Risk of myocardial infarction in patients treated with direct oral anticoagulants, network meta-analysis of randomized trials

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Potential conflicts of interest

Speaker's name: András Komocsi MD DSc

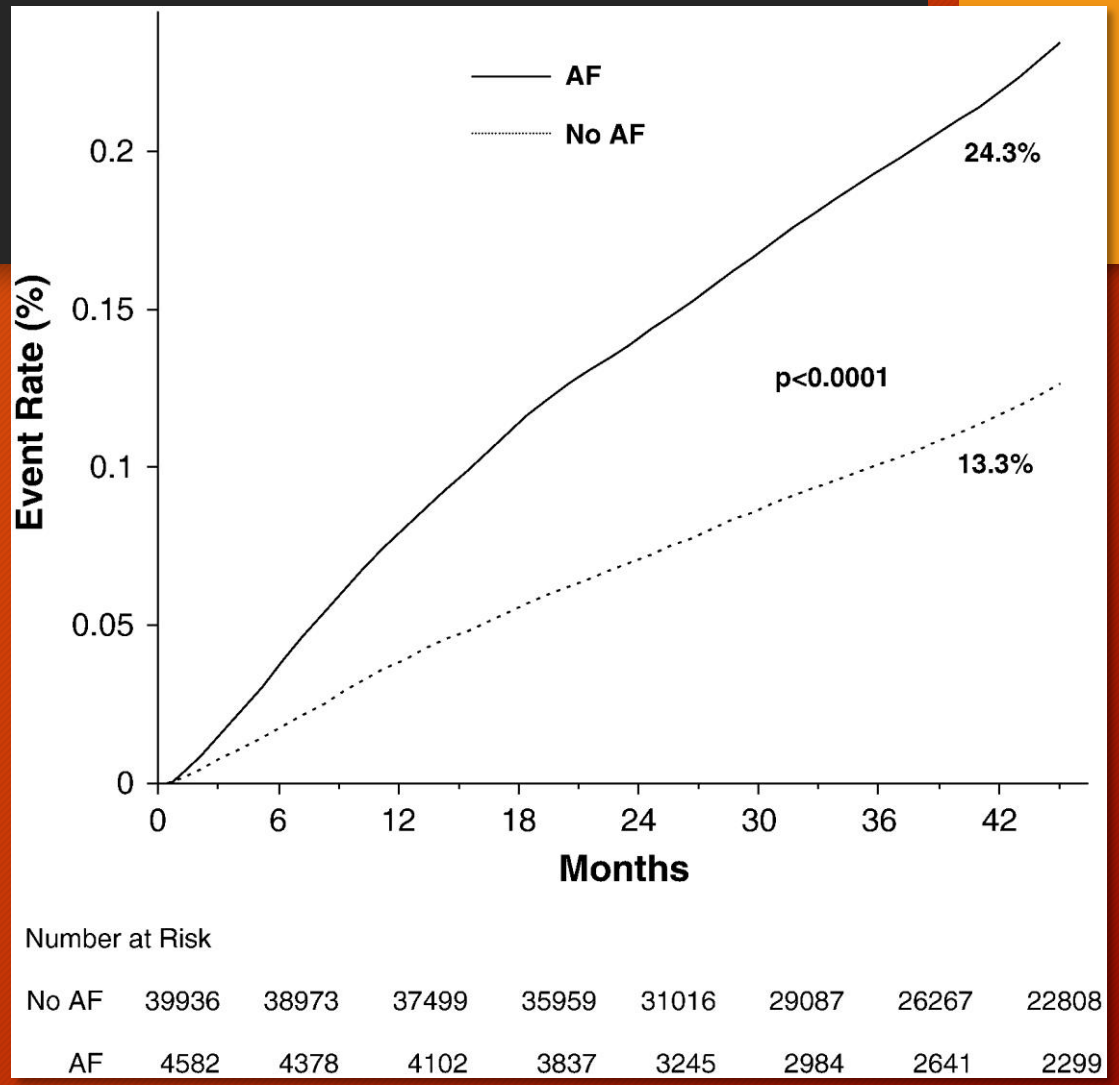
☑ I have the following potential conflicts of interest to report:

Lectures Fees, Consulting Fees or Honoraria:

Bayer Healthcare Pharmaceuticals,
Boehringer-Ingelheim,
Merk-Sharp & Dohme,
PfizerEli Lilly,
Krka

REACH Registry

Incidence of CV mortality, MI & stroke is 2x higher



(Only first events included. AF, atrial fibrillation; CV, cardiovascular; MI, myocardial infarction)

CT. Ruff et al: Long-term cardiovascular outcomes in patients with atrial fibrillation and atherothrombosis in the REACH Registry. Int J Card, Vol 170, Issue 3, 2014, 413 - 418

What AF patients die of?

- Thromboembolism is considered to be one of the most common complications in patients with AF
- The formation and detachment of the thrombus in patients with AF can increase the risks of ischemic stroke and systemic thrombosis
- It has been reported that the risk of ischemic stroke in patients with AF is 6-fold higher than that in healthy individuals and approximately 23.5% of elderly patients with AF suffer from ischemic stroke at the age of 80 to 90.

Table 2

Clinical endpoints of elderly patients with or without atrial fibrillation during follow-up.

Clinical endpoints	Atrial fibrillation (n = 194)	Nonatrial fibrillation (n = 387)	*P*
Thromboembolism	54 (27.8%)	38 (9.8%)	<.001
Ischemic stroke	11 (5.7%)	9 (2.3%)	.0370
Acute coronary syndrome	31 (16.0%)	26 (6.7%)	.0004
Other system thrombosis	24 (12.4%)	7 (1.8%)	<.001
Hemorrhage	57 (29.4%)	49 (12.7%)	<.001
Massive hemorrhage	28 (14.4%)	9 (2.3%)	<.001
Micro-hemorrhage	40 (20.6%)	43 (11.1%)	.002
All-cause death	56 (28.7%)	45 (11.6%)	<.001

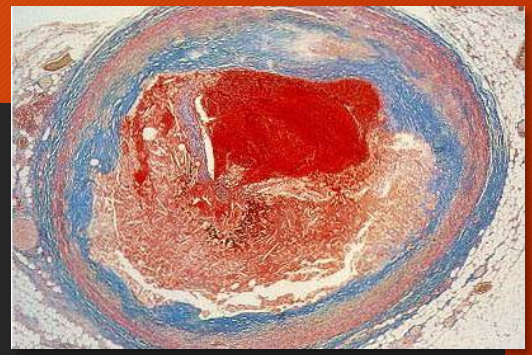
Wang et al. Medicine (Baltimore) 2017; 96(33): e7679.

Table 2 – Descriptive analysis of causes of death in clinical trials with DOACs and in the GARFIELD registry, as rate per 1000 patient-years and as percentage of total deaths.

