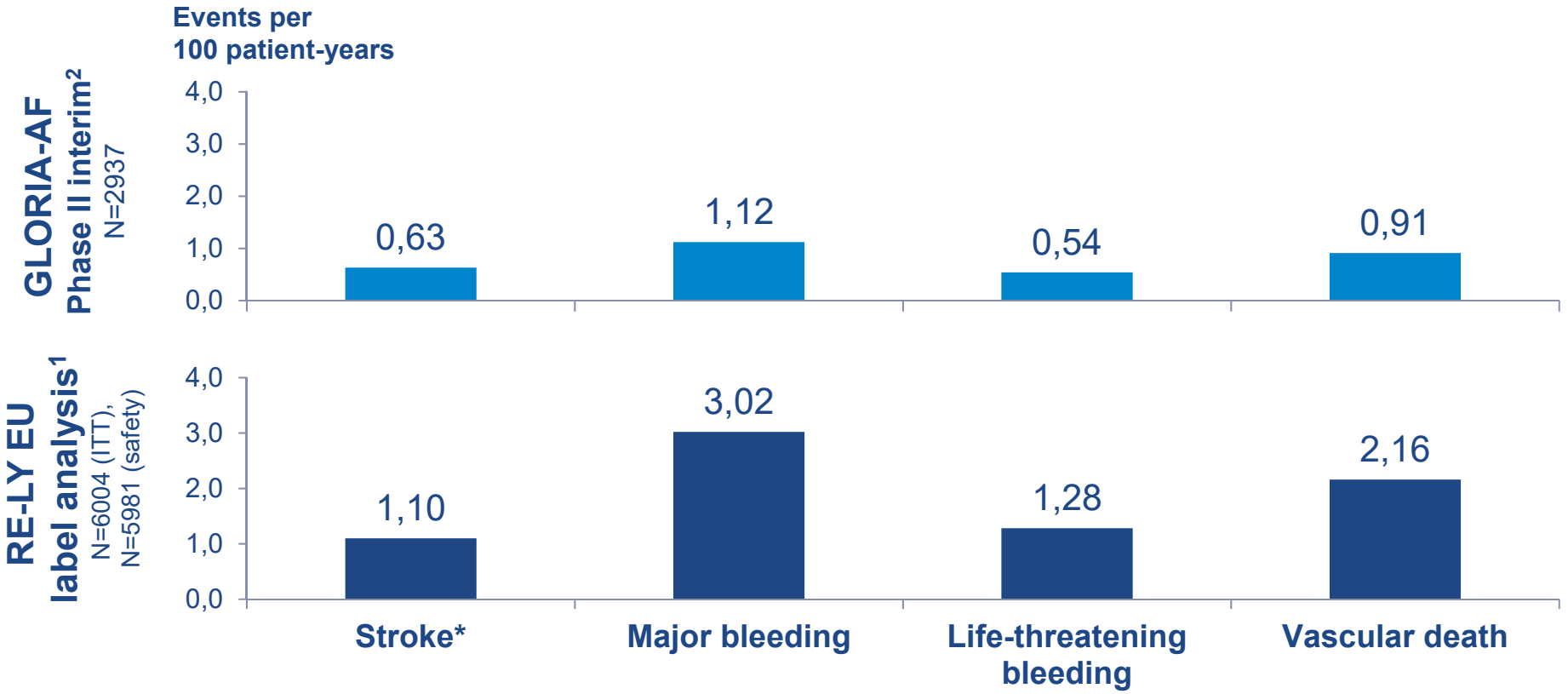
GLORIA-AF Data Confirm the Safety and Effectiveness of Dabigatran in the Real World



