Recanalization Therapy & Secondary Prophylaxis in the Elderly

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Disclosures

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Content

- Recanalization Therapies:
  - I.v. tPA & Endovascular Treatment in the Elderly
  - Pre-existing Dementia and Disability

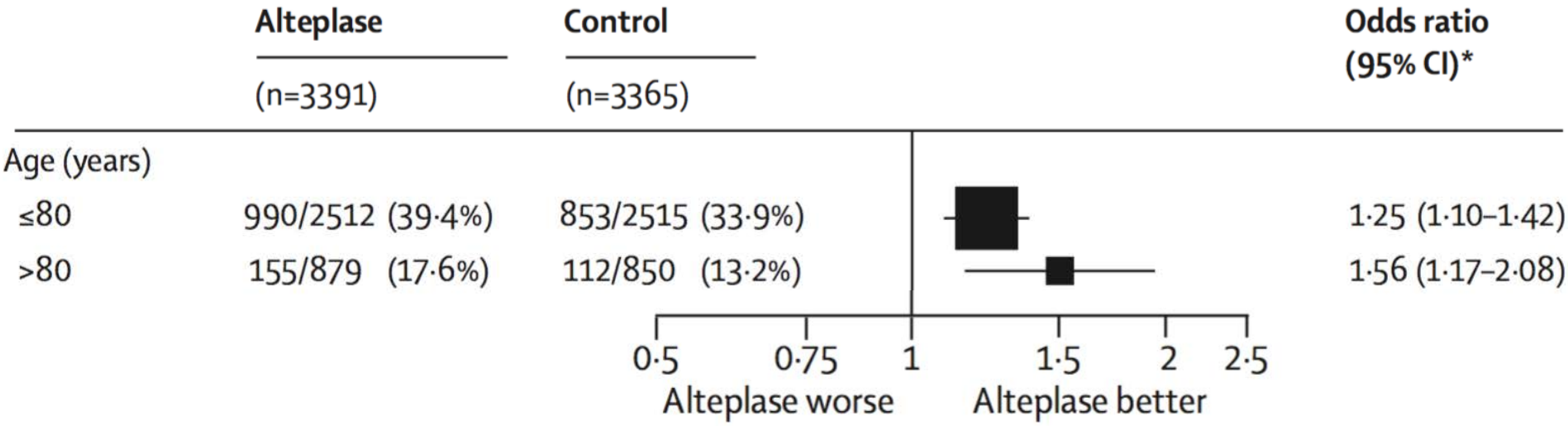
- Secondary Prophylaxis in the Elderly
  - DOAC vs. VKA
  - DOAC vs. DOAC (indirect comparisons)
  - DOAC vs. Aspirin

Stereotype #1

„Older patients do not benefit from i.v. tPA“

Patients >80 years benefit from i.v. tPA as much as patients ≤80 years

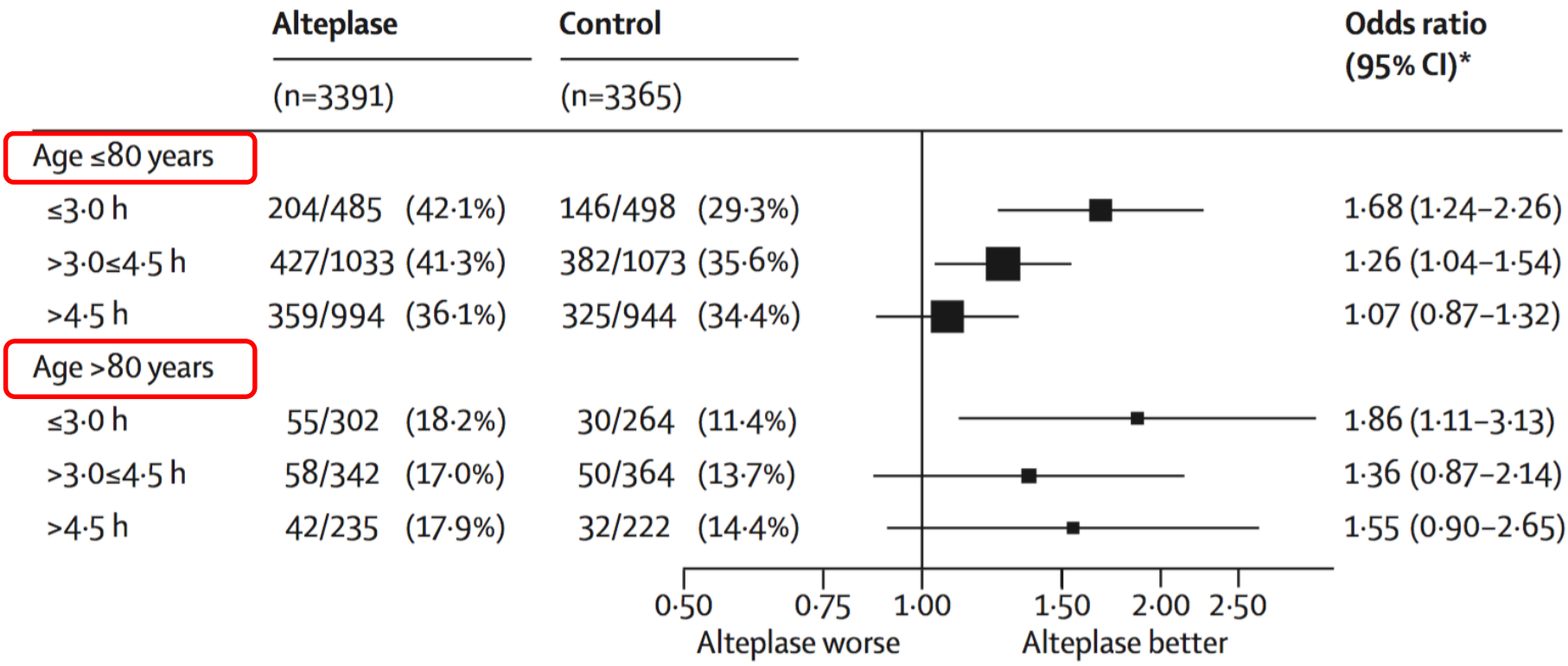
Meta-analysis of individual patient data from 6756 patients in 9 randomised trials* comparing alteplase with placebo or open control.



