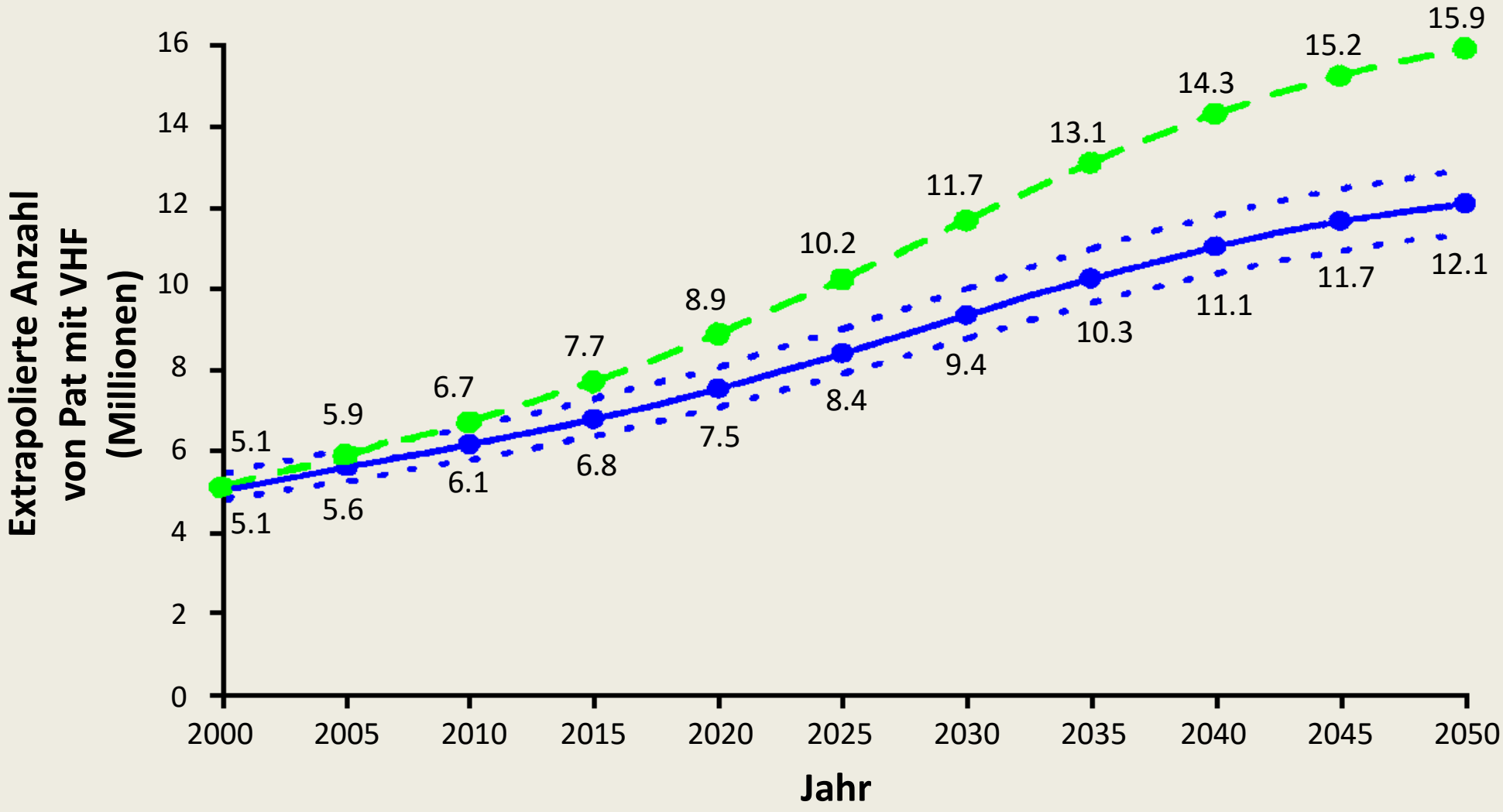
NOACs im klinischen Kontext. Operation und Intervention, Triple-Therapie, Bridging