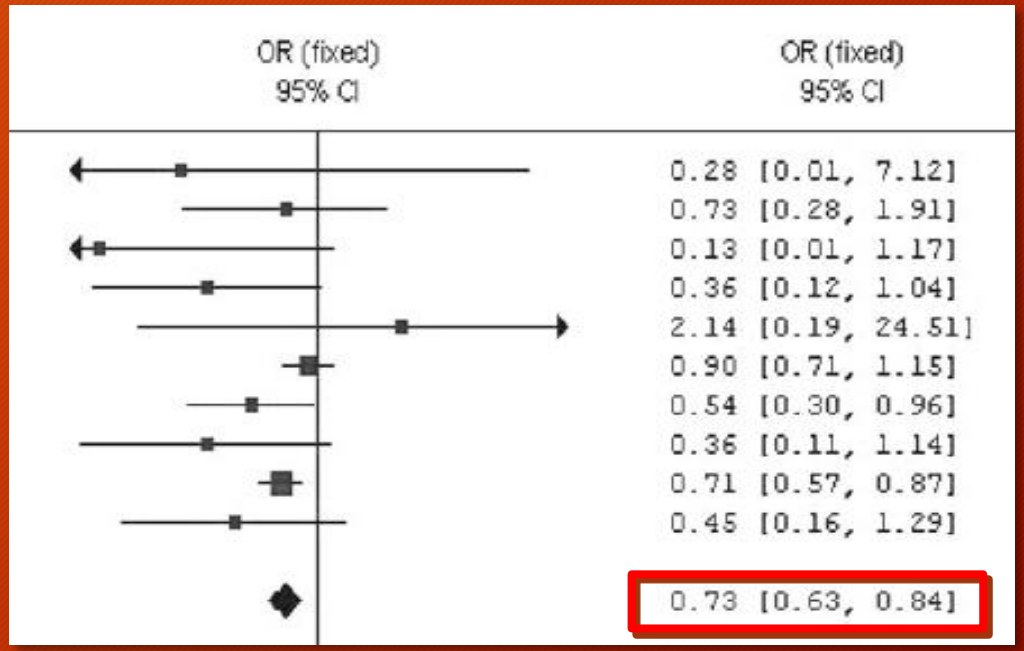
Cause of death	Meta-analysis DOAC versus warfarin [3]		GARFIELD Registry (cohorts 1 and 2) [4]	
N died	6206		1181	
N included	71,683		17,162	
Patient-years	134,046		30829	
	Death rate, ‰/y (95% CI)	% of deaths	Death rate, ‰/y (95% CI)	% of deaths
1) All-cause death	46 (40–53)	100	38 (36–41)	100
2) Cardiovascular death	29 (22–37)	64	16 (14–17)	40
• Cardiac death	21 (16–27)	46	9 (8–11)[a]	24
Sudden death/ dysrrhythmia	13 (9–17)	28	3 (2–4)[a]	8
Heart failure	7 (5–8)	15	4 (3–5)[a]	11
Myocardial infarction	1 (1–2)	3	2 (2–3)[a]	5
• Ischemic stroke/SE	3 (2–3)	6	2 (1–3)[a]	5
• Hemorrhage (all)	3 (2–4)	6	1 (0–1)[b]	2
• Other cardiovascular death[c]	3 (2–5)	6	4 (3–4)[a]	9
3) Non-cardiovascular death	14 (12–16)	30	14 (13–15)	36
• Malignancies	5 (4–6)	11	4 (3–4)[a]	10
• Infections	4 (2–6)	9	3 (2–3)[a]	7
• Respiratory	2 (1—3)	3	3 (2–4)[a]	8
• Trauma/accidental	1 (0–1)	1	N/A	N/A
• Other non-vascular death	2 (1–4)	6	4 (3–4)[a]	11
4) Undetermined death	4 (1–9)	6	9 (8–10)	24

Gómez-Outes et al. Trends in Cardiovascular Medicine 2017:27(7);494-503.

Plaque rupture, thrombosis

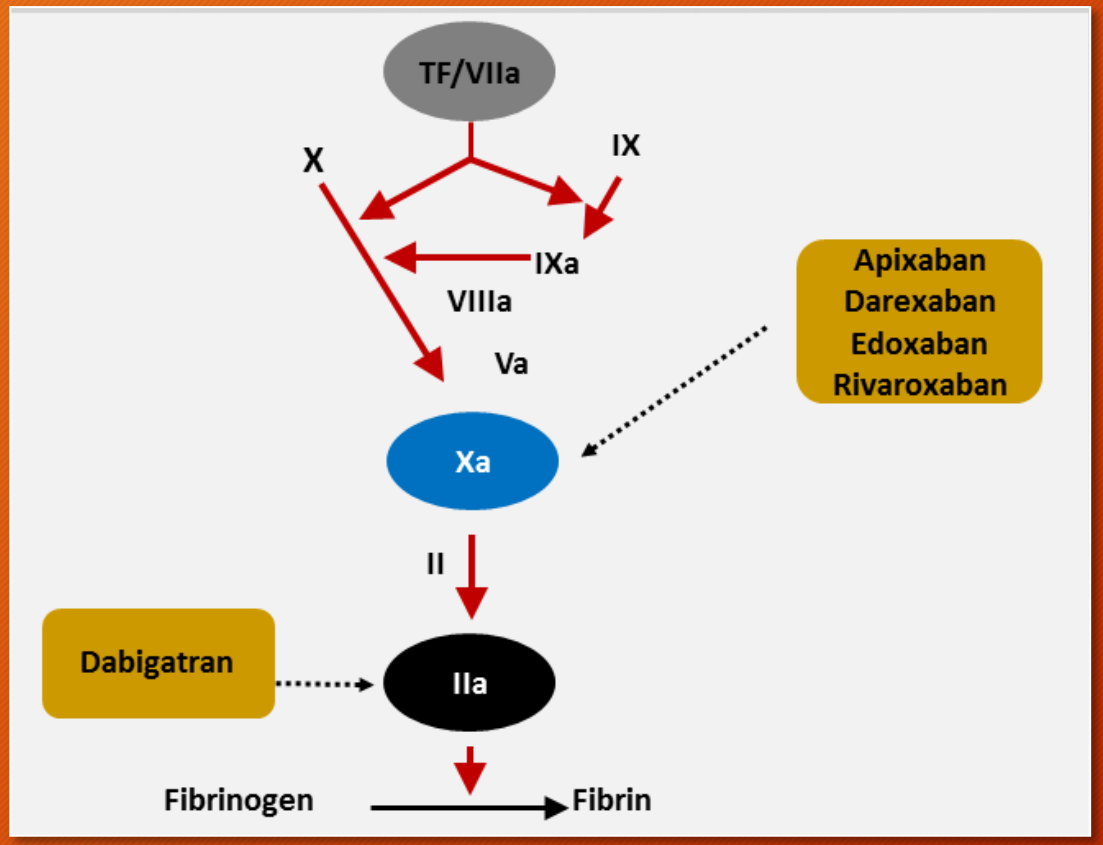


- Anticoagulation interfere with mechanisms leading to MI
- Warfarin suggested an incremental ischemic benefit when anticoagulation was applied in combination to aspirin



Andreotti F et al.: Eur Heart J. 2006;27(5):519-526.

