UNIKLINIK KÖLN

Der komplexe Gefäßpatient

Wer profitiert von einer antithrombotischen Kombinationstherapie?

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Interessenkonflikte

Vortragshonorare:
Abbott, Astra Zeneca, Bayer, BMS/Pfizer, CVRx, Daiichi-Sankyo, Medtronic, Sanofi-Aventis, Vifor

Reisekosten:
Amgen, BMS/Pfizer, Boehringer Ingelheim Fonds, CVRx, Orion Pharma, Servier

Antithrombotische Strategien

KHK
symptomatische pAVK
cAVK

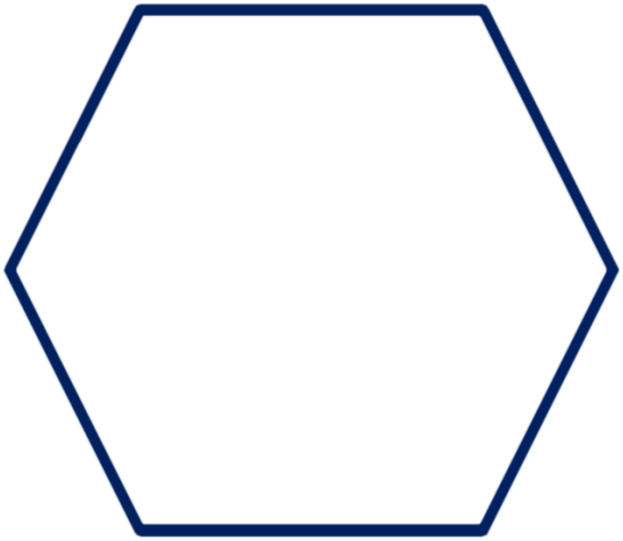
Stenting
Akutes Koronarsyndrom

Einfache Plättchenhemmung

Duale Plättchenhemmung

Wer profitiert?

