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Efficacy and Safety of Dabigatran Compared to Warfarin at Different Levels of INR Control for Stroke Prevention in 18,113 patients with Atrial Fibrillation in the RE-LY Trial

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Disclosures

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The RELY trial is sponsored by

- Boehringer-Ingelheim

Lars Wallentin has received institutional grants from

- Boehringer-Ingelheim
- BMS
- AstraZeneca
- Schering-Plough
- GSK
- Lilly

Anticoagulation in AF

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- Oral anticoagulants reduce stroke in AF
- Warfarin efficacy is related to time in treatment range (TTR) i.e. time with INR 2.0 – 3.0
- TTR varies within and between individuals, centres and countries
- Dabigatran Etexilate, an oral pro-drug, is rapidly converted to the thrombin inhibitor dabigatran
- Dabigatran is an alternative for stroke prevention in AF as shown in the RELY trial (NEJM, 2009)

RE-LY: A Non-inferiority Trial

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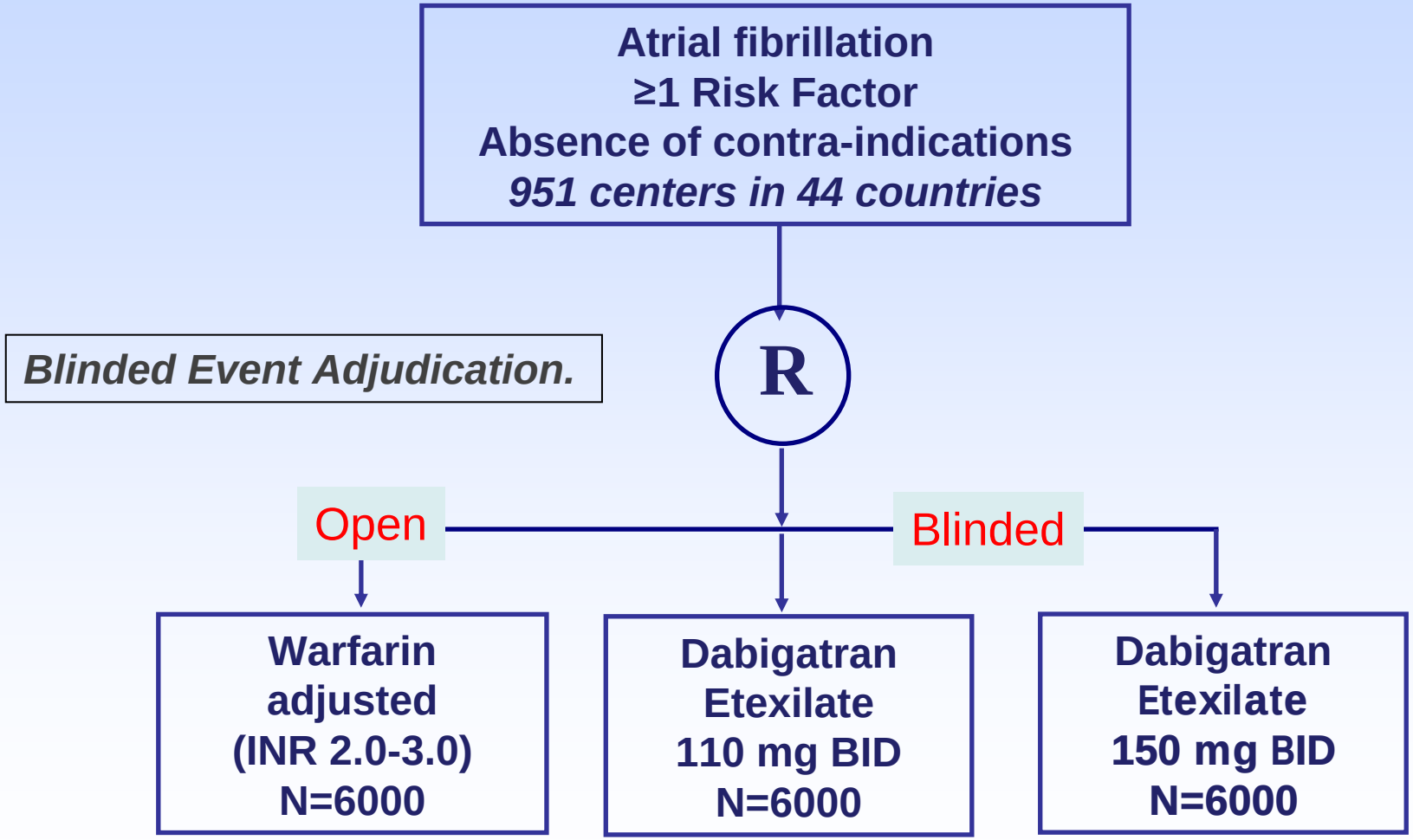