Joachim Ehrlich
St. Josefs-Hospital

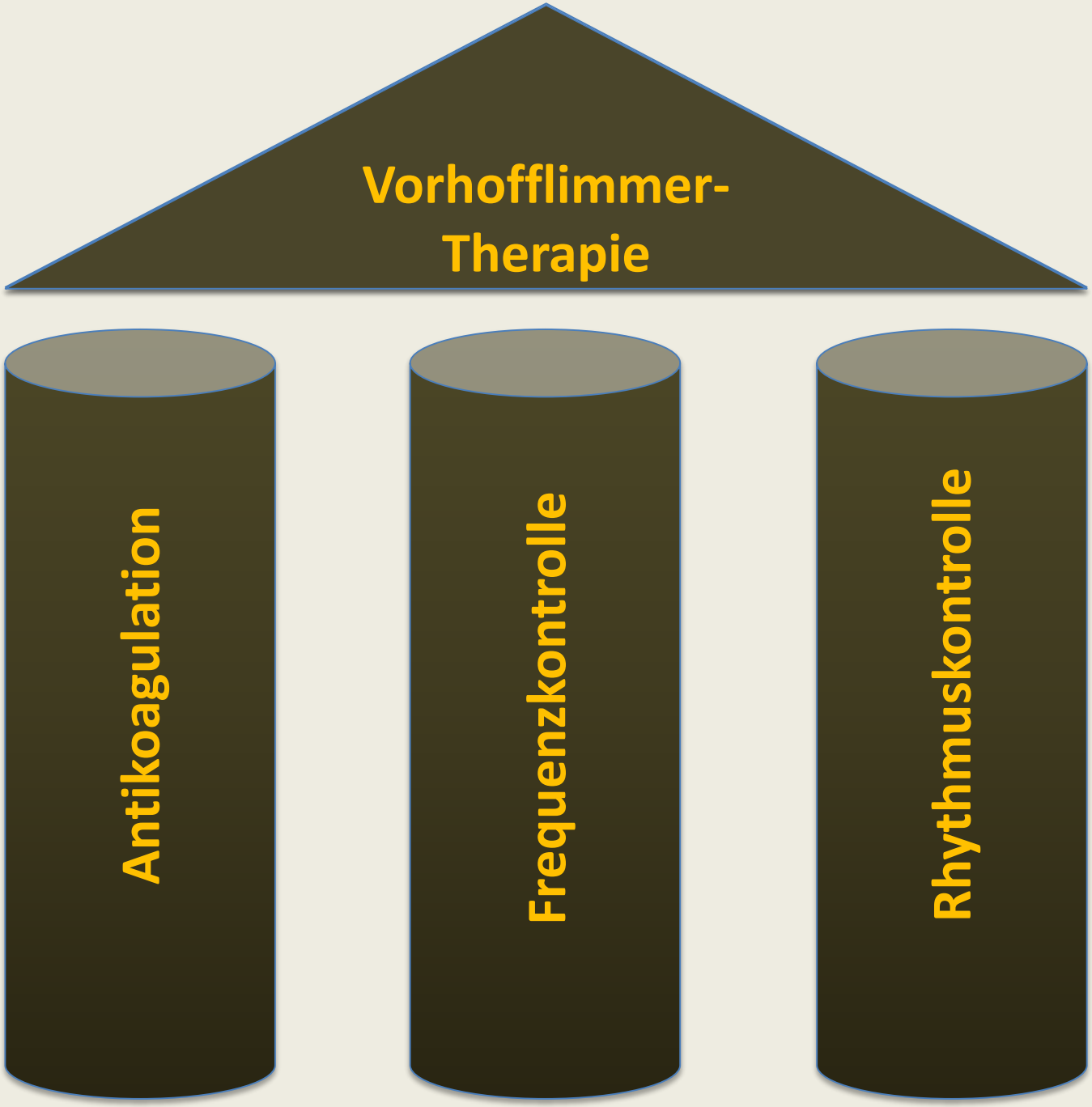
PRÄVALENZ VON VHF



solid curve: no further increase in AF incidence
dotted curve: increase in incidence rate as evident 1980 to 2000

Miyasaka et al, Circulation 2006;114:119

STANDBEINE DER VHF THERAPIE



THEMEN

Kardioversion

Ablation

Operation

Triple-Therapie

FALL

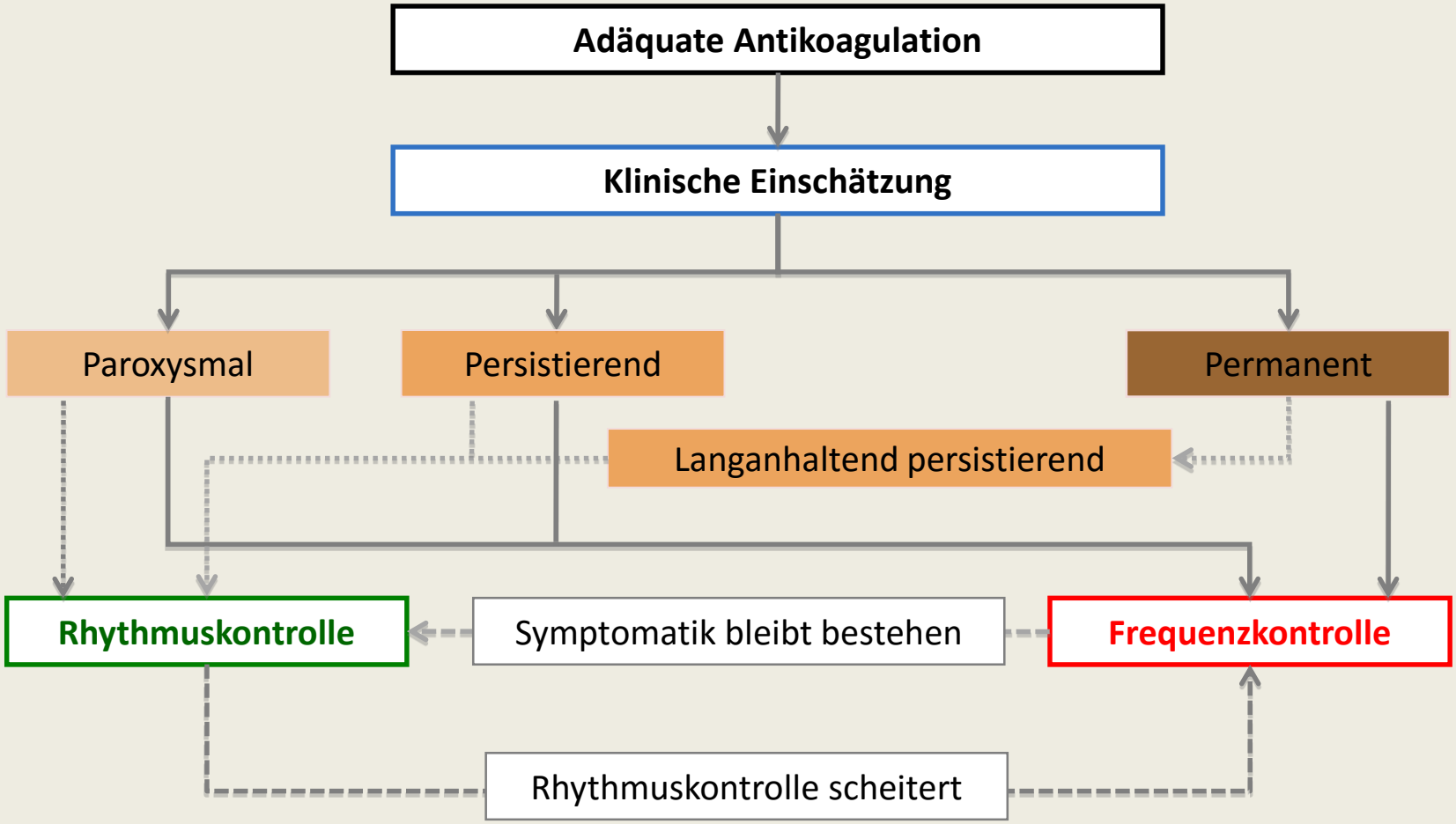
71jähriger Patient mit Hypertonie und erstmaligem VHF (CHADSVASC=2) seit gestern Abend (~18 Std.). Das VHF geht nicht weg. UND ES STÖRT….

A – Ich verschreibe Marcumar und schicke ihn heim.

B – Ich führe zusätzlich zur Antikoagulation eine Frequenzkontrolle durch und beobachte, ob der Patient symptomatisch bleibt.