ASS 100 mg +
Rivaroxaban
2x 2,5 mg



NOAK /
VKA

VHF
Thrombembolien
Kunstklappen

Kurzfristig bei sehr hohem thrombembolischen Risiko

Triple-Therapie

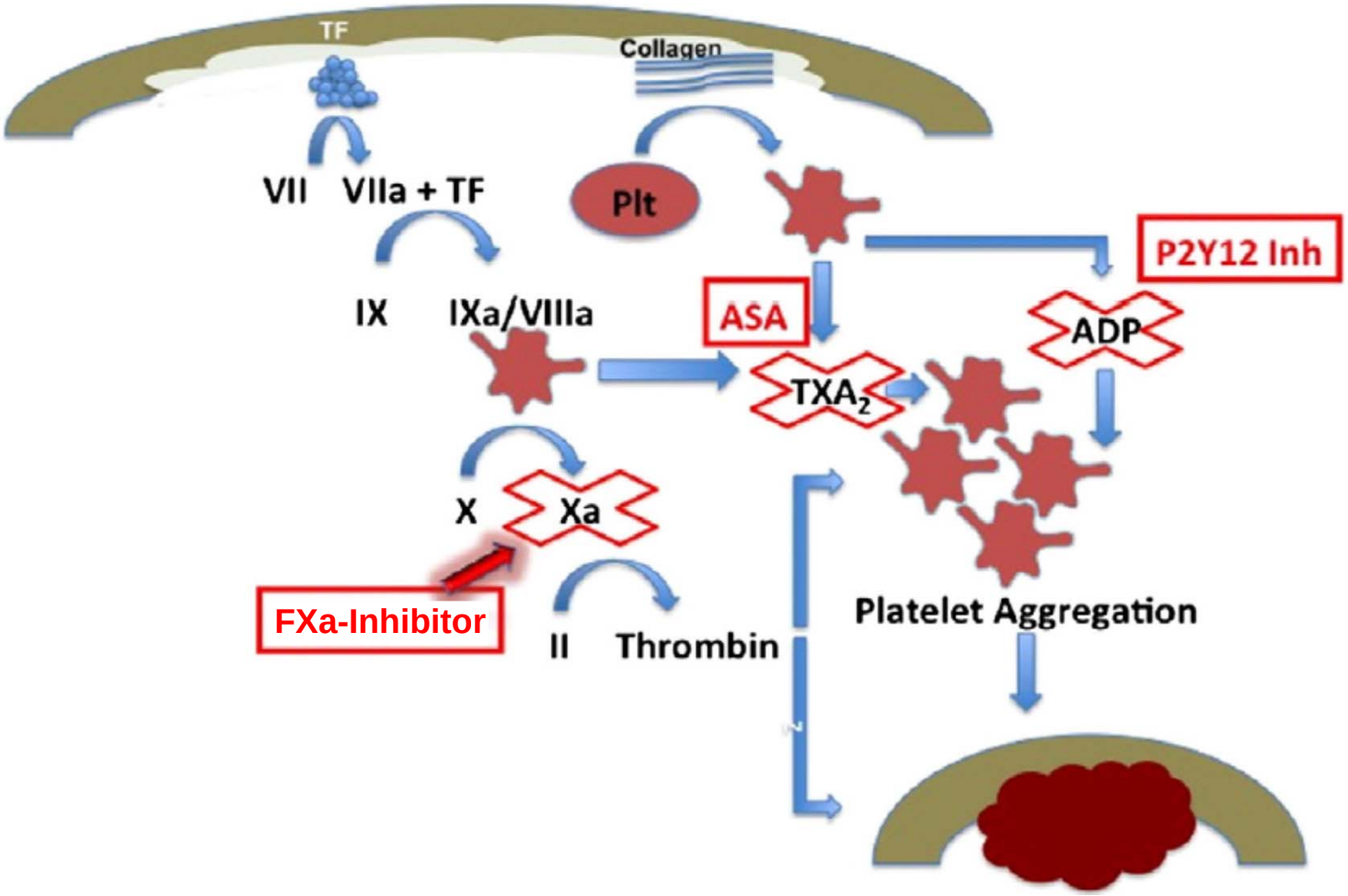
Stenting +
Indikation zur OAK

NOAK / VKA +
Clopidogrel

Stenting +
Indikation zur OAK

Standard

Rationale



Povsic et al., Am Heart J 2016

COMPASS Studie

- 27.395 Patienten mit KHK oder pAVK (inkl. Karotisstenose >50%)
- Randomisiert, doppelt verblindet
- Rivaroxaban 2x 5 mg oder ASS 1x 100 mg oder Rivaroxaban 2x 2,5 mg + ASS 1x 100 mg
- Primärer Endpunkt: kardiovaskulärer Tod, Apoplex, Myokardinfarkt

Eikelboom et al., NEJM 2017

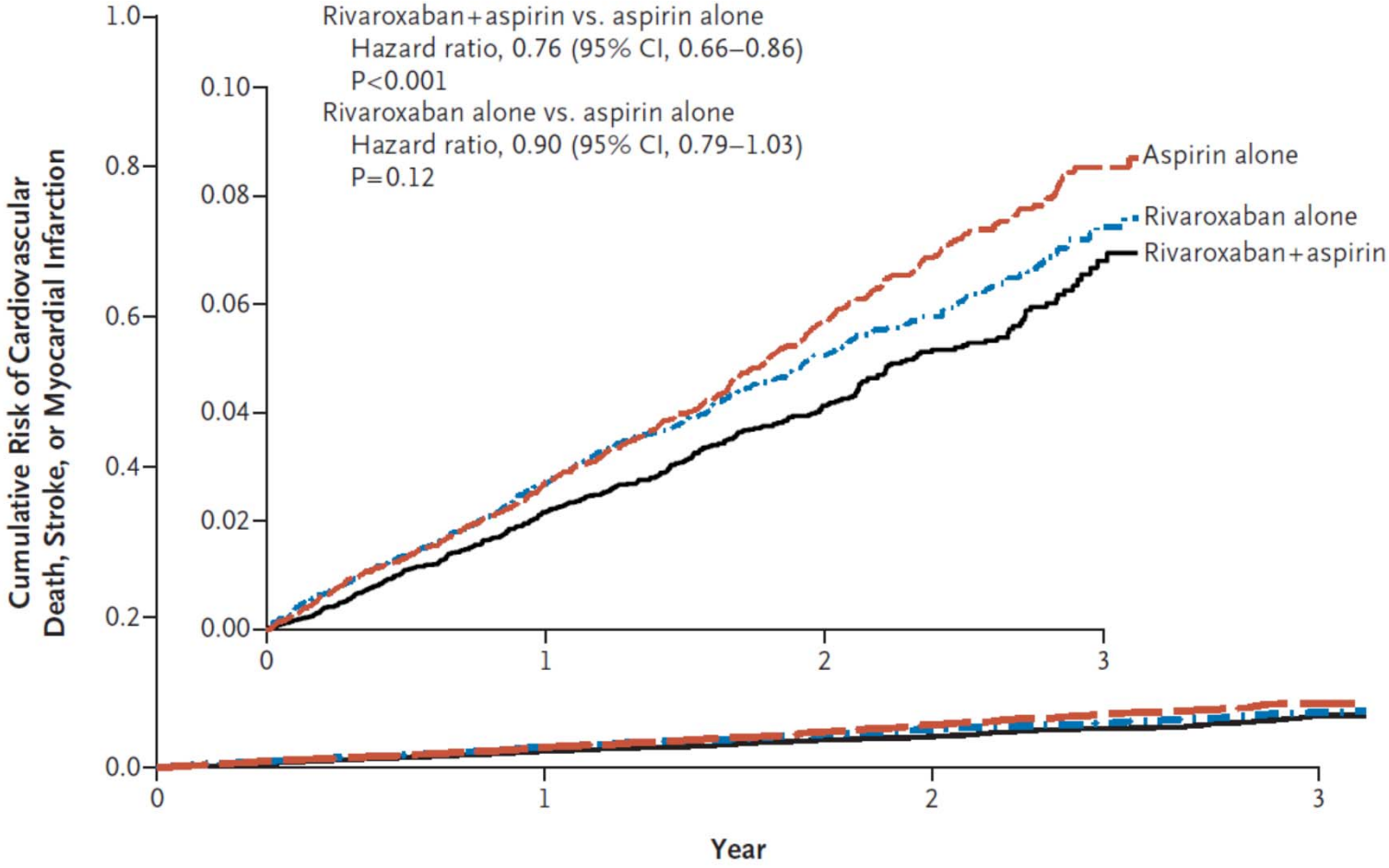
COMPASS Studie

Characteristic	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)
Age — yr	68.3±7.9	68.2±7.9	68.2±8.0
Female sex — no. (%)	2059 (22.5)	1972 (21.6)	1989 (21.8)
Body-mass index†	28.3±4.8	28.3±4.6	28.4±4.7
Blood pressure — mm Hg			
Systolic	136±17	136±18	136±18
Diastolic	77±10	78±10	78±10
Cholesterol — mmol/liter	4.2±1.1	4.2±1.1	4.2±1.1
Tobacco use — no. (%)	1944 (21.2)	1951 (21.4)	1972 (21.6)
Hypertension — no. (%)	6907 (75.5)	6848 (75.1)	6877 (75.4)
Diabetes — no. (%)	3448 (37.7)	3419 (37.5)	3474 (38.1)
Previous stroke — no. (%)	351 (3.8)	346 (3.8)	335 (3.7)
Previous myocardial infarction — no. (%)	5654 (61.8)	5653 (62.0)	5721 (62.7)
Heart failure — no. (%)	1963 (21.4)	1960 (21.5)	1979 (21.7)
Coronary artery disease — no. (%)‡	8313 (90.8)	8250 (90.5)	8261 (90.5)
Peripheral arterial disease — no. (%)§	2492 (27.2)	2474 (27.1)	2504 (27.4)
Estimated GFR — no. (%)¶			
<30 ml/min	77 (0.8)	80 (0.9)	86 (0.9)
30 to <60 ml/min	1977 (21.6)	2028 (22.2)	2028 (22.2)
≥60 ml/min	7094 (77.5)	7005 (76.8)	7012 (76.8)