***NINDS A, NINDS B, ECASS I, ECASS II, ATLANTIS A, ATLANTIS B, ECASS III, IST-3**

Lancet. 2014;384(9958):1929-35

Age does not significantly affect the interaction between i.v. tPA delay and good outcomes



P=0.08 (ie, not significant but, if anything, in the direction of lengthening, not shortening, the period during which alteplase is effective in older people)
Lancet. 2014;384(9958):1929-35

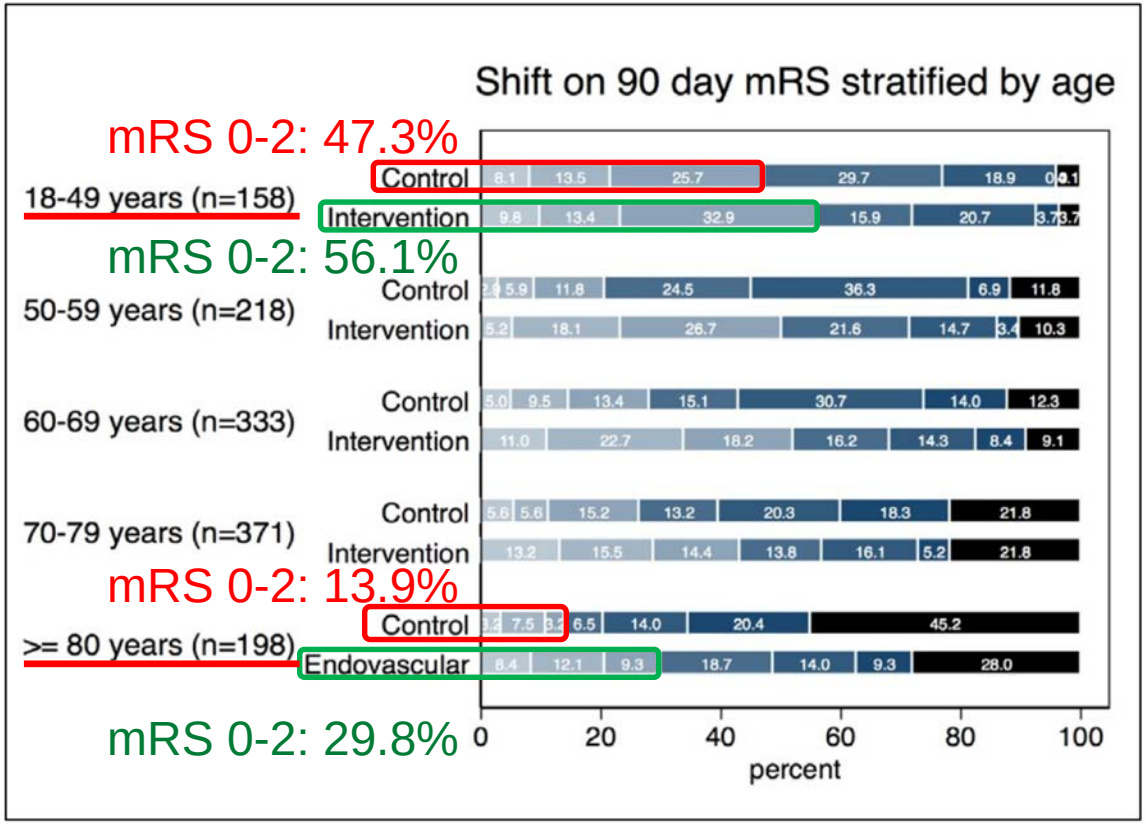
Endovascular Treatment > 80 y.o.

Stereotype #2

„Age is one of the strongest predictor of poor outcomes, so that endovascular treatments are useless in the elderly.“

Patients ≥80 years have a worse prognosis, but EVT improves their chances of a good outcome

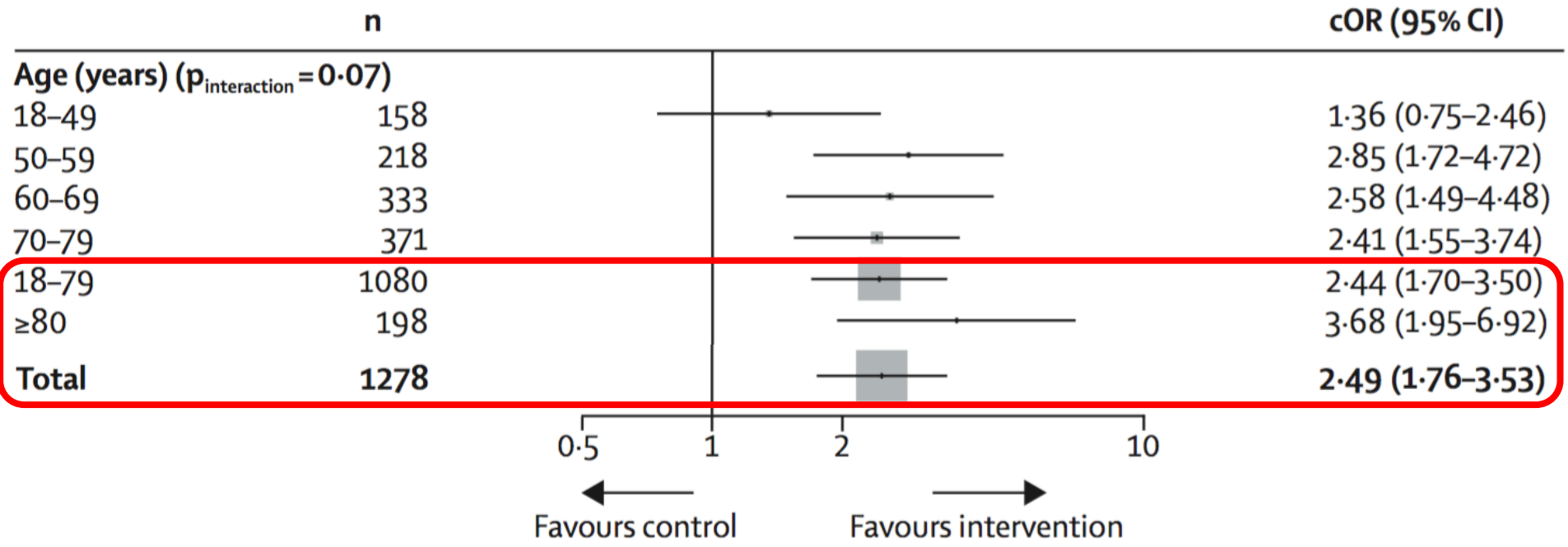
Meta-analysis of individual patient data from MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA (n=1287), HERMES collaborators



