

# Real life NOAC data: zinloze publicaties om snel te vergeten

## CONTRA

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# Disclosures for Freek W. A. Verheugt

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Research support/ principal investigator	Bayer HealthCare, Boehringer Ingelheim, Eli Lilly and Roche
Consultant	Bayer Healthcare, Eli Lilly, Daiichi-Sankyo, and Merck
Speakers' bureau	none
Honoraria	Bayer Healthcare, Eli Lilly, Daiichi-Sankyo and Merck
Scientific advisory board	AstraZeneca

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# Stelling

**Table 1. Shortcomings of Randomized Trials, Meta-Analyses, Registries, and Guidelines**

Method	Shortcomings
Randomized trial	Selection bias Generalizability
Meta-analysis	Publication bias Overestimation of treatment effect
Registry	Confounding bias
Guideline	Meta-analyses used as high level of evidence

# Wetenschappelijk bewijs

**Wat werkt in randomized controlled trials (RCTs), moet ook werken in “real life” (registries)**

# Wetenschappelijk bewijs m.b.t. NOACs

RCTs NOAC vs VKA

Registries NOAC vs VKA

Registries NOAC vs NOAC

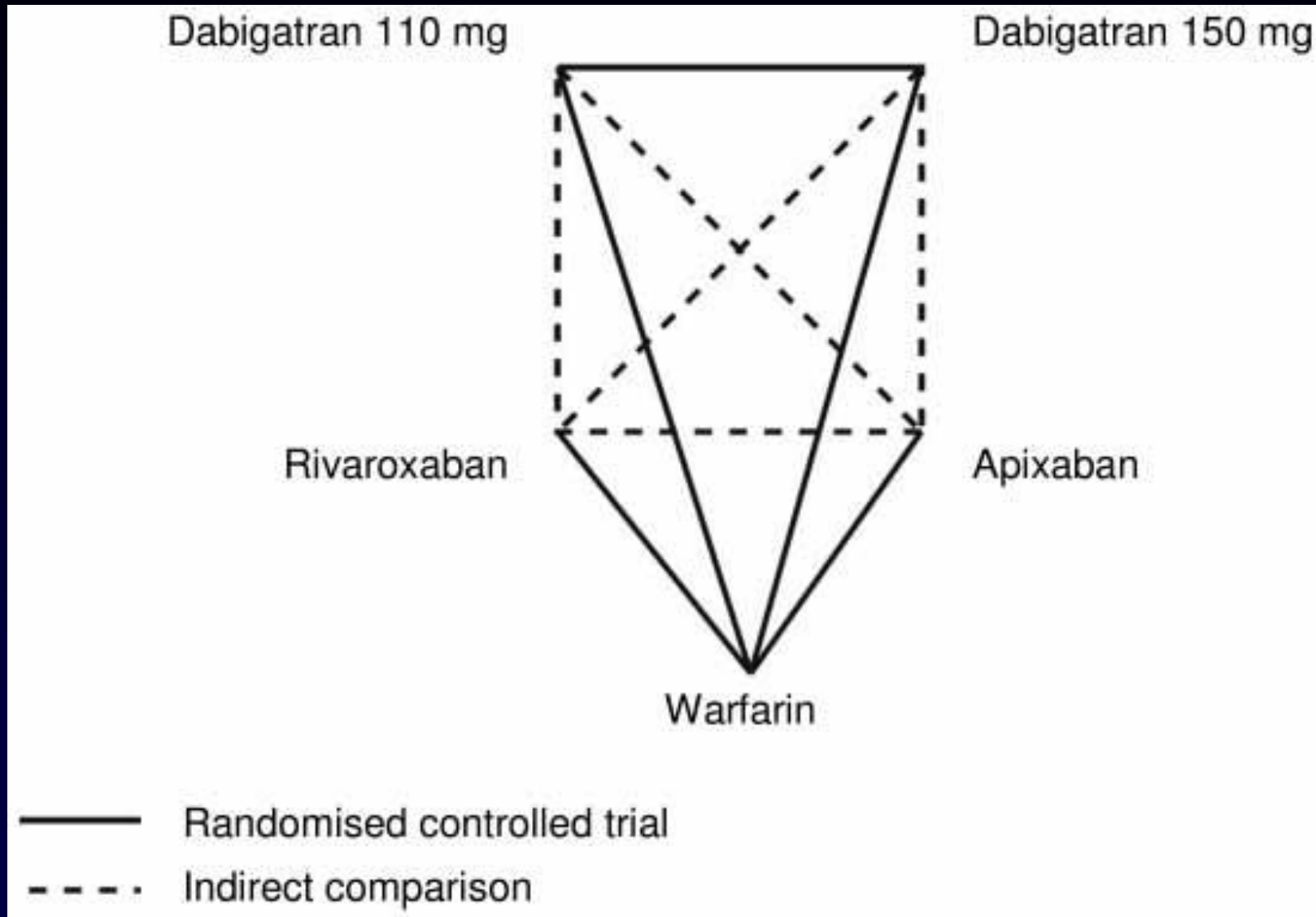
# Wetenschappelijk bewijs m.b.t. NOACs

RCTs NOAC vs VKA

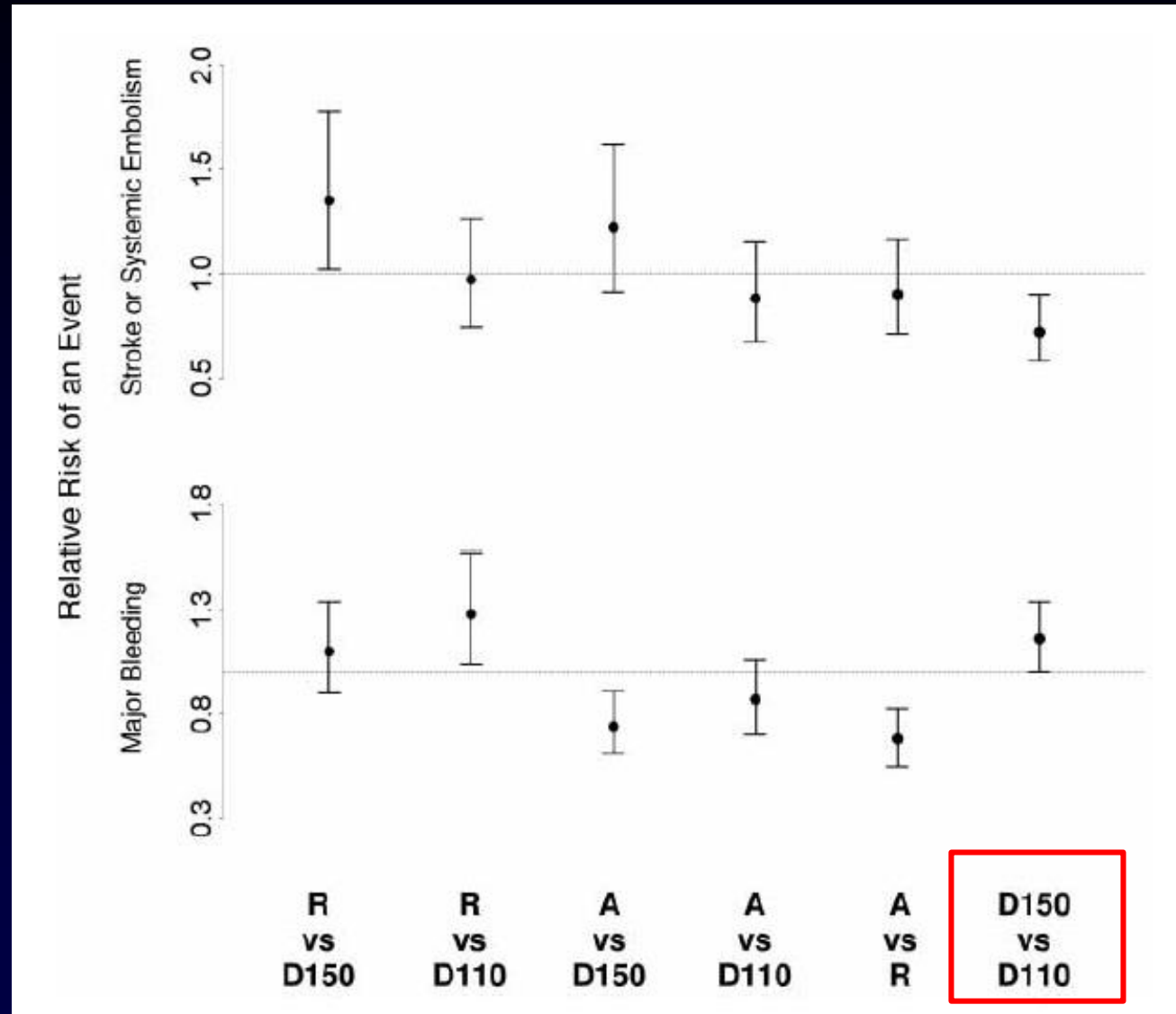
Registries NOAC vs VKA

Registries NOAC vs NOAC

# Network Meta-analysis



# Network Meta-analysis





# Wetenschappelijk bewijs m.b.t. NOACs

RCTs NOAC vs VKA

Registries NOAC vs VKA

Registries NOAC vs NOAC

# Safety of Dabigatran vs VKA in the USA

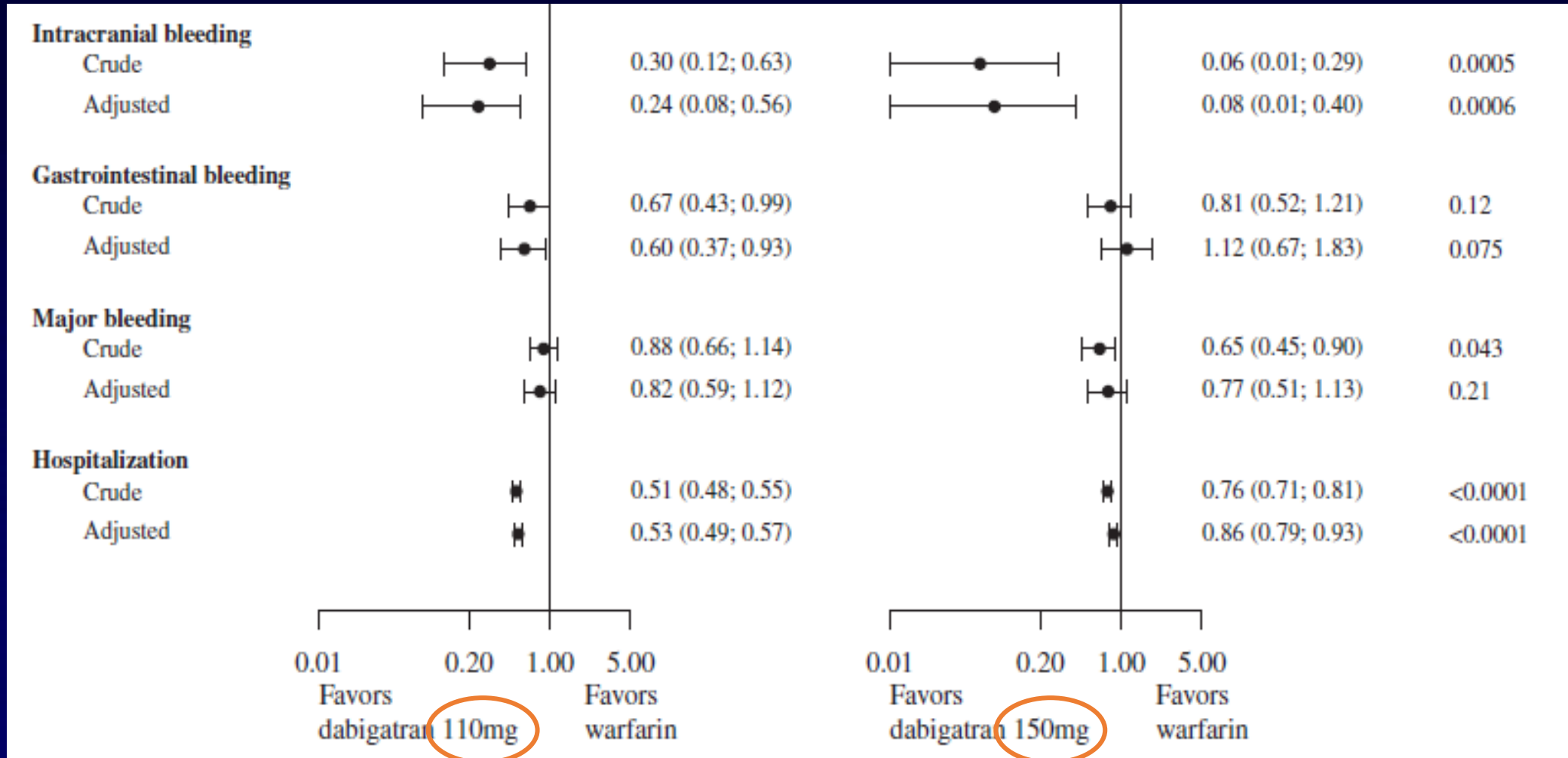
(FDA Sentinel, 6 months, n = 12,195)

**Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.\***

Analysis	Dabigatran			Warfarin		
	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)
<b>Gastrointestinal hemorrhage</b>						
Analysis with required diagnosis of atrial fibrillation	10,599	16	1.6	43,541	160	3.5
Sensitivity analysis without required diagnosis of atrial fibrillation	12,195	19	1.6	119,940	338	3.1
<b>Intracranial hemorrhage</b>						
Analysis with required diagnosis of atrial fibrillation	10,587	8	0.8	43,594	109	2.4
Sensitivity analysis without required diagnosis of atrial fibrillation	12,182	10	0.9	120,020	204	1.9

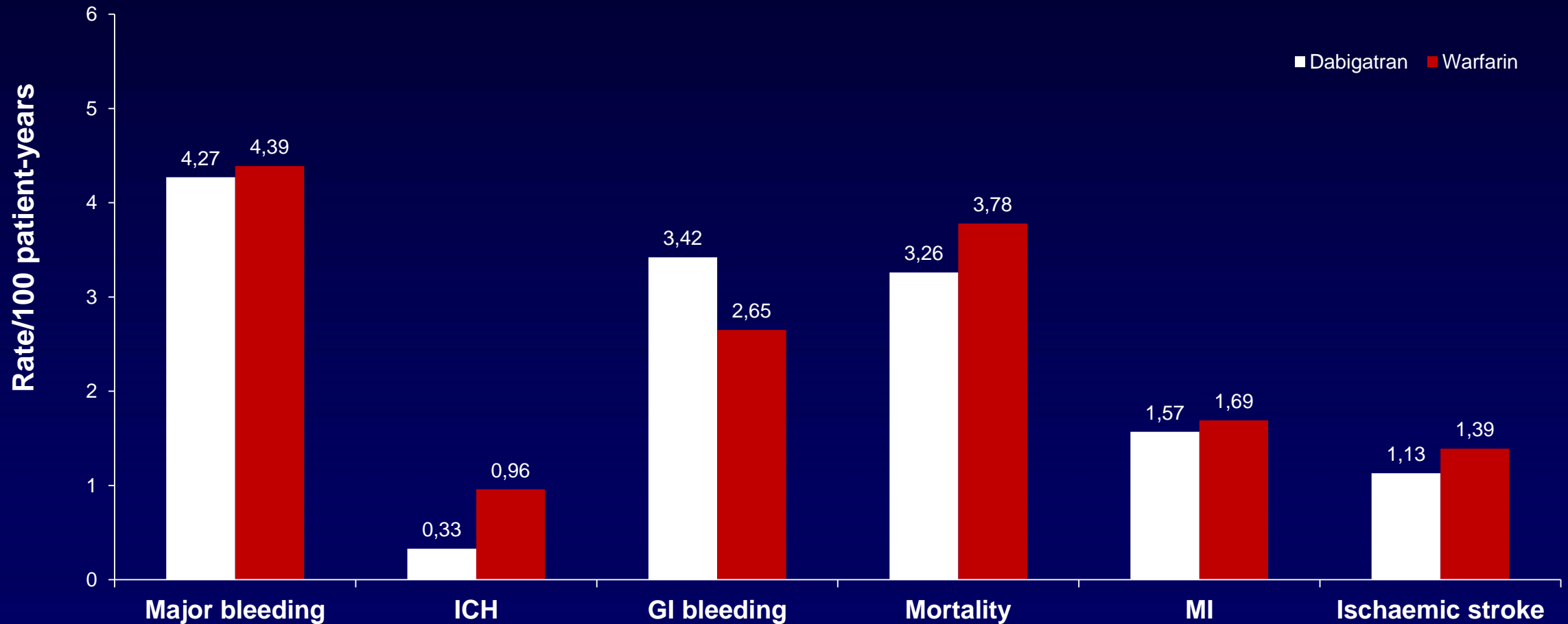
# Safety of Dabigatran vs VKA in Denmark

(National Registry, 11 months, n = 13,914)



# Safety and Efficacy of Dabigatran vs VKA in the USA

(Medicare, n = 134,414, 37,454 ptyrs)