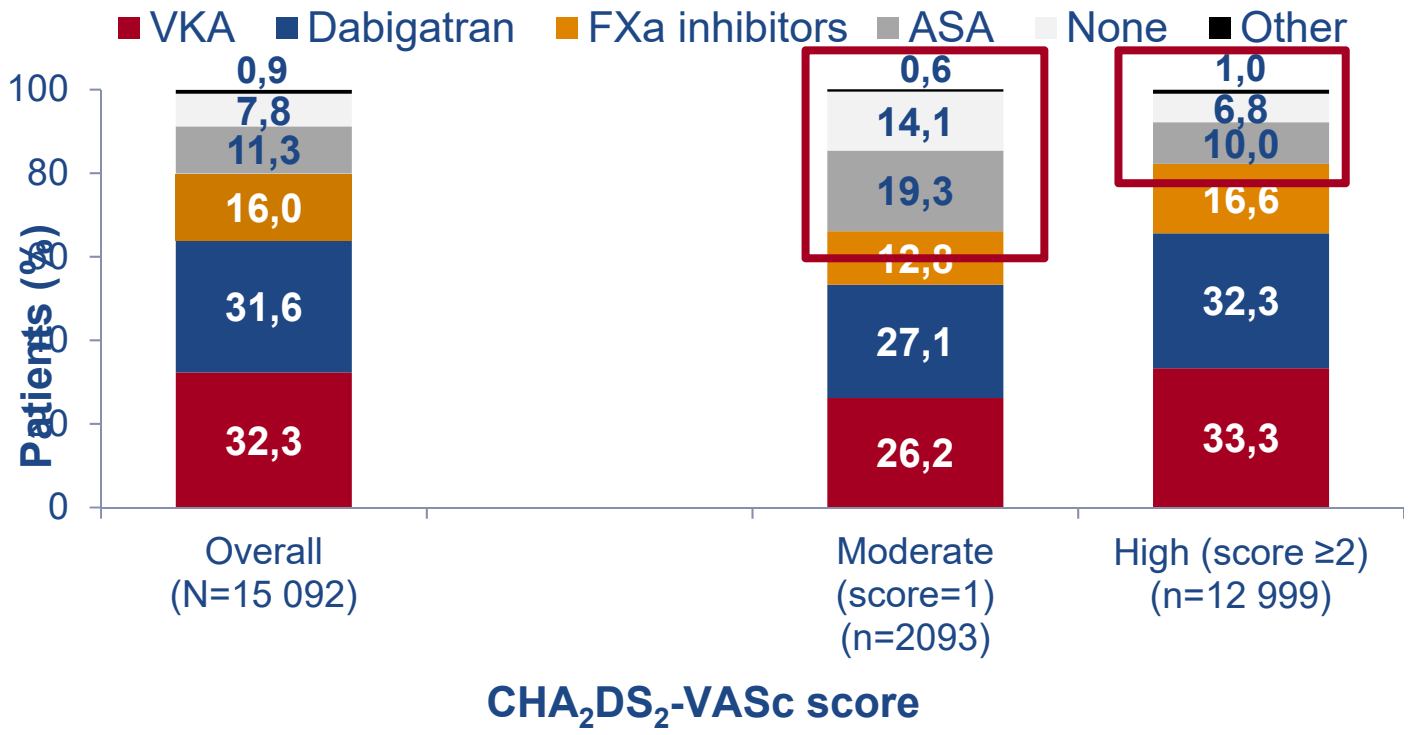
- In GLORIA-AF, where dabigatran is prescribed by physician choice, **stroke and bleeding rates were low** when compared with the RE-LY EU label post hoc analysis
- GLORIA-AF **confirms the sustained safety and effectiveness** of dabigatran over 2 years of follow-up

*Ischaemic stroke only in RE-LY analysis, ischaemic + haemorrhagic stroke in GLORIA-AF analysis

1. Lip et al. Thromb Haemost 2014; 2. Huisman et al. ESC 2016

GLORIA-AF Phase II: 34% of patients at moderate risk and 18% at high risk of stroke did not receive any OAC

Patients enrolled between Nov 2011 and Dec 2014



FXa inhibitors: rivaroxaban, apixaban, or edoxaban. ASA, acetylsalicylic acid; Huisman et al. J Am Coll Cardiol 2017

AF Pts with Acute Ischemic Stroke not Receiving Adequate Therapeutic Anticoagulation