Mean TTR 64%

Country based variation in average TTR

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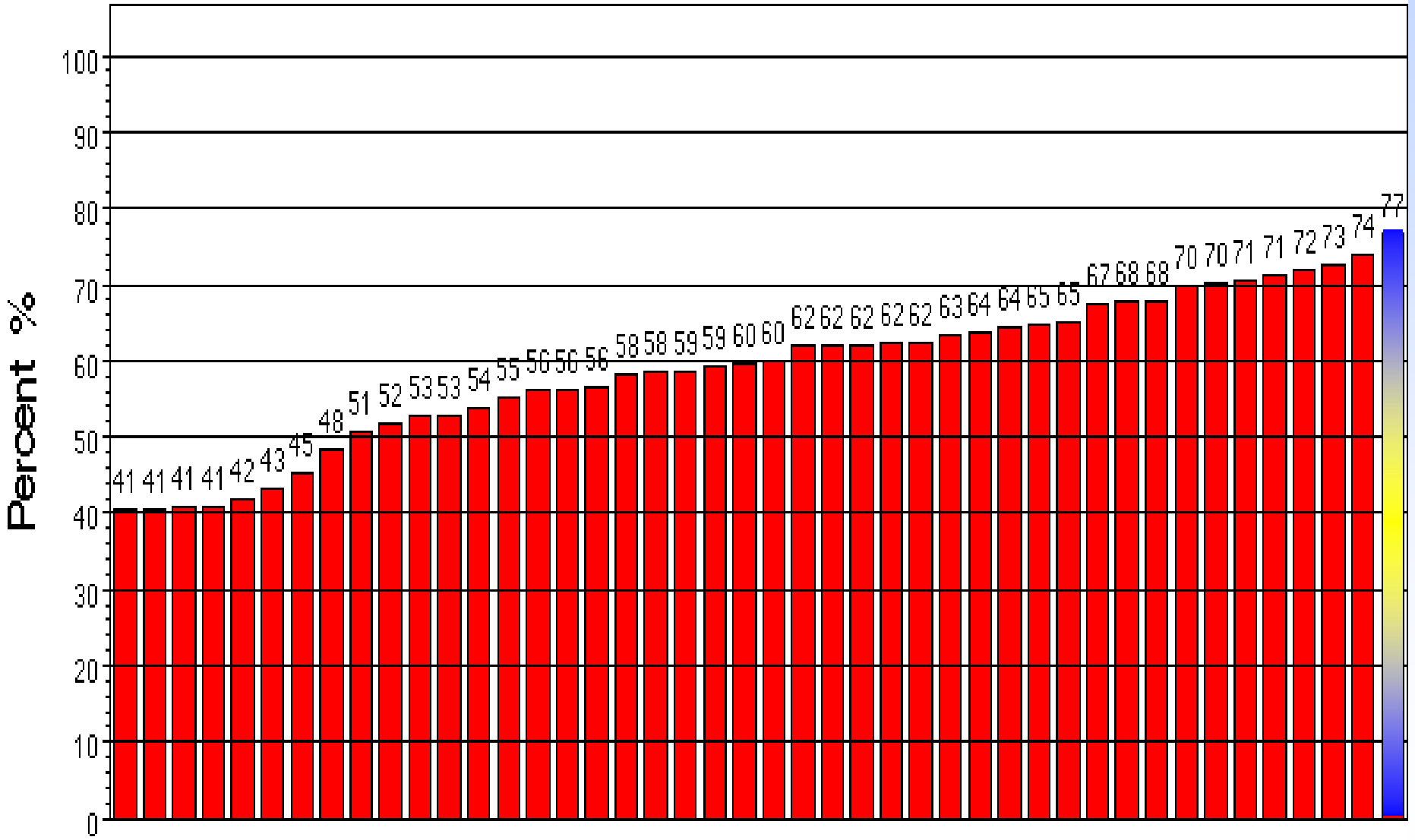

Post-hoc evaluation of outcome in relation to center based INR Control

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Hypothesis: Center level quality of INR control (TTR) during the RELY trial may influence the relative effects of dabigatran 110 mg and 150 mg vs. warfarin.