Graham DJ. Circulation 2014;131:157-164

Onze Lieve Vrouwe Gasthuis, Amsterdam

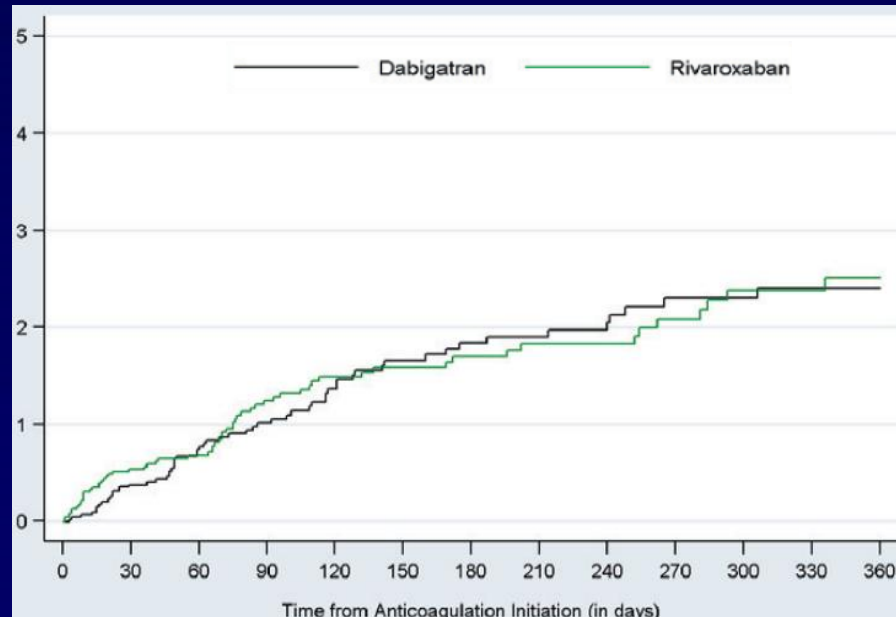
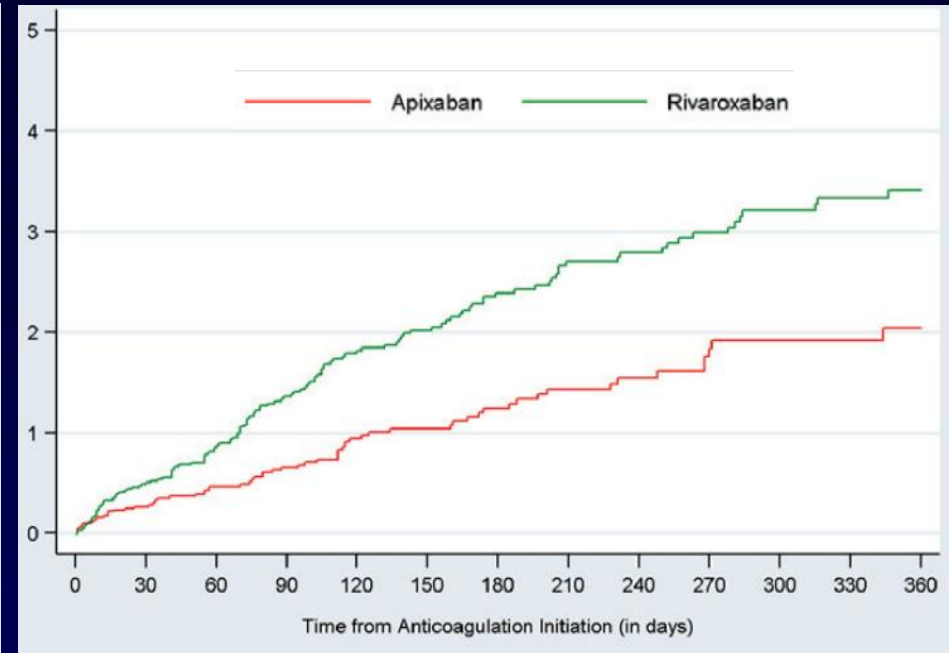
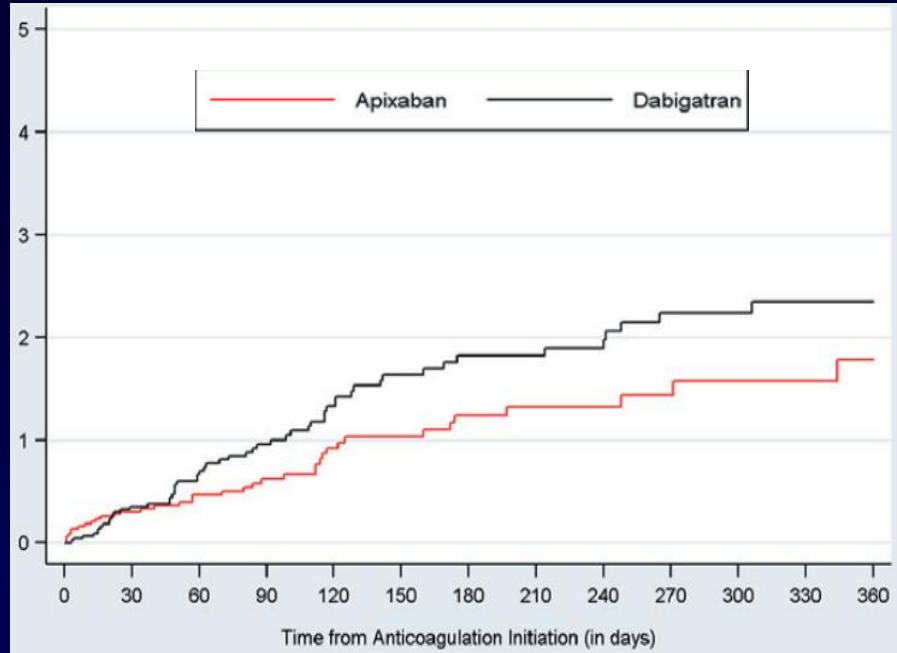
# Wetenschappelijk bewijs m.b.t. NOACs