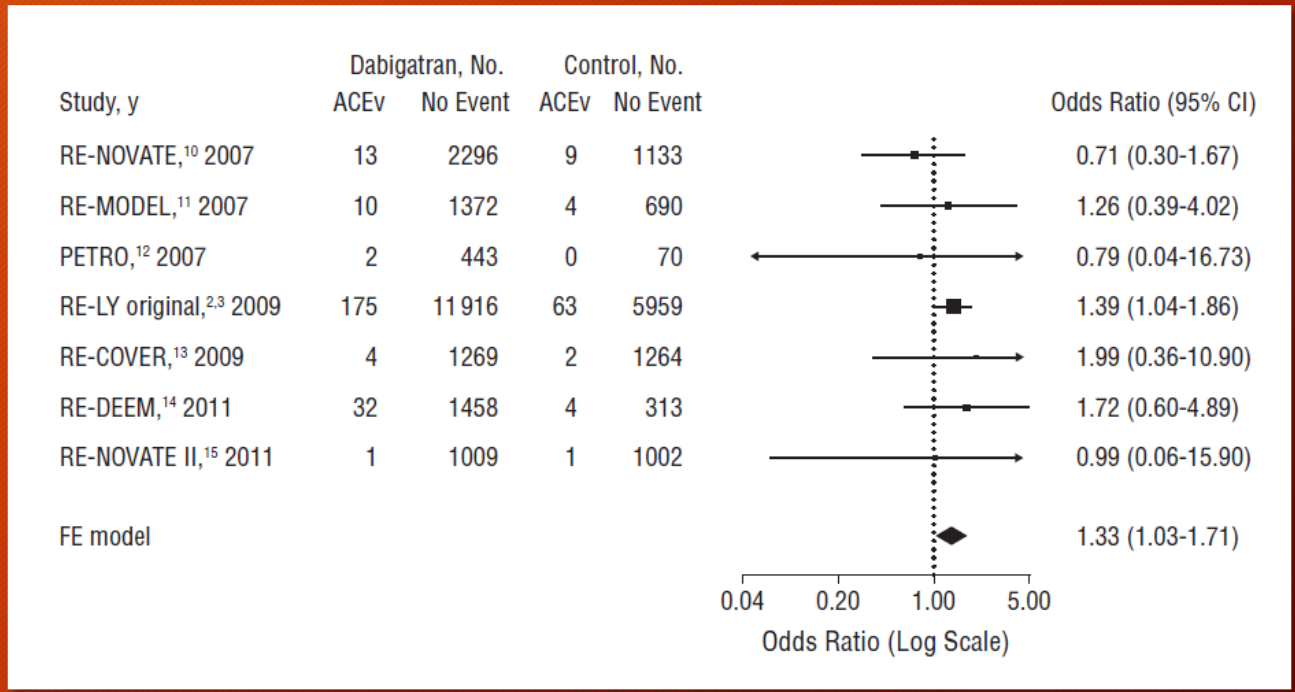
Novel generation oral anticoagulants



- Different molecular targets
- Easier clinical use
  - Drug interaction
  - Food interaction
  - Need for laboratory check-up
- Reliable effect
- Proven clinical efficacy
  - Pulmonary embolism
  - Atrial fibrillation (non-valvular)
  - PE prophylaxis & treatment

Dabigatran: Meta-analysis of seven RCTs
N=30 514

- Dabigatran was associated with a significantly **higher** risk of MI (odds ratio 1.33; 95% CI, 1.03–1.71; P= 0.05)
- No influence of „revised" RELY data (OR 1.27; 95% CI, 1.00-1.61; *P*=0.05)



Uchino K, Hernandez AV.
Arch Intern Med. 2012;172(5):397-402.

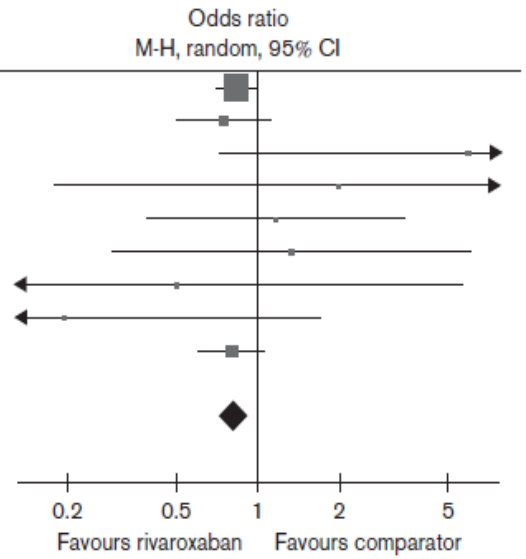
Rivaroxaban: meta-analysis of 9 RCTs
N=53 827

- Rivaroxaban was associated with a significantly **lower** risk of MI (odds ratio 0.82; 95% CI, 0.72–0.94; P= 0.004)

Study or subgroup	Rivaroxaban Events	Rivaroxaban Total	Comparator Events	Comparator Total	Weight	Odds ratio M-H, random, 95% CI
Atlas ACS 2 TIMI 51 [17]	384	10229	229	5113	60.8%	0.83 (0.70–0.98)
Atlas ACS TIMI 46	67	2331	44	1160	11.3%	0.75 (0.51–1.11)
Einstein-DVT [27]	6	1718	1	1711	0.4%	5.99 (0.72–49.83)
Einstein-PE [28]	2	2419	1	2413	0.3%	2.00 (0.18–22.03)
Record 1 [18]	7	2209	6	2224	1.4%	1.18 (0.39–3.50)
Record 2 [19]	4	1228	3	1229	0.8%	1.34 (0.30–5.98)
Record 3 [20]	1	1220	2	1239	0.3%	0.51 (0.05–5.60)
Record 4 [21]	1	1584	5	1564	0.4%	0.20 (0.02–1.69)
Rocket AF [16]	101	7111	126	7125	24.4%	0.80 (0.61–1.04)
Total (95% CI)		30049		23778	100.0%	0.82 (0.72–0.94)
Total events	573		417			

