Should novel oral anticoagulants replace warfarin in all patients with atrial fibrillation?

P. Widimsky: NO.

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P. Widimsky – Potential conflicts of interest

Occasional speakers honoraria / advisory boards:

- **AstraZeneca**
- **Bayer**
- **Boehringer Ingelheim**
- **Daiichi Sankyo**
- **Novartis**
- **Pfizer**
- **Servier**

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ORIGINAL ARTICLE

Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

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Table 1. **Baseline Characteristics of the Patients.***

Characteristic	Dabigatran (N=168)	Warfarin (N=84)
Male sex — no. (%)	107 (64)	56 (67)
Age		
Mean — yr	56.0±9.4	55.7±10.4
<50 yr — no. (%)	34 (20)	20 (24)
Creatinine clearance — ml/min	107.8±39.9	106.4±34.4
Use of aspirin or clopidogrel after surgery — no. (%)		
One agent or both	51 (30)	25 (30)
Both agents	3 (2)	1 (1)
Geographic region — no. (%)		
North America (Canada only)	15 (9)	9 (11)
Western Europe	98 (58)	42 (50)
Central Europe	55 (33)	33 (39)
Type of valve-replacement surgery — no. (%)		
Aortic	113 (67)	59 (70)
Mitral	49 (29)	22 (26)
Aortic and mitral	6 (4)	3 (4)
Baseline thromboembolic risk — no. (%)†		
Low	51 (30)	23 (27)
Intermediate or high	117 (70)	61 (73)
Population A (surgery during current hospital stay)	133 (79)	66 (79)
Population B (≥3 mo after surgery)	35 (21)	18 (21)
Coronary artery disease	39 (23)	24 (29)
Previous myocardial infarction	9 (5)	7 (8)
Previous CABG	5 (3)	4 (5)
Atrial fibrillation	37 (22)	22 (26)
Atrial flutter	7 (4)	5 (6)
New York Heart Association class ≥II	62 (37)	29 (35)
Left ventricular ejection fraction ≤40%	11 (7)	4 (5)
Hypertension	101 (60)	53 (63)
Diabetes mellitus	27 (16)	13 (15)
Hyperlipidemia	75 (45)	42 (50)
Previous stroke	5 (3)	5 (6)
Previous transient ischemic attack	4 (2)	3 (4)
Hypercoagulable condition	3 (2)	2 (2)
Logistic EuroSCORE‡	2.3±1.9	2.3±1.8
Society of Thoracic Surgeons risk score§	2.0±2.3	1.8±1.7

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Table 2. Patients Requiring Dose Escalation or Discontinuation of Dabigatran and Mean Percentage of Time above the Target Trough Plasma Level of Dabigatran.*

Dabigatran Dose	Population A (N=127)		Population B (N=35)		All Patients (N=162)	
	Patients Requiring Dose Escalation or Discontinuation† *no./total no. (%)*	Percent of Time above Target Level‡	Patients Requiring Dose Escalation or Discontinuation† *no./total no. (%)*	Percent of Time above Target Level‡	Patients Requiring Dose Escalation or Discontinuation† *no./total no. (%)*	Percent of Time above Target Level‡
All doses	47/127 (37)	84	5/35 (14)	96	52/162 (32)	86
150 mg twice daily	4 /11 (36)	99	2/13 (15)	98	6/24 (25)	98
220 mg twice daily	32/71 (45)	84	1/16 (6)	100	33 /87 (38)	87
300 mg twice daily	11/45 (24)	79	2/6 (33)	83	13/51 (25)	79

* Shown are the numbers of all patients who received at least one dose of dabigatran who required a dose escalation or discontinuation, divided by the total number of patients receiving the initial dose level. The target trough plasma level of dabigatran was 50 ng per milliliter or more. Data are from the initial 12-week treatment period.

† Doses were increased from 150 mg twice daily to 220 mg twice daily and from 220 mg twice daily to 300 mg twice daily if the steady-state trough level of dabigatran was less than 50 ng per milliliter. Among patients receiving an initial dose of 300 mg twice daily, dabigatran was discontinued if repeated measurement of the trough level was less than 50 ng per milliliter.