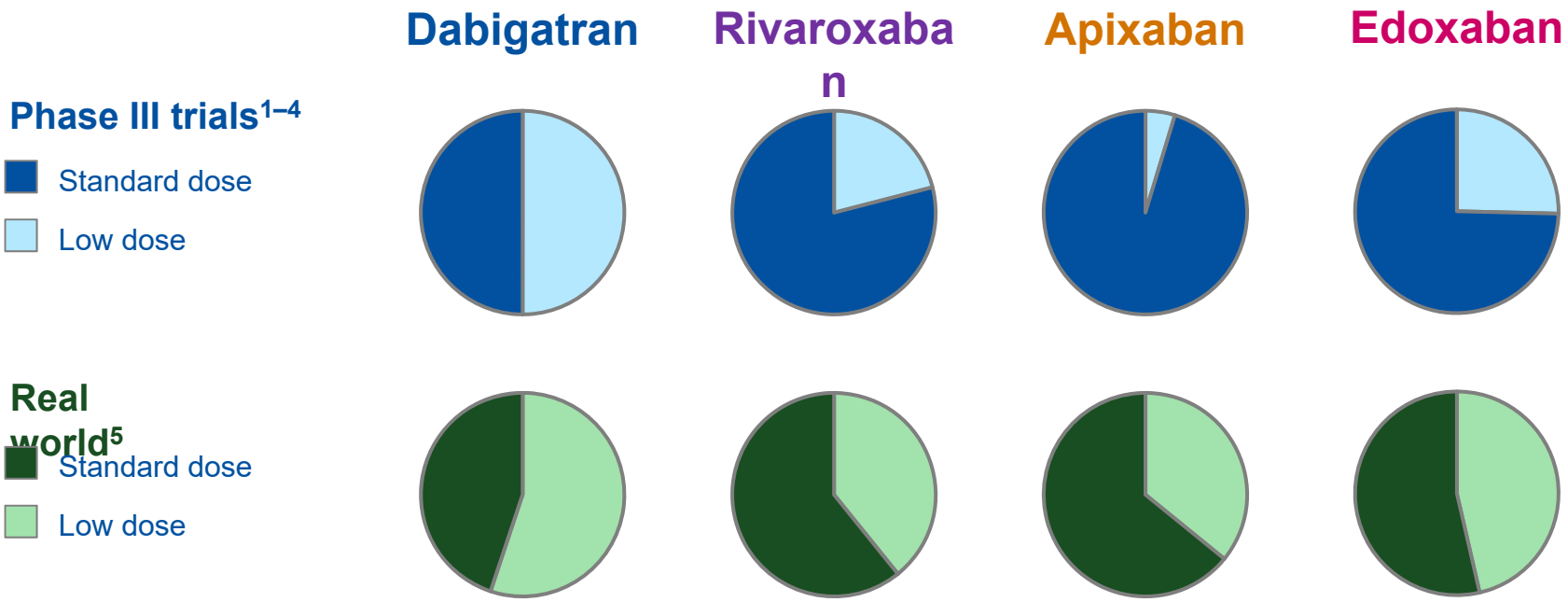
Retrospective analysis of >90 000 patients with AF who experienced acute ischemic stroke

Get With The Guidelines-Stroke program in >1600 hospitals in the USA (Oct 2012–March 2015)

*No antithrombotic treatment; antiplatelet therapy only, or subtherapeutic warfarin anticoagulation (INR <2) at the time of stroke

Xian et al. JAMA 2017

Are Patients with AF Underdosed in the Real World?