Heterogeneity: $\tau^2=0.00$; $\chi^2=6.84$, $d.f.=8$ ($P=0.55$); $I^2=0\%$

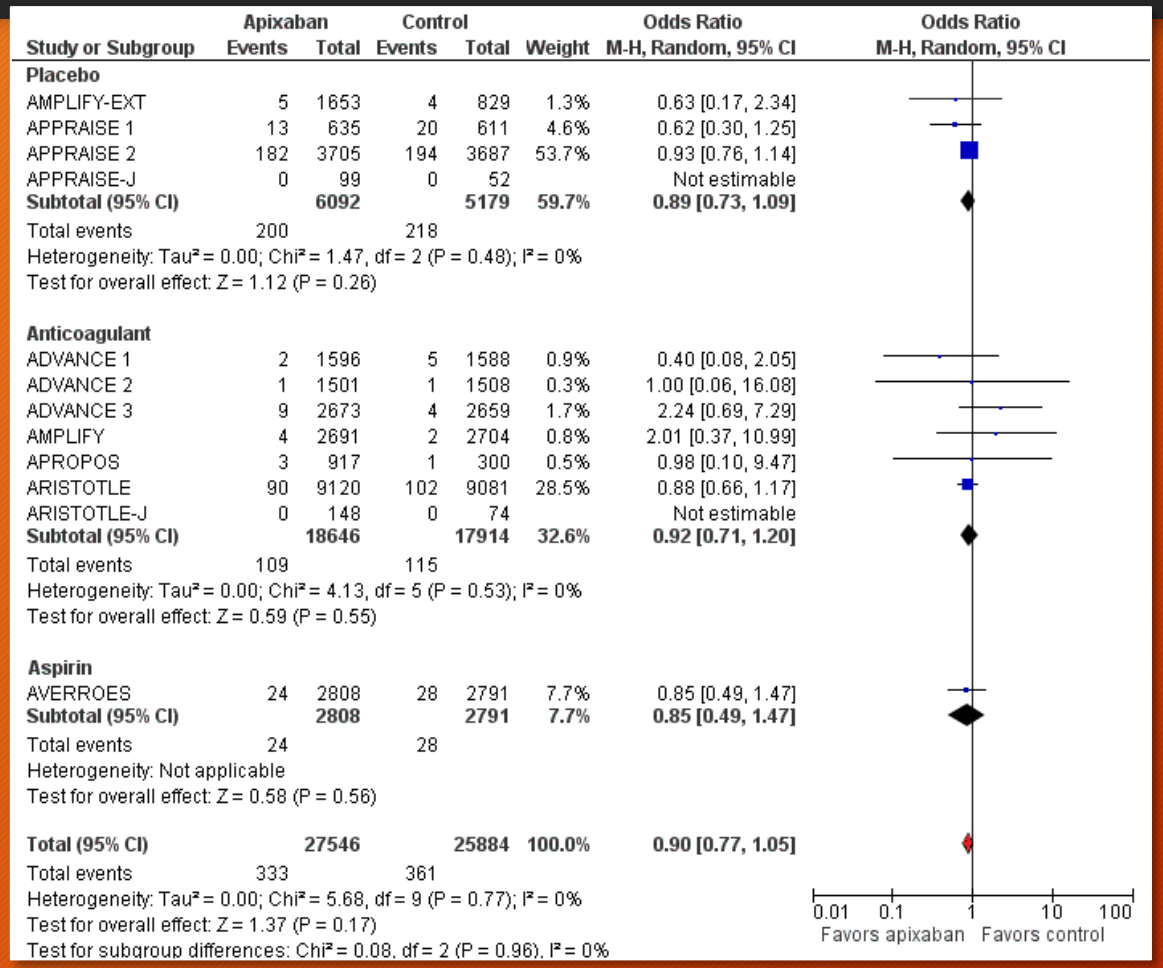
Test for overall effect: $Z=2.91$ ($P=0.004$)



Risk of myocardial infarction with rivaroxaban. 95% CI, 95% confidence interval.

Chatterjee et al. Coron Artery Dis. 2013;24(8):628-35.

Apixaban: Meta-analysis of twelve RCTs
N= 54,054



Study or Subgroup	Apixaban Events	Apixaban Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Placebo						
AMPLIFY-EXT	5	1653	4	829	1.3%	0.63 [0.17, 2.34]
APPRAISE 1	13	635	20	611	4.6%	0.62 [0.30, 1.25]
APPRAISE 2	182	3705	194	3687	53.7%	0.93 [0.76, 1.14]
APPRAISE-J	0	99	0	52		Not estimable
Subtotal (95% CI)		**6092**		**5179**	**59.7%**	**0.89 [0.73, 1.09]**
Total events	200		218			
Heterogeneity: Tau² = 0.00; Chi² = 1.47, df = 2 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.12 (P = 0.26)						
Anticoagulant						
ADVANCE 1	2	1596	5	1588	0.9%	0.40 [0.08, 2.05]
ADVANCE 2	1	1501	1	1508	0.3%	1.00 [0.06, 16.08]
ADVANCE 3	9	2673	4	2659	1.7%	2.24 [0.69, 7.29]
AMPLIFY	4	2691	2	2704	0.8%	2.01 [0.37, 10.99]
APROPOS	3	917	1	300	0.5%	0.98 [0.10, 9.47]
ARISTOTLE	90	9120	102	9081	28.5%	0.88 [0.66, 1.17]
ARISTOTLE-J	0	148	0	74		Not estimable
Subtotal (95% CI)		**18646**		**17914**	**32.6%**	**0.92 [0.71, 1.20]**
Total events	109		115			
Heterogeneity: Tau² = 0.00; Chi² = 4.13, df = 5 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.59 (P = 0.55)						
Aspirin						
AVERROES	24	2808	28	2791	7.7%	0.85 [0.49, 1.47]
Subtotal (95% CI)		**2808**		**2791**	**7.7%**	**0.85 [0.49, 1.47]**
Total events	24		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
Total (95% CI)		**27546**		**25884**	**100.0%**	**0.90 [0.77, 1.05]**
Total events	333		361			
Heterogeneity: Tau² = 0.00; Chi² = 5.68, df = 9 (P = 0.77); I² = 0%						
Test for overall effect: Z = 1.37 (P = 0.17)						
Test for subgroup differences: Chi² = 0.08, df = 2 (P = 0.96), I² = 0%						

Apixaban treatment was **not associated** with an increase in myocardial infarction.

(odds ratio 0.9; 95% CI, 0.77-1.05; P= 0.17)

Control arms included warfarin, enoxaparin, or placebo administration

Different follow-up

Tornyos A et al. J Thomb Thrombolysis 2015;40(1):1-11.