Lancet. 2016;387(10029):1723-31

Patients ≥80 years do benefit from endovascular treatment

Meta-analysis of individual patient data from MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA (n=1287), HERMES collaborators



Lancet. 2016;387(10029):1723-31

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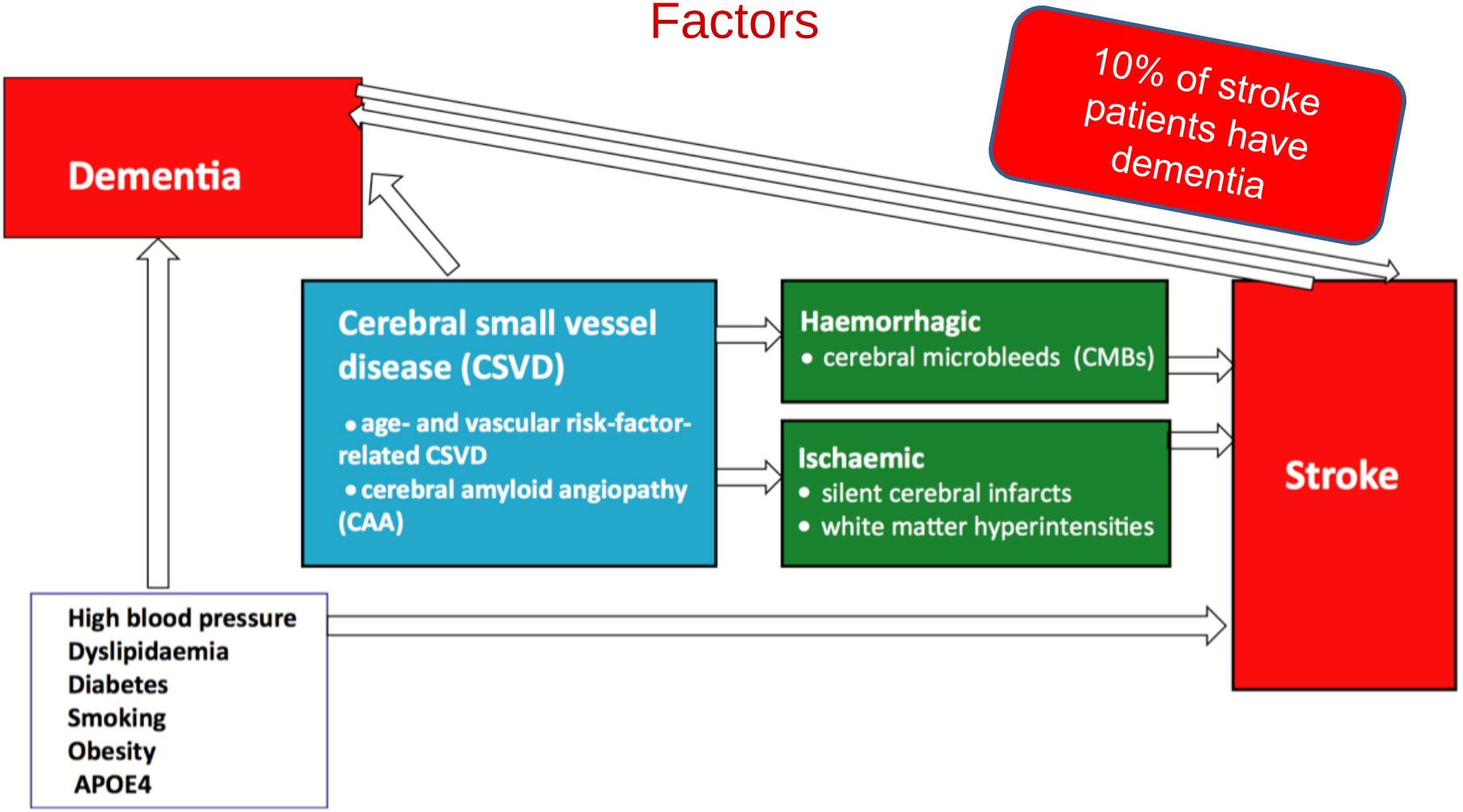
Pre-Existing Dementia & Disability

Stereotype #3

„Patients with dementia bleed more if treated with i.v. tPA“

Stroke & Dementia in the Elderly Share the Same Risk Factors



J Intern Med. 2017;281(4):348-64.