Material: All patients from the RELY study

Method: Center average TTR in the warfarin arm (Rosendaal method) applied as a proxy for all patients in each center

Statistics: Outcomes in relation to quartiles of center TTR. Interaction statistics evaluated by a multivariable approach with center based TTR as a continuous variable.

Individual and centre based quartiles of TTR and event rate in the Warfarin cohort (n=6022)

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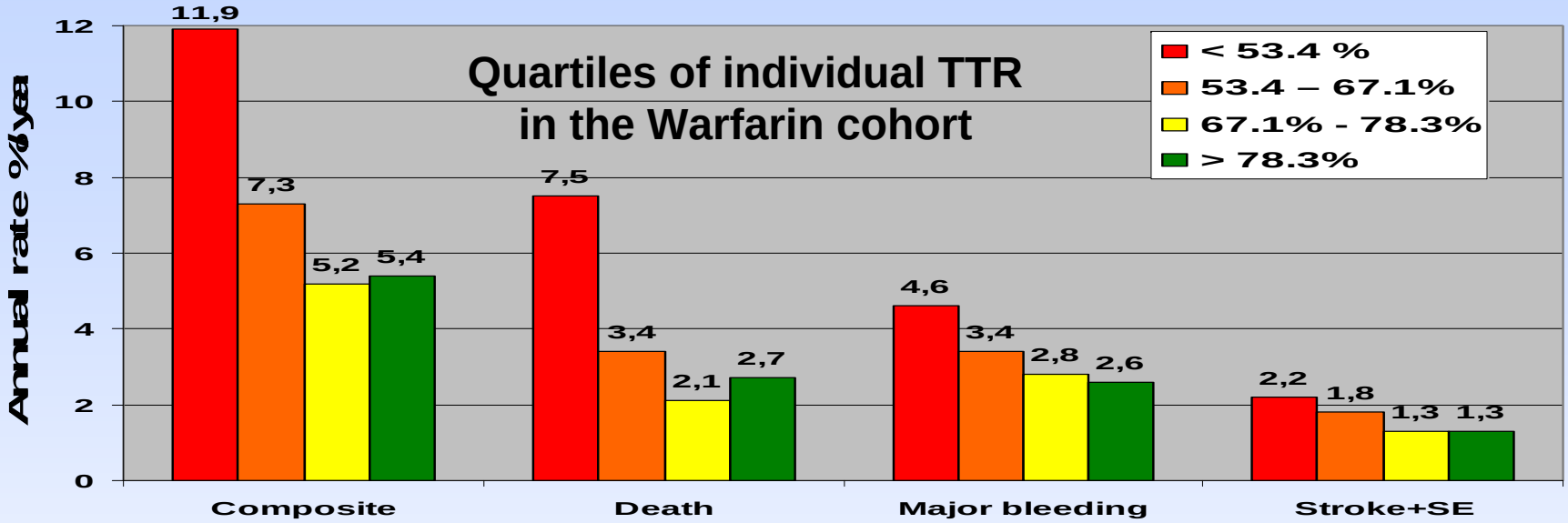

