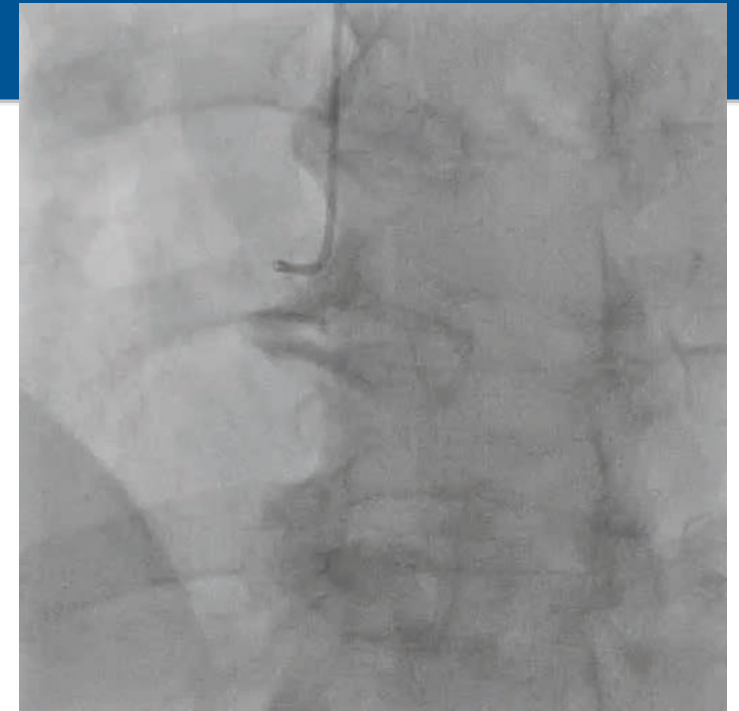
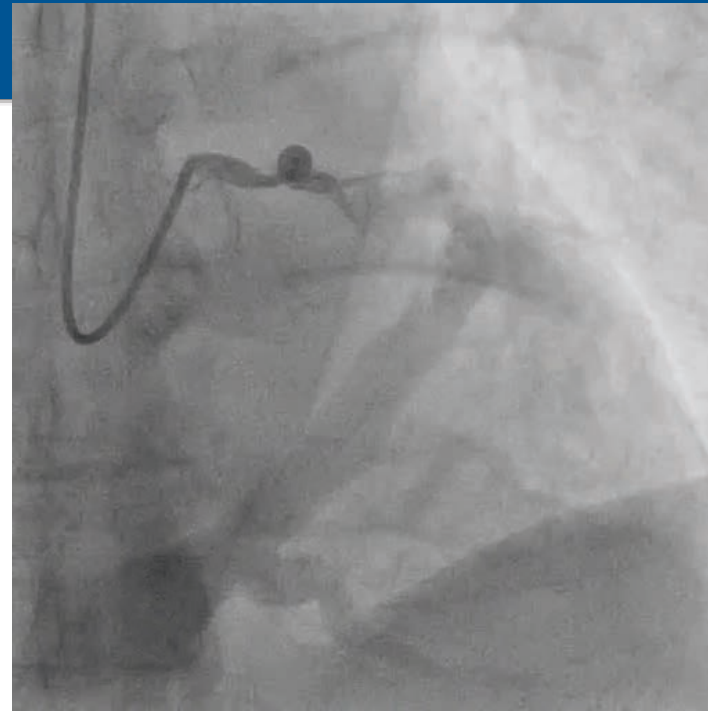
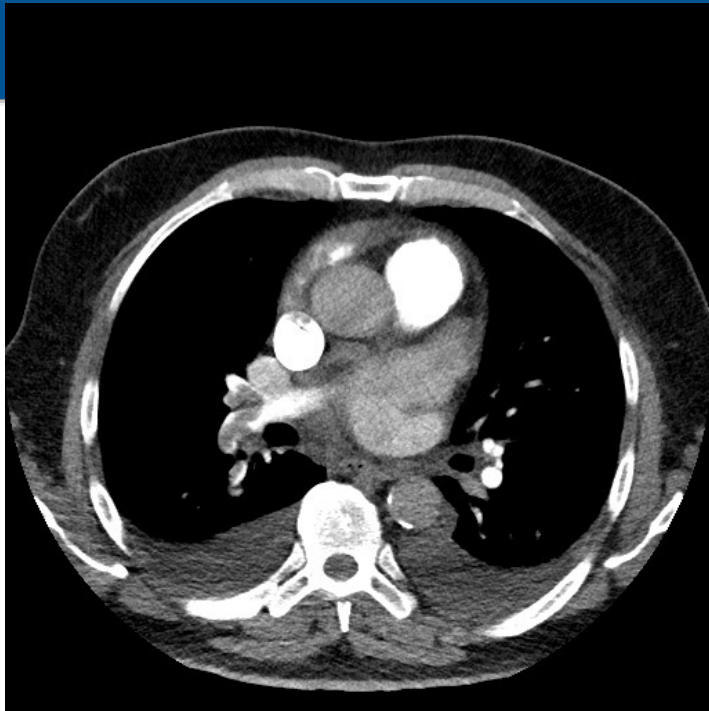


Herzinsuffizienz - Differenzierte Ansätze zur Senkung des thromboembolischen Risikos

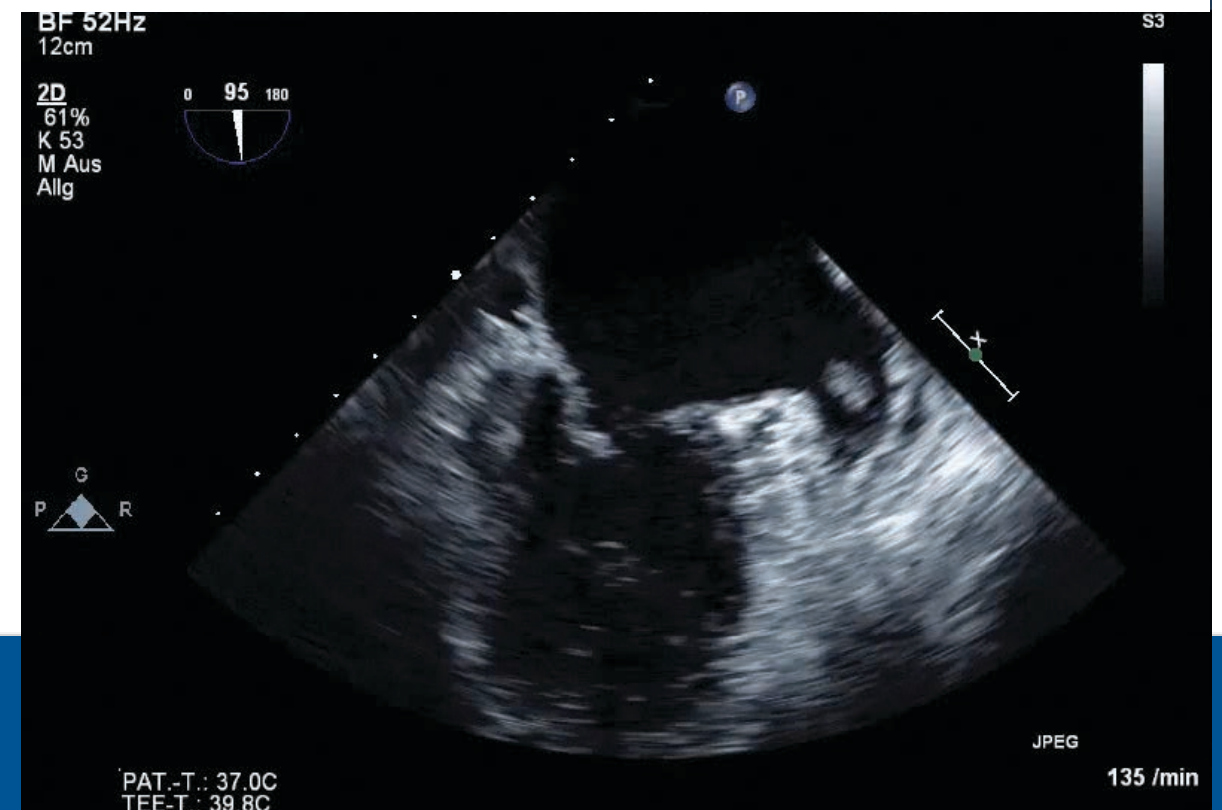
Prof. Dr. T. Geisler, Deutsches Herzkompetenzzentrum,
Klinikum der Eberhard-Karls-Universität Tübingen

Interessenkonflikte

<i>Company Name</i>	<i>Relationship</i>
<i>Eli Lilly / Daiichi Sankyo</i>	<i>Research / educational grants, honoraria, consultant</i>
<i>Astra Zeneca</i>	<i>Honoraria, consultant</i>
<i>MSD</i>	<i>Honoraria</i>
<i>The Medicines Company</i>	<i>Research grants, honoraria</i>
<i>Bristol Myers Squibb</i>	<i>Research / educational grants, honoraria, consultant</i>
<i>Bayer HealthCare</i>	<i>Research / educational grants, honoraria, consultant</i>
<i>Boehringer Ingelheim</i>	<i>Consultant, Honoraria</i>



64 jähriger Patient mit progredienter Dyspnoe



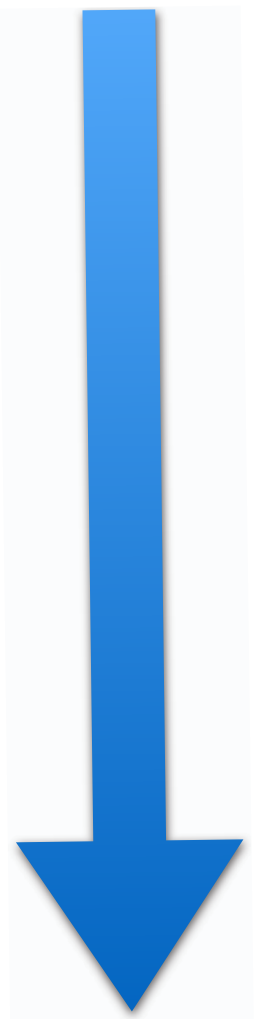
- Wie hängt das thrombembolische Risiko von der Herzinsuffizienz ab?
- Wie können wir das Risiko durch die antithrombotische Therapie beeinflussen, welche Patienten profitieren?