RCTs NOAC vs VKA

Registries NOAC vs VKA

Registries NOAC vs NOAC

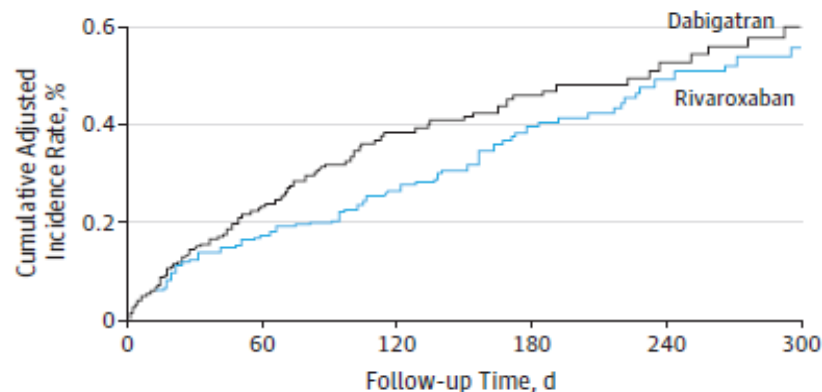
# % Major Bleeding NOAC vs NOAC after Propensity Matching in the USA (n =29,900)



*Lip GY. Thromb Haemost 2016;116:975-986*

# NOAC vs NOAC after Propensity Matching in Medicare

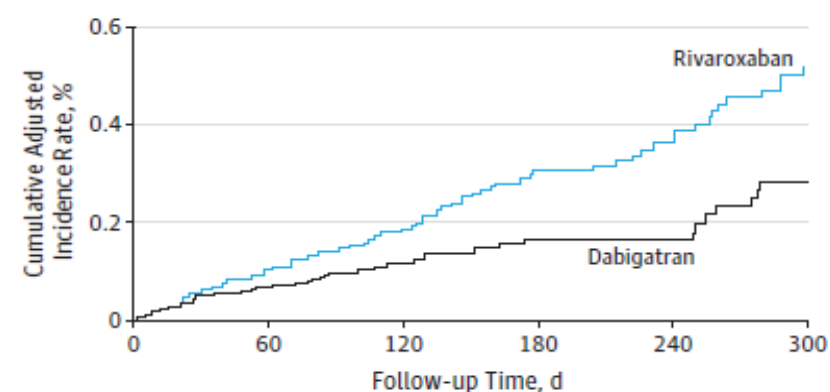
**A** Thromboembolic stroke



Weighted No.  
at risk

Dabigatran	52264	26729	13355	9236	6156	4384
Rivaroxaban	66630	35707	19527	12947	8511	5753

