

**BLEEDING IN PATIENTS WITH  
ATRIAL FIBRILLATION  
TREATED WITH  
WARFARIN, DABIGATRAN OR  
RIVAROXABAN:  
A POPULATION-BASED STUDY**

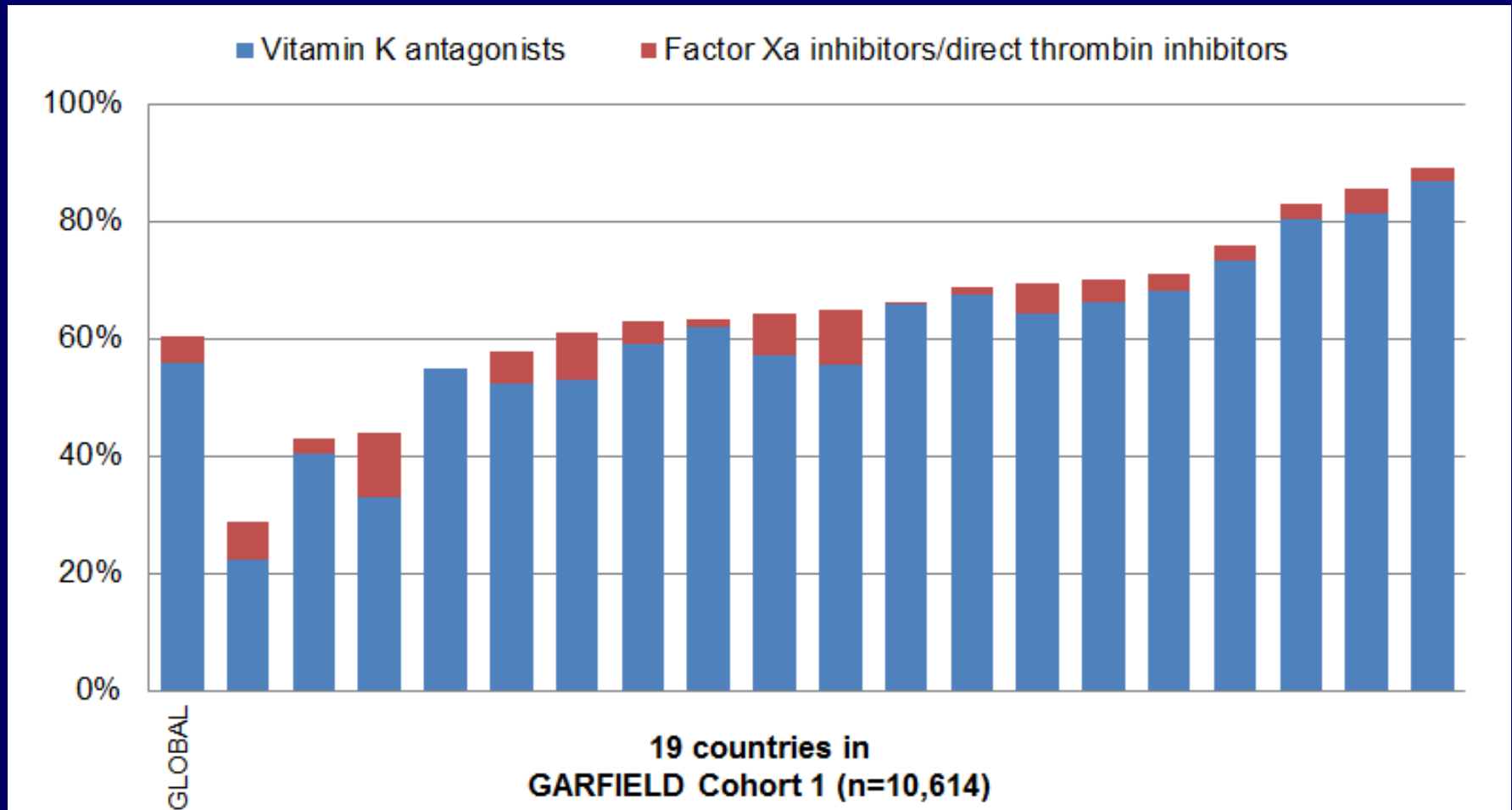
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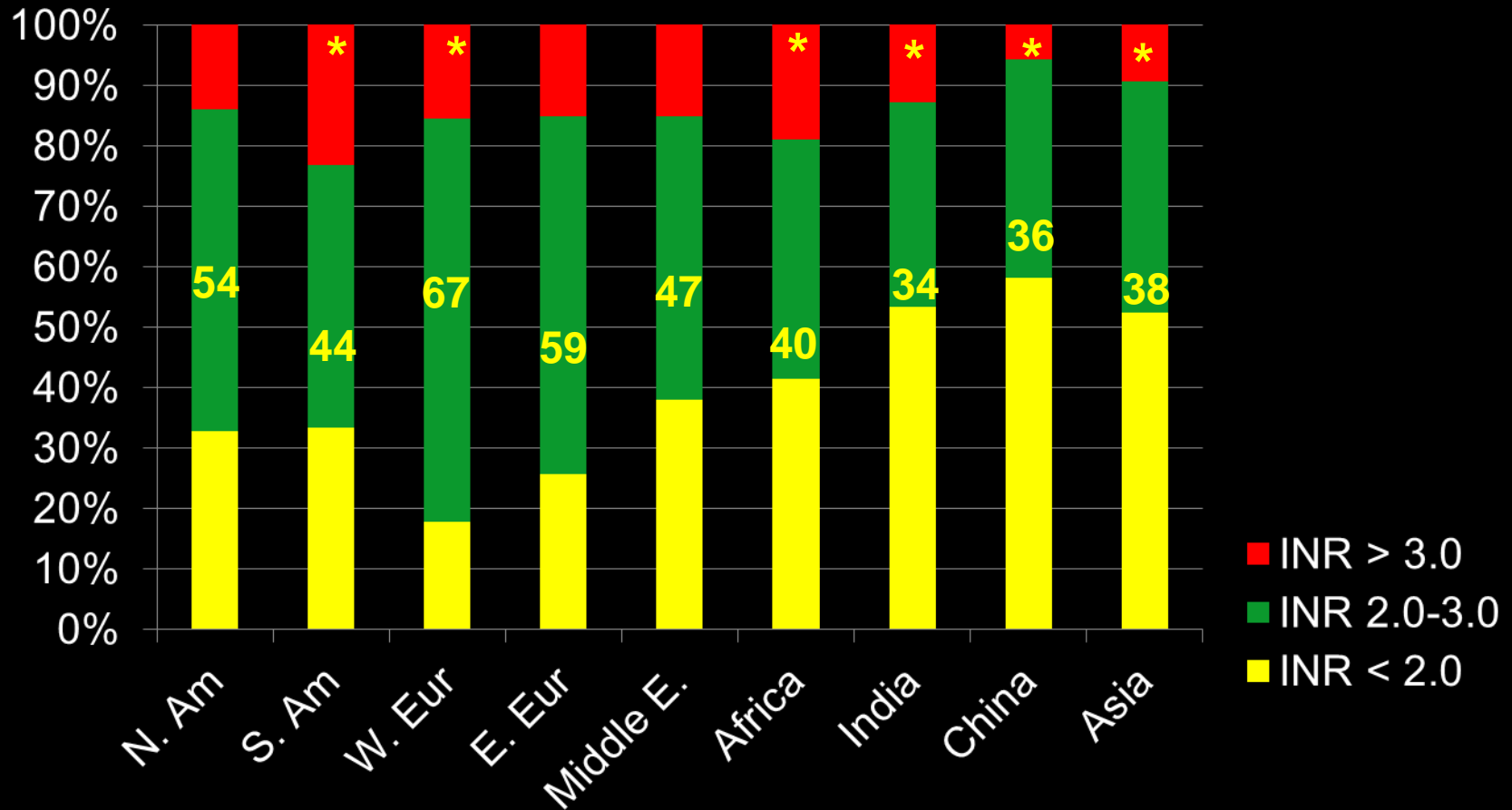
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# Anticoagulation in atrial fibrillation: the global GARFIELD Registry