Schlaganfallprävalenz bei chronischer Herzinsuffizienz ca. 10%

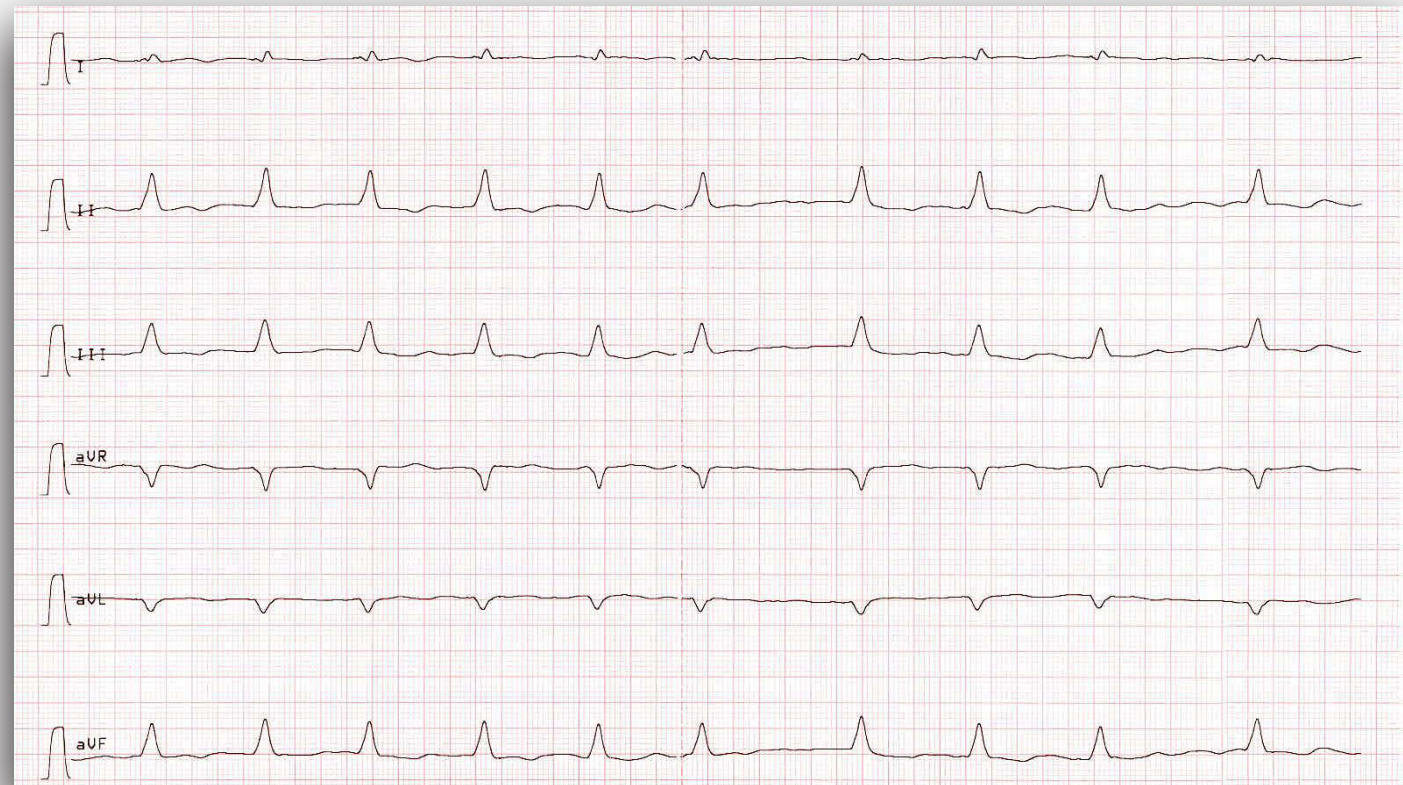
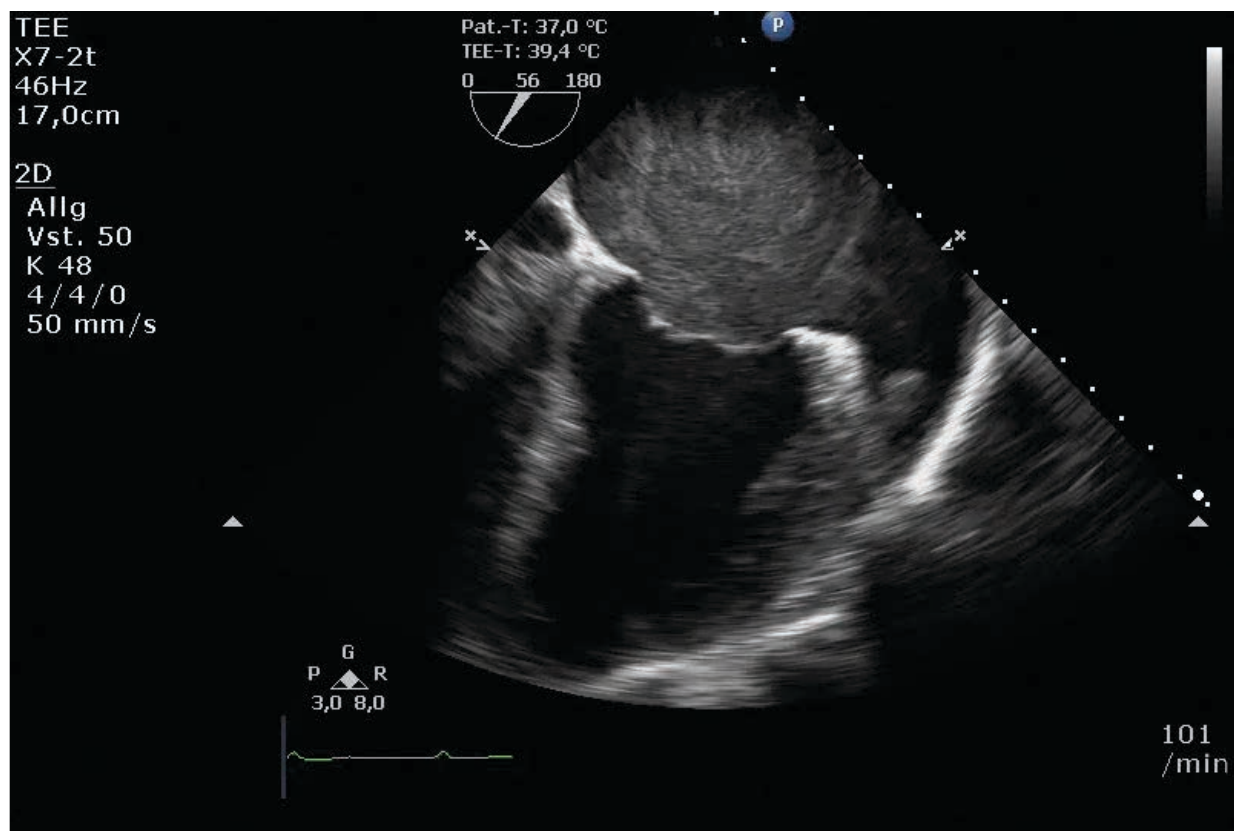
RCT	Studienpopulation	Rhythmus	Anamnese eines Schlaganfalls oder TIA
SOLVD-Treatment	2569	SR + AF (10%)	8%
CHARM-Added	2548	SR + AF (26%)	9%
SHIFT	6505	SR	8%
EMPHASIS-HF	2737	SR + AF (31%)	10%
TIME-CHF	499	SR + AF (32%)	Alter 60-74 Jahre: 9,5%; Alter >75 Jahre: 19,4%
PARADIGM-HF	8442	SR + AF (37%)	9%
Register			
ESC-HFLT Register	5039	SR + AF	9,4%
ESC HF Pilot Survey	1992	SR + AF	10,5%

Schlaganfallrate und NYHA Klasse

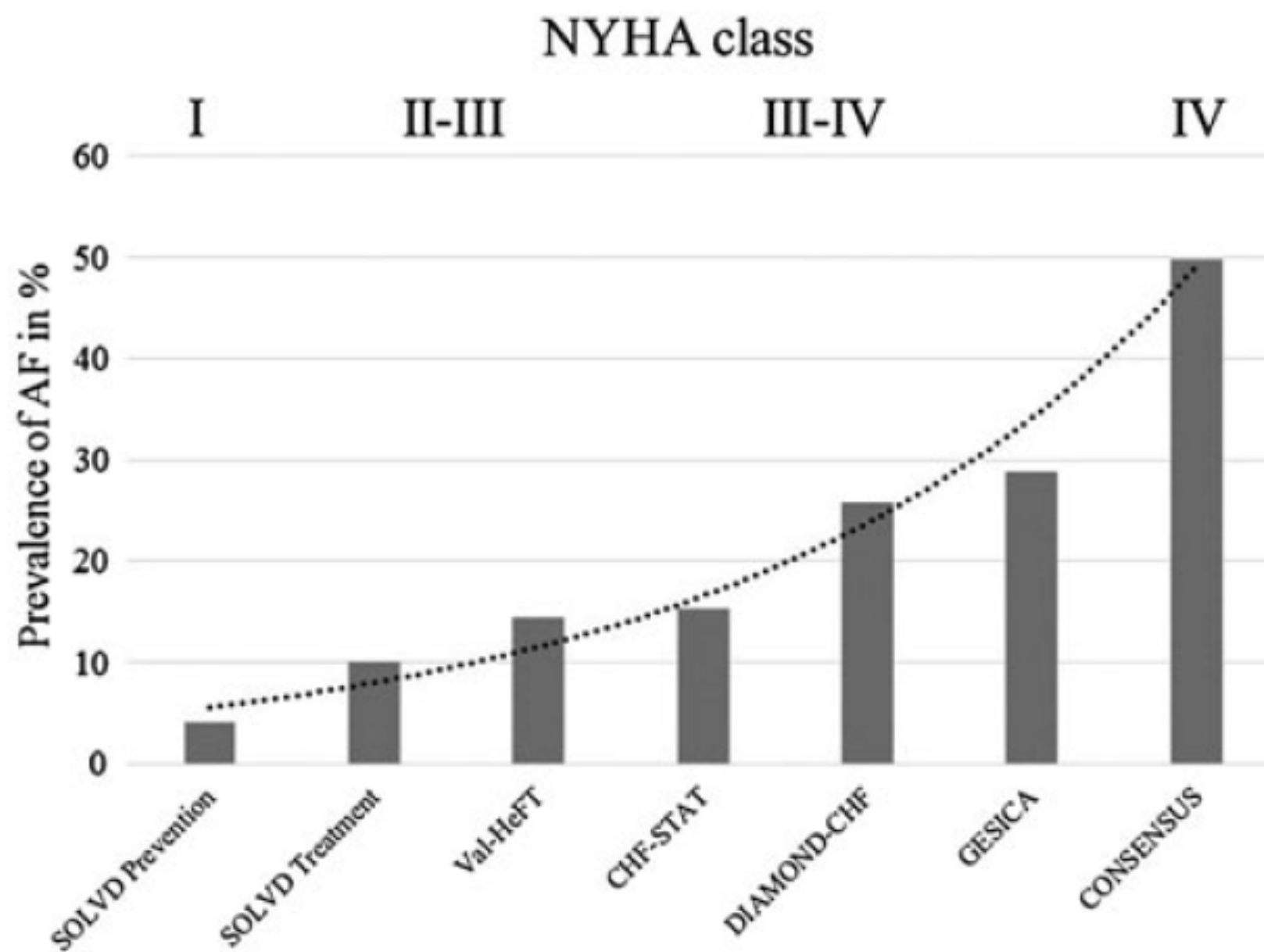
	NYHA Klasse	Ejektionsfraktion	Jährliche Schlaganfallrate
SAVE	1	31%	1,5%
SOLVD	1,77	27%	1,3%
Katz et al.	2,5	27%	1,7%
V-Heft I	2-3	30%	2,0%
PROMISE	3,4	21%	3,5%



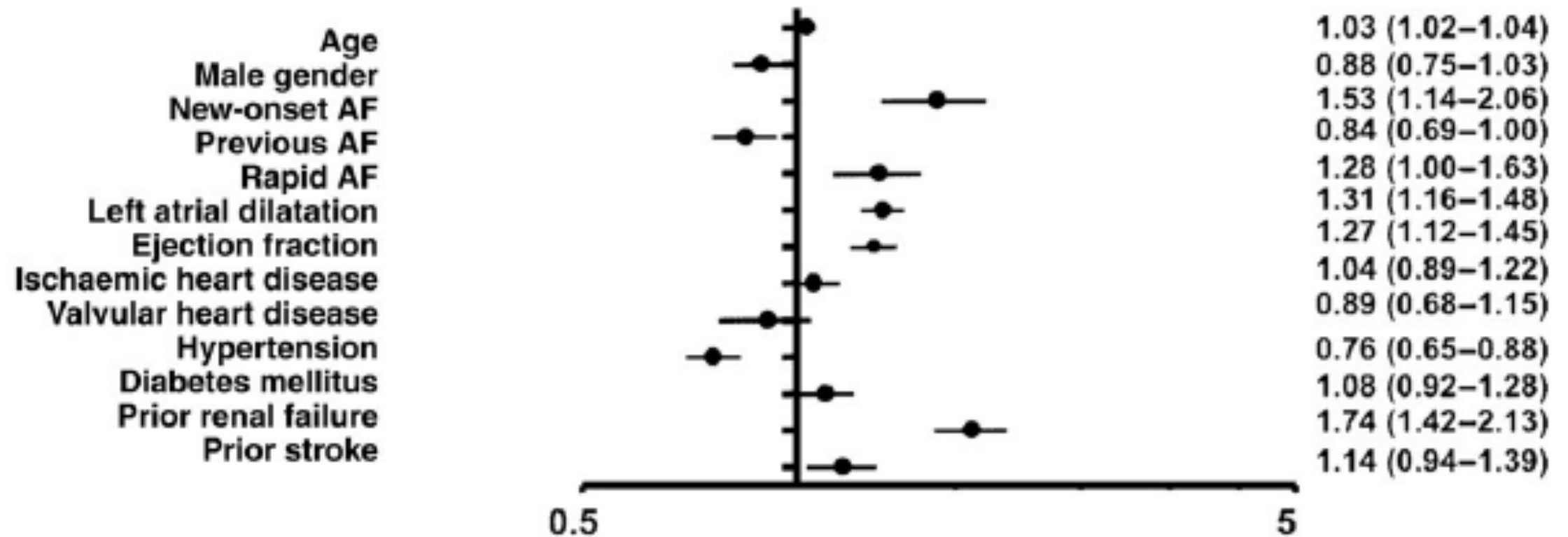
52 jähriger Patient mit rezidivierenden TIAs