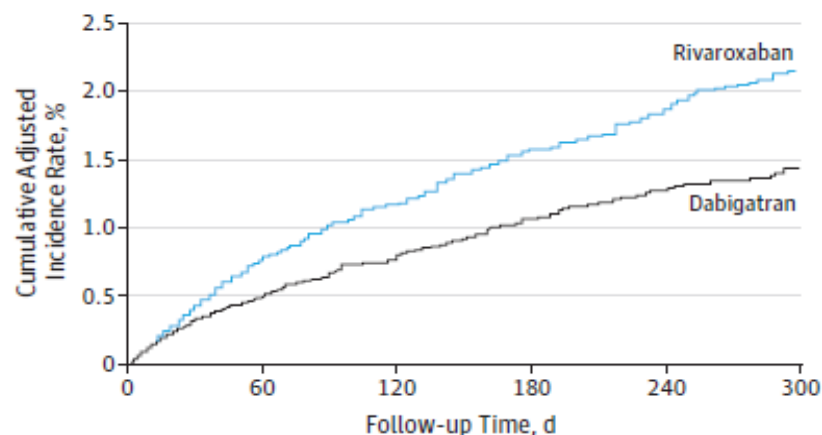
**B** Intracranial hemorrhage



Weighted No.  
at risk

Dabigatran	52264	26729	13355	9236	6156	4384
Rivaroxaban	66630	35707	19527	12947	8511	5753

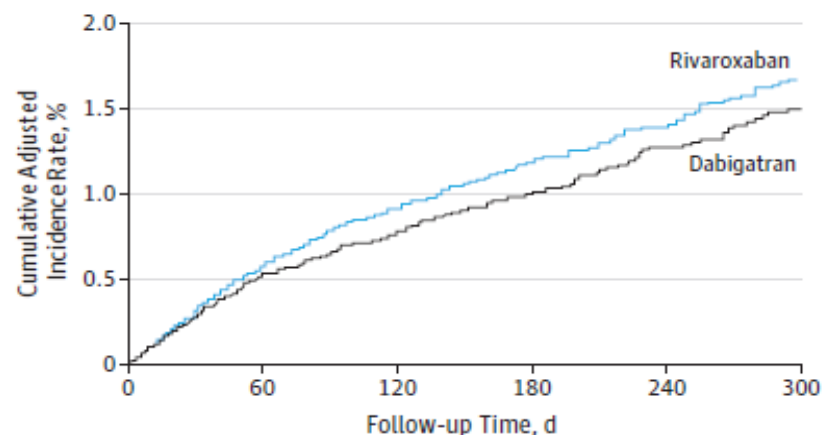
**C** Major gastrointestinal bleeding



Weighted No.  
at risk

Dabigatran	52264	26729	13355	9236	6156	4384
Rivaroxaban	66630	35707	19527	12947	8511	5753

**D** Death



Weighted No.  
at risk

Dabigatran	52264	26824	13389	9260	6165	4393
Rivaroxaban	66630	35905	19593	12996	8542	5767

# Wetenschappelijk bewijs

**Geen head-to head vergelijkende trials bekend, maar zullen zeker komen. Bloedingen zouden het primaire eindpunt moeten zijn**