‡ The percentage of time above the target level was calculated with the use of the Rosendaal method on the basis of trough levels of dabigatran, as measured on high-performance liquid chromatography–tandem mass spectrometry. Excluded from this calculation were three patients for whom no measurements were available during the initial study period.

Table 4. Adjudicated Efficacy and Safety Outcomes in the Initial and Extended Trials in the Intention-to-Treat Population.*

Outcome	Population A		Population B		All Patients		Hazard Ratio (95% CI)†	P Value‡
	Dabigatran (N=133)	Warfarin (N=66)	Dabigatran (N=35)	Warfarin (N=18)	Dabigatran (N=168)	Warfarin (N=84)		
	number of patients (percent)							
Death	1 (1)	2 (3)	0	0	1 (1)	2 (2)	0.25 (0.02–2.72)	0.26
Stroke	9 (7)	0	0	0	9 (5)	0	NA	NA
Systemic embolism	0	0	0	0	0	0	NA	NA
Transient ischemic attack	2 (2)	2 (3)	1 (3)	0	3 (2)	2 (2)	0.75 (0.13–4.49)	0.75
Myocardial infarction	1 (1)	0	2 (6)	0	3 (2)	0	NA	NA
Death, stroke, systemic embolism, or myocardial infarction	11 (8)	2 (3)	2 (6)	0	13 (8)	2 (2)	3.37 (0.76–14.95)	0.11
Death, stroke, transient ischemic attack, systemic embolism, or myocardial infarction	12 (9)	4 (6)	3 (9)	0	15 (9)	4 (5)	1.94 (0.64–5.86)	0.24
Valve thrombosis without symptoms	2 (2)	0	3 (9)	0	5 (3)	0	NA	NA
Bleeding								
Any	35 (26)	8 (12)	10 (29)	2 (11)	45 (27)	10 (12)	2.45 (1.23–4.86)	0.01
Major	7 (5)	2 (3)	0	0	7 (4)	2 (2)	1.76 (0.37–8.46)	0.48
Major with pericardial location	7 (5)	2 (3)	0	0	7 (4)	2 (2)	1.76 (0.36–8.45)	0.48

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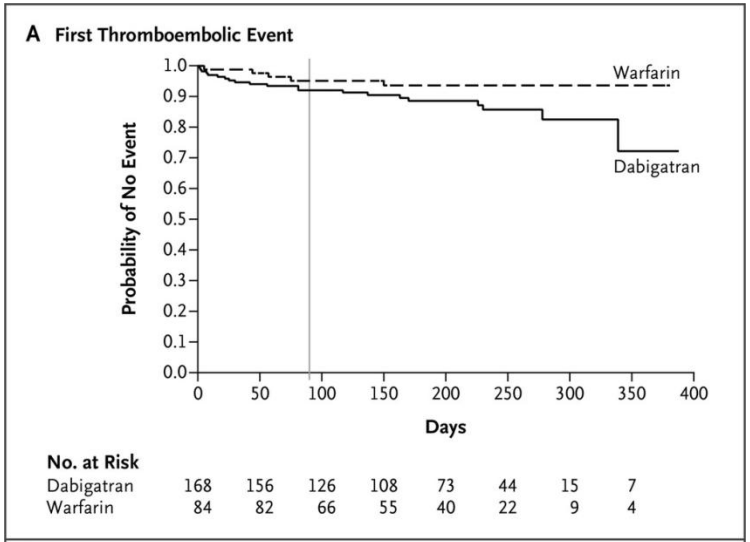