Prevalence of atrial fibrillation with increasing heart failure symptoms

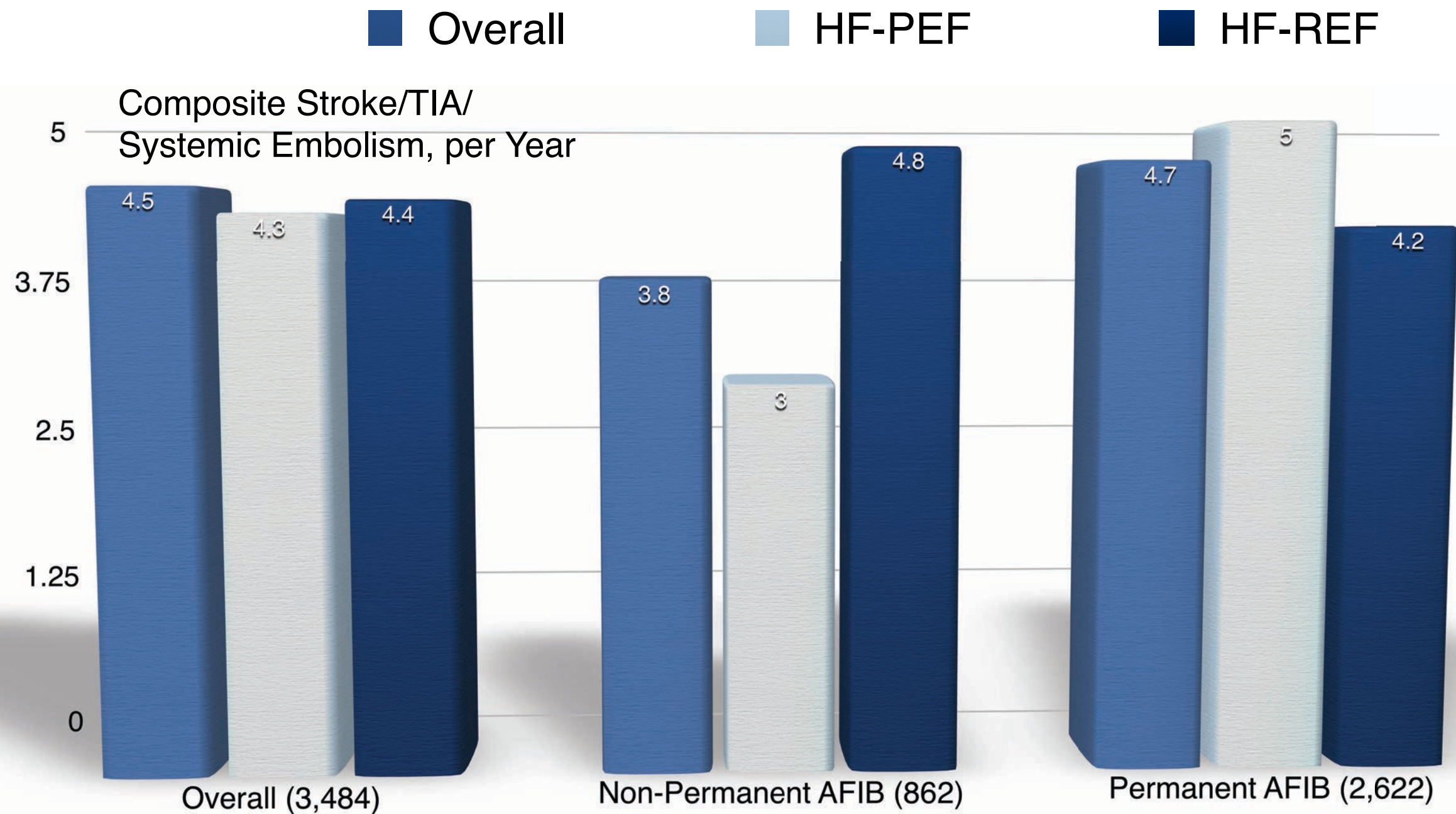


Neu auftretendes Vorhofflimmern ist ein starker Prädiktor der Mortalität bei Patienten die mit einer Herzinsuffizienz hospitalisiert werden.

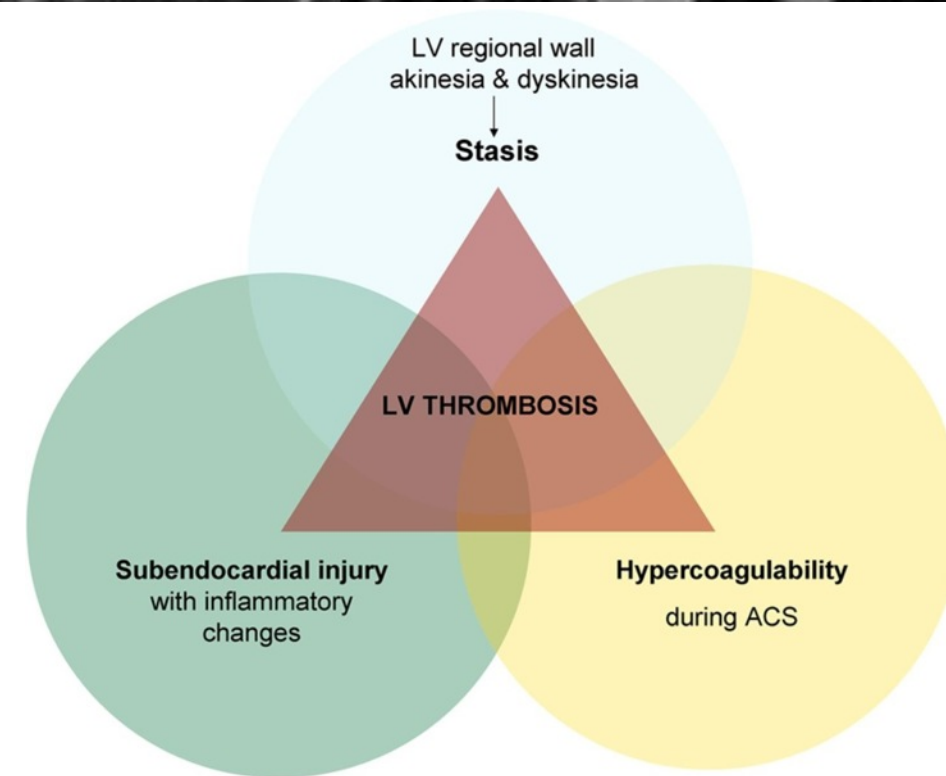
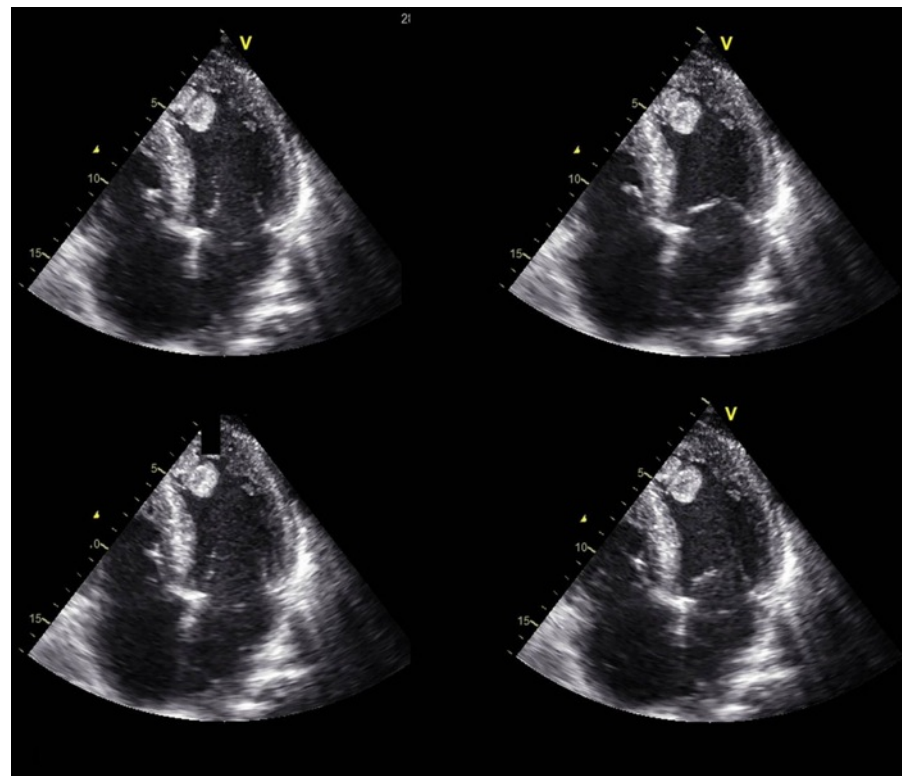
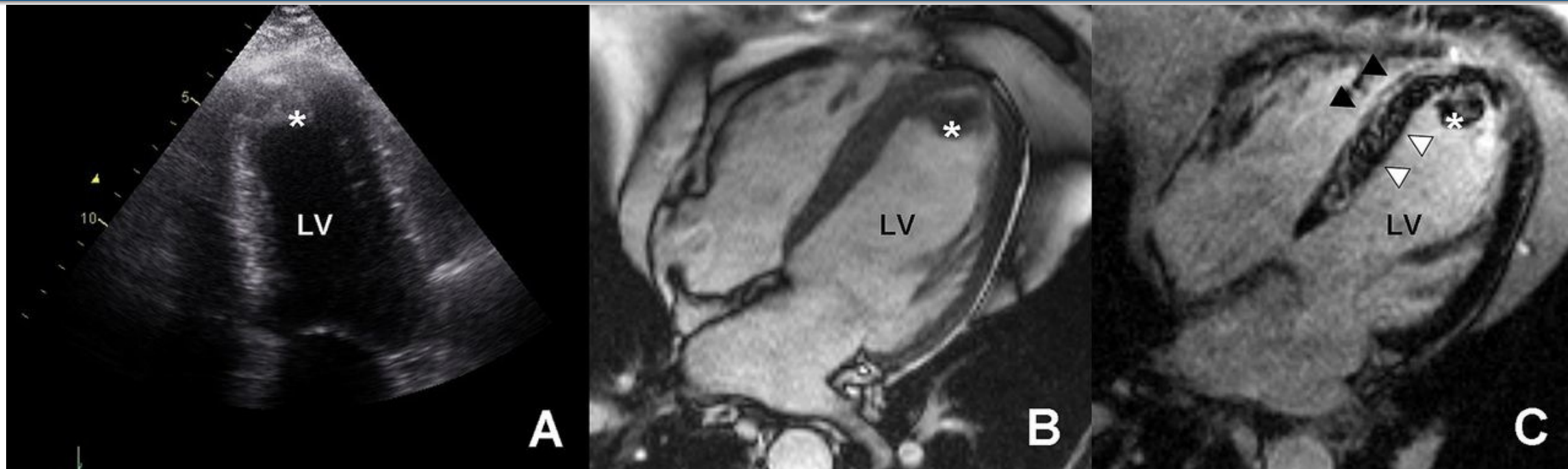


*No AF used as reference group.