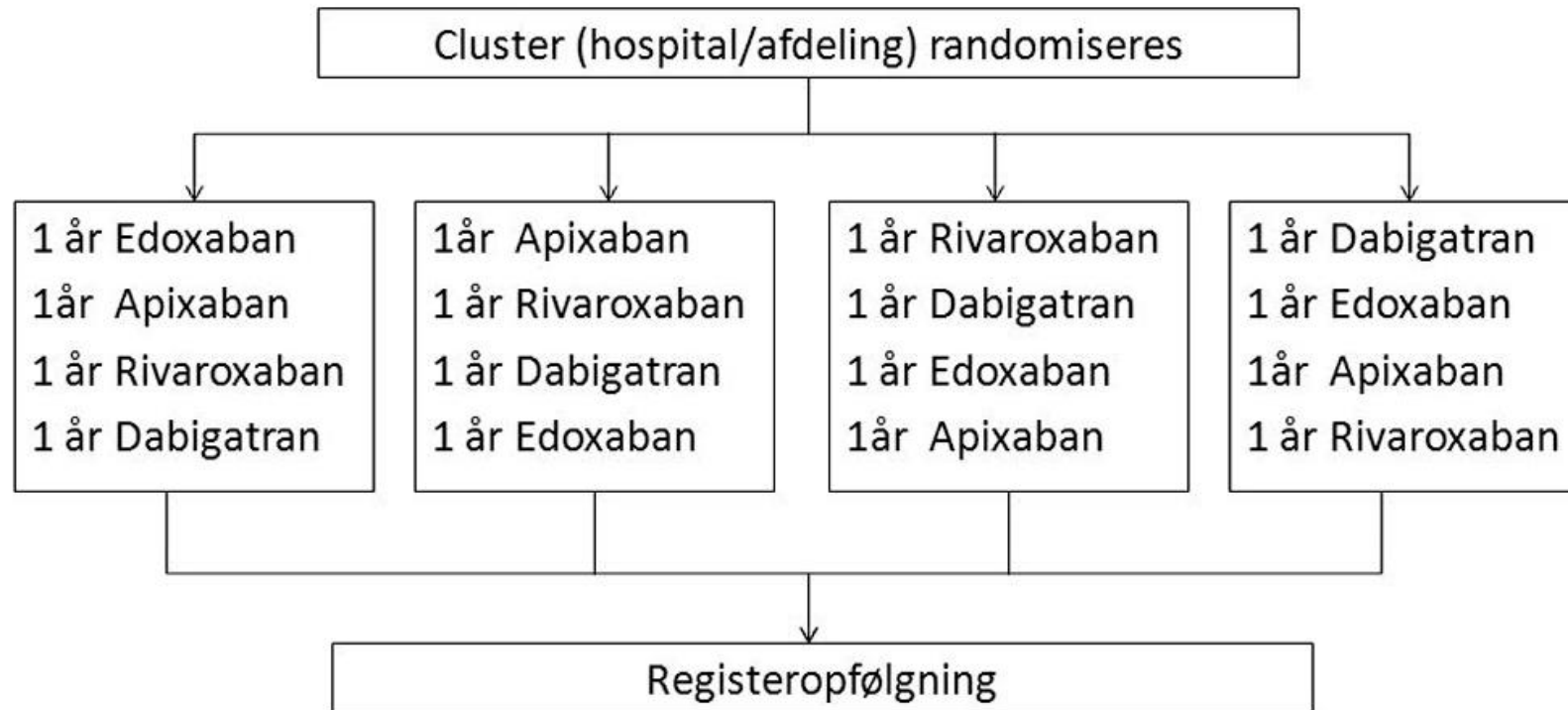
# DANNOAC-AF (n =11,000)

NTC 03129490

## Metode



2 years {



## Primaire effectiviteits eindpunt

Stroke, systemische embolie, myocardinfarct of totale sterfte

## Secundair eindpunten

Ziekenhuisopname wegens bloeding, of de primaire eindpunten  
ieder afzonderlijk

## Wetenschappelijk bewijs

### Antithrombotic Treatment Patterns in Patients with Newly Diagnosed Nonvalvular Atrial Fibrillation: The GLORIA-AF Registry, Phase II



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**AJM 2015;128:1306-1313**

### The Changing Landscape for Stroke Prevention in AF



#### Findings From the GLORIA-AF Registry Phase 2

Menno V. Huisman, MD, PhD,<sup>a</sup> Kenneth J. Rothman, Dr PH,<sup>b</sup> Miney Paquette, MSc,<sup>c</sup> Christine Teutsch, MD,<sup>d</sup> Hans-Christoph Diener, MD,<sup>e</sup> Sergio J. Dubner, MD,<sup>f</sup> Jonathan L. Halperin, MD,<sup>g</sup> Chang Sheng Ma, MD,<sup>h</sup> Kristina Zint, PhD,<sup>i</sup> Amelie Elsaesser, PhD,<sup>j</sup> Dorothee B. Bartels, PhD,<sup>k,l</sup> Gregory Y.H. Lip, MD,<sup>m</sup> on behalf of the GLORIA-AF Investigators

**JACC 2017;69:777-785**

# Conclusies

1. In de 4 grote RCTs blijken NOACs veiliger en non-inferior t.o.v. VKA bij de preventie van ischemische beroerte bij AF
2. In “real life” blijken registries mét hun inherente tekortkomingen dit ook aan te tonen in Denemarken en USA
3. Máár, vergelijkingen tussen NOACs in registries gaan mank aan hun inherente confounding by indication, en zijn dus niet betrouwbaar
4. Dus, direct vergelijkende RCTs tussen NOACs bij AF zijn dringend nodig, waarbij de nadruk op bloedingen moet komen te liggen