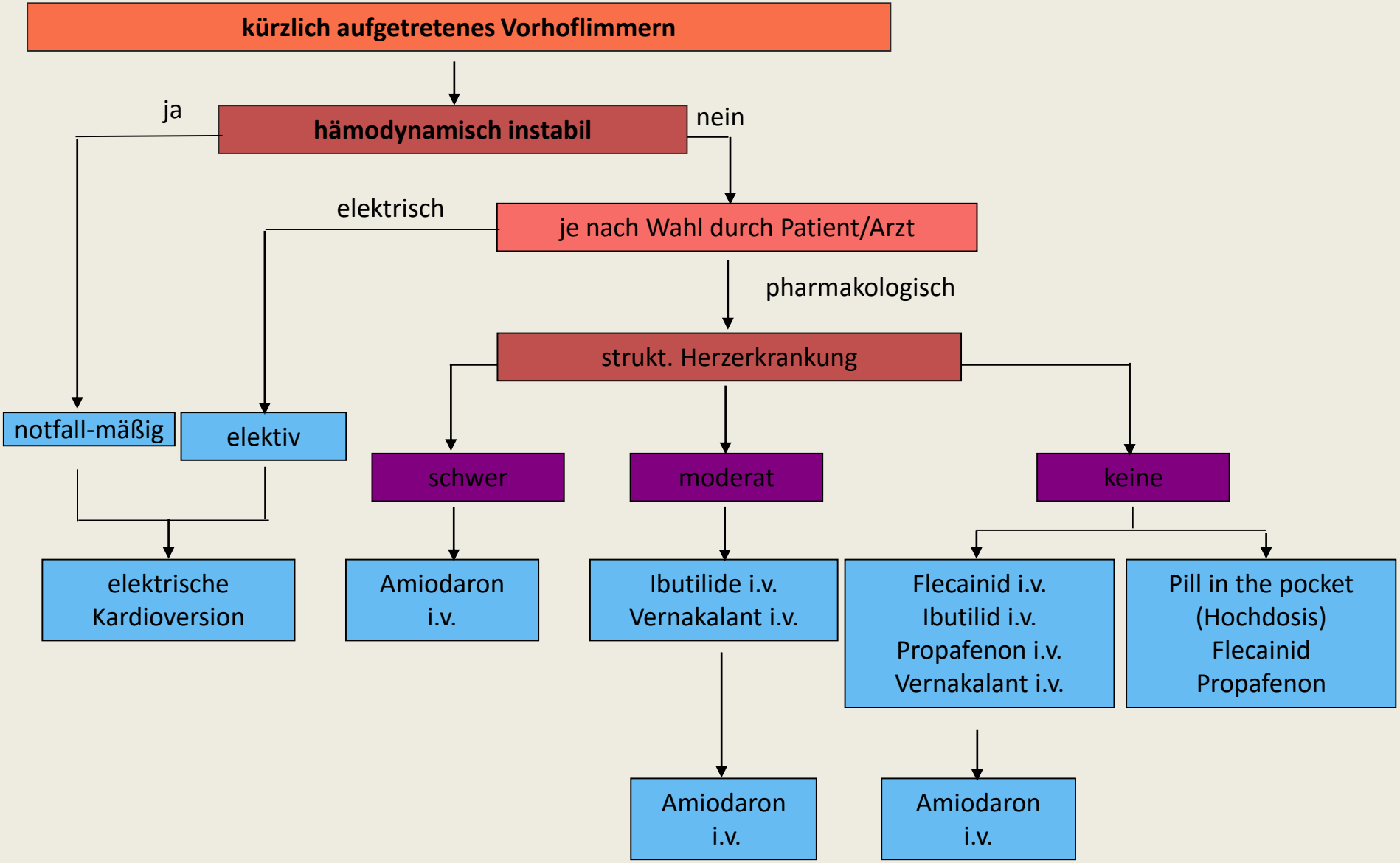
C – Klarer Fall: primäre Pulmonalvenenisolation.

BEHANDLUNGSPFAD



Camm et al, Eur Heart J 2010; 31(19):2369-429

INDIKATION ZUR KARDIOVERSION



Modifiziert nach Camm et al, Eur Heart J 2012;33(21):2719-47

Exclusion criteria

AF or atrial flutter due to r
Clinically significant (moc
Increased bleeding risk b
anticoagulation (eg,
Conditions other than AF t
(eg, prosthetic mecha
Persistent uncontrolled hyp
Active infective endocard
Planned major surgery
Planned AF or atrial flutte
Use of unapproved invest
Required aspirin >165 m
Simultaneous treatment w
(eg, clopidogrel, ticlo
Severe comorbid conditio
Active alcohol or drug ab
participation impract
Recent stroke (within 7 d)
Severe renal insufficiency
creatinine clearance
ALT or AST >2 × ULN or c
causative factor [eg,
Platelet count ≤100,000/
Hemoglobin level <9 g/d
Inability to comply with INR monitoring

ECG, Electrocardiogram; *CH* ... *LV*, left ventricular; *LVEF*, left ventricular ejection fraction; *S* ... *DBP*, diastolic blood pressure; ALT, alanine transaminase; AST, aspartate transaminase; *ULN*, upper limit of normal; *wk*, weeks; *mo*, months.

ARISTOTLE

6. Plan to p
7. Severe r
8. Active i
9. Active li
a. Persiste
b. Known
c. Active
d. Active
10. Wome
use a me
11. Anemi
count <1
12. Patient
to ximelo
13. Patient
14. Patien
expectan
concomit
investiga
addiction

ALT, alanine aminotransferase; *AST*, aspartame aminotransferase; *Alk phos*, alkaline phosphatase; *HCV*, hepatitis C virus; *HBs*, hepatitis B surface; *HBc*, hepatitis B core; *IgM*, immunoglobulin M.

Exclusion Criteria:

1. Transient AF secondary to other reversible disorders (e.g., thyrotoxicosis, cardiac or thoracic surgery, pneumonia, severe anemia);
2. Subjects with moderate or severe mitral stenosis, unresected atrial myxoma, or a mechanical heart valve (subjects with bioprosthetic heart valves and/or valve repair can be included);
3. Subjects for whom the AF management plan is rhythm control with subsequent discontinuation of oral anticoagulation if sinus rhythm is restored or maintained, including subjects in whom successful electrical or surgical ablation has been performed or is planned during the course of the study;
4. Subjects with a ... for anticoagulant agents;

ENGAGE-AF

...ous malformation, or aneurysm

...ntrolled bleeding, including major surgery

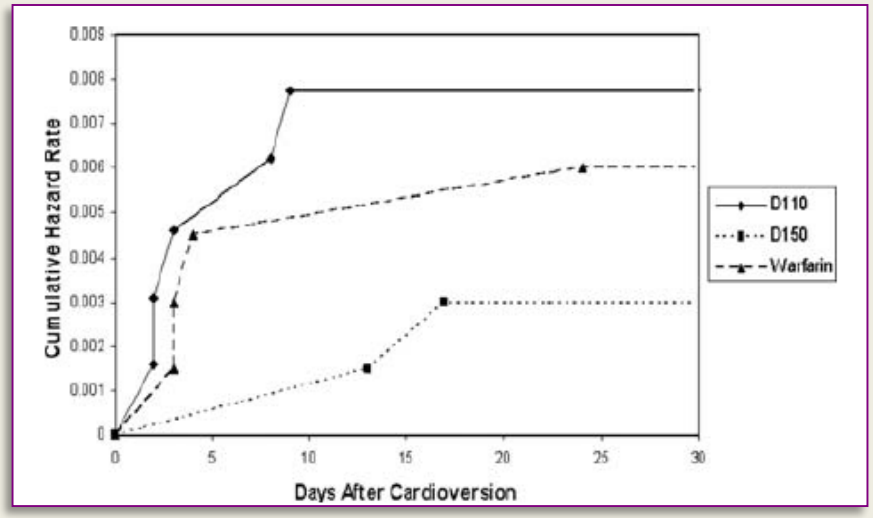
...Hg or diastolic blood pressure ≥100

ROCKET-AF

Supplement to: Patel et al. N Engl J Med. 2011;365:883-891
Ezkowitz MD et al. Am Heart J. 2009;157:805-810
Lopes RD et al., Am Heart J 2010;159:331-9