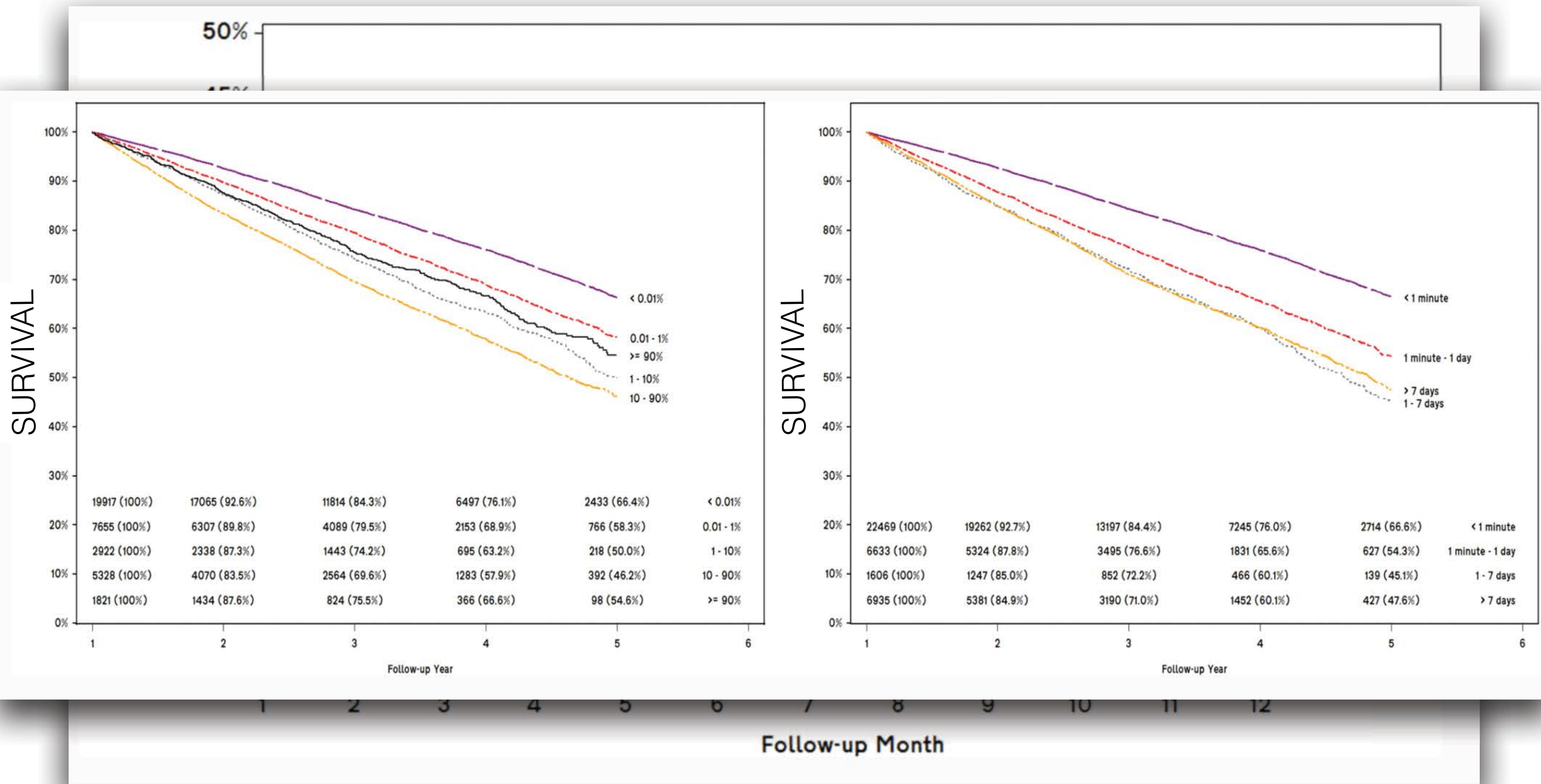
Das Risiko für thrombembolische Ereignisse ist unabhängig von der Art der Herzinsuffizienz (HF-PEF vs. HF-REF) wird aber beeinflusst vom Vorhofflimmer Typ



CHF – hohes Risiko für intrakardiale Thromben auch bei Sinusrhythmus



Device detektiertes Vorhofflimmern bei Herzinsuffizienz-Patienten - Auswertungen der ALTITUDE Studie an CRT-D 63.886 Patienten





C-SPIN

Canadian Stroke Prevention Intervention Network

ARTESiA

**APIXABAN FOR THE REDUCTION OF THROMBO-EMBOLISM
DUE TO SUB-CLINICAL ATRIAL FIBRILLATION**

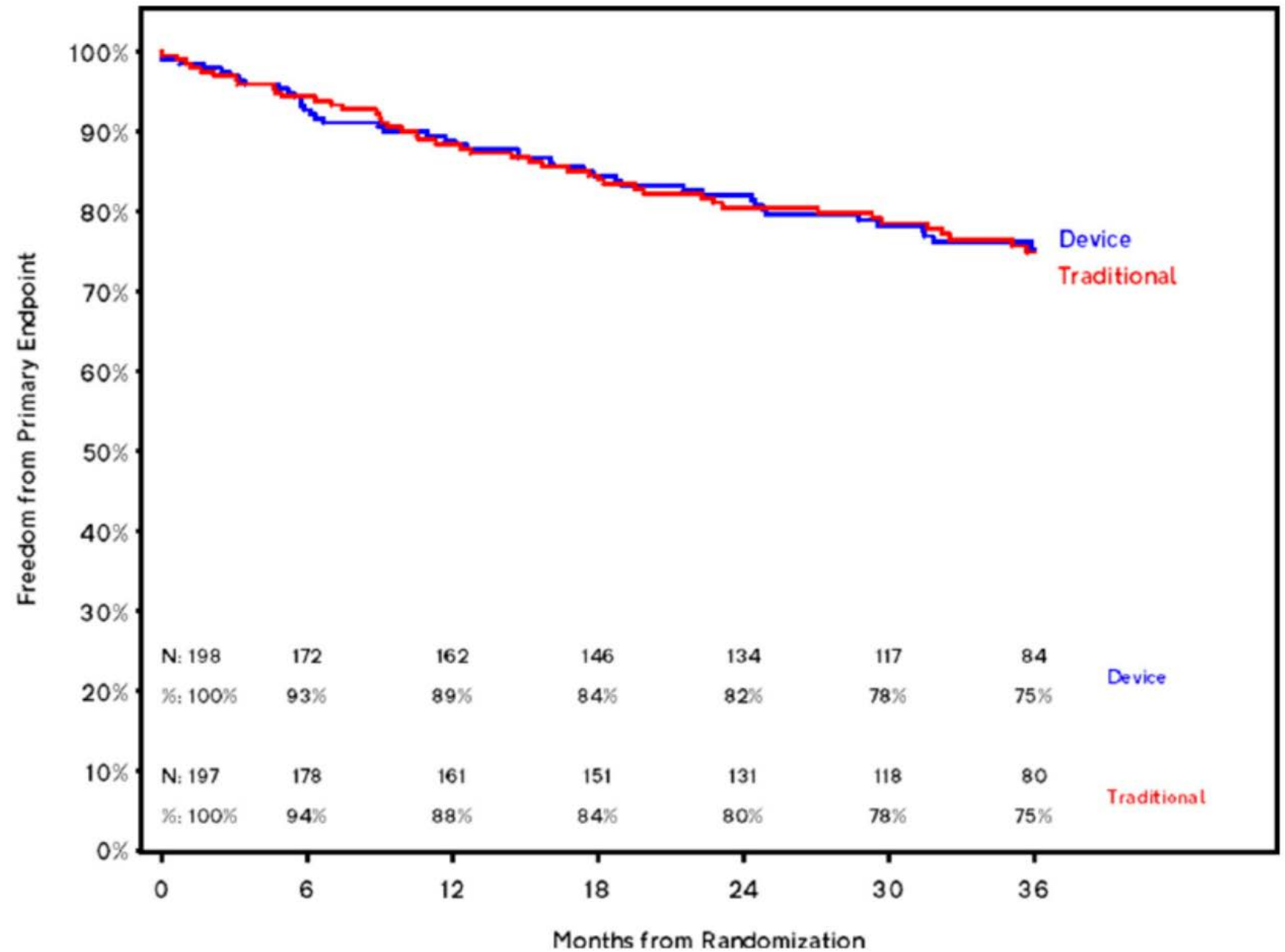
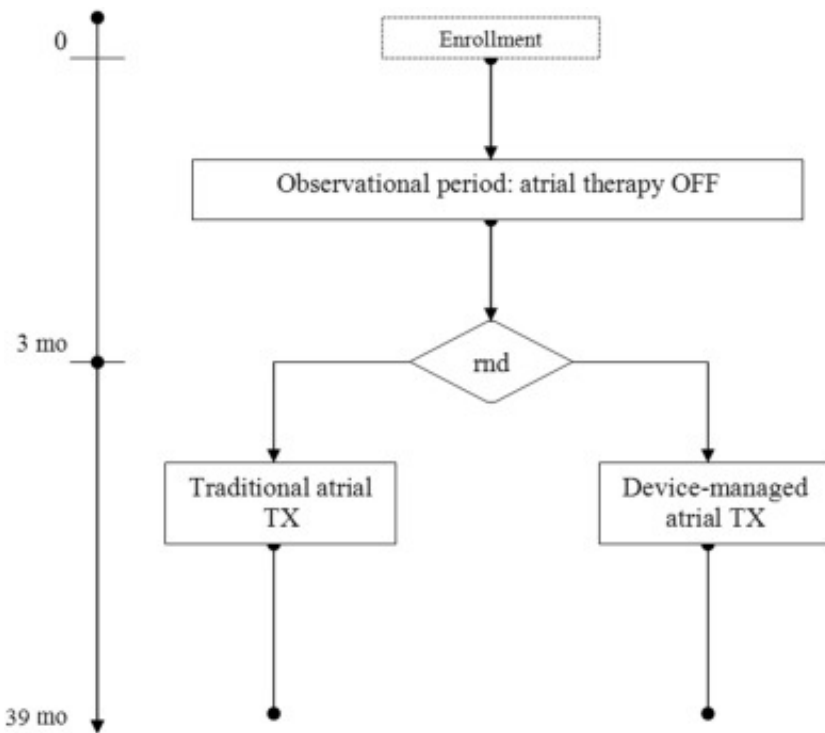
Non-vitamin K
antagonist Oral
anticoagulants
in patients with
Atrial High rate
episodes



Device (CRT-D) Therapie des Vorhofflimmerns bei Herzinsuffizienz

Therapie verändert nicht die Prognose - Hinweis für Vorhofflimmern als Risikomarker der Erkrankung anstatt eines modifizierbaren Risikofaktors

TRADE-HF Studie (n=355 Patienten)



Assoziation der Herzinsuffizienz und Thrombembolien ist vielmehr abhängig von klinischen Faktoren als von der Präsenz des Vorhofflimmern

Research

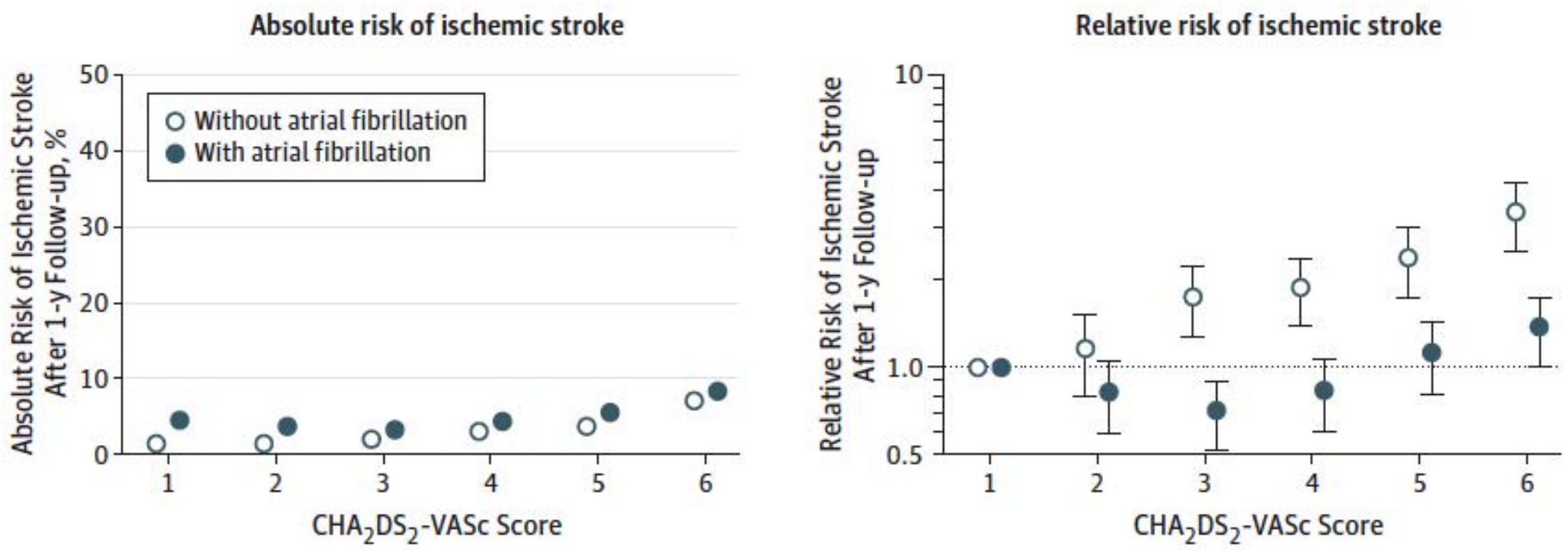
Original Investigation

Assessment of the CHA₂DS₂-VASc Score in Predicting Ischemic Stroke, Thromboembolism, and Death in Patients With Heart Failure With and Without Atrial Fibrillation