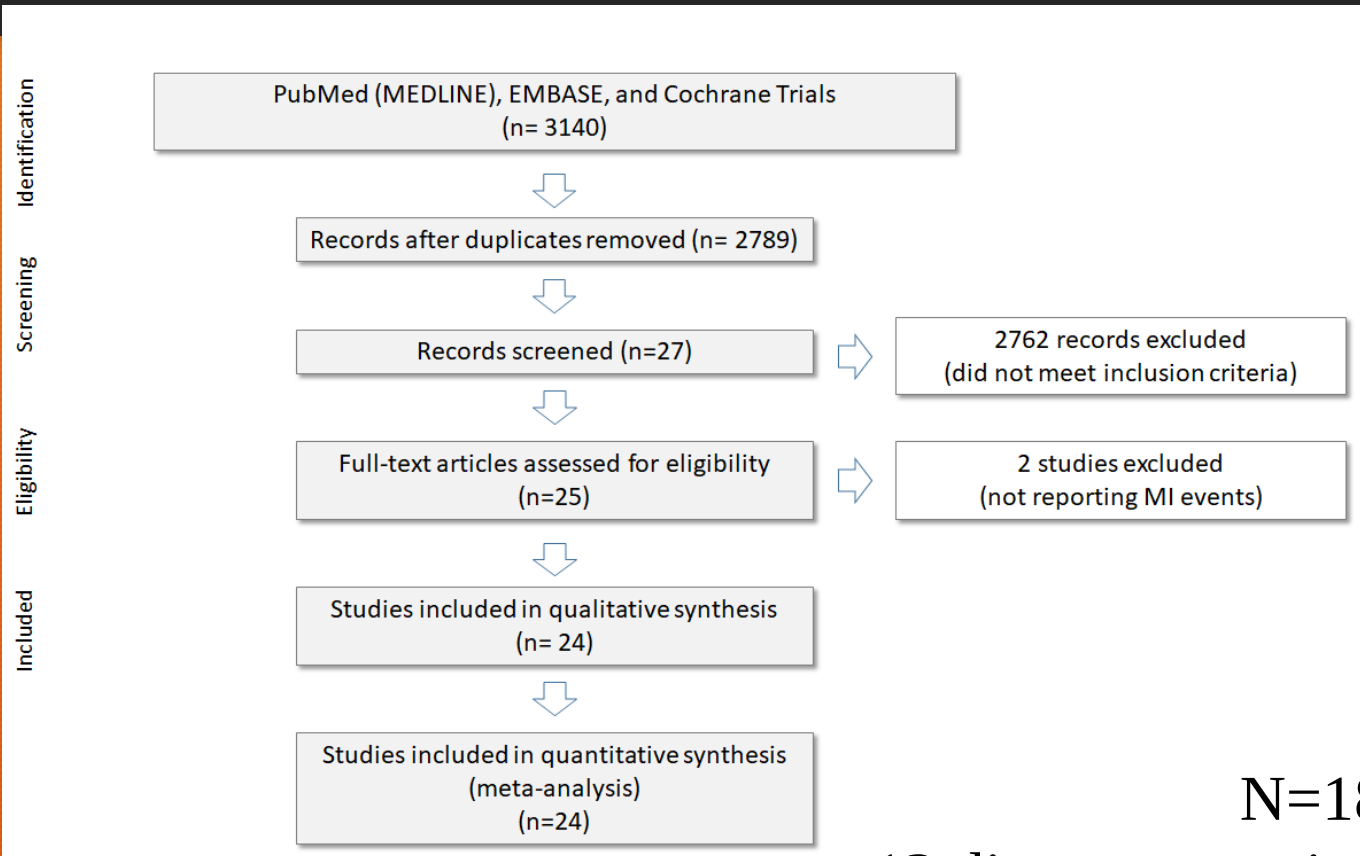
Purpose

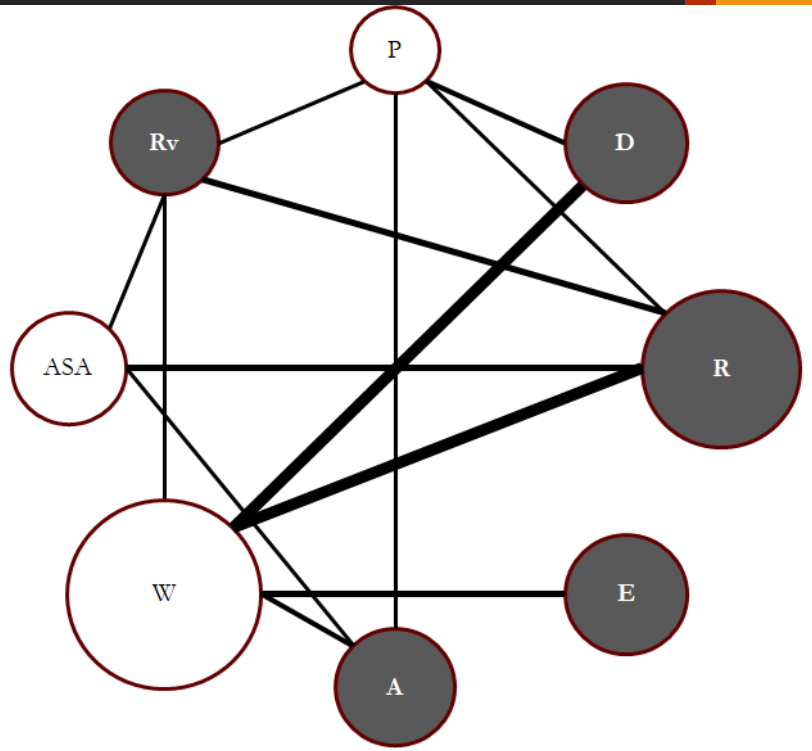
- **The relative safety of oral anticoagulants continues to be debated**
- **Data regarding cardiovascular safety of the different direct oral anticoagulants (DOACs) are inconsistent. Our aim was to examine cardiovascular safety of long-term DOAC treatment.**
- **The relative safety and efficacy of the approved oral anticoagulants** (dabigatran apixaban, rivaroxaban and edoxaban) **in using a network meta-analysis.**

Methods

- Inclusion criteria
  - (1) randomized controlled trial assessed the clinical efficacy and/or safety of one or more approved DOAC;
  - (2) control groups were applied with oral anticoagulation and/or antiplatelet and/or placebo treatment;
  - (3) the frequency of acute coronary syndromes during follow-up was reported.
- Electronic database: MEDLINE, Scopus, and Cochrane
- The primary end-point of the analysis was the occurrence of myocardial infarction (MI).
- Random-effects model within a Bayesian framework using Markov Chain Monte Carlo simulation to calculate pooled odds ratio (OR) and 95% credibility intervals (CI).
- Ranking therapies by their likelihood of leading to the best results for the outcomes.

Results: Study selection and network layout





N=180,300

13 direct comparison of the 28 possible

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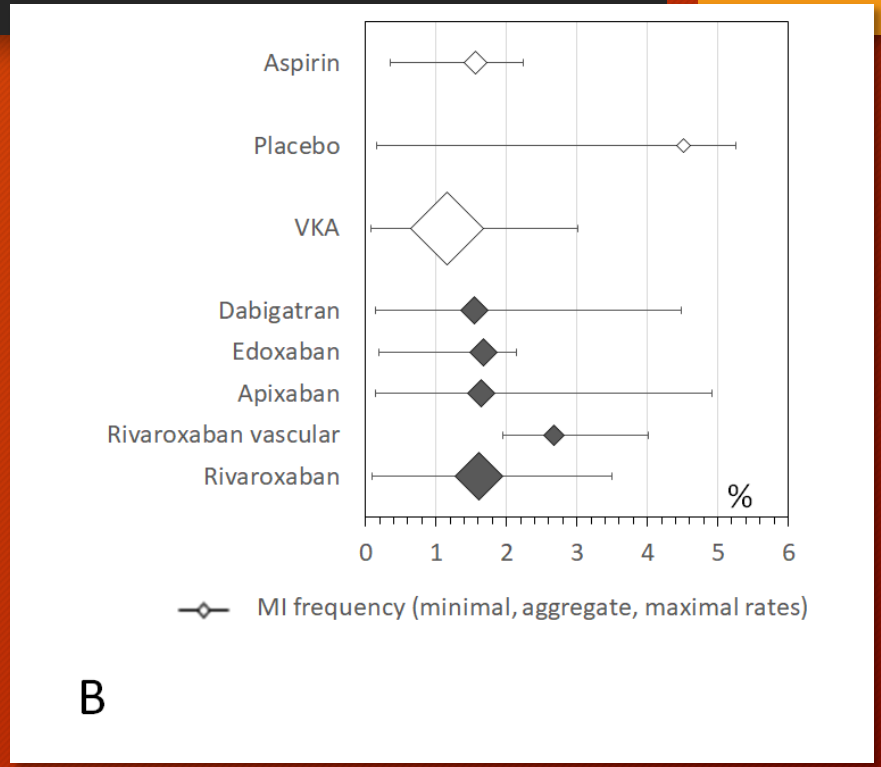
MI frequency

3,142 MI occurred
VKA arm with lowest rate (1.16%) and in the placebo arms with the highest rate (4.52%)

DOAC-treated patients had numerically fewer MI compared to various controls.