KARDIOVERSION IN RELY

	D110		D150		Warfarin	
	n	%	n	%	n	%
Total randomized	6015		6076		6022	
Cardioversions performed	647*		672		664	
Electric	554	85.63	550	81.85	553	83.28
Pharmacological	91	14.06	122	18.15	111	16.72
TEE	165	25.50	162	24.11	88	13.25
Normal sinus rhythm at discharge	566	87.48	596	88.69	595	89.61
Stroke and systemic embolism	5	0.77	2	0.30	4	0.60
<30 d after cardioversion						
Major bleeding	11	1.70	4	0.60	4	0.60
<30 d after cardioversion						



RELY: 18,113 Patienten, medianes F/U: 2,0 Jahre

Nagarakanti et al, Circulation 2011;123:131-136

KARDIOVERSION IN ROCKET-AF

Table 6 Outcomes After ECV, PCV, or Catheter Ablation According to Randomized Treatment

Endpoint Following ECV, PCV, or Ablation	Rivaroxaban (N = 160)	Warfarin (N = 161)	All (N = 321)
Stroke or systemic embolism	3 (1.88)	3 (1.86)	6 (1.87)
CV death	2 (1.25)	4 (2.48)	6 (1.87)
All-cause death	3 (1.88)	6 (3.73)	9 (2.80)
Hospitalization	50 (31.25)	48 (29.81)	98 (30.53)
Stroke or systemic embolism or CV death	5 (3.13)	7 (4.35)	12 (3.74)
Stroke or systemic embolism or death from any cause	6 (3.75)	9 (5.59)	15 (4.67)
Major or NMCR bleeding	30 (18.75)	21 (13.04)	51 (15.89)

Values are numbers of events following cardioversion or ablation; percentages of patients with cardioversion or ablation in the given treatment group are shown in parentheses.

CV = cardiovascular; ECV = electrical cardioversion; NMCR = non-major clinically relevant; PCV = pharmacologic cardioversion.

ROCKET-AF: 14.264 Patienten, medianes F/U: 2,1 Jahre

143 Pat. – 181 el. CV; 142 Pat. – 194 pharm. CV; 79 Pat. – 85 PVI

Picini et al. JACC 2013;61:1998–2006

KARDIOVERSION IN ARISTOTLE

Table 2 Clinical Outcomes After Any Cardioversion, Within 30 Days, in Patients Assigned to Either Warfarin or Apixaban

Outcomes	Warfarin (n = 412)	Apixaban (n = 331)	Total (n = 743)
Stroke or systemic embolism	0	0	0
Myocardial infarction	1 (0.2)	1 (0.3)	2 (0.2)
Major bleeding	1 (0.2)	1 (0.3)	2 (0.2)
Death	2 (0.5)	2 (0.6)	4 (0.5)

Values are n (%).

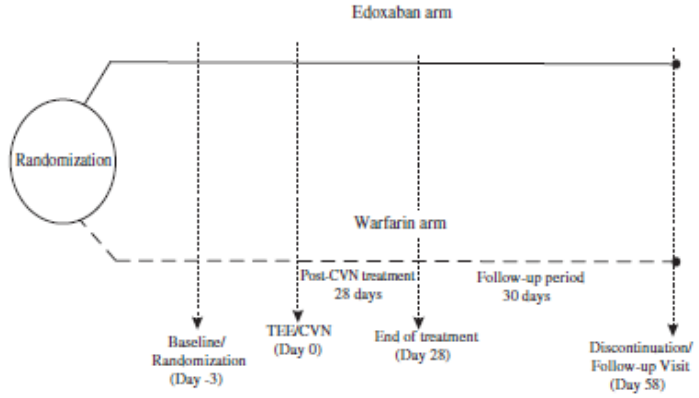
ARISTOTLE: 18.201 Patienten, medianes F/U: 1,8 Jahre

Flaker et al. J Am Coll Cardiol 2014;63:1082–7

KARDIOVERSIONEN MIT EDOXABAN

A) Study Flow Diagram for TEE-Guided Stratum

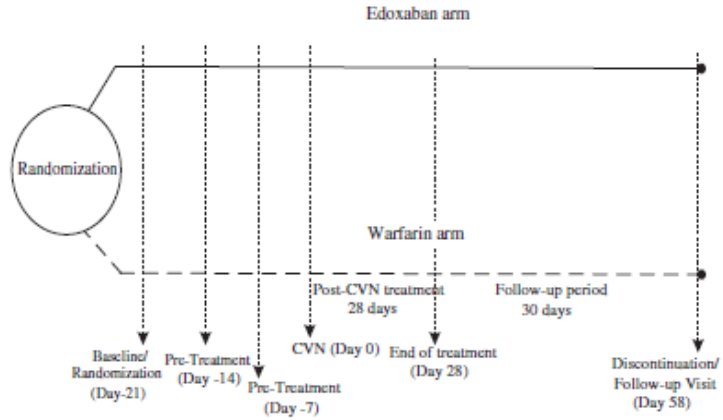
DU176b-F-E308: A randomized, open-label parallel group study comparing edoxaban or enoxaparin followed by warfarin in subjects undergoing planned electrical cardioversion of non-valvular atrial fibrillation



CVN=Cardioversion; TEE= Transesophageal Echocardiography

B) Study Flow Diagram for Non-TEE-Guided Stratum

DU176b-F-E308: A randomized, open-label parallel group study comparing edoxaban or enoxaparin followed by warfarin in subjects undergoing planned electrical cardioversion of non-valvular atrial fibrillation