Eikelboom et al., NEJM 2017

COMPASS Studie

Abbruch wegen Überlegenheit nach 23 Monaten *follow-up*



Eikelboom et al., NEJM 2017

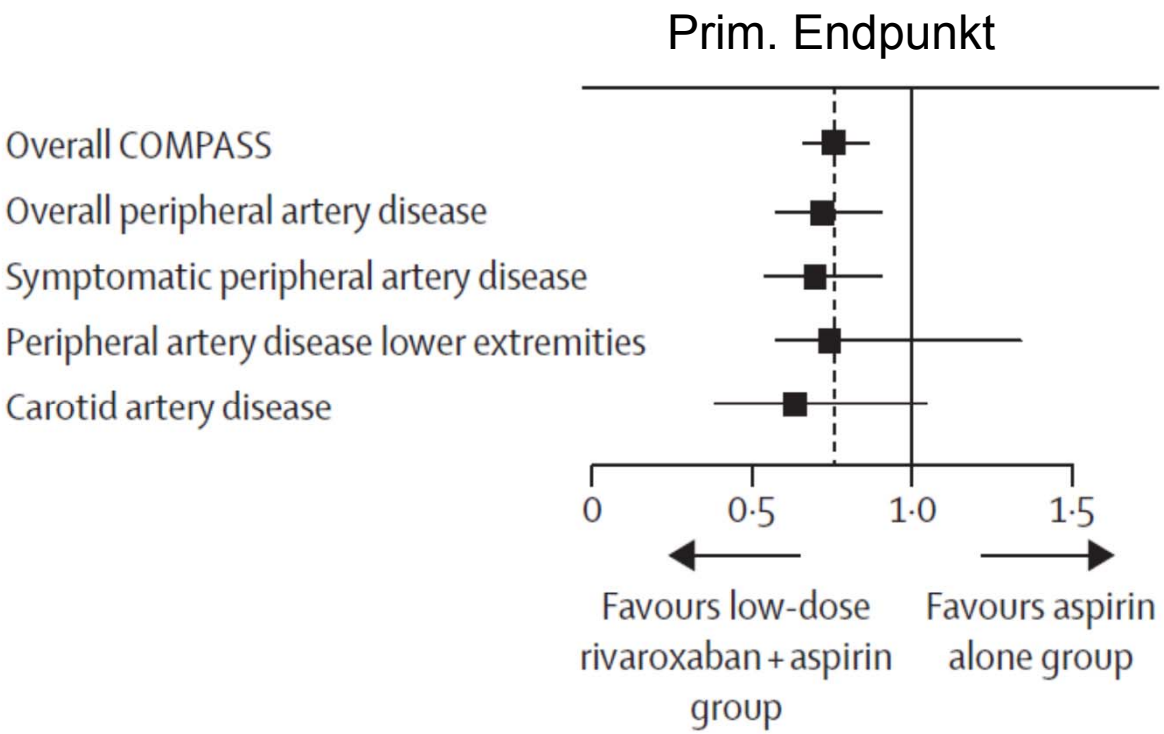
COMPASS Studie

Outcome	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)	Rivaroxaban plus Aspirin vs. Aspirin Alone		Rivaroxaban Alone vs. Aspirin Alone	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
		number (percent)					
Major and minor bleeding							
Major bleeding	288 (3.1)	255 (2.8)	170 (1.9)	1.70 (1.40–2.05)	<0.001	1.51 (1.25–1.84)	<0.001
Fatal bleeding†	15 (0.2)	14 (0.2)	10 (0.1)	1.49 (0.67–3.33)	0.32	1.40 (0.62–3.15)	0.41
Nonfatal symptomatic ICH†	21 (0.2)	32 (0.4)	19 (0.2)	1.10 (0.59–2.04)	0.77	1.69 (0.96–2.98)	0.07
Nonfatal, non-ICH, symptomatic bleeding into critical organ†	42 (0.5)	45 (0.5)	29 (0.3)	1.43 (0.89–2.29)	0.14	1.57 (0.98–2.50)	0.06
							0.001
Fa							0.05
Fa							0.006
Ma							0.001
Tra							0.03
Mi							0.001
Site of							
Gastrointestinal	140 (1.5)	91 (1.0)	65 (0.7)	2.15 (1.60–2.89)	<0.001	1.40 (1.02–1.93)	0.04
Intracranial	28 (0.3)	43 (0.5)	24 (0.3)	1.16 (0.67–2.00)	0.60	1.80 (1.09–2.96)	0.02
Skin or injection site	28 (0.3)	28 (0.3)	12 (0.1)	2.31 (1.18–4.54)	0.01	2.34 (1.19–4.60)	0.01
Urinary	13 (0.1)	30 (0.3)	21 (0.2)	0.61 (0.31–1.23)	0.16	1.43 (0.82–2.50)	0.20
Net-clinical-benefit outcome: CV death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ	431 (4.7)	504 (5.5)	534 (5.9)	0.80 (0.70–0.91)	<0.001	0.94 (0.84–1.07)	0.36