Dementia→thrombolysis rate 0.56%–10% vs 1–16% in the general population

Table 4 Reasons thrombolysis was not administered[a]

Reason thrombolysis was not given	Dementia (n = 628)	No dementia (n = 7, 250)	Standardized difference	*p* Value
Arrival more than 3 hours after stroke onset (%)[b]	27.1	29.4	0.05	0.29
Patient condition too mild (e.g., deficit resolved, rapidly improving, or low NIHSS)	13.2	16.8	0.10	0.054
Patient condition too severe (e.g., decreased level of consciousness or high NIHSS)	4.3	1.4	0.23	<0.001
Delay in decision to treat	1	0.6	0.04	0.51
Other contraindications to thrombolysis	7.0	6.0	0.04	0.31
Physician decision	13.5	7.5	0.22	<0.001
No reason stated	39.8	41.3	0.03	0.48

I.v. Thrombolysis in Patients with Pre-existing Dementia

Alshekhlee A *et al* *Neurology* 2011;76:1575–1580	**Dementia (n=207)**	**Non-Dementia (n=621)**	***P***
sICH	5.8%	4.5%	0.45
Hospital Mortality	17,4%	14.5%	0.31
Saposnik G *et al* J Neurol 2012;259:2366–2375	**Dementia (n=99)**	**Non-Dementia (n=99)**	***P***
sICH	11.1%	11.1%	n.s.
Hospital Mortality	22.2%	26.3%	n.s.
Gensicke H et al Stroke 2016; 47:450–456	**NO Pre-existing Disability (n=7430)**	**Pre-existing Disability (n=489)**	***P***
sICH	4.8%	4.5%	n.s.
3-month poor outcome	**a**OR 0.95; 95% CI, 0.75-1.21		

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Oral Anticoagulation in the Elderly

Oral Anticoagulation in the Elderly

- 1/10 person ≥75 years has atrial fibrillation
- ↑Age = ↑Stroke Risk
- Age≥75 y. = 2 points in the CHA_2DS_2-Vasc Score→OAC recommended

BUT:

- Risk of VKA-related bleeding in patients ≥75 y.o.: 5%
- Poor cognitive functions→VKA-nonadeherence
- DOAC are increasingly prescribed in the elderly

→ What do we know on the efficacy and safety of DOACs and VKA among patients with atrial fibrillation and ≥75 y.o.?

Group characteristics of trials on atrial fibrillation

Trial Name (Year)	Patients ≥75 years included in the trial
ROCKET AF (2011) Rivaroxaban vs. Warfarin	43%
RE-LY (2009) Dabigatran vs. Warfarin	31%
ENGAGE AF-TIMI 48 (2013) Edoxaban vs. Warfarin	40%
ARISTOTLE (2011) Apixaban vs. Warfarin	31%

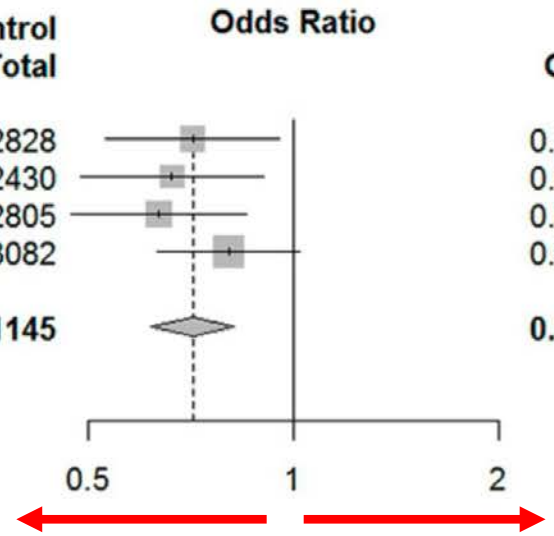
DOAC in ***full*** Dose vs. VKA, ≥75 y.o.
Endpoint = Any Stroke or Systemic Embolism

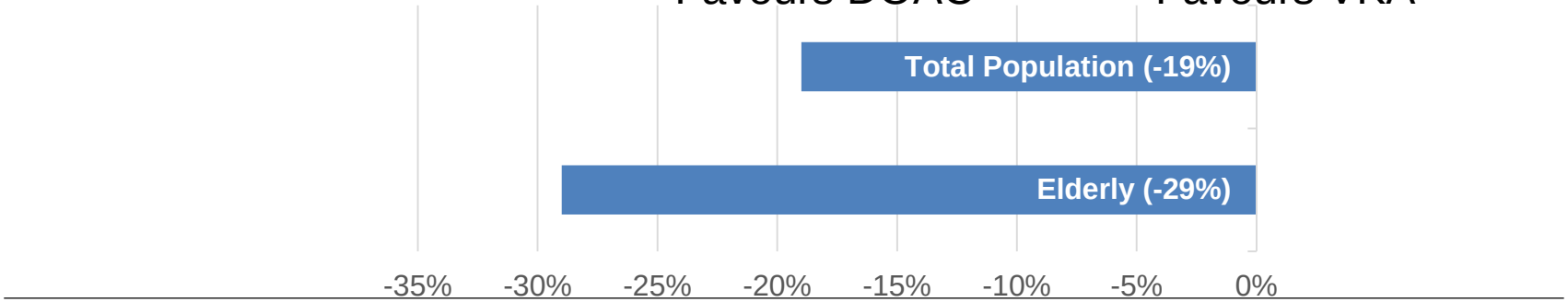
Meta-Analysis of the 4 RCTs comparing DOAC to VKA in AFIB (n=22‘381)

Substance (Study)	Experimental Events	Experimental Total	Control Events	Control Total	OR	95%-CI	W(fixed)
Apixaban (ARISTOTLE)	79	2850	109	2828	0.71	[0.53; 0.95]	22.9%
Dabigatran 150 mg (RELY)	69	2466	101	2430	0.66	[0.49; 0.91]	20.4%
Edoxaban 60 mg (ENGAGE AF-TIMI 48)	75	2838	115	2805	0.63	[0.47; 0.85]	22.7%
Rivaroxaban (ROCKET)	125	3082	154	3082	0.80	[0.63; 1.02]	34.0%
Fixed effect model	**348**	**11236**	**479**	**11145**	**0.71**	**[0.62; 0.82]**	**100%**