# INR Control by Region

Based on three most recent INR values (%)



\*  $P \leq 0.005$  vs. N. America

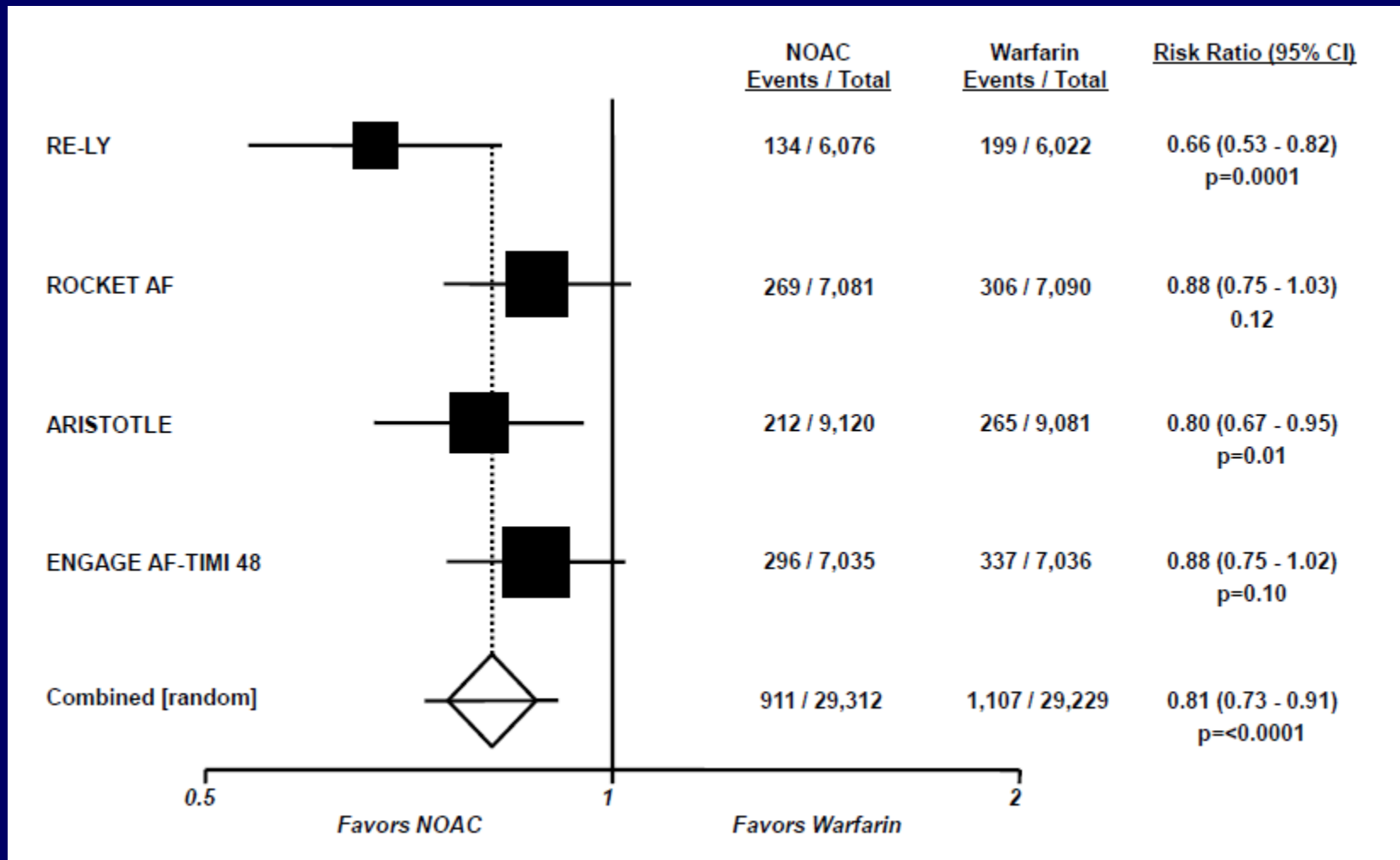
# Novel oral anticoagulants (NOACs)

	<b>Apixaban</b>	<b>Rivaroxaban</b>	<b>Dabigatran</b>
<b>Brand name</b>	<b>Eliquis</b>	<b>Xarelto</b>	<b>Pradaxa</b>
<b>Target</b>	<b>Factor Xa</b>	<b>Factor Xa</b>	<b>Factor IIa</b>
<b>T max, h</b>	<b>1-3</b>	<b>2-4</b>	<b>1.25-3</b>
<b>Half-life, h</b>	<b>8-15</b>	<b>9-13</b>	<b>12-14</b>
<b>Renal</b>	<b>25%</b>	<b>60%</b>	<b>80%</b>