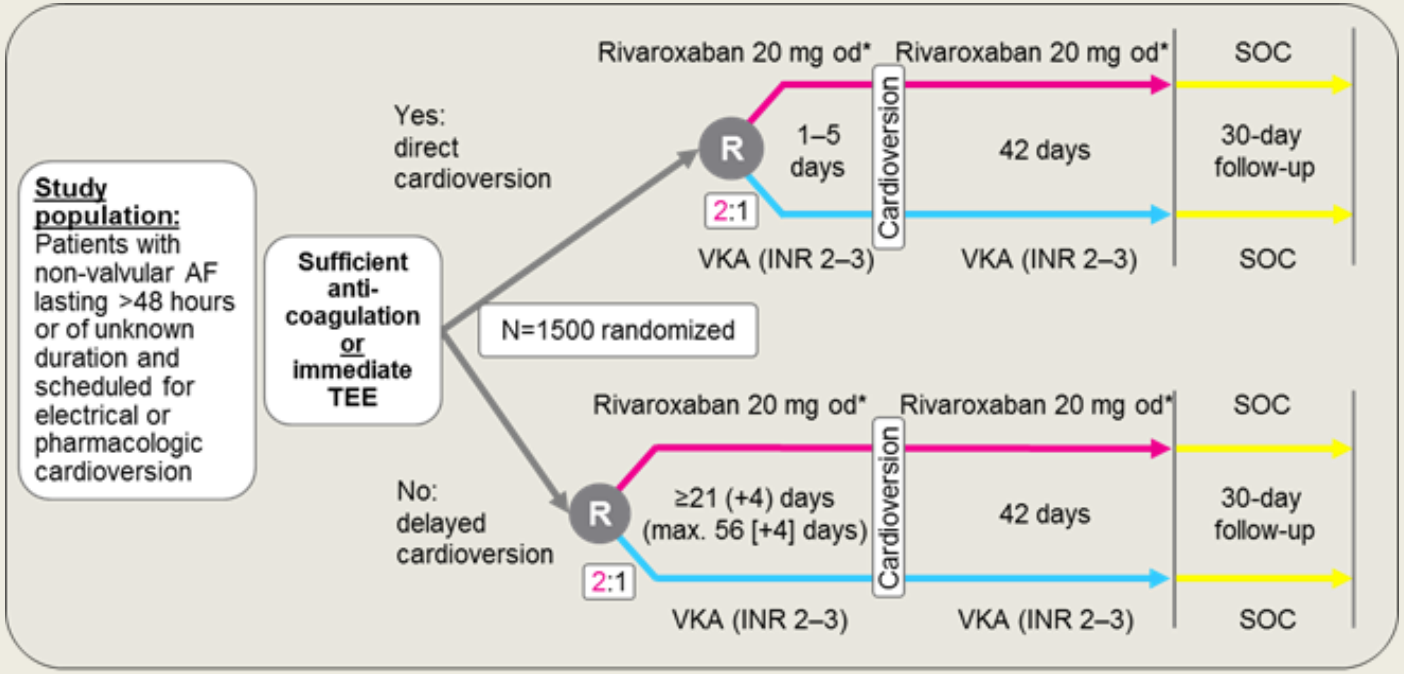


CVN=Cardioversion

Lip et al. Am Heart J 2015;169:597-604.

X-VERT

Phase IIIb, prospektive, randomisierte, open-label Studie bei Kardioversion



*CrCl 30–49 ml/min: 15 mg once daily

AF, atrial fibrillation; CrCl, creatinine clearance; INR, international normalized ratio; od, once daily; R, randomization; SOC, standard of care; TEE, transesophageal echocardiogram: VKA, vitamin K antagonist

Ziel: Wirksamkeit und Sicherheit von Rivaroxaban bei Patienten mit nicht-valvulärem VHF bei elektiver Kardioversion

Cappato et al. Eur Heart J 2014;35(47):3346-55

X-VERT

	Total by treatment			Early (1-5 Tage)		Delayed (3-8 Wochen)	
	Rivaroxaban	VKA	RR (95% CI)	Rivaroxaban	VKA	Rivaroxaban	VKA
Efficacy, *n* (%)[a]	*n* = 978	*n* = 492		*n* = 567	*n* = 277	*n* = 411	*n* = 215
Primary end-point	5 (0.51)	5 (1.02)	0.50 (0.15–1.73)	4 (0.71)	3 (1.08)	1 (0.24)	2 (0.93)
Stroke	2 (0.20)	2 (0.41)		2 (0.35)	1 (0.36)	0	1 (0.47)
Haemorrhagic stroke	2 (0.20)	0		2 (0.35)	0	0	0
Ischaemic stroke	0	2 (0.41)		0	1 (0.36)	0	1 (0.47)
TIA	0	0		0	0	0	0
SE	0	1 (0.20)		0	1 (0.36)	0	0
MI	1 (0.10)	1 (0.20)		1 (0.18)	0	0	1 (0.47)
Cardiovascular death	4 (0.41)	2 (0.41)		3 (0.53)	2 (0.72)	1 (0.24)	0
All-cause death	5 (0.51)	3 (0.61)		3 (0.53)	3 (1.08)	2 (0.49)	0
Safety, *n* (%)[b]	*n* = 988	*n* = 499		*n* = 575	*n* = 284	*n* = 413	*n* = 215
Major bleeding	6 (0.61)	4 (0.80)	0.76 (0.21–2.67)	3 (0.52)	3 (1.06)	3 (0.73)	1 (0.47)
Fatal	1 (0.10)	2 (0.40)		1 (0.17)	2 (0.70)	0	0
Critical site	2 (0.20)	3 (0.60)		2 (0.35)	2 (0.70)	0	1 (0.47)
ICH	2 (0.20)	1 (0.20)		2 (0.35)	0	0	1 (0.47)
Hb decrease ≥2 g/dL	4 (0.40)	1 (0.20)		1 (0.17)	1 (0.35)	3 (0.73)	0
Transfusion ≥2 units RBCs or whole blood	3 (0.30)	1 (0.20)		1 (0.17)	1 (0.35)	2 (0.48)	0

Primärer Endpunkt: Schlaganfall, TIA, periph. Embolie, Myokardinfarkt, CV Tod

Cappato et al. Eur Heart J 2014;35(47):3346-55

KARDIOVERSION MIT NOACS

Die Daten sind ermutigend.
Überprüfung der Compliance der Patienten ist wichtig.

Recommendations for Prevention of thromboembolism in NVAF: Peri-Cardioversion

Recommendations	Class	Level
For patients with AF of ≥48 hours duration, or when the duration of AF is unknown, OAC therapy (eg, VKA with INR 2-3 or dabigatran) is recommended for ≥3 weeks prior to and for ≥4 weeks after cardioversion, regardless of the method (electrical or oral/IV pharmacological).	I	B
In patients with risk factors for stroke or AF recurrence, OAC therapy, whether with dose-adjusted VKA (INR 2-3) or a NOAC, should be continued lifelong irrespective of the apparent maintenance of sinus rhythm following cardioversion.	I	B

INR = international normalization ratio; IV = intravenous; OAC = oral anticoagulant

Camm et al. Eur Heart J 2012;33(21):2719-47

FALL

71jähriger Patient mit Hypertonie und erstmaligem VHF (CHADSVASC=2) seit gestern Abend (~18 Std.). Das VHF geht nicht weg. UND ES STÖRT….