Heterogeneity: I-squared=0%, tau-squared=0, p=0.6283

Test for overall effect: p<0.0001





Swiss Med Wkly. 2016;146:w14356
Lancet. 2014;383(9921):955-62

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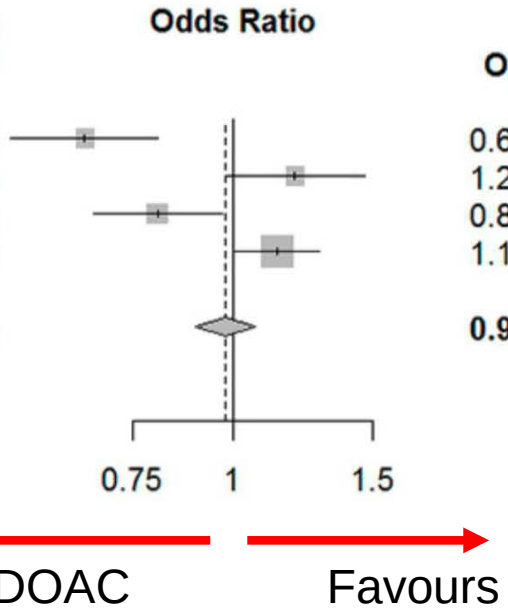
DOAC in ***full*** Dose vs. VKA, ≥75 y.o.
Endpoint = Major and Clinically Relevant Non-Major Bleeding

Substance (Study)	Experimental Events	Experimental Total	Control Events	Control Total	OR	95%-CI	W(fixed)
Apixaban (ARISTOTLE)	151	2836	224	2819	0.65	[0.53; 0.81]	15.7%
Dabigatran 150 mg (RELY)	227	2145	188	2088	1.20	[0.98; 1.47]	17.2%
Edoxaban 60 mg (ENGAGE AF-TIMI 48)	224	2838	270	2805	0.80	[0.67; 0.97]	20.8%
Rivaroxaban (ROCKET)	693	2688	633	2702	1.14	[1.00; 1.29]	46.3%
Fixed effect model	**1295**	**10507**	**1315**	**10414**	**0.98**	**[0.90; 1.06]**	**100%**

Heterogeneity: I-squared=89.1%, tau-squared=0.0662, p<0.0001

Test for overall effect: p=0.5999



→ No difference between DOAC and VKA in the elderly and total population (OR 0.86, 95%-CI 0.73–1.00)

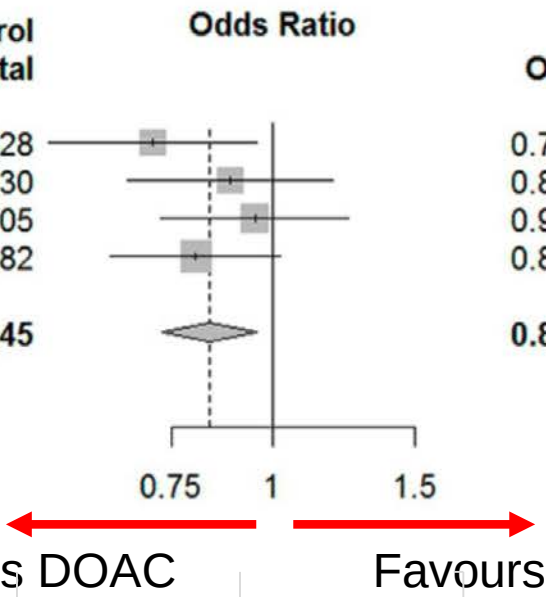
DOAC in ***low*** Dose vs. VKA, ≥75 y.o.
Endpoint = Any Stroke or Systemic Embolism

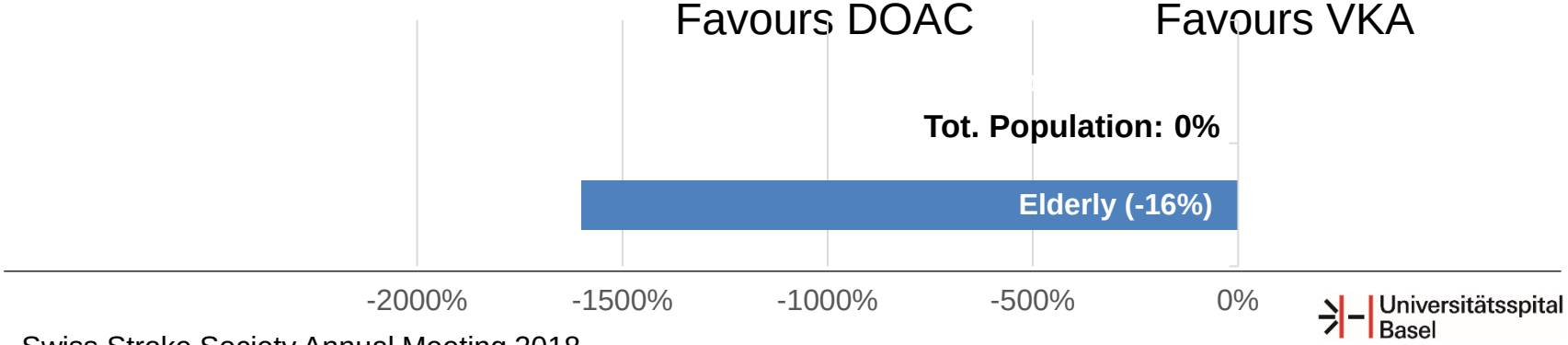
CAVE: Increased risk of ischemic stroke with low dose DOAC

Substance (Study)	Experimental Events	Experimental Total	Control Events	Control Total	OR	95%-CI	W(fixed)
Apixaban (ARISTOTLE)	79	2850	109	2828	0.71	[0.53; 0.95]	21.2%
Dabigatran 110 mg (RELY)	87	2349	101	2430	0.89	[0.66; 1.19]	21.5%
Edoxaban 30 mg (ENGAGE AF-TIMI 48)	109	2789	115	2805	0.95	[0.73; 1.24]	25.7%
Rivaroxaban (ROCKET)	125	3082	154	3082	0.80	[0.63; 1.02]	31.6%
Fixed effect model	**400**	**11070**	**479**	**11145**	**0.84**	**[0.73; 0.96]**	**100%**