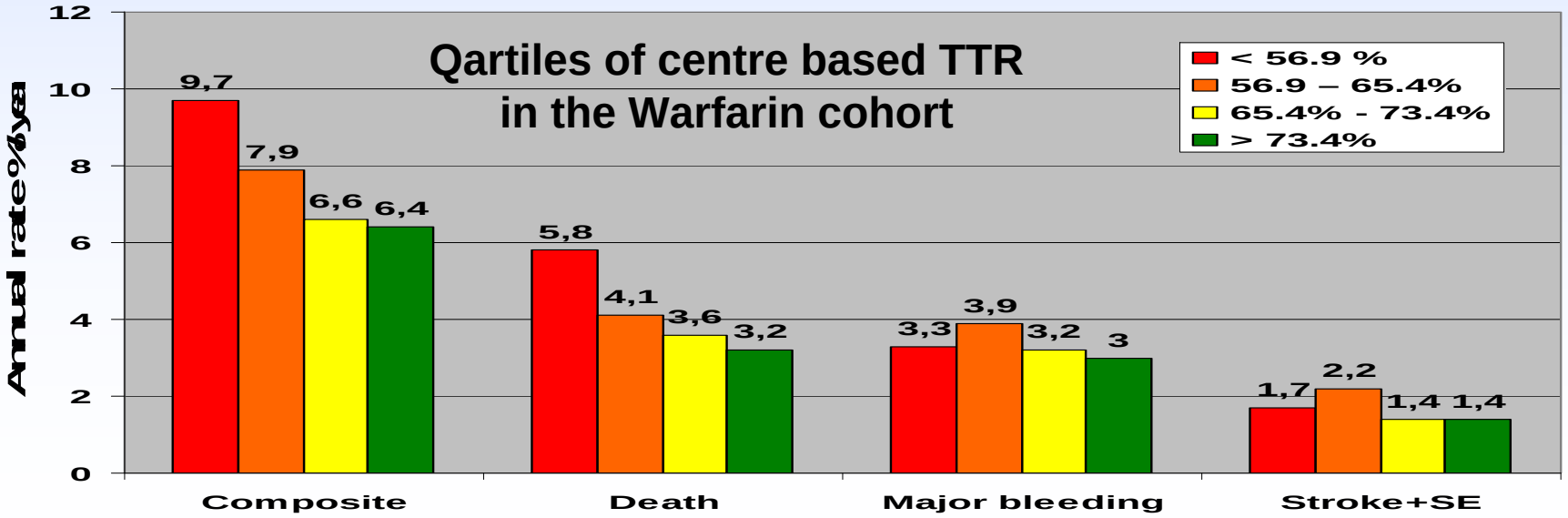

Composite = composite of stroke, systemic embolism, MI, pulmonary embolism, death and major bleeding

Baseline Characteristics vs c_TTR

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Centre based TTR	< 56.9%	56-9-65.4%	65.4-72.4%	> 72.4%	p
TTR warfarin group	50.1	62.8	70.0	78.7	
All randomized	4511	4522	4497	4494	
Mean age (years)	70.0	71.3	72.2	72.6	<0.001
Male (%)	59.6	65.0	65.0	65.0	0.037
CHADS2 score (mean)	2.2	2.2	2.1	2.0	
0-1 (%)	27.9	31.7	32.2	32.2	<0.001
2 (%)	36.9	35.0	35.0	35.0	
3+ (%)	35.2	33.3	32.8	32.9	
Prior stroke (%)	15.3	13.1	11.6	11.6	<0.001
Prior MI (%)	14.2	17.3	17.8	17.8	<0.001
CHF (%)	38.5	33.5	29.1	29.1	<0.001
Baseline ASA (%)	43.0	42.2	37.9	37.9	<0.001

1^0 endpoint – Stroke or Systemic Embolism

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	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
Center TTR	**Annual rate**	**Annual rate**	**Annual rate**	**RR 95% CI**	**P***	**RR 95% CI**	**P**
All patients	1.5 %	1.1 %	1.7 %	0.91 0.74-1.11	0.34	0.66 0.53-0.82	<0.001
< 56.9%	**1.9%**	**1.1%**	**1.7%**	**1.1 0.73-1.6**		**0.61 0.39-0.96**	
56.9 – 65.4%	**1.6%**	**1.1%**	**2.2%**	**0.74 0.51-1.1**		**0.48 0.32-0.74**	
65.4% - 72.4%	**1.4%**	**1.1%**	**1.4%**	**1.0 0.65-1.5**		**0.76 0.48-1.21**	
> 72.4%	**1.3%**	**1.3%**	**1.4%**	**0.88 0.57-1.4**		**0.88 0.57-1.37**	
Int P					**0.27***		**0.41***

***Interaction p evaluated by a multivariable approach with center based TTR as a continuous variable.**

Intracranial Bleeding

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	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
Center TTR	Annual rate	Annual rate	Annual rate	RR 95% CI	P*	RR 95% CI	P
All patients	0.23%	0.30%	0.74%	0.31 0.20-0.47	<0.001	0.40 0.27-0.60	<0.001
< 56.9%	0.28%	0.31%	0.50%	0.56 0.23-1.3		0.62 0.27-1.4	
56.9 – 65.4%	0.27%	0.40%	1.0%	0.25 0.12-0.55		0.38 0.19-0.74	
65.4% - 72.4%	0.13%	0.27%	0.60%	0.22 0.07-0.65		0.44 0.19-1.0	
> 72.4%	0.24%	0.23%	0.77%	0.31 0.13-0.73		0.30 0.13-0.71	
Int P					0.51		0.68