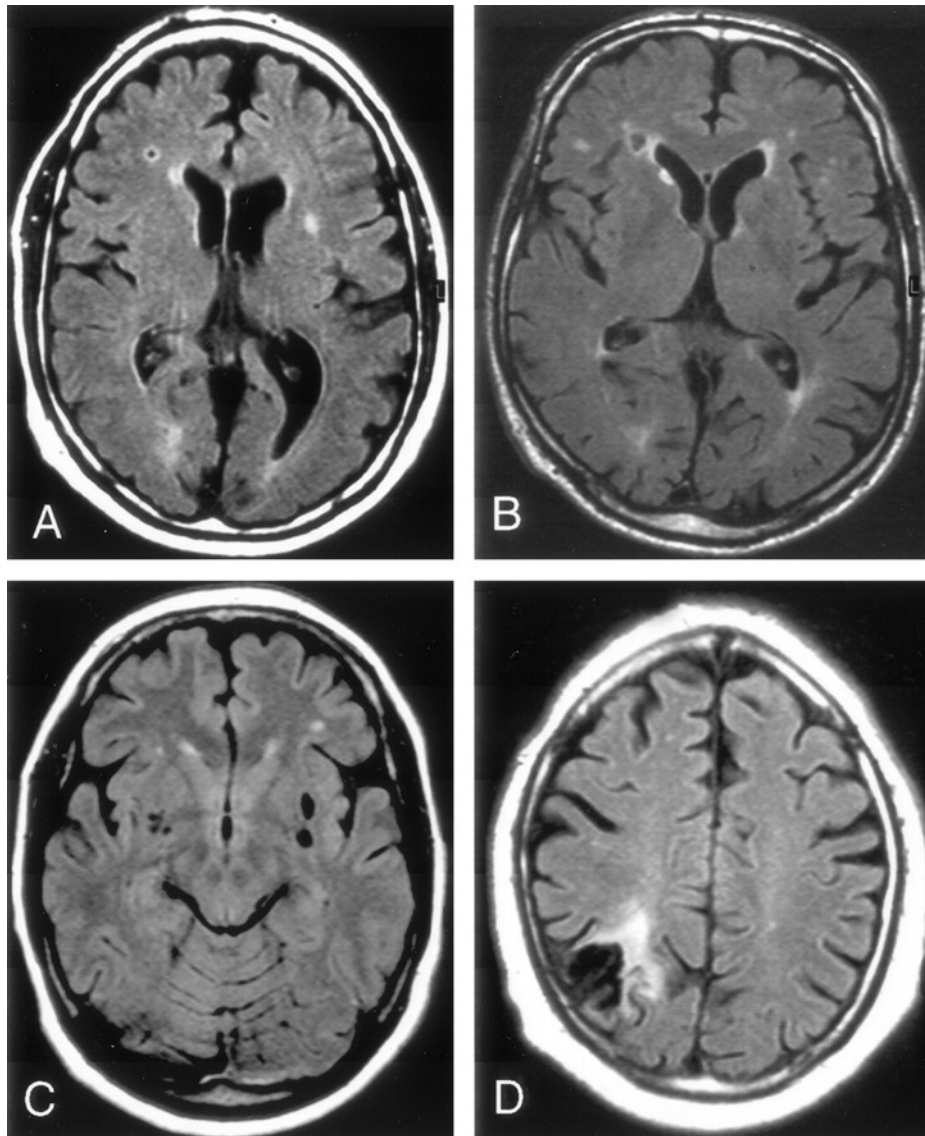
Dänische Registerstudie an 42 987 Herzinsuffizienzpatienten

Line Melgaard, MSc; Anders Gorst-Rasmussen, MSc, PhD; Deirdre A. Lane, PhD; Lars Hvilsted Rasmussen, MD, PhD; Torben Bjerregaard Larsen, MD, PhD; Gregory Y. H. Lip, MD

Figure 2. Absolute Risks and Relative Risks by CHA₂DS₂-VASc Score Components During the First Year of Follow-up, Stratified According to Prior Diagnosis of Atrial Fibrillation



Eine chronische Herzinsuffizienz begünstigt das Auftreten von silenten ischämischen Läsionen



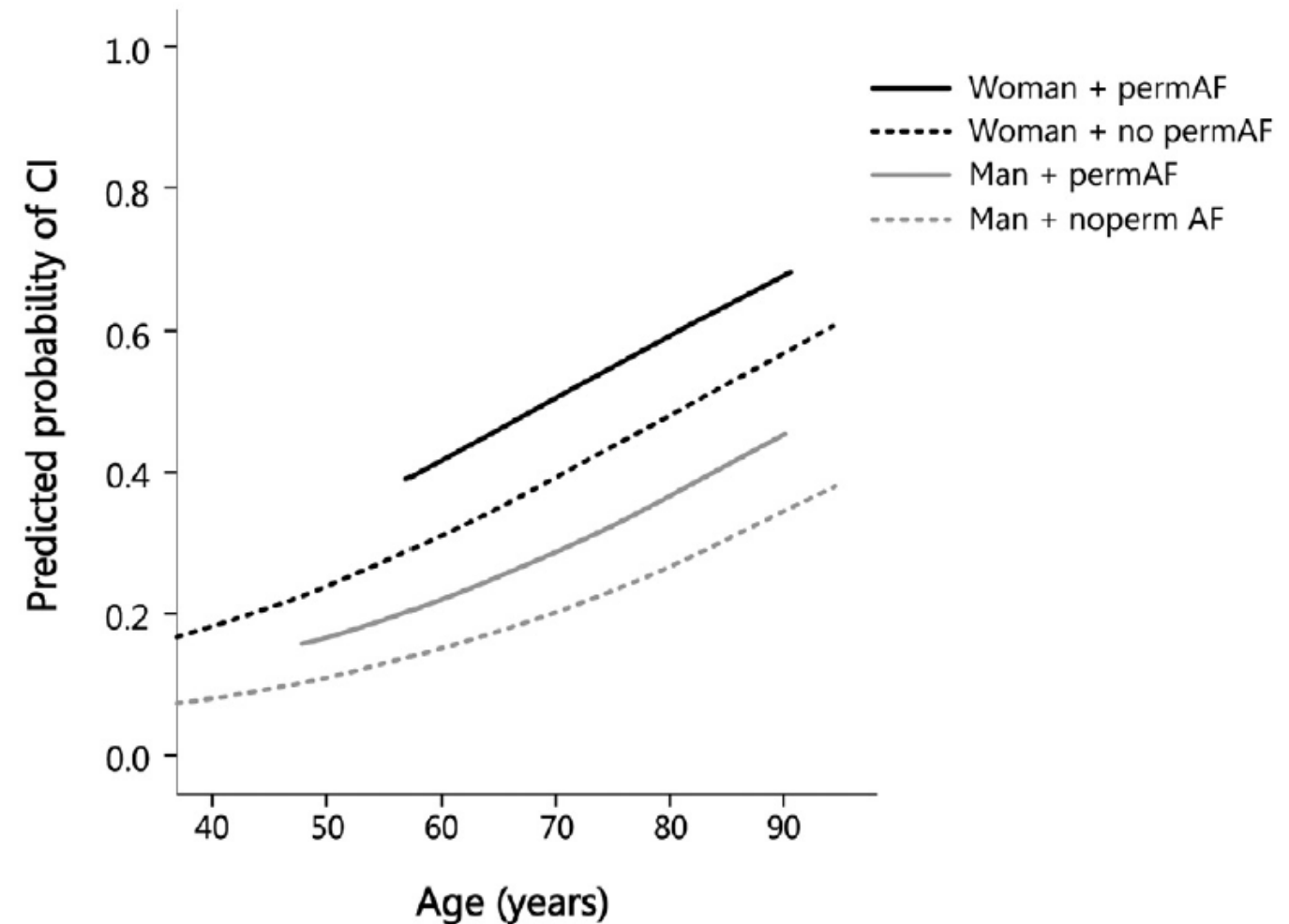
	n	mittleres Alter	Silente cerebrale Ischämien	
			bei Herzinsuffizienzpatienten	Kontrollen
Schmidt et al., 1991	20	40 Jahre	20%	0
Siachos et al., 2005	117	51 Jahre	34%	-
Vogels et al., 2007	58	69 Jahre	42%	12%
Kozdag et al., 2008	72	62 Jahre	35%	3,6%

Kognitive Funktion bei Herzinsuffizienzpatienten

Table 2. Relation between the Presence of Silent Brain Infarcts at Base Line, the Severity of Periventricular and Subcortical White-Matter Lesions, and the Risk of Dementia.

Variable	Hazard Ratio (95% Confidence Interval)	
	Adjusted for Age, Sex, and Level of Education	Adjusted for Age, Sex, Level of Education, and MRI Measures*
Silent brain infarcts (yes vs. no)	2.26 (1.09–4.70)	2.03 (0.91–4.55)
Severity of periventricular white-matter lesions (per SD increase)	1.59 (1.13–2.25)	1.47 (0.92–2.35)
Severity of subcortical white-matter lesions (per SD increase)	1.21 (0.96–1.53)	0.92 (0.65–1.29)

Assoziation Vorhofflimmern / Geschlecht und Alter mit der kognitiven Verschlechterung bei Herzinsuffizienz-Patienten



CHA₂DS₂-VASc Risk Score

KNOW YOUR STROKE RISK			
CHA ₂ DS ₂ -VASc Risk	Score	CHA ₂ DS ₂ -VASc Score	Adjusted stroke rate (% / year)
		0	0
CHF or LVEF <40%	1	1	1.3
Hypertension	1	2	2.2
Age > 75	2	3	3.2
Diabetes	1	4	4
Stroke / TIA / Thromboembolism	2	5	6.7
Vascular Disease	1	6	9.8
Age 65-74	1	7	9.6
Female	1	8	6.7
		9	15.2

*CHF = congestive heart failure; TIA - transient ischemic attack;
LVEF = left ventricular ejection fraction.*

Herzinsuffizienz ist ein Risiko Faktor für Schlaganfälle = geringster RF von allen



Novel Clinical Risk Factors

Chronic kidney disease

Obstructive sleep apnea

AF burden

Serum Biomarkers

Natriuretic peptides

Troponin

Established Clinical Risk Factors (CHADS-VASc)