Heterogeneity: I-squared=0%, tau-squared=0, p=0.5095

Test for overall effect: p=0.0093





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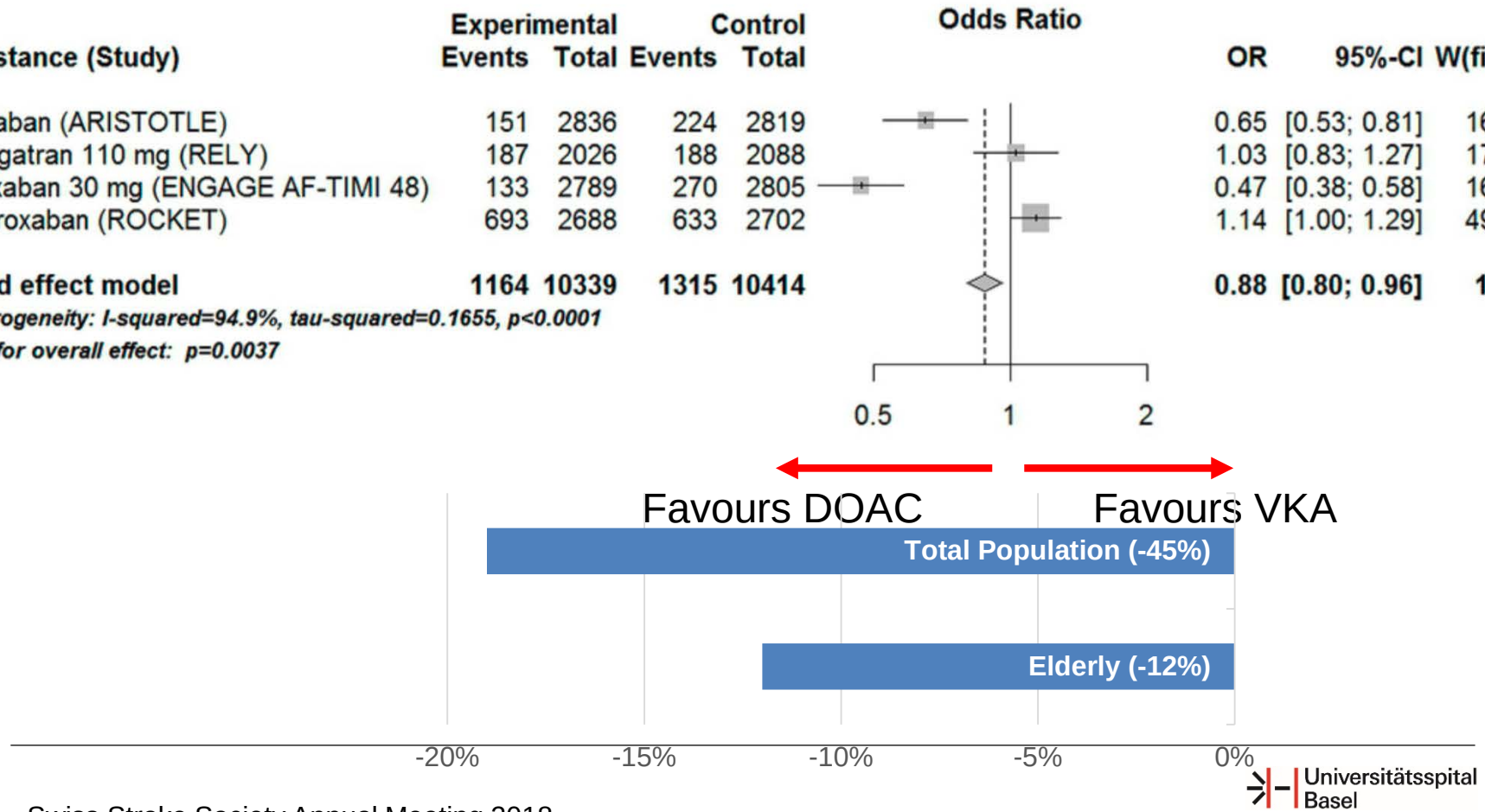
DOAC in ***low*** Dose vs. VKA, ≥75 y.o.
Endpoint = Major and Clinically Relevant Non-Major Bleeding

Substance (Study)	Experimental Events	Experimental Total	Control Events	Control Total	OR	95%-CI	W(fixed)
Apixaban (ARISTOTLE)	151	2836	224	2819	0.65	[0.53; 0.81]	16.8%
Dabigatran 110 mg (RELY)	187	2026	188	2088	1.03	[0.83; 1.27]	17.0%
Edoxaban 30 mg (ENGAGE AF-TIMI 48)	133	2789	270	2805	0.47	[0.38; 0.58]	16.6%
Rivaroxaban (ROCKET)	693	2688	633	2702	1.14	[1.00; 1.29]	49.7%
Fixed effect model	**1164**	**10339**	**1315**	**10414**	**0.88**	**[0.80; 0.96]**	**100%**