Major Bleeding

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	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
Major bleeding	Annual rate	Annual rate	Annual rate	RR 95% CI	P*	RR 95% CI	P
All patients	2.7 %	3.1 %	3.4 %	0.80 0.69-0.93	0.003	0.93 0.81-1.07	0.31
< 56.9%	2.2%	2.4%	3.3%	0.66 0.48-0.91		0.74 0.54-1.0	
56.9 – 65.4%	3.1%	3.2%	3.9%	0.79 0.60-1.0		0.84 0.64-1.1	
65.4% - 72.4%	2.9%	3.6%	3.2%	0.90 0.67-1.2		1.12 0.85-1.5	
> 72.4%	2.5%	3.2%	3.0%	0.84 0.62-1.1		1.08 0.81-1.4	
Int P					0.22*		0.10*

*Interaction p evaluated by a multivariable approach with center based TTR as a continuous variable.

Total death

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	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
Center TTR	**Annual rate**	**Annual rate**	**Annual rate**	**RR 95% CI**	**P***	**RR 95% CI**	**P**
All patients	3.8 %	3.6 %	4.1 %	0.91 0.80-1.03	0.13	0.88 0.77-1.00	0.051
< 56.9%	4.1 %	3.9%	5.8%	0.71 0.56-0.90		0.68 0.54-0.86	
56.9 – 65.4%	3.9%	3.7%	4.1%	0.96 0.75-1.24		0.91 0.70-1.2	
65.4% - 72.4%	3.3%	3.6%	3.6%	0.92 0.70-1.21		1.0 0.78-1.3	
> 72.4%	3.6%	3.3%	3.2%	1.1 0.87-1.5		1.0 0.78-1.4	
Int P					0.02*		0.02*

*Interaction p evaluated by a multivariable approach with center based TTR as a continuous variable.

All cardiovascular events

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	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
Center TTR	**Annual rate**	**Annual rate**	**Annual rate**	**RR 95% CI**	**P***	**RR 95% CI**	**P**
All patients	7.1 %	6.9 %	7.6 %	0.92 0.84-1.02	0.10	0.91 0.82-1.00	0.04
< 56.9%	7.4%	6.7%	9.7%	0.75 0.62-0.89		0.69 0.57-0.82	
56.9 – 65.4%	7.4%	7.0%	7.9%	0.93 0.78-1.1		0.88 0.73-1.1	
65.4% - 72.4%	6.9%	7.2%	6.6%	1.1 0.87-1.3		1.1 0.92-1.4	
> 72.4%	6.5%	6.7%	6.4%	1.0 0.83-1.2		1.0 0.85-1.3	
Int P					0.04*		0.002*

*Interaction p evaluated by a multivariable approach with center based TTR as a continuous variable.

All cardiovascular events include vascular events, death and major bleeding

Limitations

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Post-hoc analyses including several secondary end-points

Centre based INR control has many limitations

- **does not appropriately reflect individual patients INR control**
- **does not reflect the full effect of INR control in individual patients**
- **does not reflect impact of good and poor responders to dabigatran**
- **does not reflect effects of treatment discontinuations**
- **constitutes as post-randomization defined variable**
- **associated with differences in other variables between centres**

The analyses verify the well-known effects of individual and centre based INR control on outcome events in the Warfarin arm – but the identification of the appropriate control patients in the other arms is challenging.

Summary

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- For stroke prevention in AF Dabigatran 110 seems non-inferior and Dabigatran 150 superior to Warfarin irrespective of centre based INR control.
- Concerning intracranial hemorrhage Dabigatran 110 and 150 seem superior to warfarin irrespective of centre based INR control.
- Concerning major bleeding Dabigatran 110 seems superior and Dabigatran 150 similar to Warfarin irrespective of centre based INR control .
- Concerning all vascular events and mortality Dabigatran 110 and 150 seem superior to Warfarin at sites with poor and similar at average - good INR ctrl.

Conclusions

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- For the primary efficacy and safety endpoints, the main RELY study results are consistent showing reductions in stroke and major bleeding with Dabigatran compared Warfarin irrespective of centre based INR control

- For secondary outcomes such as all vascular events and mortality the advantages of Dabigatran may be greater at sites with poorer INR control