Prior stroke/TIA

Age

Hypertension

Diabetes

Heart failure

Female sex

Vascular disease

Echo Parameters

LA volume

LA and LAA Function



Advanced Imaging

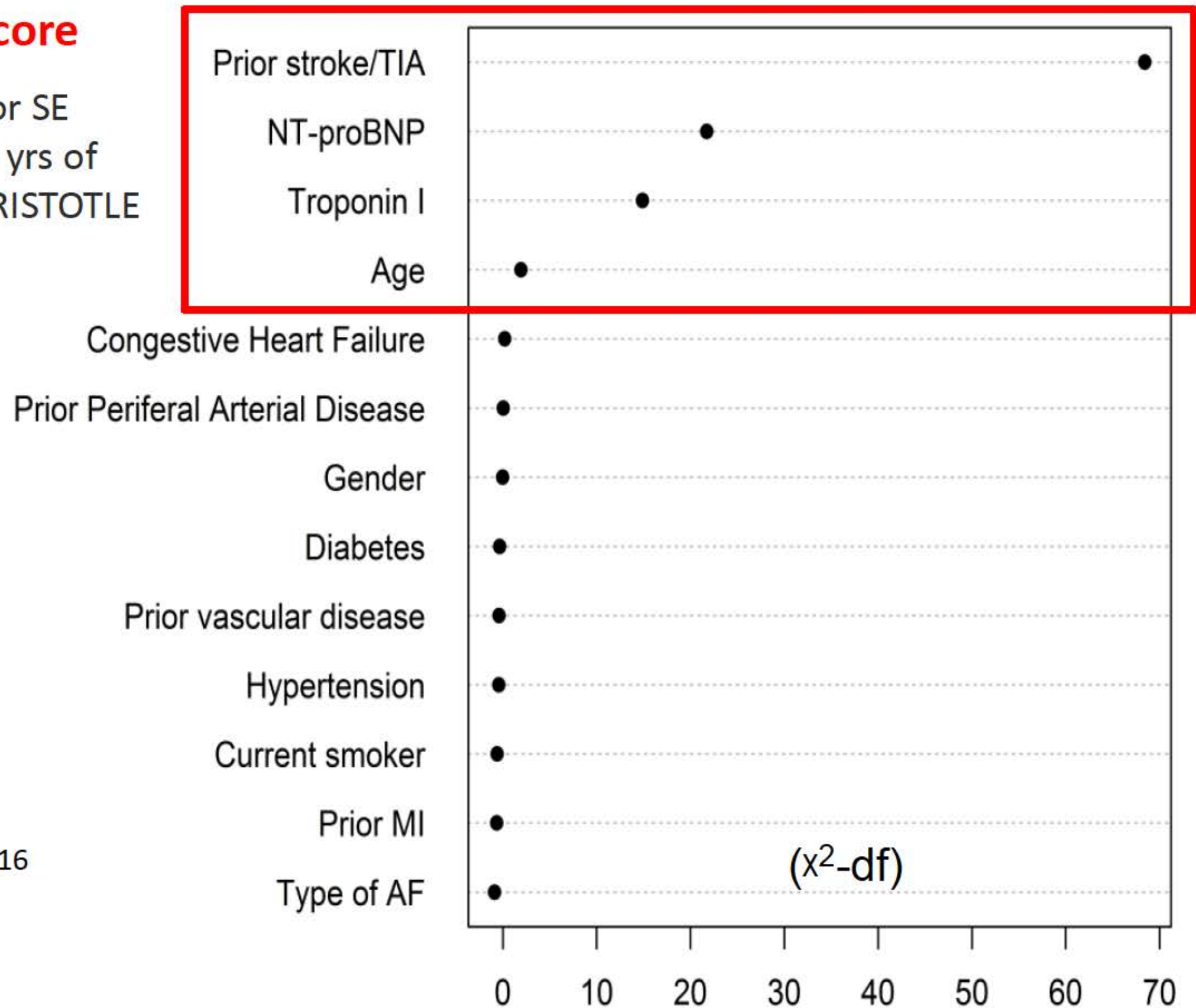
LA fibrosis

LAA morphology



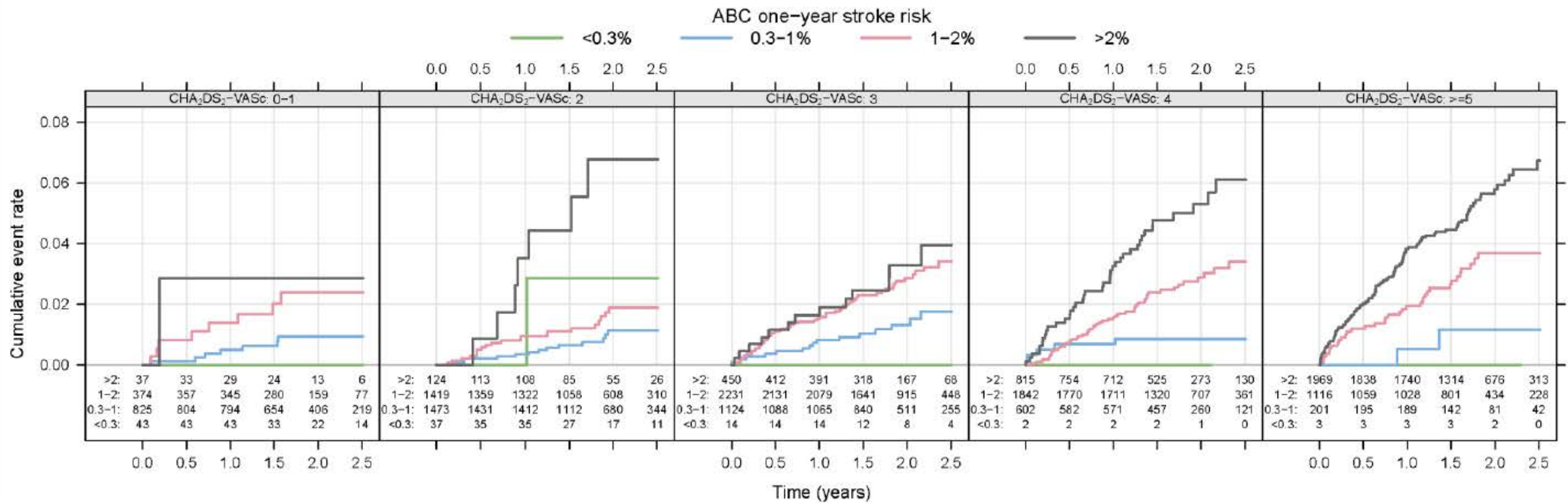
ABC-stroke score

Based on 391 stroke or SE during 27,929 person yrs of follow-up from the ARISTOTLE trial



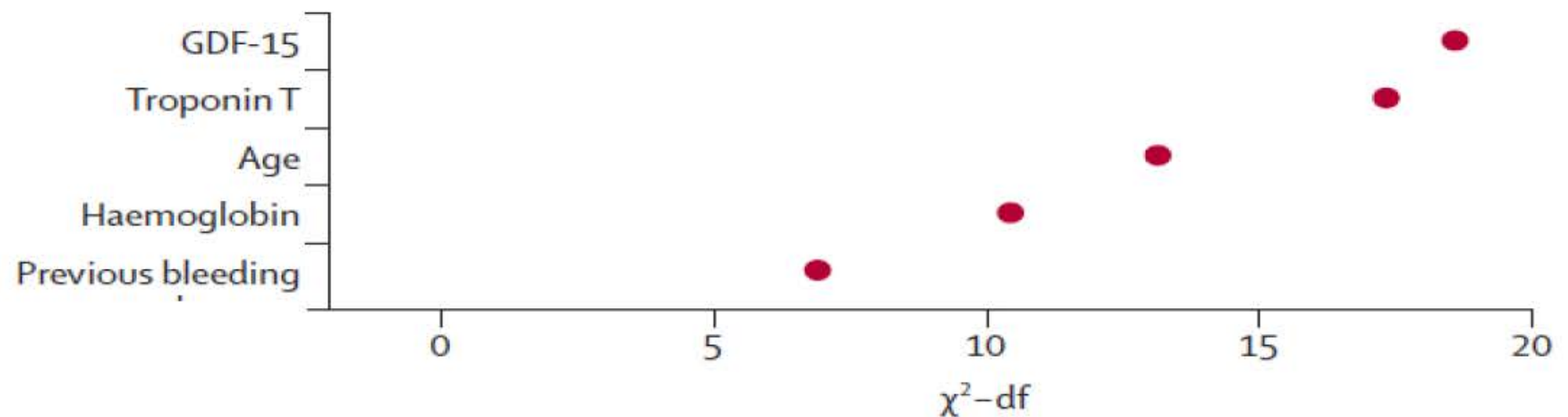
Mehrwert des ABC Score für die Schlaganfallrisikoprädiktion im Vergleich zum CHA₂DS₂-Vasc Score

Event rates by the three ABC-stroke risk classes (low, medium, and high) for the CHA₂DS₂-VAsc score (panel): 0-1 points, 2 points, and ≥3 points.

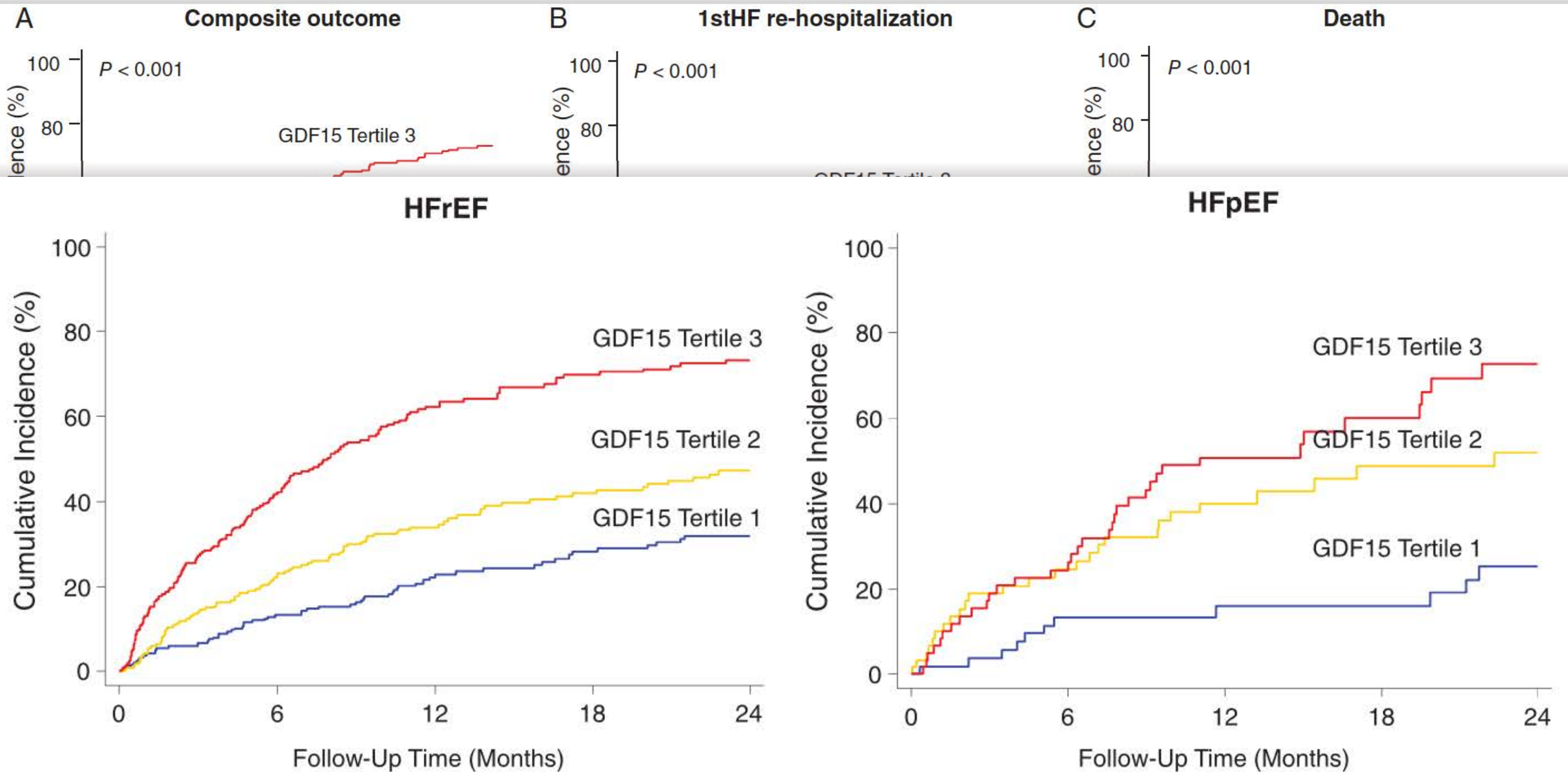


The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study

ABC-bleeding score (age, biomarkers [GDF-15, cTnT-hs (or creat clearance), and hemoglobin], and clinical history [previous bleeding]) score yielded a higher c-index than HAS-BLED and ORBIT scores for major bleeding in both the derivation (0.68 vs 0.61 vs 0.65) and validation (0.71 vs 0.62 vs 0.68) cohorts



Biomarker GDF-15 und Prognose bei Herzinsuffizienz



Herzinsuffizienz ist assoziiert mit einem erhöhten Blutungsrisiko unter OAK

Daten aus der AFFIRM-Studie an 4060 Patienten

Table IV. Covariates significantly associated with major bleeding

Covariate	P	Hazard ratio	HR: 95% confidence limits		Increase/decrease in risk
			Lower	Upper	
Age at entry	<.0001	1.05	1.04	1.07	+5%*
Congestive heart failure	.0108	1.43	1.09	1.89	+43%
Diabetes	.0152	1.44	1.07	1.93	+44%
Hepatic or renal disease	.0021	1.93	1.27	2.93	+93%
First episode of AF	.0476	1.30	1.00	1.68	+30%
Warfarin use	.0073	1.78	1.17	2.70	+78%
Aspirin use	<.0001	2.01	1.45	2.77	+101%

*Per year of age.

Impact of demographics and co-morbidities on likelihood of lower time in therapeutic range

Characteristic	OR (95% CI)	p
Age ≥ 75 (vs < 75) (yrs)	0.94 (0.88–1.01)	NS
Men (vs women)	0.78 (0.73–0.83)	< 0.001
United States region		
Northeast	1.00 (Referent)	—
West	1.39 (1.26–1.54)	< 0.001
South	1.38 (1.26–1.52)	< 0.001
Midwest	1.04 (0.95–1.14)	NS
Co-morbidities (vs not present)		
Heart failure	1.41 (1.28–1.56)	< 0.001
Diabetes	1.28 (1.19–1.38)	< 0.001
Previous stroke	1.15 (1.04–1.27)	0.0075
Hypertension	0.86 (0.80–0.93)	< 0.001

CI = confidence interval; OR = odds ratio.