Heterogeneity: I-squared=94.9%, tau-squared=0.1655, p<0.0001

Test for overall effect: p=0.0037



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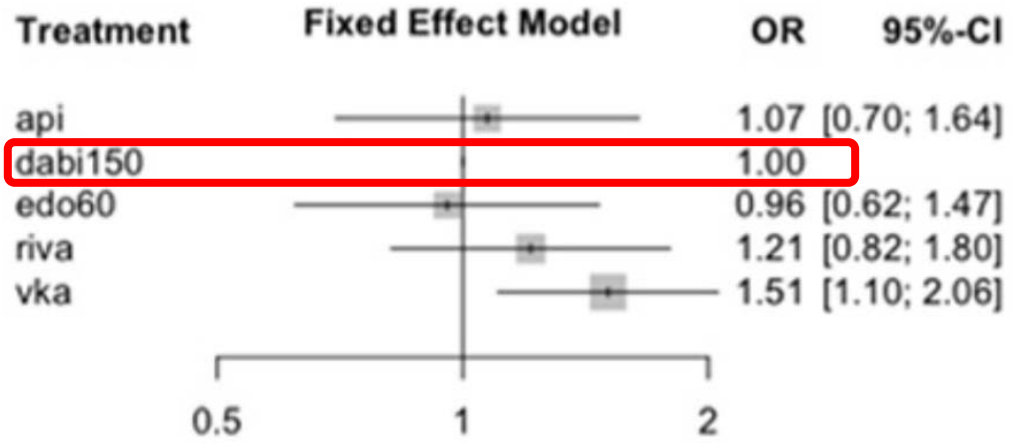
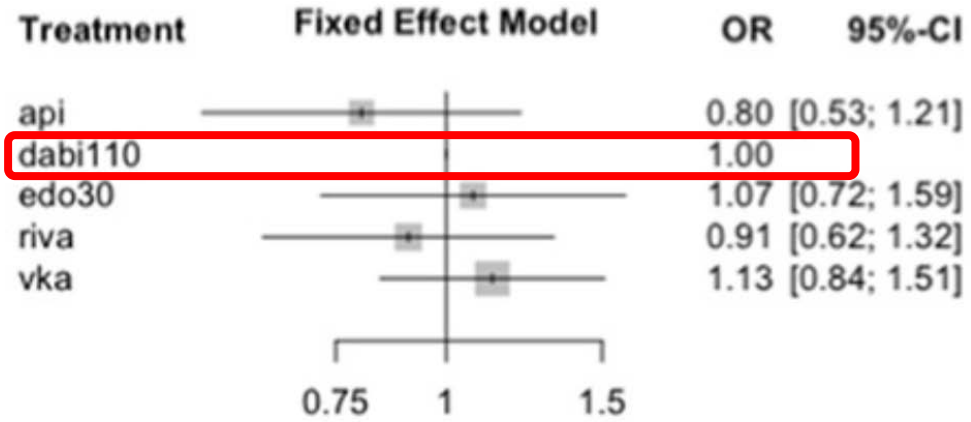
Indirect Comparison of DOAC, ≥75 y.o.

Indirect comparison of DOAC, ≥75 y.o.

- No RCT available comparing DOACs to each other.
- Indirect comparisons between DOACs using data from RCT are biased.
- Conflicts of interest may influence the interpretation of data.

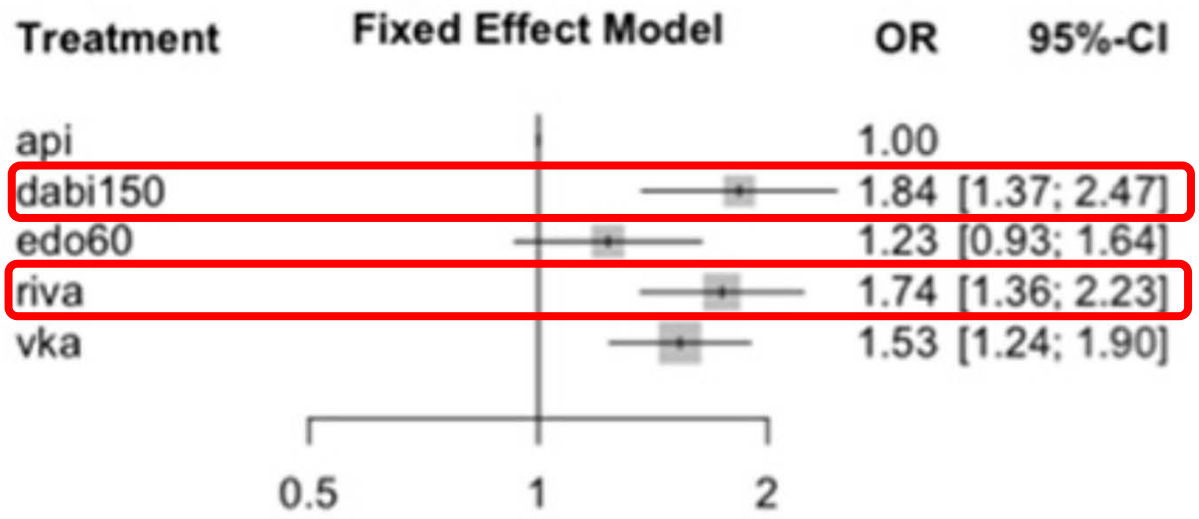
Indirect Comparison of DOAC, ≥75 y.o.
Endpoint = Any Stroke or Systemic Embolism





No significant difference between DOACs in the prevention of SSE

Indirect Comparison of DOAC, ≥75 y.o. Endpoint = Major or Clinically Significant Bleeding



Indirect Comparison: Compared to Apixaban, *apparently* elevated bleeding risk under D150mg (***+84%***), D110mg (***+58%***), and Rivaroxaban (***+74%***). ***However:***

- In patients ≥75 y.o.: lower CHADS2 score in ARISTOTLE (2.7) than in ROCKET (3.7)
- Patients on Aspirin: ARISTOTLE: 31%, RELY: 40%, ROCKET: 40%
- In the RCTs on VTE, Apixaban not shown to be safer

  → ***Differences in the trial populations may explain the apparently better safety profile of apixaban.***

Indirect Comparison of DOAC, ≥75 y.o.
Endpoint = Major or Clinically Significant Bleedding

DOAC1	*vs*	DOAC2	OR for Bleeding
D150mg	*vs*	Edo 60mg	**1.49**, 95% CI 1.13-1.96
D110mg	*vs*	Edo 30mg	**2.19**, 95% CI 1.62-2.96
→*However*, Patients on Aspirin: RELY: 40%, ENGAGE-AF TIMI: 29%			

RCT populations do not entirely reflect the clinical population

- Patients with reduced life expetancy (1 to 2 years depending on the trial) were excluded.