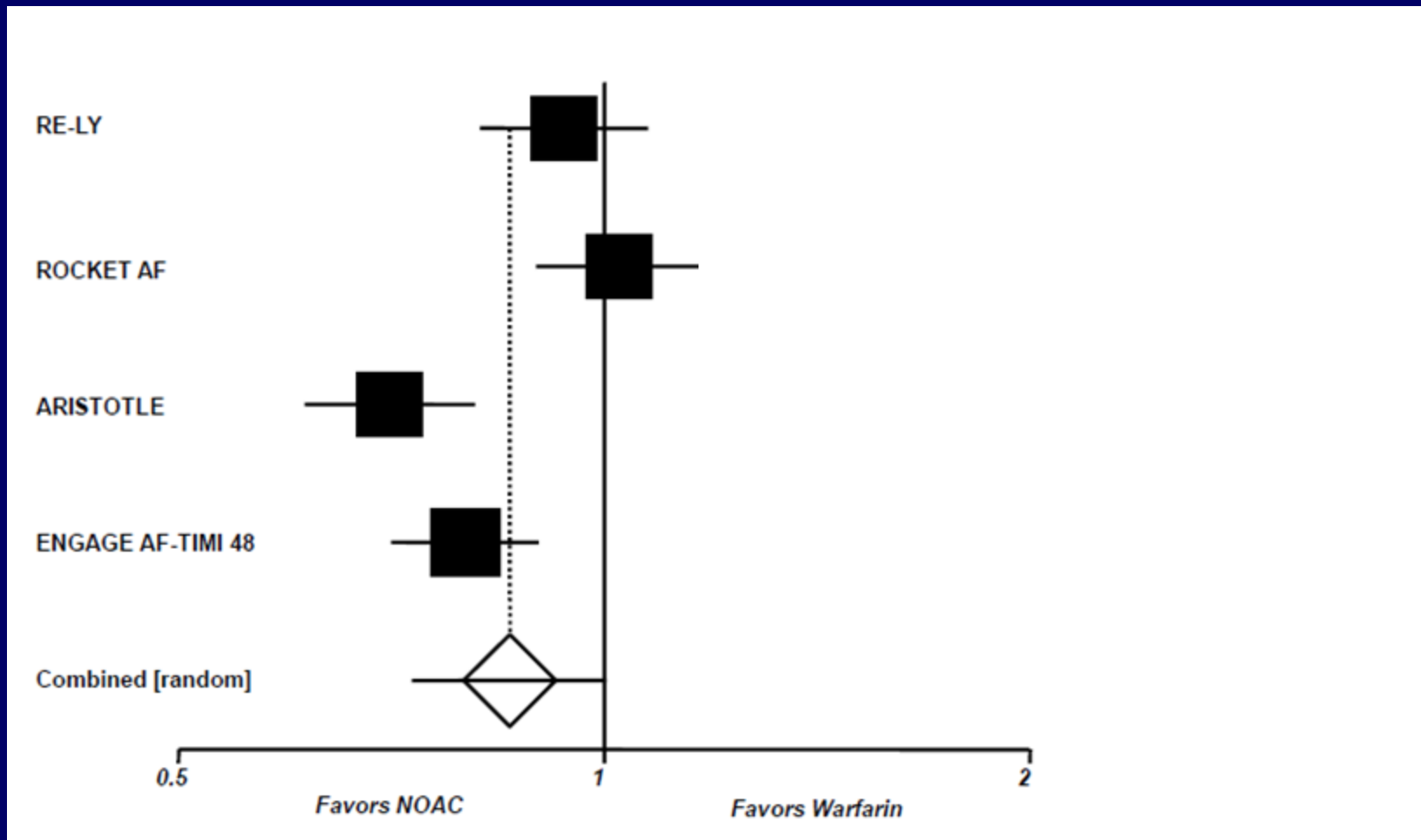
# Meta-analysis: NOAC higher doses

## Stroke or systemic embolism



# Higher doses of NOACs vs warfarin

## Major bleeding



# RCTs vs “Real-world” use

- Patient selection
- Relative risk reduction vs. absolute risk reduction
- Personalized approach recommended

Israel:

Dabigatran 150 mg bid – standard dose

Dabigatran 110 mg bid - older patients, high  
bleeding risk

(Clalit Health Services Pharmacopoeia)