Unterschiede der Definition der Herzinsuffizienz in den NOAK Studien zur Thrombembolieprophylaxe bei Vorhofflimmern

Table 2 Definition of heart failure in atrial fibrillation NOAC trials and potential for improvement

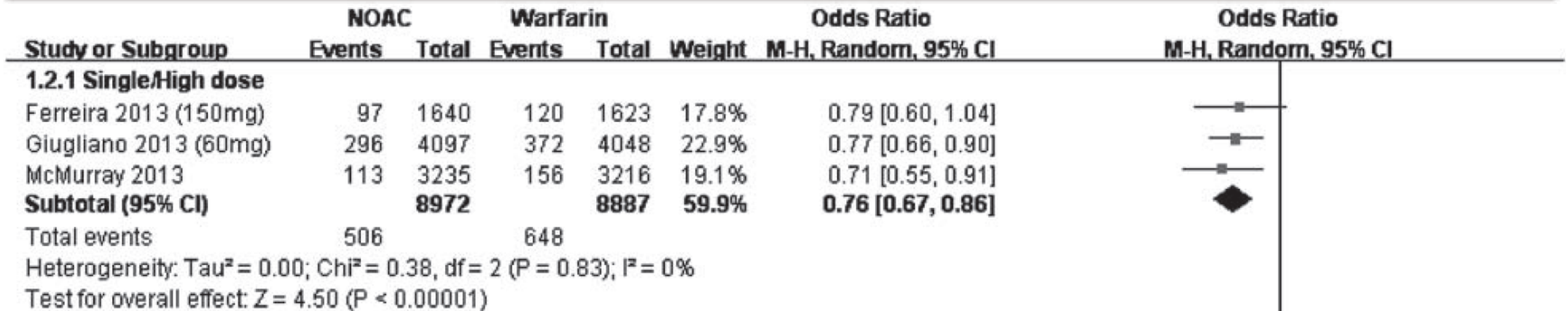
Trial	HF definition	Potential for improvement
RELY	NYHA class \geq II LVEF	HF aetiology HF treatment
ROCKET-HF	HF history LVEF < 40%	Volume status Loop diuretic dose
ENGAGE-HF TIMI 48	HF history NYHA class	Previous HF hospitalizations IV loop diuretics during index hospitalization
ARISTOTELE	HF history LVEF < 40%	Natriuretic peptide levels Concomitant antiplatelet agents

NOAC, non-vitamin K antagonist anticoagulant; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; HF, heart failure; IV, intra-venous.

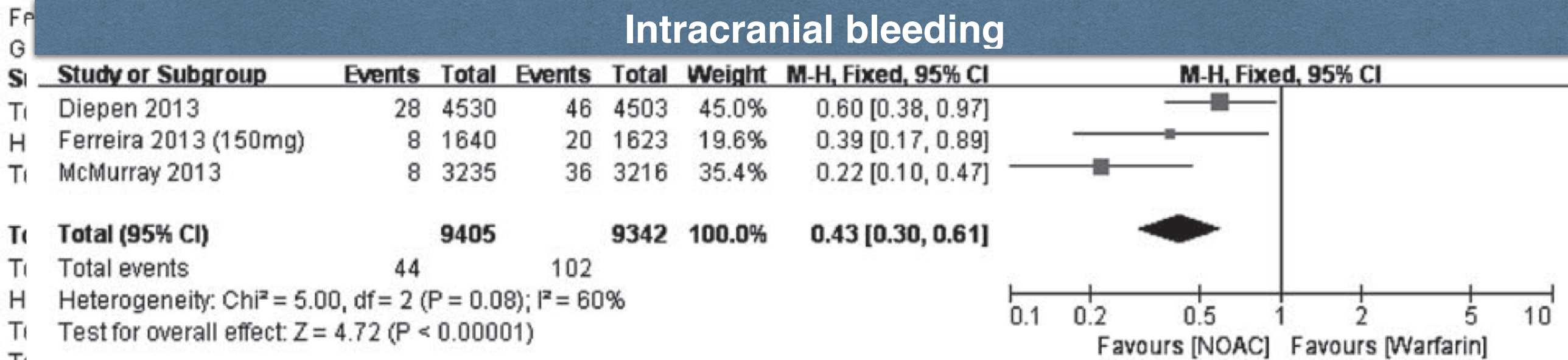
NOAKs im Vergleich zu VKA bei Patienten mit Herzinsuffizienz und Vorhofflimmern - Metanalysis aus den NOAK Landmark Studien

Stroke / Systemic embolism

Major Hemorrhage



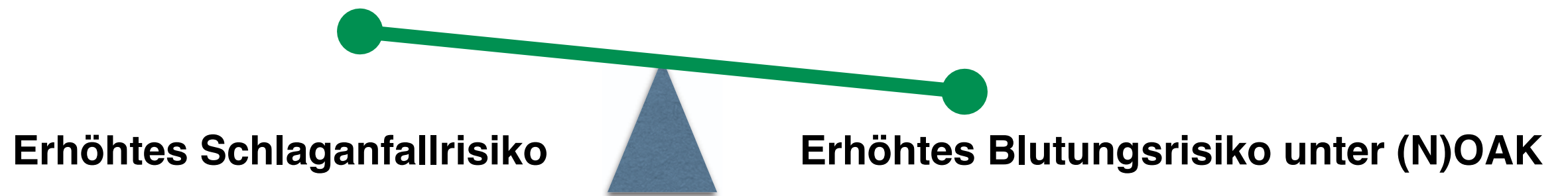
1.2.2 Low Dose



Intracranial Haemorrhages

Was tun bei Patienten mit Herzinsuffizienz und Sinusrhythmus?

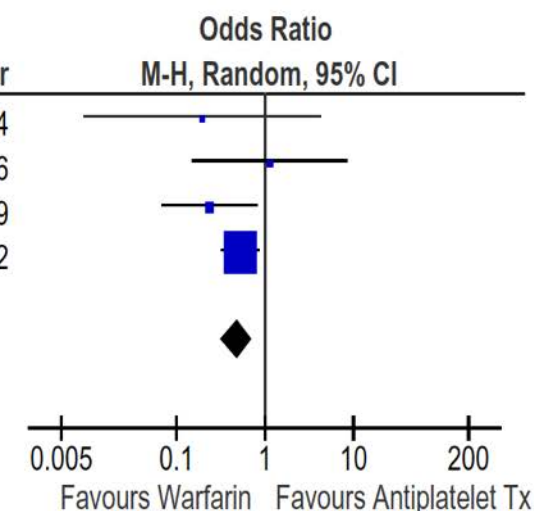
- Nicht adressiert in den Leitlinien



Meta analysis of RCT's Warfarin vs antiplatelet therapy in HF

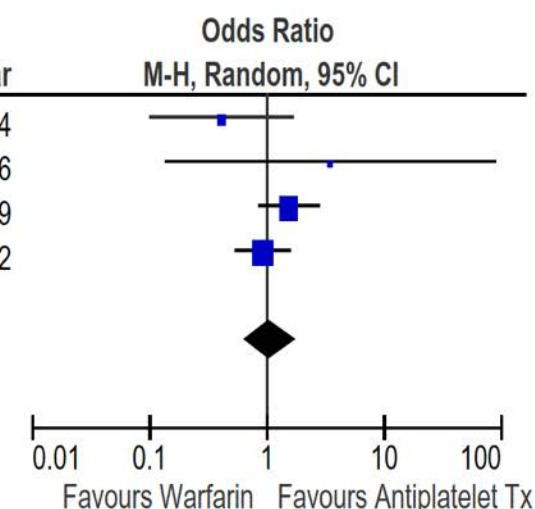
Stroke

Study or Subgroup	Warfarin		Antiplatelet Therapy		Weight	Odds Ratio		Year
	Events	Total	Events	Total		M-H, Random, 95% CI	Year	
WASH	0	80	2	80	1.8%	0.20	[0.01, 4.13]	2004
HELAS	2	54	2	61	4.3%	1.13	[0.15, 8.34]	2006
WATCH	3	540	24	1047	11.8%	0.24	[0.07, 0.79]	2009
WARCEF	29	1142	55	1163	82.0%	0.52	[0.33, 0.83]	2012
Total (95% CI)		1816		2351	100.0%	0.49	[0.32, 0.73]	
Total events	34		83					
Heterogeneity: Tau ² = 0.00; Chi ² = 2.53, df = 3 (P = 0.47); I ² = 0%								
Test for overall effect: Z = 3.42 (P = 0.0006)								



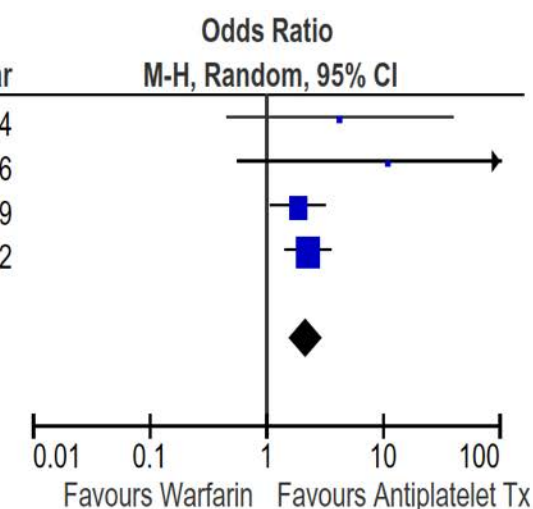
Mortality

Study or Subgroup	Warfarin		Antiplatelet Therapy		Weight	Odds Ratio		Year
	Events	Total	Events	Total		M-H, Random, 95% CI	Year	
WASH	3	80	7	80	11.3%	0.41	[0.10, 1.63]	2004
HELAS	1	54	0	61	2.3%	3.45	[0.14, 86.44]	2006
WATCH	21	540	27	1047	40.6%	1.53	[0.86, 2.73]	2009
WARCEF	28	1142	31	1163	45.7%	0.92	[0.55, 1.54]	2012
Total (95% CI)		1816		2351	100.0%	1.06	[0.64, 1.75]	
Total events	53		65					
Heterogeneity: Tau ² = 0.07; Chi ² = 4.16, df = 3 (P = 0.24); I ² = 28%								
Test for overall effect: Z = 0.24 (P = 0.81)								