18% Reduktion der Gesamtmortalität

Eikelboom et al., NEJM 2017

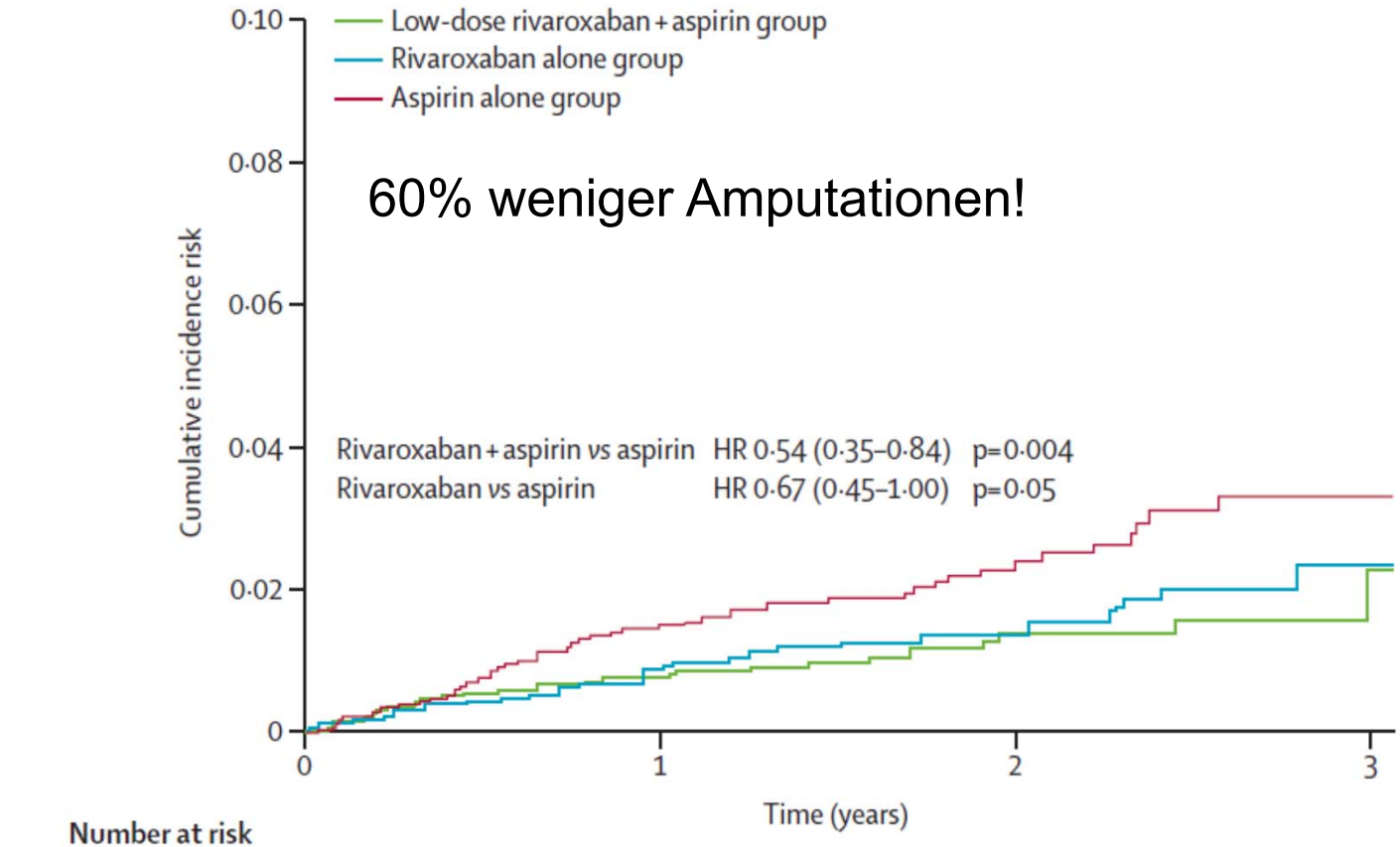
COMPASS Studie – pAVK/cAVK



Anand et al., Lancet 2018

COMPASS Studie – pAVK/cAVK

Major adverse limb events including major amputation



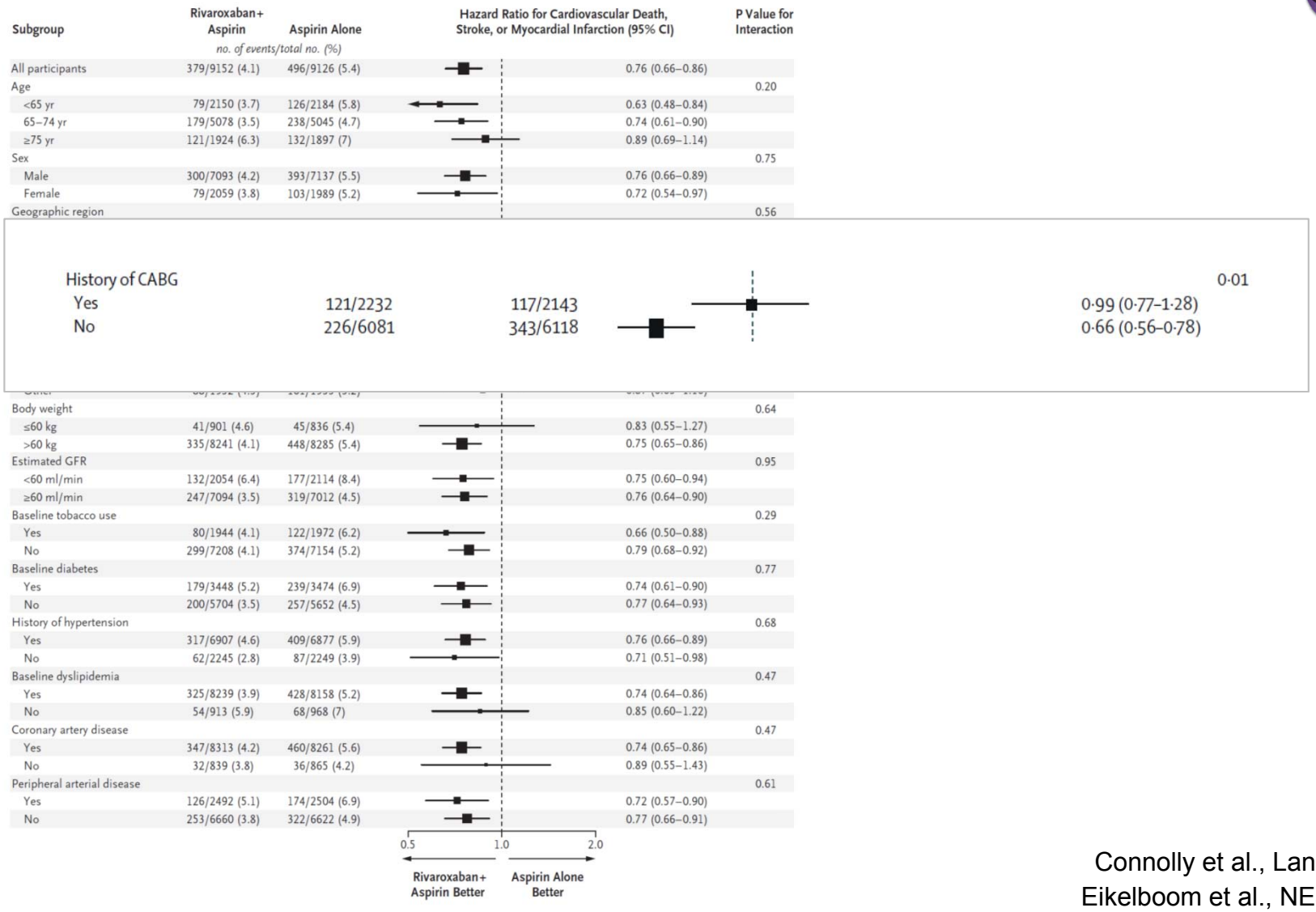
Anand et al., Lancet 2018

Low dose NOAK + ASS für alle

Zulassung:
Rivaroxaban 2,5 mg zweimal täglich in Kombination mit ASS 75-100 mg einmal täglich zur Prophylaxe atherothrombotischer Ereignisse bei erwachsenen Patienten mit KHK oder symptomatischer pAVK und einem hohen Risiko für ischämische Ereignisse

~1.200 €/J
~6,5 Millionen Patienten in D
~7,7 Milliarden €/J
~3,5% der GKV Ausgaben

COMPASS Studie – Subgruppenanalysen



Subgroup	Rivaroxaban+ Aspirin	Aspirin Alone	Hazard Ratio for Cardiovascular Death, Stroke, or Myocardial Infarction (95% CI)	P Value for Interaction
	no. of events/total no. (%)			
All participants	379/9152 (4.1)	496/9126 (5.4)	0.76 (0.66–0.86)	
Age				0.20
<65 yr	79/2150 (3.7)	126/2184 (5.8)	0.63 (0.48–0.84)	
65–74 yr	179/5078 (3.5)	238/5045 (4.7)	0.74 (0.61–0.90)	
≥75 yr	121/1924 (6.3)	132/1897 (7)	0.89 (0.69–1.14)	
Sex				0.75
Male	300/7093 (4.2)	393/7137 (5.5)	0.76 (0.66–0.89)	
Female	79/2059 (3.8)	103/1989 (5.2)	0.72 (0.54–0.97)	