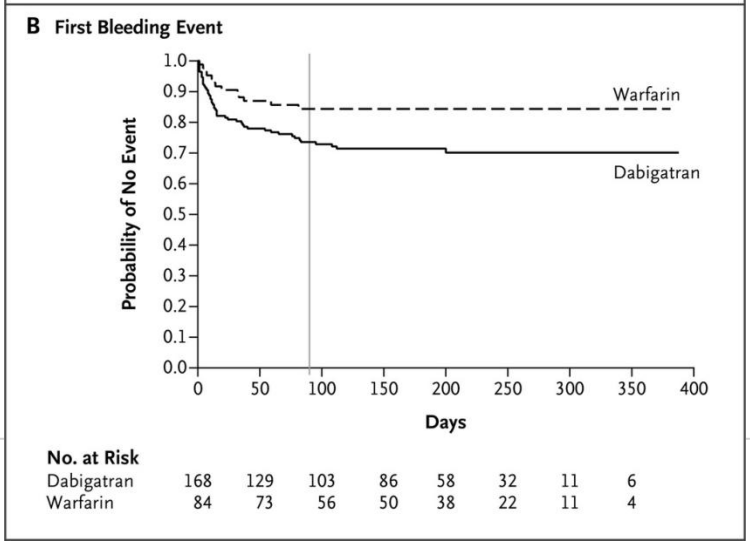

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Why dabigatran failed in the RE-ALLIGN trial ?

Most thromboembolic events in the dabigatran group occurred in patients who had **started a study drug within 7 days after valve surgery**, with fewer occurring in patients who had undergone valve implantation more than 3 months before randomization. Excess bleeding events among patients receiving dabigatran occurred in the two study populations.

Warfarin inhibits the activation of both **tissue factor–induced coagulation** (by inhibiting the synthesis of coagulation factor VII) and **contact pathway–induced coagulation** (by inhibiting the synthesis of factor IX), as well as inhibiting the synthesis of factor X and thrombin in the common pathway, whereas dabigatran exclusively inhibits thrombin. If contact activation is intense, the resulting thrombin generation may overwhelm local levels of dabigatran, which can lead to thrombus formation on the surface of the valve and related embolic complications.

The results may also be relevant to studies of other new oral anticoagulants in patients with mechanical heart valves. **Data from AF trials cannot be extrapolated to patients with mechanical heart valves because the mechanisms of thrombosis are different.**

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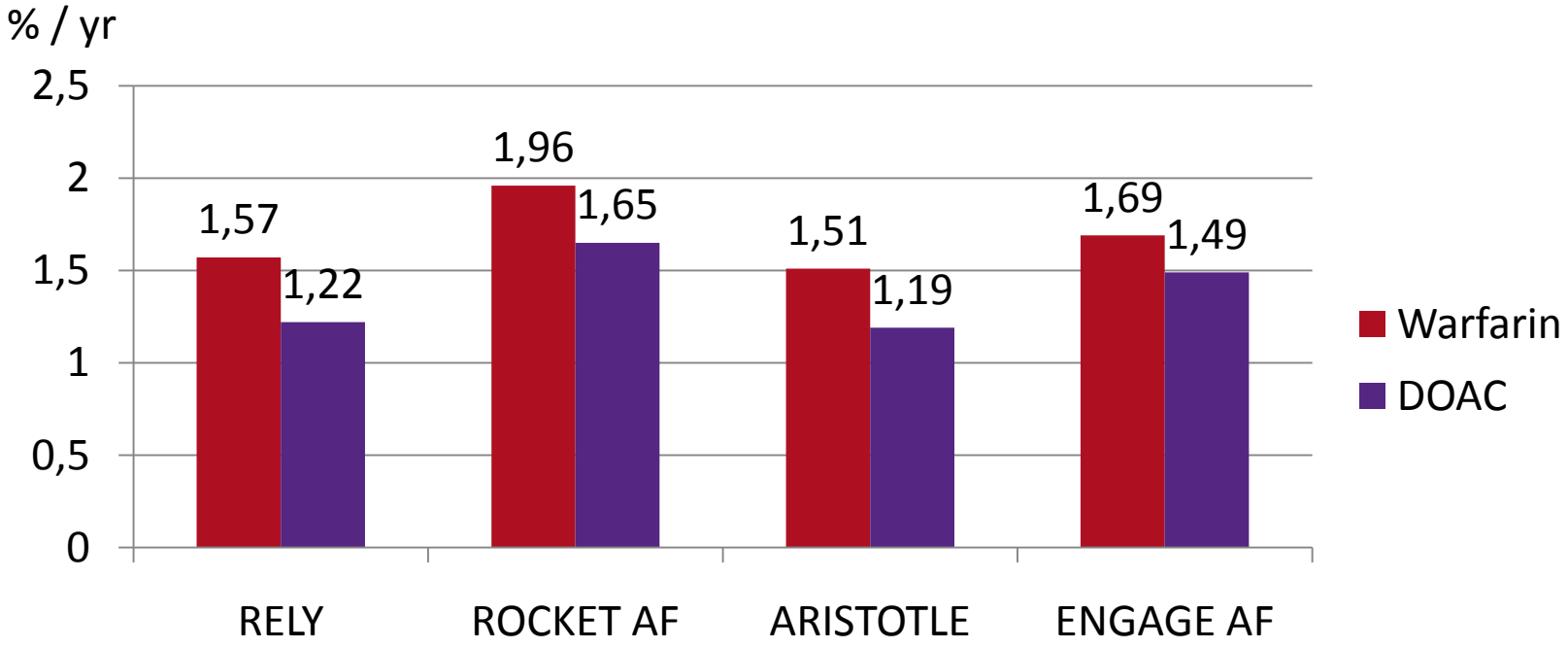
Any stroke in the main AF trials