Heterogeneity analysis showed consistent results within treatment groups (dabigatran I^2: 26%, x^2: p=0.23, and I^2 0%, x^2: p≥0.53 for all other DOACs) while high heterogeneity among DOAC subgroups (I^2 64.2%, x^2: p=0.02).

Exclusion of the Secondary Prevention of Venous Thrombo Embolism (RE-MEDY) or the Management of Myocardial Injury After Noncardiac Surgery (MANAGE) trial but none of the others corrected the I^2 value in the dabigatran subgroup to zero. (data not shown)



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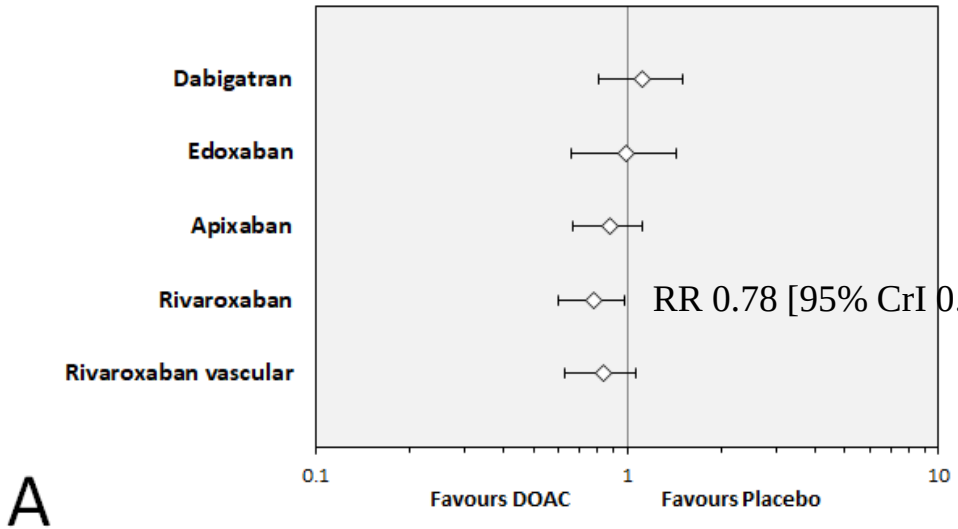

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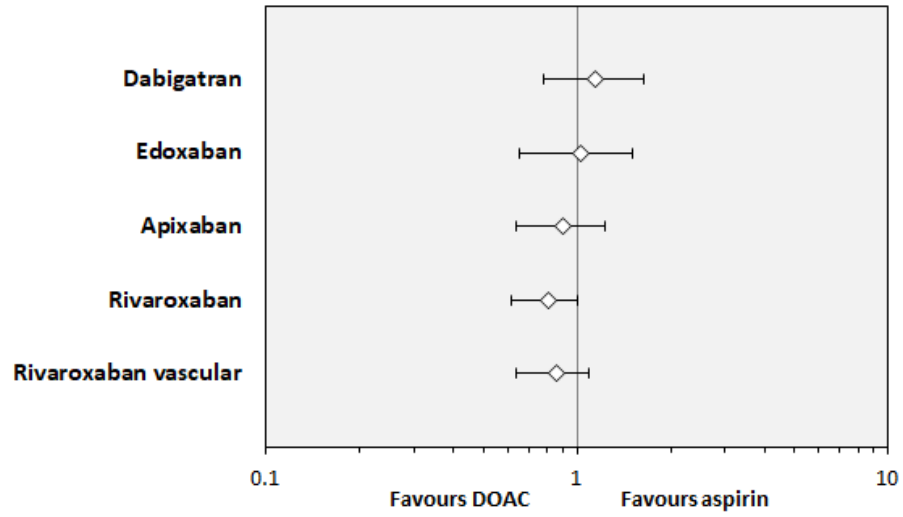

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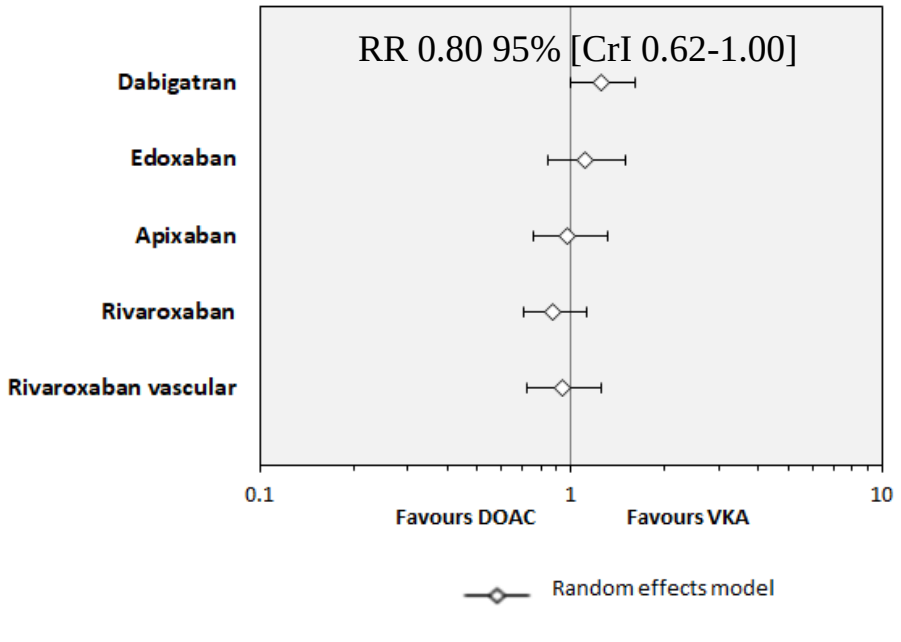
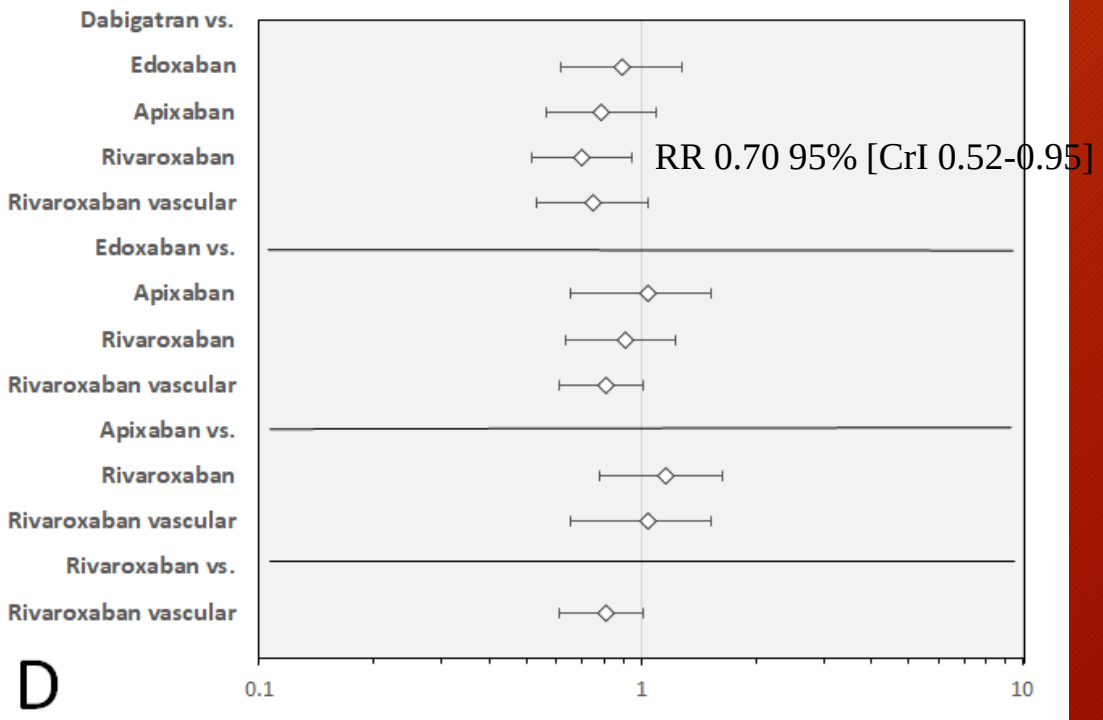