Geographic region				0.56
History of CABG				0·01
Yes	121/2232	117/2143	0·99 (0·77–1·28)	
No	226/6081	343/6118	0·66 (0·56–0·78)	
Body weight				0.64
≤60 kg	41/901 (4.6)	45/836 (5.4)	0.83 (0.55–1.27)	
>60 kg	335/8241 (4.1)	448/8285 (5.4)	0.75 (0.65–0.86)	
Estimated GFR				0.95
<60 ml/min	132/2054 (6.4)	177/2114 (8.4)	0.75 (0.60–0.94)	
≥60 ml/min	247/7094 (3.5)	319/7012 (4.5)	0.76 (0.64–0.90)	
Baseline tobacco use				0.29
Yes	80/1944 (4.1)	122/1972 (6.2)	0.66 (0.50–0.88)	
No	299/7208 (4.1)	374/7154 (5.2)	0.79 (0.68–0.92)	
Baseline diabetes				0.77
Yes	179/3448 (5.2)	239/3474 (6.9)	0.74 (0.61–0.90)	
No	200/5704 (3.5)	257/5652 (4.5)	0.77 (0.64–0.93)	
History of hypertension				0.68
Yes	317/6907 (4.6)	409/6877 (5.9)	0.76 (0.66–0.89)	
No	62/2245 (2.8)	87/2249 (3.9)	0.71 (0.51–0.98)	
Baseline dyslipidemia				0.47
Yes	325/8239 (3.9)	428/8158 (5.2)	0.74 (0.64–0.86)	
No	54/913 (5.9)	68/968 (7)	0.85 (0.60–1.22)	
Coronary artery disease				0.47
Yes	347/8313 (4.2)	460/8261 (5.6)	0.74 (0.65–0.86)	
No	32/839 (3.8)	36/865 (4.2)	0.89 (0.55–1.43)	
Peripheral arterial disease				0.61
Yes	126/2492 (5.1)	174/2504 (6.9)	0.72 (0.57–0.90)	
No	253/6660 (3.8)	322/6622 (4.9)	0.77 (0.66–0.91)	

Connolly et al., Lancet 2018
Eikelboom et al., NEJM 2017

Low dose NOAK + ASS für alle?