# Aims

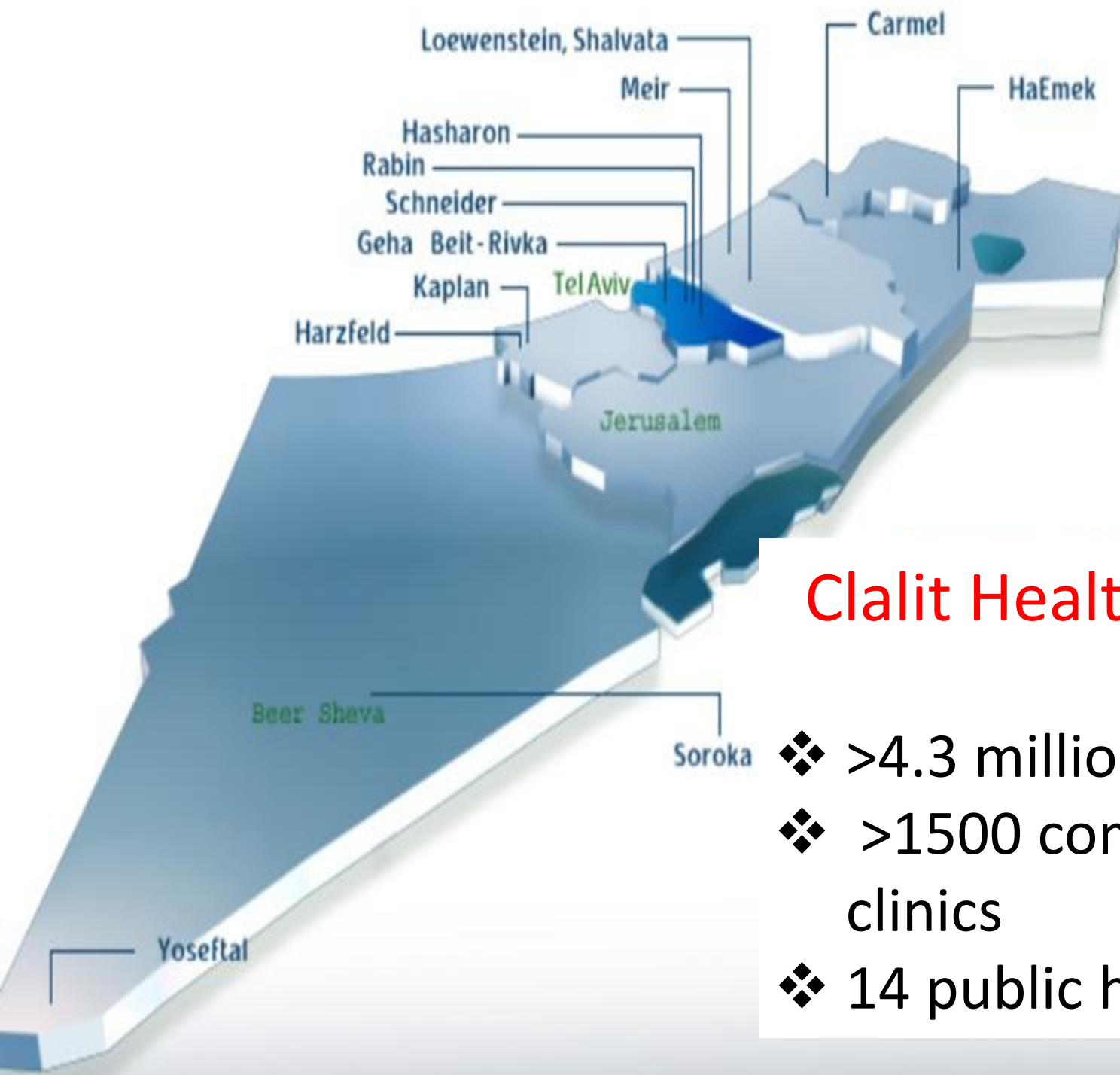
## Primary

- Determine the rates for major bleeding in “real-world” patients with AF beginning treatment with dabigatran, rivaroxaban or warfarin

## Secondary

- Determine the organ-specific pattern of bleeding





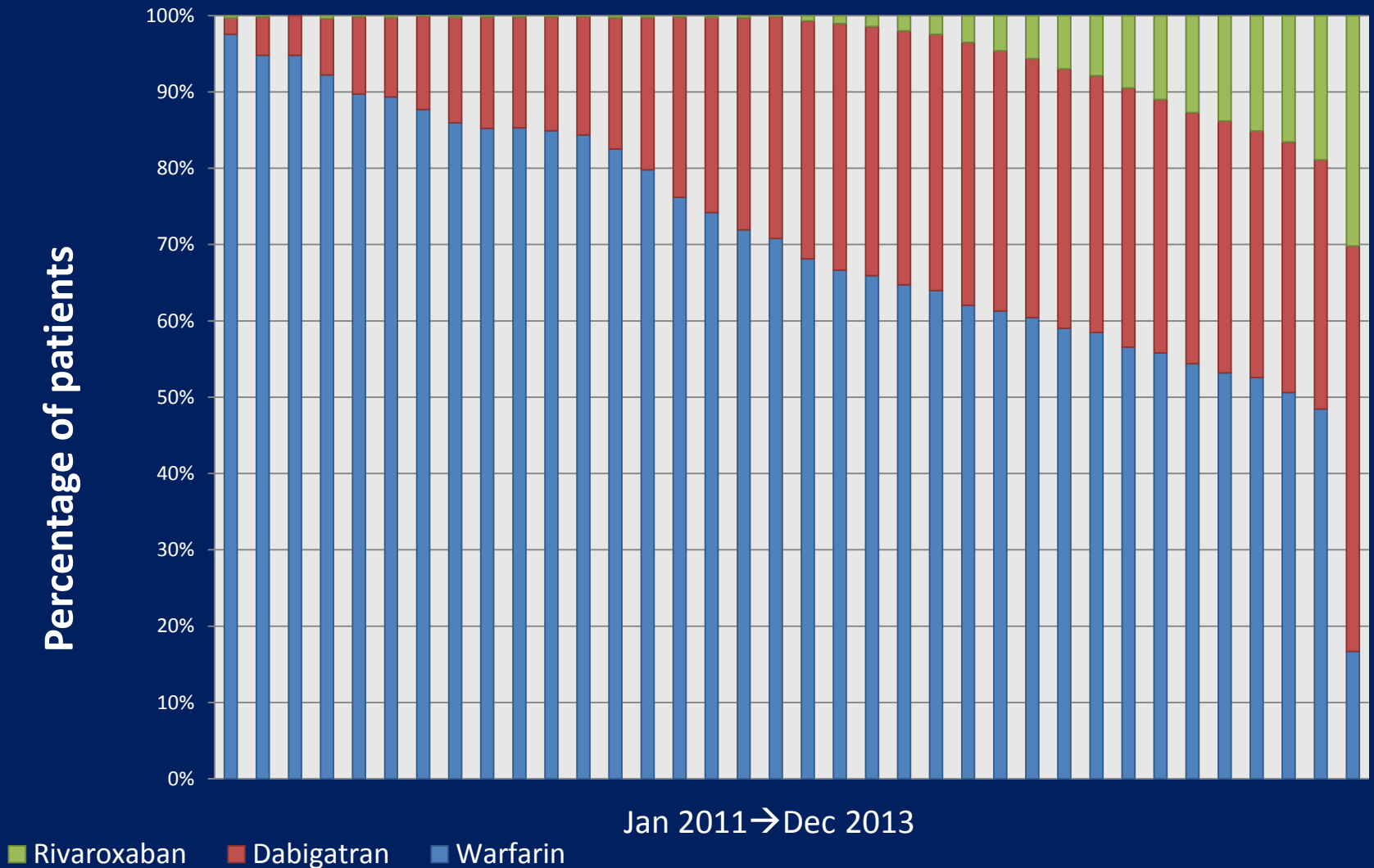
## Clalit Health Services

- ❖ >4.3 million members
- ❖ >1500 community clinics
- ❖ 14 public hospitals

# Methods

- Consecutive, unselected patients initiating anticoagulation for AF from 1/2011 to 12/2013
- Charts of patients hospitalized because of bleeding (= bleeding endpoint) reviewed
- Bleeding events calculated as rate per 100 patient-years of treatment
- Organ specific bleeding calculated as rate per 100 patient-years of treatment