Eine elektrische Kardioversion ist geplant.

A – Ich antikoaguliere den Patienten mit unfraktioniertem Heparin und kardiovertiere ihn elektrisch.

B – Ich antikoaguliere den Patienten mit Marcumar und kontrolliere, dass die INR 3 Wochen therapeutisch ist. Dann kardiovertiere ich.

C – Ich antikoaguliere den Patienten mit einem NOAK, mache eine TEE Untersuchung und kardiovertiere ihn.

TEE VOR KARDIOVERSION

4.1.7.1 Transoesophageal echocardiogram-guided cardioversion

The mandatory 3-week period of OAC prior to cardioversion can be shortened if TOE reveals no LA or LAA thrombus. TOE may not only show thrombus within the LAA or elsewhere in the left atrium, but may also identify spontaneous echo-contrast or complex aortic plaque. A TOE-guided cardioversion strategy is recommended as an alternative to 3-week pre-cardioversion anticoagulation if experienced staff and appropriate facilities are available, and, when early cardioversion is neede
OAC is not indicated due to patient choice c
risks, or when there is a high risk of LA/LAA

If no LA thrombus is detected on TOE, UF
be started prior to cardioversion and contin
the target INR is achieved with OAC.

If TOE detects a thrombus in the left atrium
2.0–3.0) treatment is required for at least 3 w
should be repeated. If thrombus resolution is evic
sion can be performed, and post-cardioversion OAC is continued lifelong. If thrombus is still evident, the rhythm control strategy may be changed to a rate control strategy, especially when AF-related symptoms are controlled, since there is a high risk of thrombo-embolism if cardioversion is performed (*Figure 5*).

In patients with a definite AF onset <48 h, cardioversion can be performed expediently under the cover of UFH administered i.v. followed by infusion or subcutaneous LMWH. In patients with risk factors for stroke (see Section 4.1.1), OAC should be started after cardioversion and continued lifelong. UFH or LMWH should be continued until the INR is at the therapeutic level
thro

Kardioversion ohne TEE möglich, wenn VHF <48 Stunden besteht

Camm et al. Eur Heart J 2012;33(21):2719-47

TEE-GEFÜHRTE KARDIOVERSION

Variable	Transesophageal-Echocardiography Group (N=619)	Conventional-Treatment Group (N=603)	Relative Risk (95% CI)	P Value
All embolic events — no. (%)	5 (0.8)	3 (0.5)	1.62 (0.39–6.76)	0.50
Cerebrovascular accident	4 (0.6)	2 (0.3)	1.95 (0.36–10.60)	0.43
Transient ischemic attack	1 (0.2)	1 (0.2)	0.97 (0.06–15.54)	0.99
Peripheral embolism	0	0	—	—
Hemorrhagic events — no. (%)	18 (2.9)†	33 (5.5)	0.53 (0.30–0.93)	0.03
Major	5 (0.8)	9 (1.5)	0.54 (0.18–1.61)	0.26
Minor	14 (2.3)	24 (4.0)	0.57 (0.30–1.09)	0.08
Death from all causes — no. (%)	15 (2.4)	6 (1.0)	2.44 (0.95–6.24)	0.06
Cardiac-related	8 (1.3)	4 (0.7)	1.95 (0.59–6.44)	0.27
Noncardiac-related	5 (0.8)	2 (0.3)	2.44 (0.47–12.50)	0.27
Unknown cause	2 (0.3)	0	4.87 (0.23–101.25)	0.16
Sinus rhythm — no. (%)				
Restored immediately after DC cardioversion	370/461 (80.3)	266/333 (79.9)	1.01 (0.94–1.08)	0.90
Restored within 8 wk	440 (71.1)	393 (65.2)	1.09 (1.01–1.18)	0.03
Maintained at 8-wk follow-up	326 (52.7)	304 (50.4)	1.05 (0.95–1.16)	0.43
Functional status at 8 wk — DASI score‡	27.4±18.3	26.7±18.6	—	0.50

Klein et al, N Engl J Med 2001;344:1411-20

FRÜHE KARDIOVERSION OHNE TEE

Thromboembolische Komplikationen bei Patienten, die <48 Std. nach Beginn des VHF elektrisch kardiovertiert wurden.

Retrospektive Betrachtung von 2481 Patienten, 5116 erfolgreiche Kardioversionen ohne Antikoagulation.

	Total No. of Patients	No. (%) of Patients by Time to Cardioversion[b]			P Value[c]
		<12 h (n = 2440)	12-<24 h (n = 1840)	24-<48 h (n = 836)	
		No. (%) [95% CI] of Patients by Time to Cardioversion			
Thromboembolic complications	38	8 (0.3) [0.1-0.6]	21 (1.1) [0.7-1.6]	9 (1.1) [0.4-1.8]	.004
By sex					
Female	22	3 (0.4) [0-0.8]	13 (2.4) [1.1-3.6]	6 (2.5) [0.5-4.6]	.001
Male	16	5 (0.3) [0-0.6]	8 (0.6) [0.2-1.0]	3 (0.5) [0-1.1]	.48
By $CHADS_2$ score					
0-1	25	4 (0.2) [0-0.4]	15 (1.0) [0.5-1.5]	6 (0.9) [0.2-1.6]	.006
>1	13	4 (1.0) [0-2.0]	6 (2.0) [0.4-3.7]	3 (1.9) [0-4.1]	.50
By CHA_2DS_2-VASc score					
0-1	10	2 (0.2) [0-0.4]	4 (0.4) [0-0.8]	4 (0.9) [0-1.8]	.06
>1	28	6 (0.5) [0.1-0.9]	17 (2.0) [1.1-2.9]	5 (1.2) [0.2-2.3]	.008

Nuotio et al, JAMA 2014; 312:647-648

FALL

71jähriger Patient mit Hypertonie und erstmaligem VHF (CHADSVASC=2) seit gestern Abend (~18 Std.). Das VHF geht nicht weg. UND ES STÖRT….