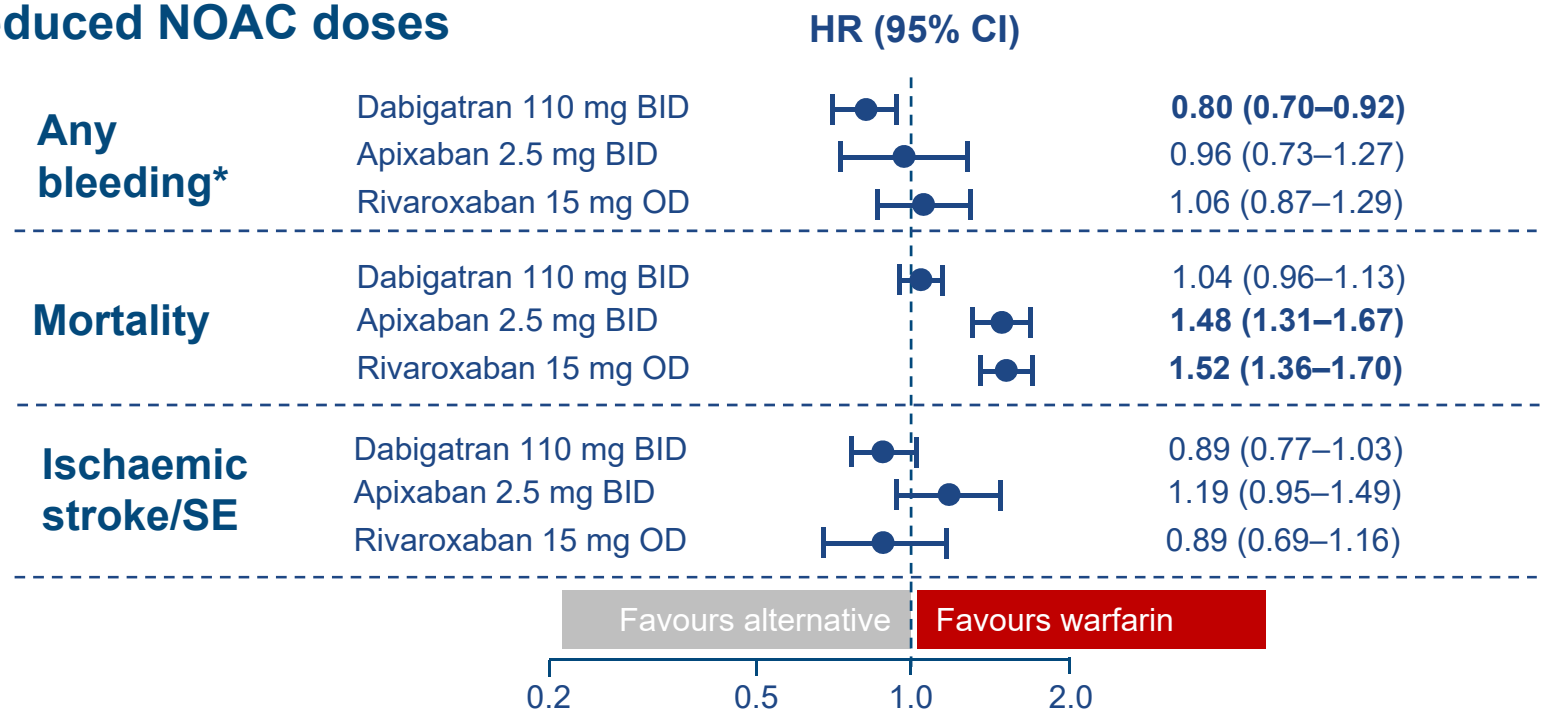


'The right dose needs to be prescribed for the right patient in order to obtain, in real-life practice, the benefits of NOACs that have been demonstrated in RCTs'[6]

1. Connolly et al. N Engl J Med 2009; 2. Fox et al. Eur Heart J 2011; 3. Granger et al. N Engl J Med 2011; 4. Giugliano et al. N Engl J Med 2013; 5. IMS MIDAS data from Q1 2018 from all countries for which data were available; 6. Dillinger et al. Arch Cardiovasc Dis 2018

Effectiveness and Safety of *Reduced Dose* NOAC and Warfarin in AF

Safety and Effectiveness at one-year follow-up
Reduced NOAC doses



N=61,348

*Haemorrhagic stroke, major gastrointestinal bleeding; SE, systemic embolism; Propensity-weighted cohort study of three nationwide Danish registries of OAC-naïve patients with AF, safety outcomes at one year follow-up; dabigatran 110 mg BID, n=8875; apixaban 2.5 mg BID, n=4400; rivaroxaban 15 mg OD, n=3476; warfarin, n=38 893

Nielsen PB, et al. BMJ 2017;356:j510

Summary

- Real-world evidence complements data from RCTs, providing insights into treatment outcomes in everyday clinical practice and varied settings
- Real-world evidence confirms the safety and efficacy profile of NOACs over VKAs, even in frail subgroups
- Underuse and underdosing of anticoagulants may leave patients at risk of stroke