# Percentage of patients beginning anticoagulants during study period



# Demographic and clinical features

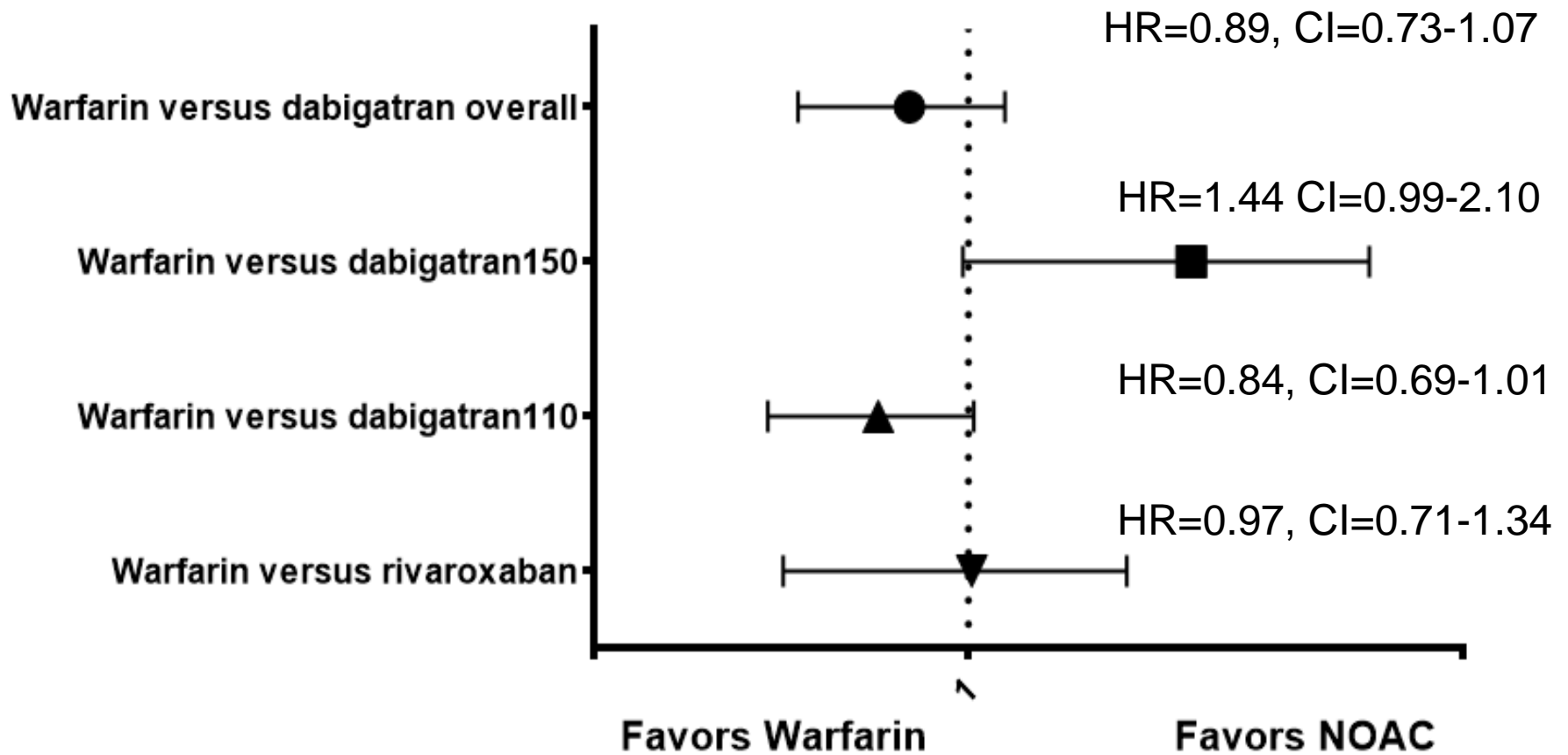
## N=18249

	Warfarin	Dabigatran150	Dabigatran110	Rivaroxaban
Patients (N)	9564	1806	4170	2709
Patient-years	9451	1079	3215	1086
Age in years Median (Range)	79 (27-99)	78 (52-89)	82 (55-95)	82 (58-91)
Women (%)	43.8	45.1	47	38.6
CHADS <sub>2</sub> score Median (Range)	3 (0-6)	3 (1-6)	4 (2-6)	4 (2-6)
Serum creatinine mg/dL Median (Range)	1.2 (0.3-11.6)	1.0 (0.5-4.4)	1.2 (0.5-4.1)	1.3 (0.5-3.5)
Anti platelet drug use (%)	52	50	35	55