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Warfarin dosage in the main AF trials

	Warfarin
RE-LY	Open, adjusted to INR 2.0 - 3.0
ROCKET-AF	Blinded, adjusted to INR 2.0 - 3.0
ARISTOTLE	Blinded, adjusted to INR 2.0 - 3.0
ENGAGE AF	Blinded, adjusted to INR 2.0 - 3.0

Patients risk profiles in the main AF trials

	$CHADS_2$
RE-LY	2.1 ± 1.1 (>2: 32%)
ROCKET AF	3.5 ± 0.9 (>2: 87%)
ARISTOTLE	2.1 ± 1.1 (>2: 30%)
ENGAGE AF	2.8 ± 1.0 (>**3**: 23%)

Pulmonary embolism and myocardial infarction rates in the main AF trials

	Pulmonary embolism	Myocardial infarction
RE-LY	W 0.09%/yr vs. Dabi 0.14%/yr (ns)	W 0.53%/yr vs. Dabi 0.73%/yr (ns)
ROCKET AF	N.A.	W 1.12%/yr vs. Riva 0.91%/yr (ns)
ARISTOTLE	W 0.05%/yr vs. Api 0.04%/yr (ns)	W 0.61%/yr vs. Api 0.53%/yr (ns)
ENGAGE AF	N.A.	W 0.75%/yr vs. Edo 0.70%/yr (ns)

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Gastro-intestinal bleeding in the main AF trials

	Warfarin	Direct OAC
RE-LY	1.02%/yr	1.32%/yr
ROCKET AF	2.2%	3.2%
ARISTOTLE	0.86%/yr	0.76%/yr
ENGAGE AF	1.23%/yr	1.51%/yr

Study drug discontinuation in the main AF trials

	Warfarin	Direct OAC
RE-LY	17%	21% (more frequently than W for GI symptoms)
ROCKET-AF	22.2%	23.7%
ARISTOTLE	27.5%	25.3%
ENGAGE AF	34.5%	34.4%

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Advantages of direct oral anticoagulants (DOACs)

Stable and predictable dosage

Short halflife – quick fading of anticoagulant effect in case of bleeding

No need for laboratory controls

Lower risk of fatal bleeding complications (incl. hemorhagic stroke)

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Warfarin advantages over DOACs

Long halflife – stable anticoagulant effect (missing doses carries only minor risk of ischemic event)

Wide availability - low price

Regular laboratory controls may increase the adherence to medication

Better protection in the highest-risk situations (e.g. prosthetic valves)

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