Einschlusskriterien COMPASS

CAD or PAD plus at least one of the following:

- Age ≥65
- Age <65 plus documented atherosclerosis in two vascular beds or at least 2 additional risk factors

  Additional risk factors are:

  - Current smoker
  - Diabetes mellitus
  - Renal dysfunction with estimated glomerular filtration rate <60 ml/min
  - Heart failure
  - Non-lacunar ischemic stroke ≥1 month ago

Low dose NOAK + ASS für alle?

Ausschlusskriterien COMPASS

High risk of bleeding

Stroke within 1 month or any history of hemorrhagic or lacunar stroke

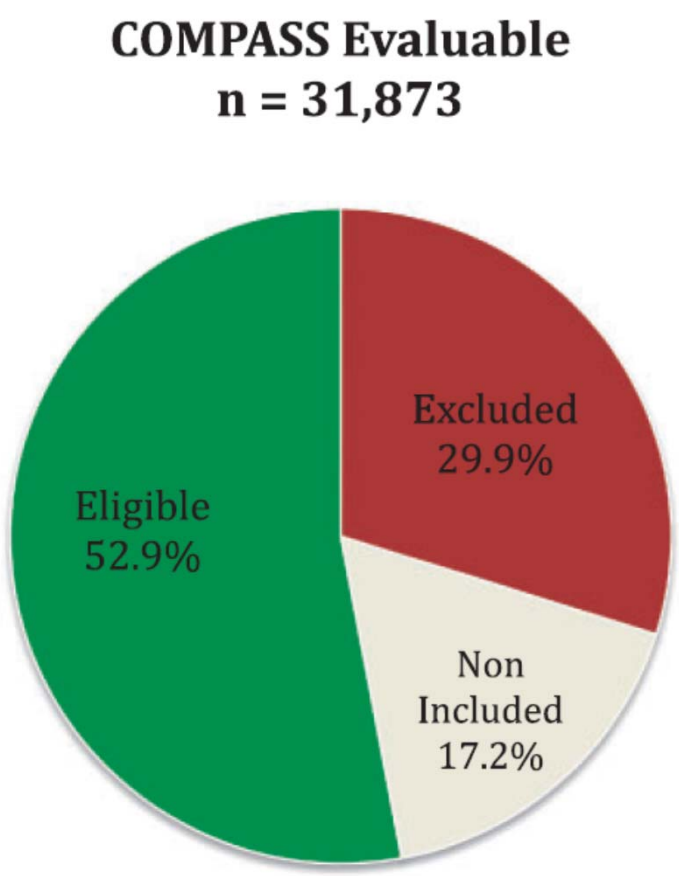
Severe heart failure with known ejection fraction <30% or New York Heart Association (NYHA) class III or IV symptoms

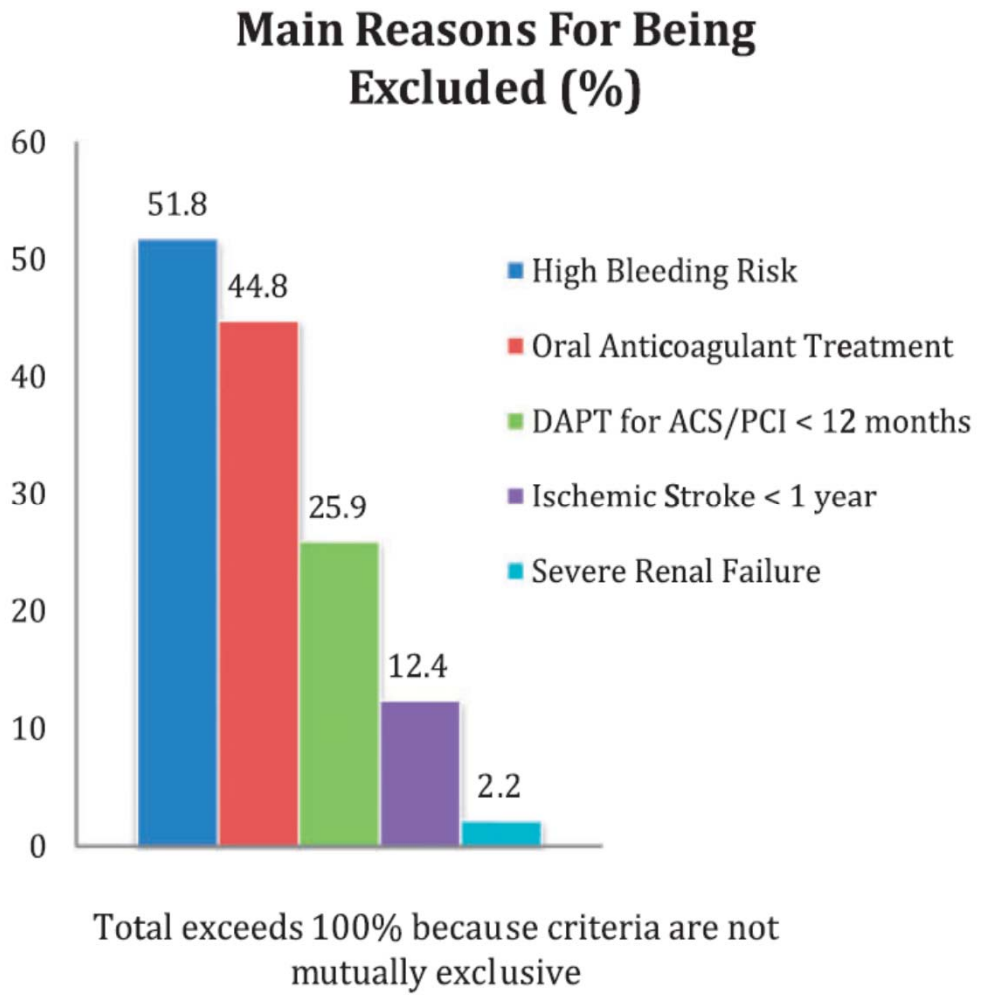
Estimated glomerular filtration rate (eGFR)<15 mL/min

Need for dual antiplatelet therapy, other non-aspirin antiplatelet therapy or oral anticoagulant therapy

uvm.