C



D

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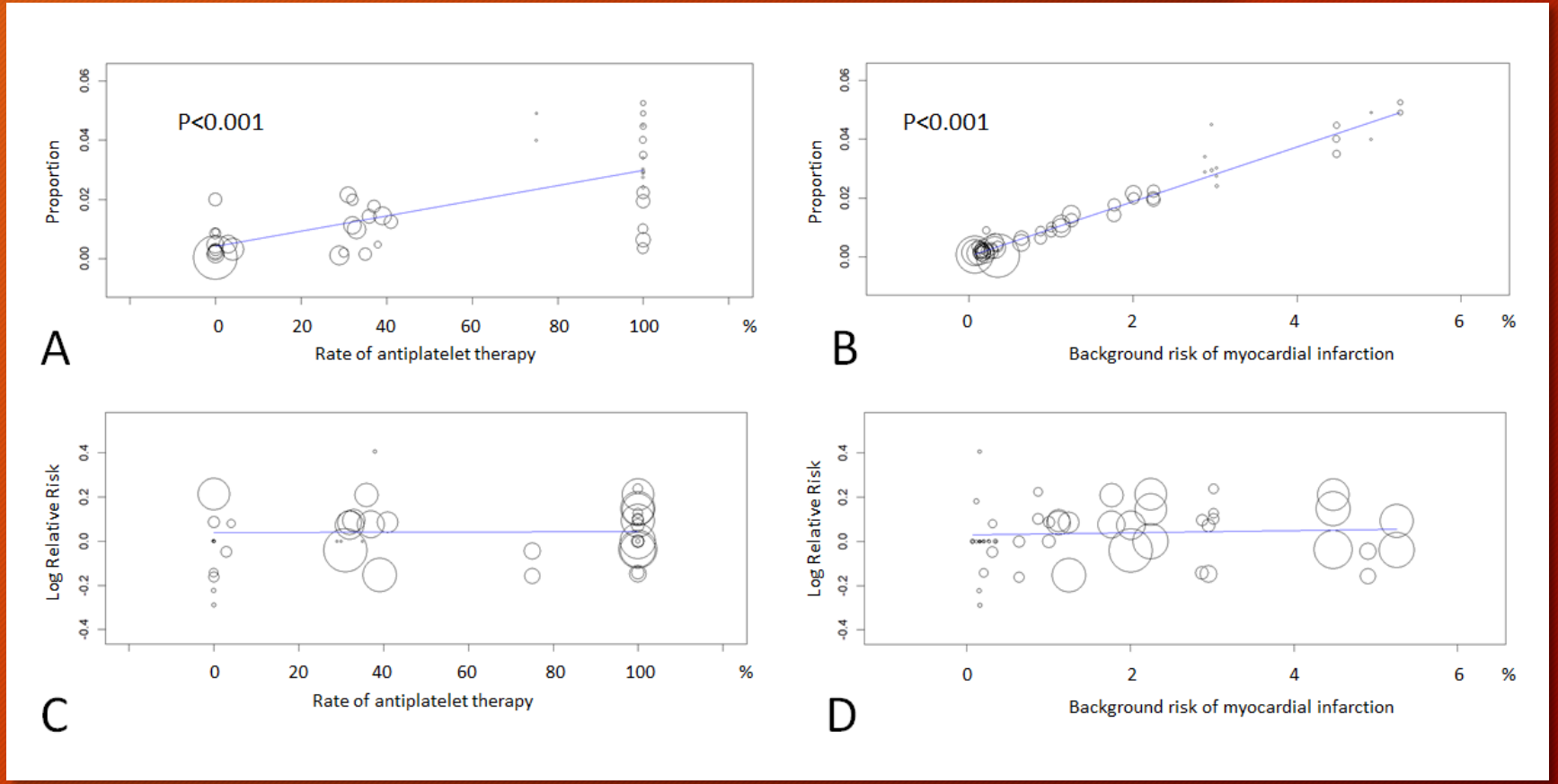
Background risk and antiplatelet therapy

Rate of MI events correlated to the rate of antiplatelet use, and to the higher background MI rate of the respective control groups.
In multiple regression analysis only background risk prevailed as a significant determinant.

Risk ratio against aspirin computed from the network, showed correlation neither to the antiplatelet use nor to the background risk.



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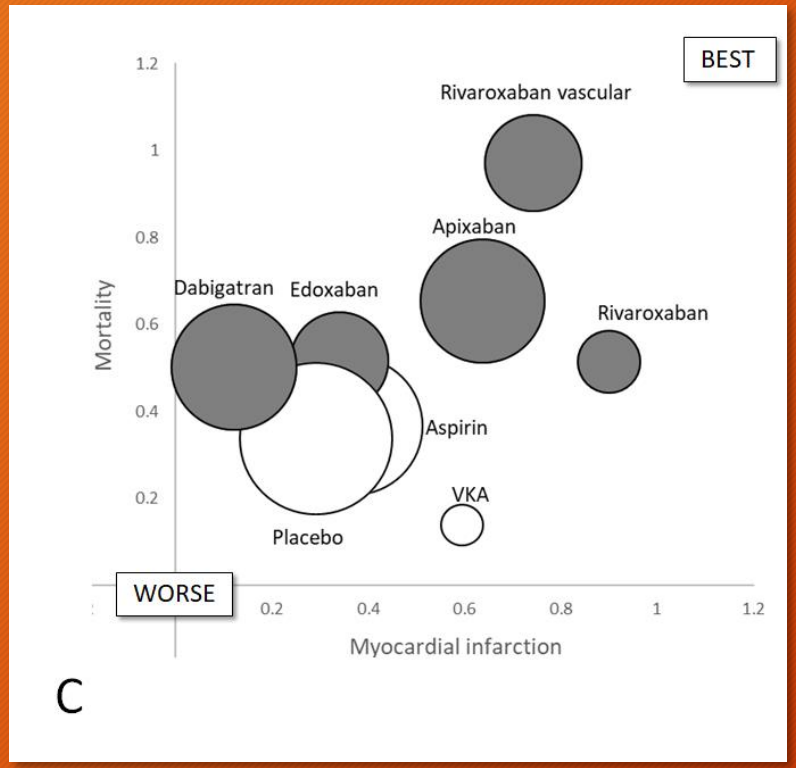
Ranking