- Likely exclusion of people with dementia (challenging informed consent process), as well as people with psychosocial issues or living in nursing homes for whom follow-up could be difficult

→ We need more clinical studies on DOAC for the elderly, without excluding frail people

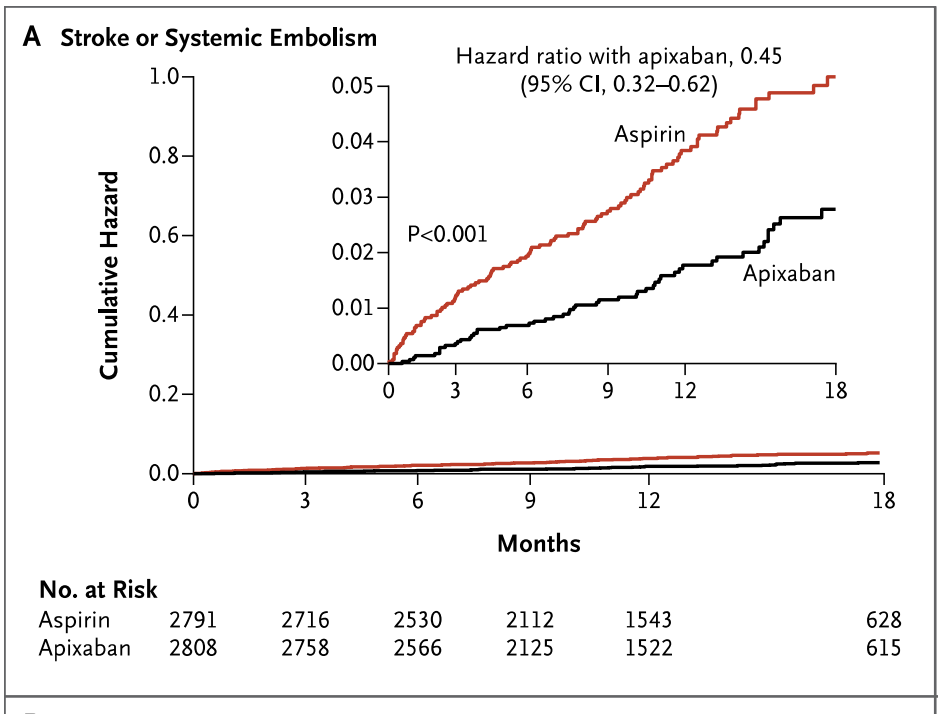
Stereotype #4

„Older people fall more often, so that we treat them with aspirin instead of oral anticoagulants regardless of their CHADS-Score.“

What if the patients is unsuited to VKA – No oral anticoagulation at all?

- Double-blind randomized clinical trial (AVERROES)
- 5599 patients with atrial fibrillation for whom VKA was unsuitable
- Apixaban (2*5mg) vs. Aspirin (81 to 324 mg/d)

Stroke or Systemic Embolism

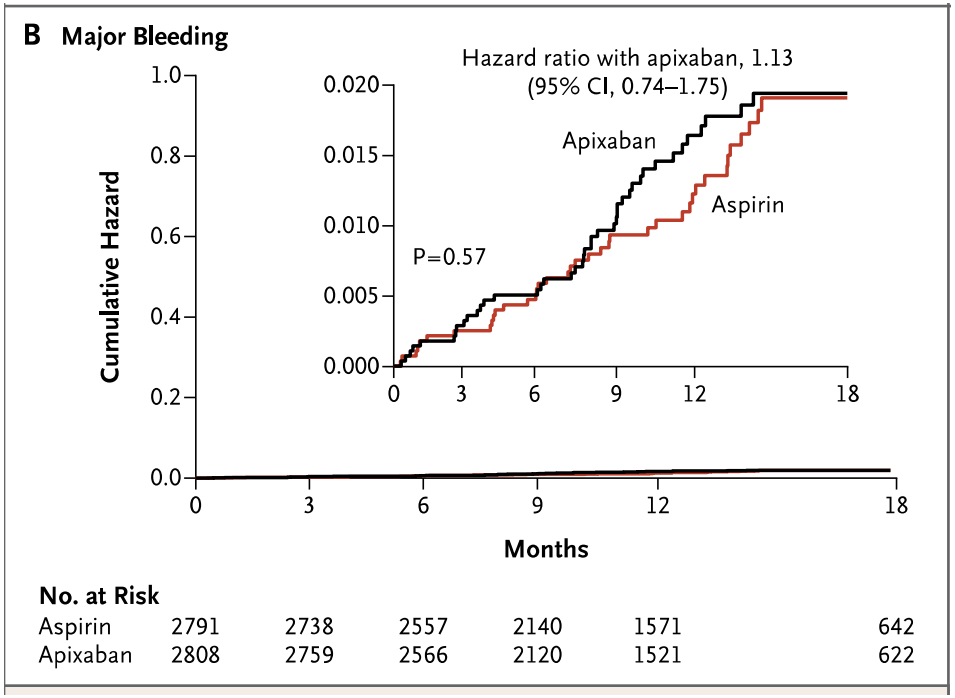


N Engl J Med. 2011;364(9):806-817

What if the patients is unsuited to VKA – No oral anticoagulation at all?

„Treating 1000 patients for 1 year with apixaban rather than with aspirin would **prevent 21 strokes** or systemic emboli, **9 deaths**, and **33 hospitalizations** for cardiovascular causes, at the **cost of 2 major bleeding events**“.

Major Bleeding



N Engl J Med. 2011;364(9):806-817

Summary

- Age alone should not be an exclusion reason for IV tPA or EVT.
- Neither should mild pre-existing dementia, unless this treatment is precluded because of other reasons.
- Not all patients with dementia are suitable for all interventions.
- All DOACs are effective and safe also in the elderly
- Indirect DOAC to DOAC comparisons are misleading because of baseline imbalances.
- Older people with atrial fibrillation for whom VKA does not seem a safe option can still benefit from DOACs.

Thank you to the Stroke Team and Many More!