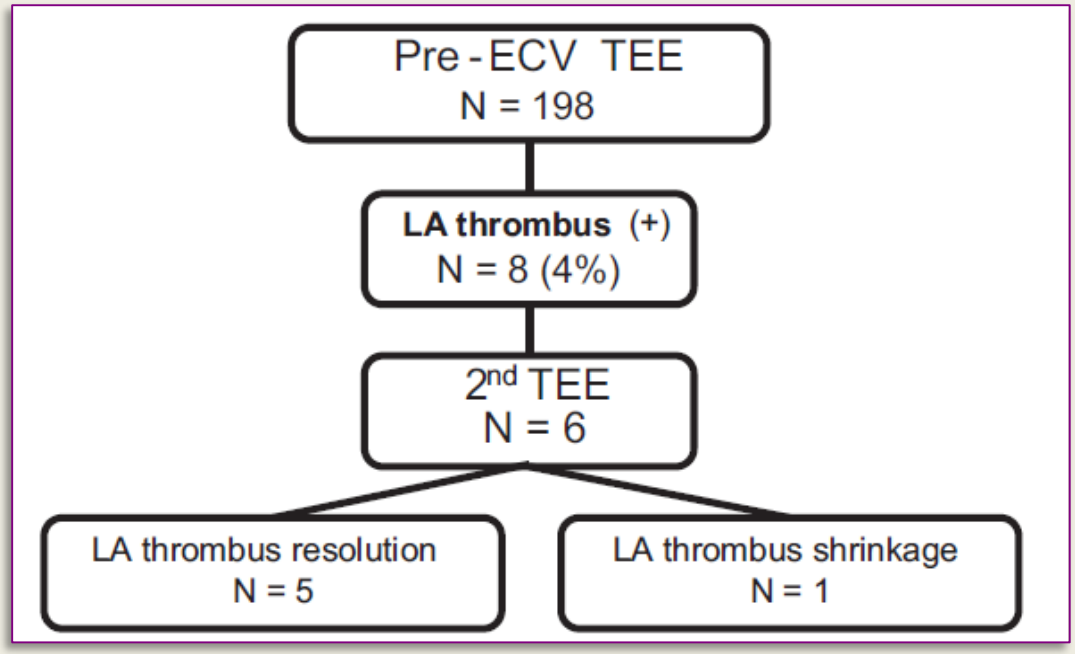
Sie haben Dabigatran 2x110 mg gegeben. Es findet sich ein LAA-Thrombus.

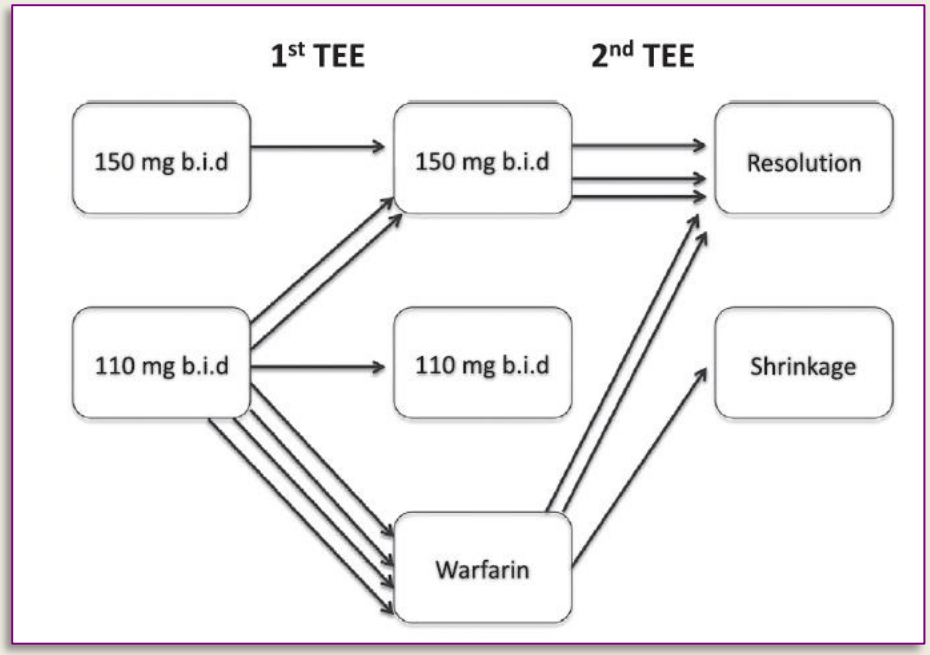
A – Ich warte 4 Wochen und untersuche erneut mittels TEE.

B – Ich erhöhe die Dosis auf 2x150 mg.

C – Ich setze auf Marcumar um.