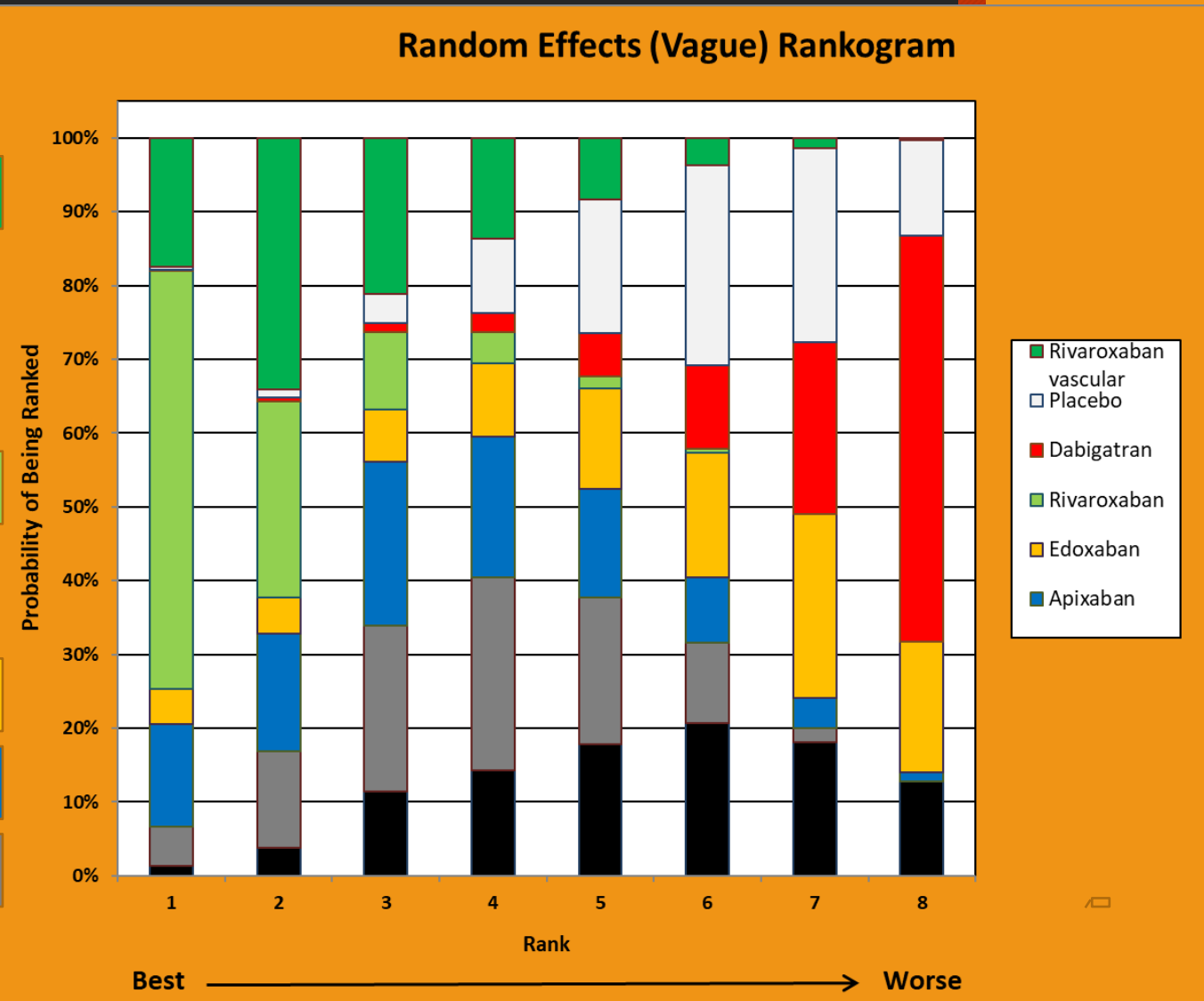
17.5%

56.6%

4.8%

14.0%

5.3%



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Limitations

- None of the trials had MI as primary end-point
- Low incidence of MI among groups (~1%)
- The method used does not allow computation of absoluted risk reduction and NNT values

Conclusion

- There is a considerable heterogeneity regarding cardiac safety among oral anticoagulants
- Treatment with rivaroxaban is associated with reduced rate of MI
- Differences in risk of myocardial infarction may influence the choice of treatment

Thank your very much for your attention!

EHRA Practical Guide on the use of NOACs in patients with non-valvular AF

Table 12 Recommendations concerning new onset AF in patients with a recent (<1 year) ACS

1. In patients with low or moderate atherothrombotic risk (GRACE risk <118), VKAs in monotherapy could be considered after 1–3 months (or 6 months in case of DES), especially when the bleeding risk is elevated (HAS-BLED ≥3)
2. In patients with high atherothrombotic risk (GRACE risk >118), additional single antiplatelet therapy (preferably clopidogrel) might be necessary, especially when their bleeding risk is acceptable (HAS-BLED <3)
3. Dual antiplatelet therapy without additional anticoagulation might be an alternative for patients with a low CHA_2DS_2-VASc score (i.e. ≤1) but high residual atherothrombotic risk (i.e. GRACE risk score >118)
4. If a NOAC would be indicated, a FXa inhibitor might be preferred in view of the small but insignificant increase in the risk of myocardial infarction with dabigatran, but this needs to be weighed against the overall perceived clinical effect (which was not impacted for dabigatran)
5. If dabigatran would be indicated, a lower dose (110 mg bid) might be preferred, in combination with low-dose aspirin or with clopidogrel
6. Ultra-low-dose rivaroxaban (2.5 mg BID or 5 mg BID) in combination with DAPT has not been evaluated in the setting of AF and can currently not be recommended

Table 13 Recommendations concerning new onset AF in patients with a remote (>1 year) ACS

1. As VKAs alone are superior to aspirin post-ACS, anticoagulation without additional antiplatelet agents is considered sufficient for most AF patients with stable CAD
2. As the advantages of NOACs over VKAs are likely to be preserved in stable CAD patients with AF, NOACs may be safe and effective alternatives to VKAs
3. In general, no preference is given to either one of the NOACs although a small increase was noted with dabigatran (but without impacting overall clinical benefit)
4. If dabigatran is chosen, a lower dose (110 mg bid) plus low-dose aspirin might be a sensible option (or clopidogrel in case of allergy to aspirin) especially in patients with high atherothrombotic risk and low bleeding risk

ACS, acute coronary syndrome; bid, twice daily; CAD, coronary artery disease.