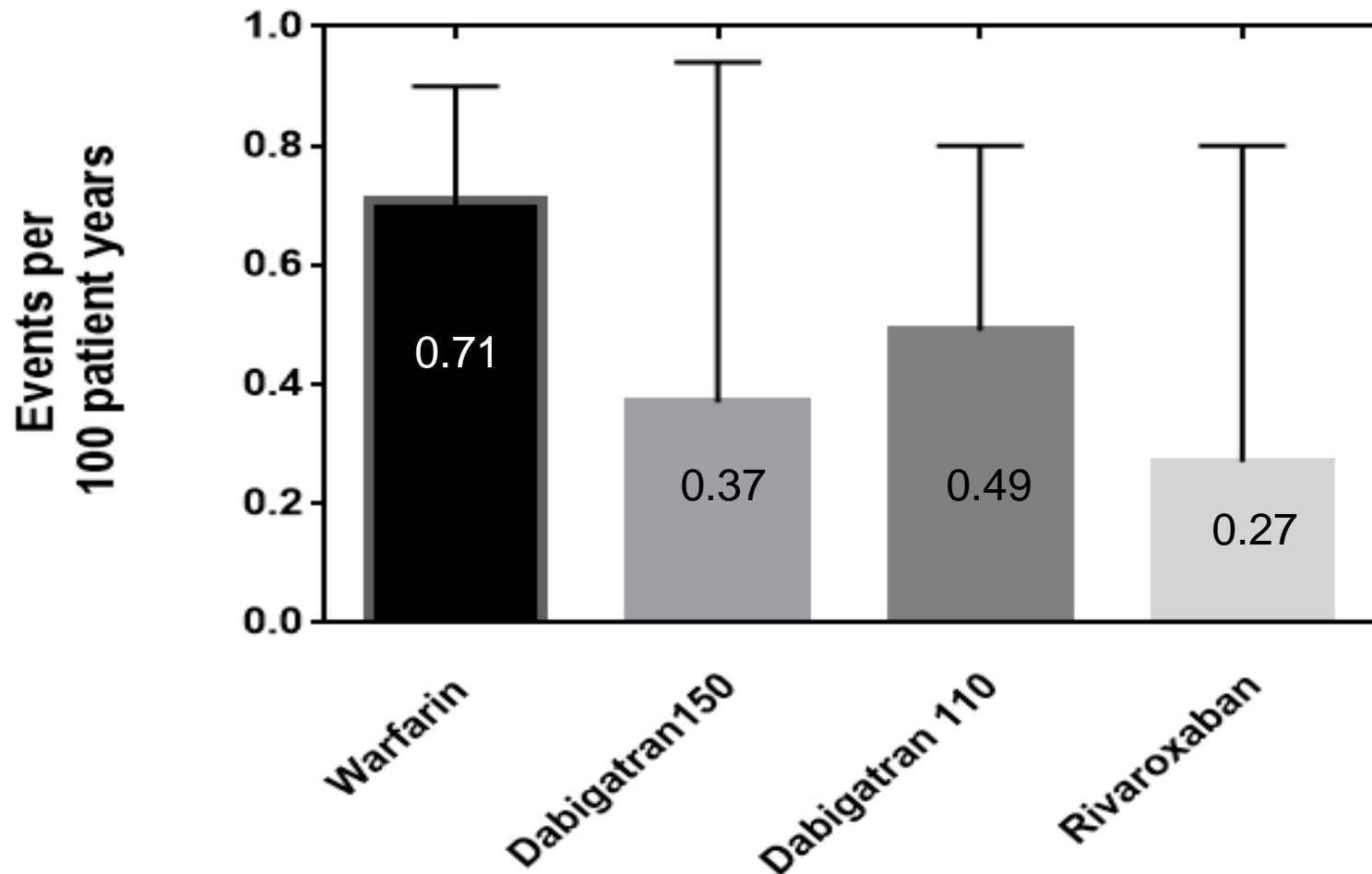
# Major bleeding rates

Rate per 100 patient years (95% CI)	Warfarin	Dabigatran overall	Dabigatran 150	Dabigatran 110	Rivaroxaban
<b>Major bleeding</b>	3.96 (3.64-4.42)	4.24 (3.68-4.89)	2.85 (2.04-3.92)	4.69 (4.03-5.44)	4.10 (3.04-5.32)