Low dose NOAK + ASS für alle?





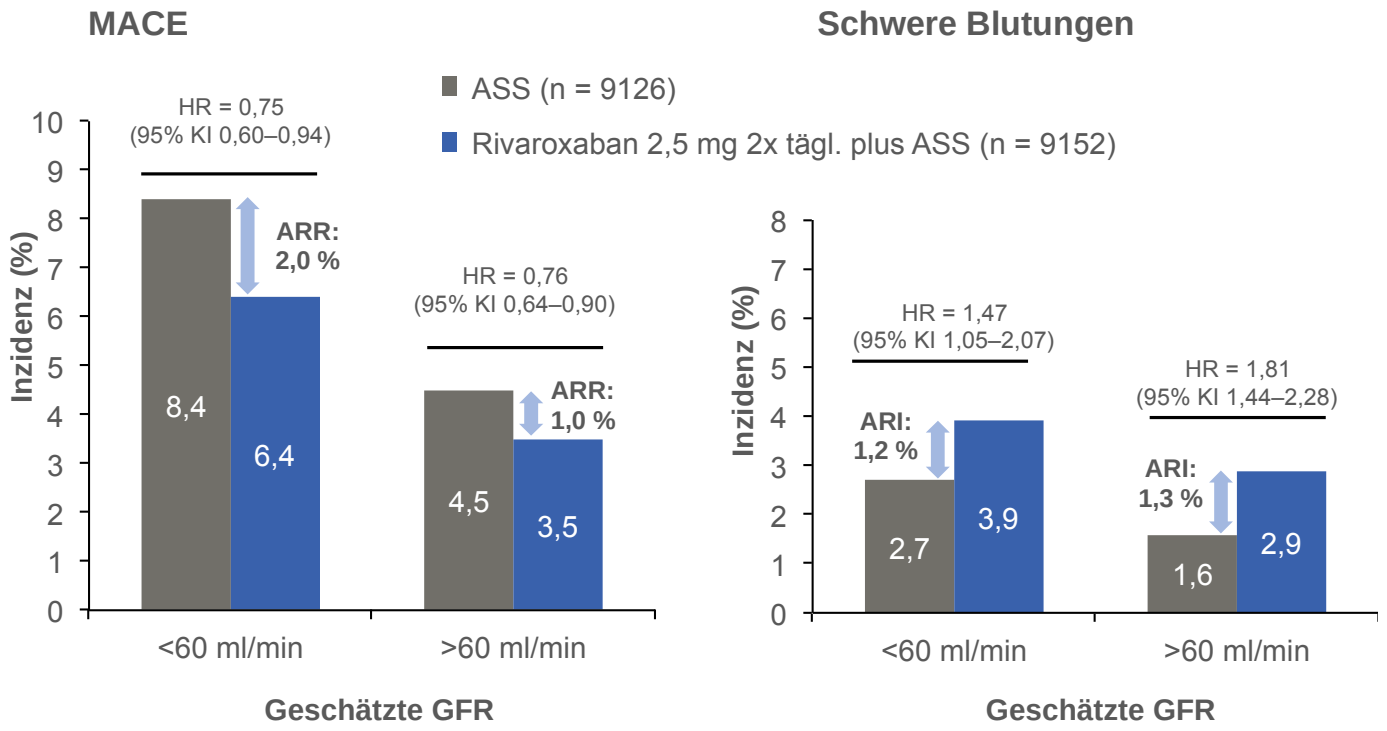
Darmon et al., Eur Heart J 2017

Low dose NOAK + ASS für alle?

Vergleichbare relative Risikoreduktion in den meisten Subgruppen

→ Je höher das absolute Risiko, desto größer der absolute Benefit

→ Hochrisiko-Patienten profitieren besonders (Niereninsuffizienz, Diabetes, KHK+pAVK)



Low dose NOAK + ASS für alle?

Bedeutung des Alters

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Age				0.20
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≥75 yr	121/1924 (6.3)	132/1897 (7)	0.89 (0.69–1.14)	

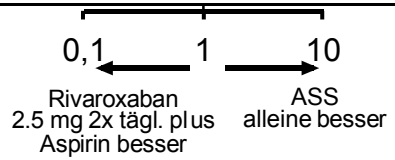
Variable	Efficacy endpoints (MACE outcome)			NNT-B	Safety endpoints (Major Bleedings)			NNT-H	LHH[d]
Age	Event rate (%)		Absolute risk difference[c] (%)		Event rate (%)		Absolute risk difference[c] (%)		
<65 yrs [N = 4334]	R + A[a] [N = 2150] 3.7	A[b] [N = 2184] 5.8	−2.1	48	R + A[a] [N = 2150] 1.4	A[b] [N = 2184] 1.2	0.2	500	11
> 65 yrs [N = 13,944]	R + A[a] [N = 7002] 4.2	A[b] [N = 6942] 5.3	−1.1	91	R + A[a] [N = 7002] 3.6	A[b] [N = 6942] 2.0	1.6	63	0.7

Eikelboom et al., NEJM 2017
Darmon et al., Eur Heart J 2017

Low dose NOAK + ASS für alle?