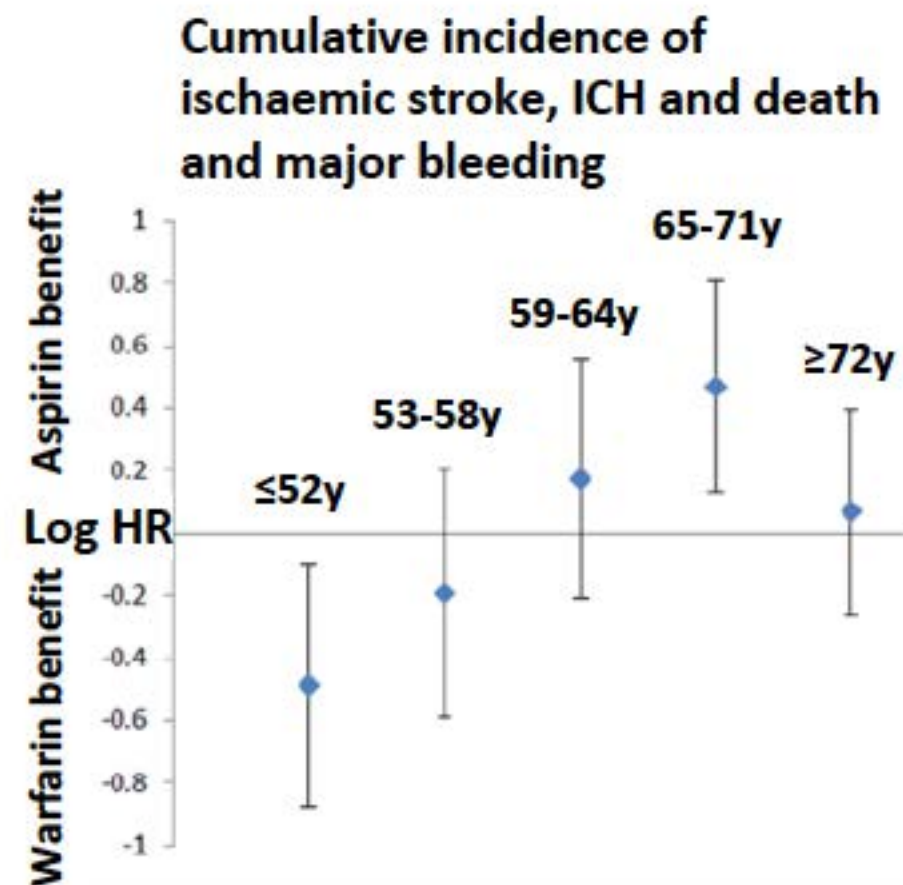
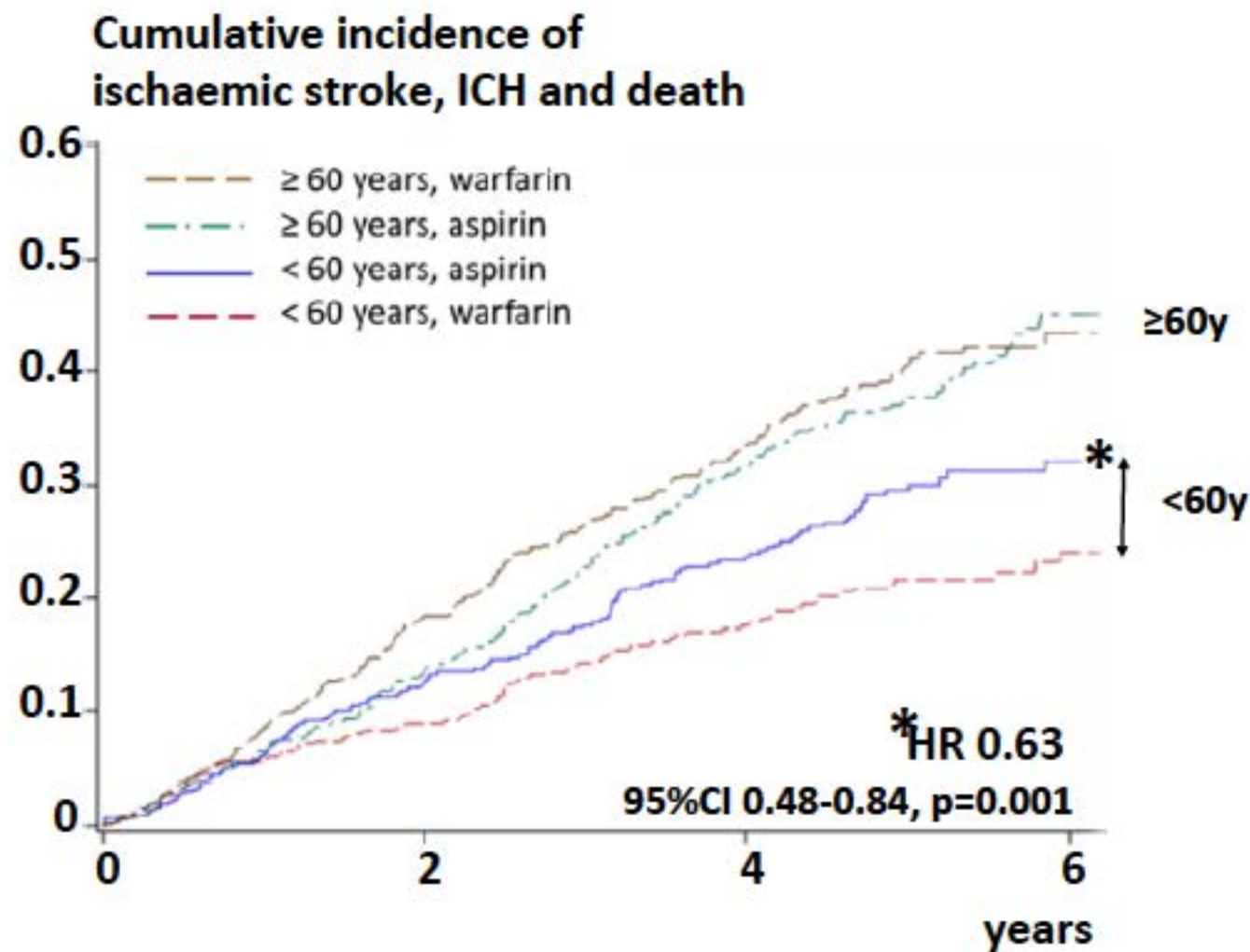


Major Bleeding

Study or Subgroup	Warfarin		Antiplatelet Therapy		Weight	Odds Ratio		Year
	Events	Total	Events	Total		M-H, Random, 95% CI	Year	
WASH	4	89	1	91	2.2%	4.24	[0.46, 38.66]	2004
HELAS	4	54	0	61	1.2%	10.96	[0.58, 208.44]	2006
WATCH	28	540	30	1047	39.2%	1.85	[1.10, 3.14]	2009
WARCEF	66	1142	31	1163	57.3%	2.24	[1.45, 3.46]	2012
Total (95% CI)		1825		2362	100.0%	2.15	[1.55, 2.99]	
Total events	102		62					
Heterogeneity: Tau ² = 0.00; Chi ² = 1.89, df = 3 (P = 0.59); I ² = 0%								
Test for overall effect: Z = 4.56 (P < 0.00001)								



WARCEF – Subgruppen Analyse: Wer profitiert ?



< 60 Jahre: VKA vorteilhaft
> 60 years: Aspirin vorteilhaft

OAK bei Herzinsuffizienz und reduzierter LV-Funktion

Table 5 Randomized controlled trials of anticoagulation with warfarin in patients with heart failure and reduced ejection fraction without atrial fibrillation and characteristic comparison with the COMMANDER-HF trial

Trial	n	Study design	Population	Comparison group	Mean follow-up (months)	Primary endpoint	Major bleeding rate (safety)
WASH (Warfarin/Aspirin Study in Heart Failure)	279	Open-label	LVEF \leq 35%	ASA 300 mg vs. warfarin vs. no treatment	27	No significant differences in composite of death, MI, or stroke	Warfarin 4% ASA 1% No treatment 0%
HELAS (Heart failure Long-Term Antithrombotic Study)	197	Placebo-controlled, double-blinded	LVEF \leq 35% 59% IHD, 41% DCM	IHD: ASA 325 mg vs. warfarin; DCM: warfarin vs. placebo	IHD: 19 DCM: 20	No significant differences in incidence of MI or death	IDH: warfarin 7% ASA 0% DCM: warfarin 8% placebo 0%
WATCH (Warfarin and Antiplatelet Therapy in Chronic Heart Failure)	1587	Double-blind, double-dummy (ASA and clopidogrel), and open-label (warfarin)	LVEF \leq 35%	ASA 162 mg vs. clopidogrel 75 mg vs. warfarin	23	No significant difference in the composite endpoint of death, MI, or stroke	Warfarin 5.2% ASA 3.6% Clopidogrel 2.1%
WARCEF (Warfarin vs. Aspirin in patients with Reduced Cardiac Function)	2306	Double-blind, double-dummy	LVEF \leq 35%	Warfarin vs. ASA 325 mg	42	No significant difference in the composite endpoint of ischemic stroke, intracerebral haemorrhage, or death	Warfarin 1.78%/year ASA 0.87%/year
COMMANDER-HF	~5000	Double-blind, placebo-controlled	LVEF \leq 40%, recent HF exacerbation, increased NP, CAD	Rivaroxaban 2.5 mg b.i.s. vs. placebo	Event driven	Primary endpoint: death from any cause, MI, or stroke	Clinically relevant bleeding

LVEF, left ventricular ejection fraction; ASA, aspirin; IHD, ischaemic heart disease; DCM, dilated cardiomyopathy; MI, myocardial infarction; NP, natriuretic peptide.

2012 Consensus Document from the ESC Heart Failure Association and the ESC Working Group on Thrombosis

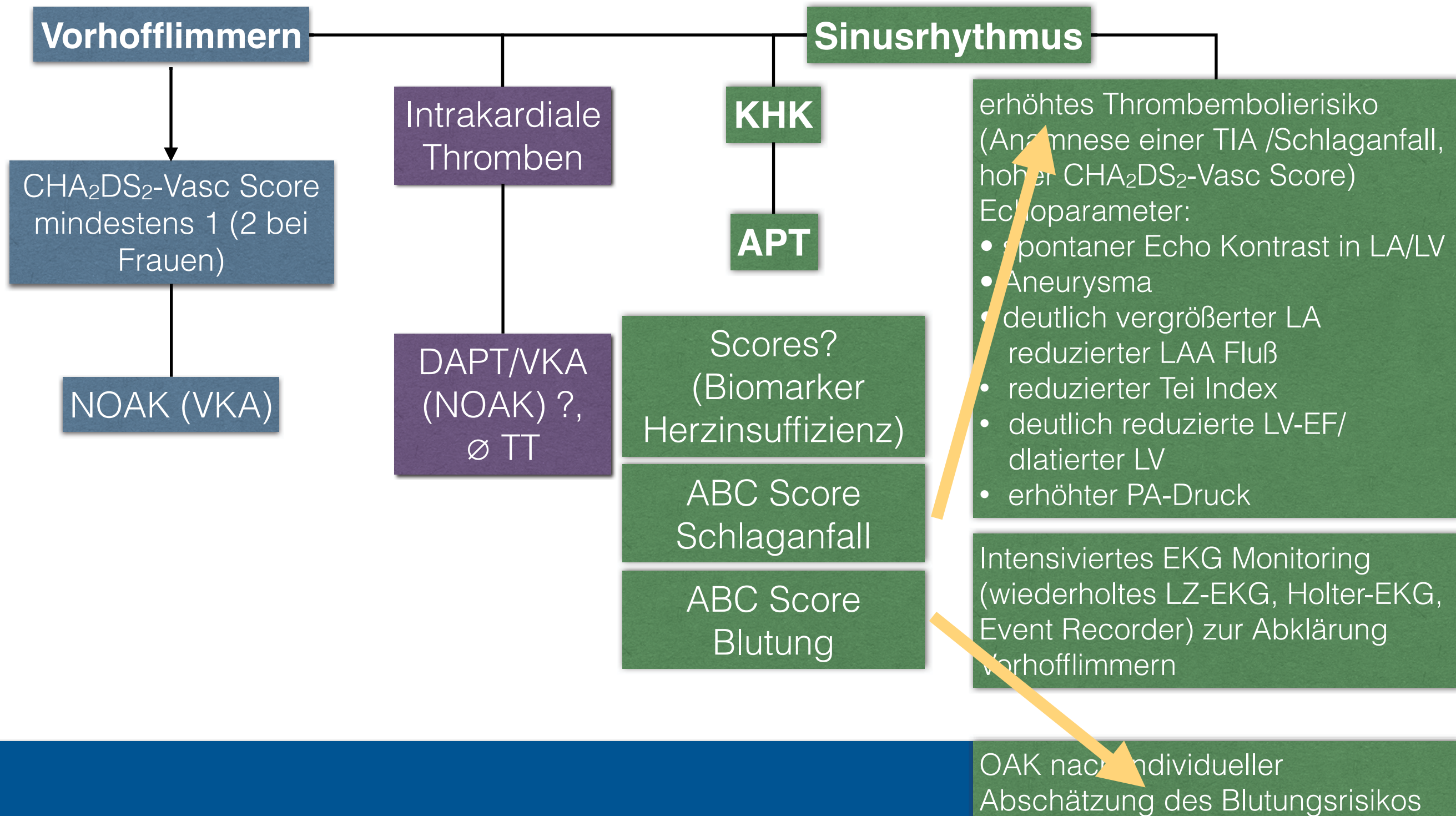
- In the absence of a specific indication, such as documented coronary artery disease, aspirin should not be initiated.
- Given no overall benefit of warfarin on rates of death and stroke, with an increase in major bleedings despite the potential for a reduction in ischemic stroke - there is currently no compelling reason to use warfarin routinely for all HF patients in sinus rhythm.
- Until more evidence becomes available, clinical decisions to treat patients with HF in sinus rhythm with anticoagulants must be made on a patient-by-patient basis, balancing the individual benefits against the risks of treatment, especially amongst high risk patients.
- Clinical trials are needed to see if the new oral anticoagulants (oral direct thrombin inhibitors, oral Factor Xa inhibitors) that may offer a different risk–benefit profile compared with warfarin could offer the reduction in ischemic stroke with less risk of major bleeding.
- Anticoagulation may potentially be considered by some clinicians in the following HF patient groups: HFrEF with previous thrombo-embolism (stroke, transient ischemic attack, VTE), newly diagnosed intracardiac thrombus, and right heart failure with pulmonary hypertension, but evidence is limited and more research is needed to ascertain the long-term risk–benefit ratio.

2012 Consensus Document from the ESC Heart Failure Association and the ESC Working Group on Thrombosis

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Herzinsuffizienz - Differenzierte Ansätze zur Senkung des thromboembolischen Risikos

Herzinsuffizienz HF-REF (HF-PEF?)



Vielen Dank für die Aufmerksamkeit!