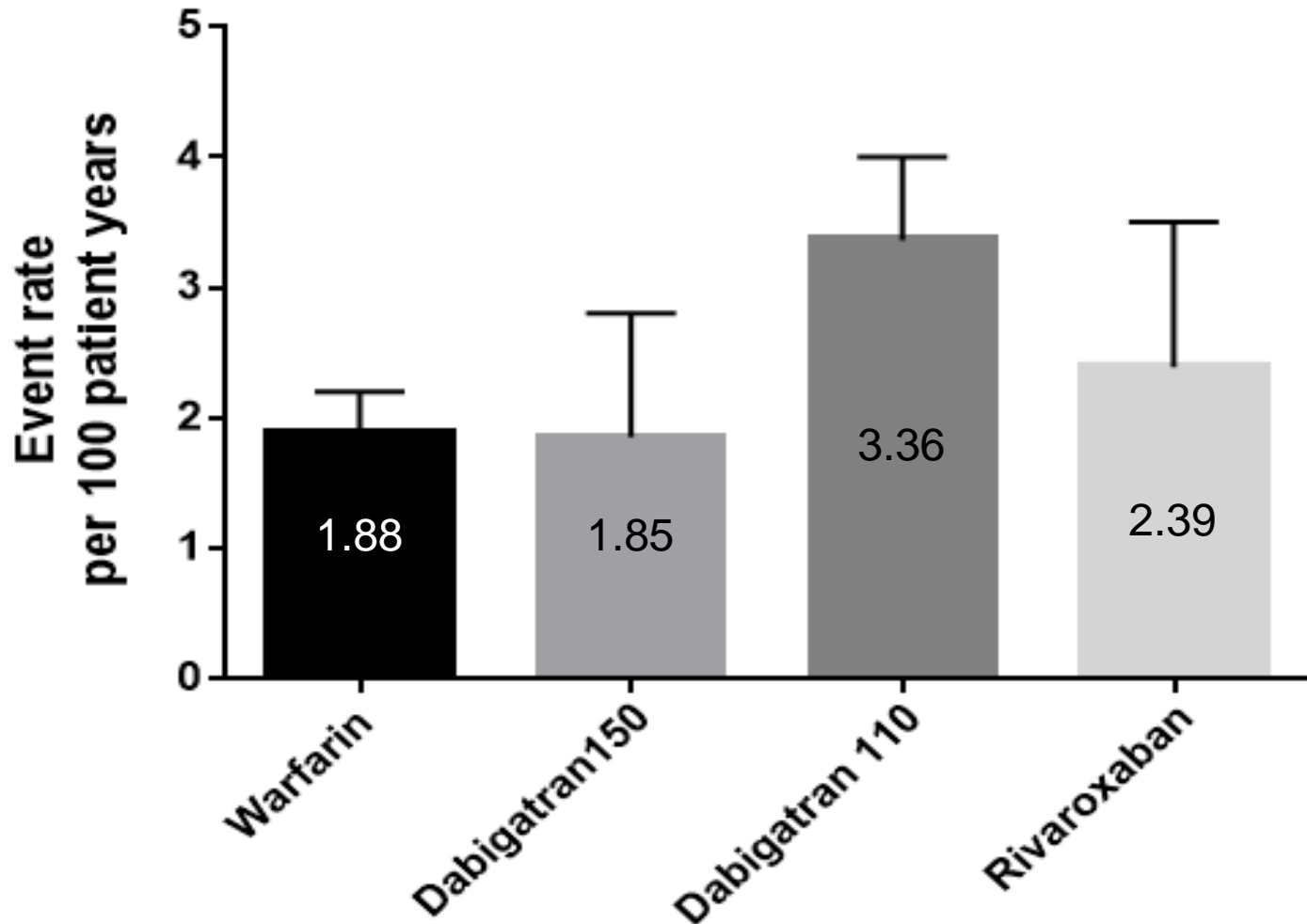
# Hazard ratios: Warfarin vs NOACs



# Site-specific bleeding rates: Intracranial hemorrhage



# Site-specific bleeding rates: Gastrointestinal hemorrhage





# Population-based studies

	Number of patients	Major hemorrhage (per 100 pt years)	Excess bleeding with dabi vs warfarin?
Danish <i>JACC 2011</i> (Patient and pharmacy reg.)	Warf=8936 Dabi=4978	Warf=2.9 Dabi150=2.2 Dabi110=2.8	No
Danish <i>BMJ Open 2013</i> (Patient and pharmacy reg.)	Warf=49640 Dabi150=1114 Dabi110=1612	Warf=4.29 Dabi150=3.75 <b>Dabi110=11.05</b>	<b>Yes for dabi110</b>
Medicare <i>JAMA Int Med 2014</i>	Warf=8102 Dabi=1302	Warf=5.9% <b>Dabi=9%</b>	<b>Yes</b>
Medicare <i>Circulation 2014</i>	Warf= 67207 Dabi=67494	Warf= 4.39 Dabi= 4.27	No
Israeli (HMO database, individual chart review)	Warf=9564 Dabi150=1806 Dabi110=4170 Riva=2709	Warf=3.9 Dabi150=2.8 Dabi110=4.6 Riva=4.1	No

# Conclusions

- Israeli physicians now start over 50% of new AF patients on a NOAC (using dose stratification for dabigatran)
- Major hemorrhage rate was not greater with dabigatran or rivaroxaban compared to warfarin
- Results are consistent with RCTs and some but not all population studies
- High risk versus low risk patients distinguished – plausible reason for greater bleeding risk in dabigatran 110mg group & reduced risk in dabigatran 150 mg group

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