Nutzen bei Herzinsuffizienz

		Rivaroxaban 2,5 mg 2x tägl. plus ASS (N=9152)	ASS Monotherapie (N=9126)	Rivaroxaban 2,5 mg 2xtägl. plus ASS vs ASS alleine			
		n/N (%)	n/N (%)	HR (95% KI)	HR (95% KI)	*p*-Wert	p int
MACE (KV Tod, Schlaganfall, MI)	Keine HI	271/7189 (3,8 %)	339/7147 (4,7 %)		0,79 (0,68–0,93)	0,004	0,28
	HI	108/1963 (5,5 %)	157/1979 (7,9 %)		0,68 (0,53–0,86)	0,002	
Schwere Blutungen (mod. ISTH)	Keine HI	239/7189 (3,3 %)	134/7147 (1,9 %)		1,79 (1,45–2,21)	<0,0001	0,26
	HI	49/1963 (2,5 %)	36/1979 (1,8 %)		1,36 (0,88–2,09)	0,16	
Klinischer Nettonutzen*	Keine HI	315/7189 (4,4 %)	369/7147 (5,2 %)		0,85 (0,73–0,99)	0,03	0,15
	HI	116/1963 (5,9 %)	165/1979 (8,3 %)		0,69 (0,55–0,88)	0,002	

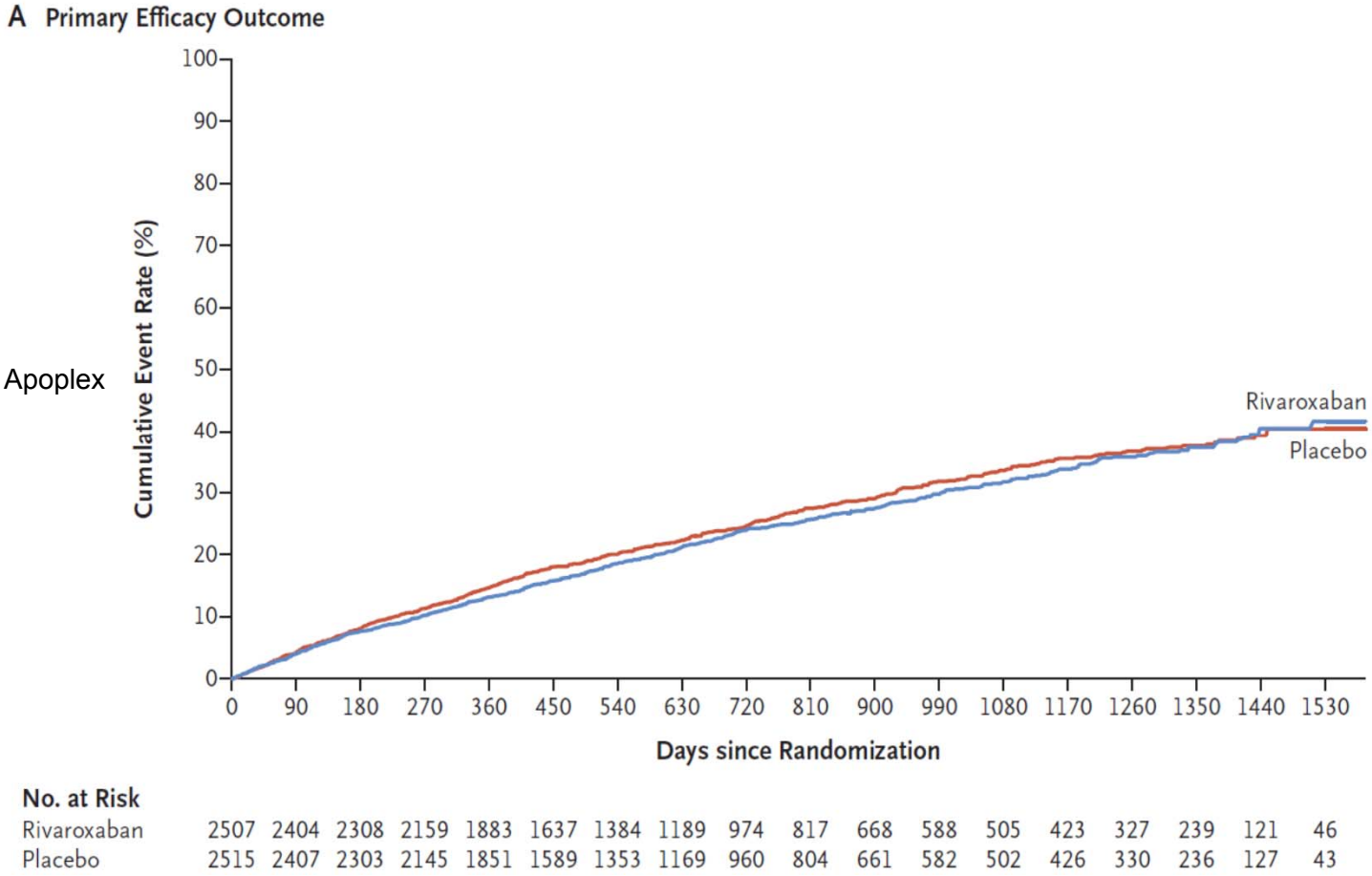


Branch et al., ESC-HF 2018, Abstract 1591

Low dose NOAK + ASS für alle?

COMMANDER HF: EF<40%, KHK, Verschlechterung der Herzinsuffizienz in den letzten 21 Tagen

Tod, Infarkt, Apoplex



Zannad et al., NEJM 2018

Zusammenfassung

***Low dose* NOAK in der Sekundärprävention**

- Nur ohne Indikation zur Vollantikoagulation
- Kardiovask. Tod, Myokardinfarkt, Apoplex ↓
- Blutungen ↑
- Netto Benefit
- V.a. erwägen bei niedrigem Blutungsrisiko, jungen Patienten, sehr hohem kardiovaskulären Risiko
- Nicht geben bei hohem Blutungsrisiko oder HFrEF

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Vielen Dank für Ihre Aufmerksamkeit!