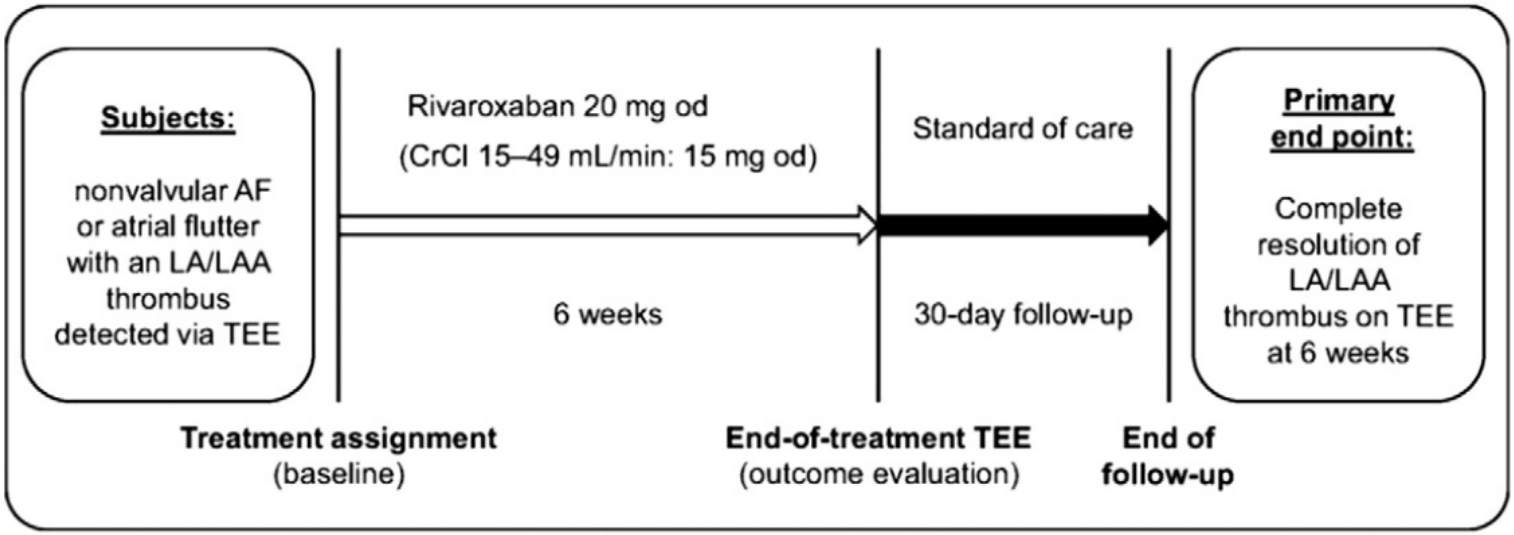
LA THROMBUS UND DABIGATRAN



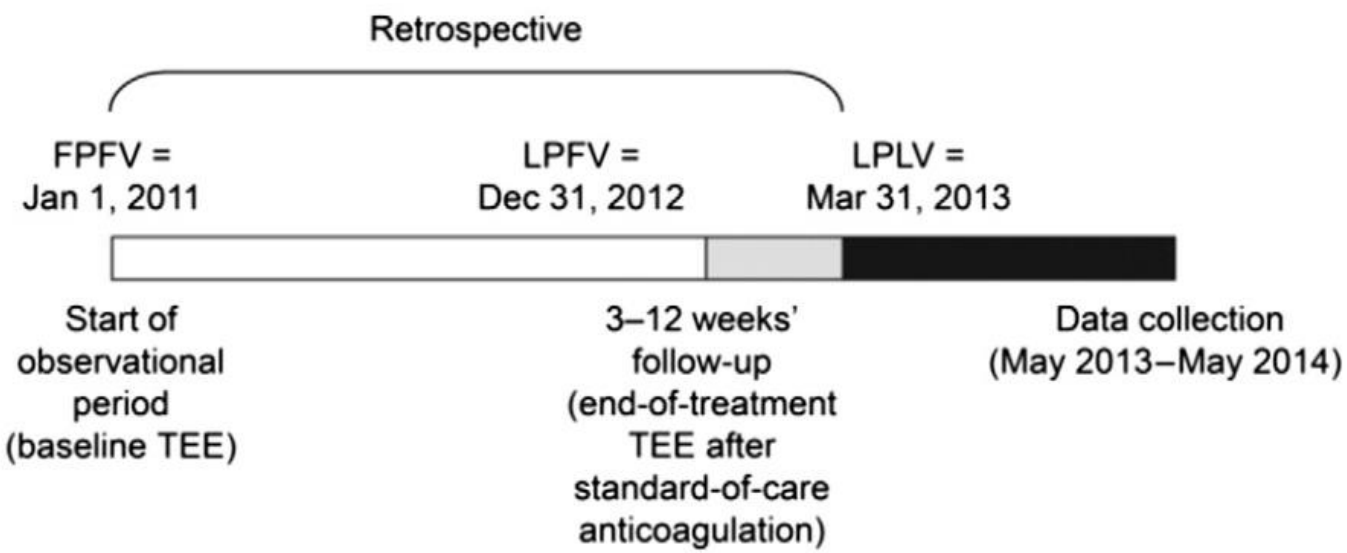


Mitamura et al. J Arrhythm 2015;(31):226–231

X-TRA AND CLOT-AF



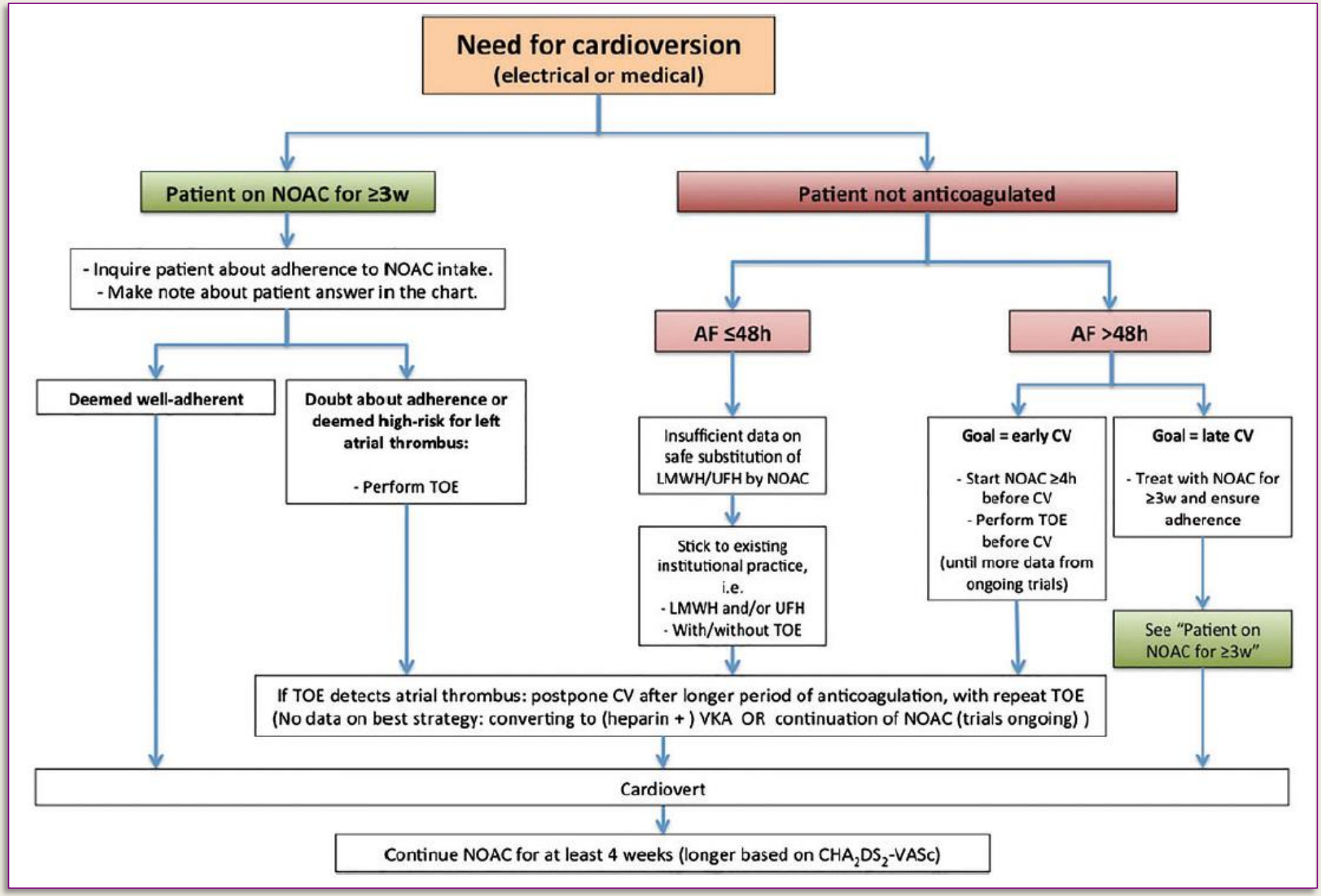
X-TRA study design. *CrCl*, creatinine clearance; *od*, once daily.



Overview of CLOT-AF registry. *FPFV*, first patient, first visit; *LPFV*, last patient, first visit; *LPLV*, last patient, last visit.

Lip et al. Am Heart J 169;(4):464–471

EHRA PRACTICAL GUIDE CARDIOVERSION



Heidbuchel et al, Europace (2015) 17, 1467–1507

THEMEN

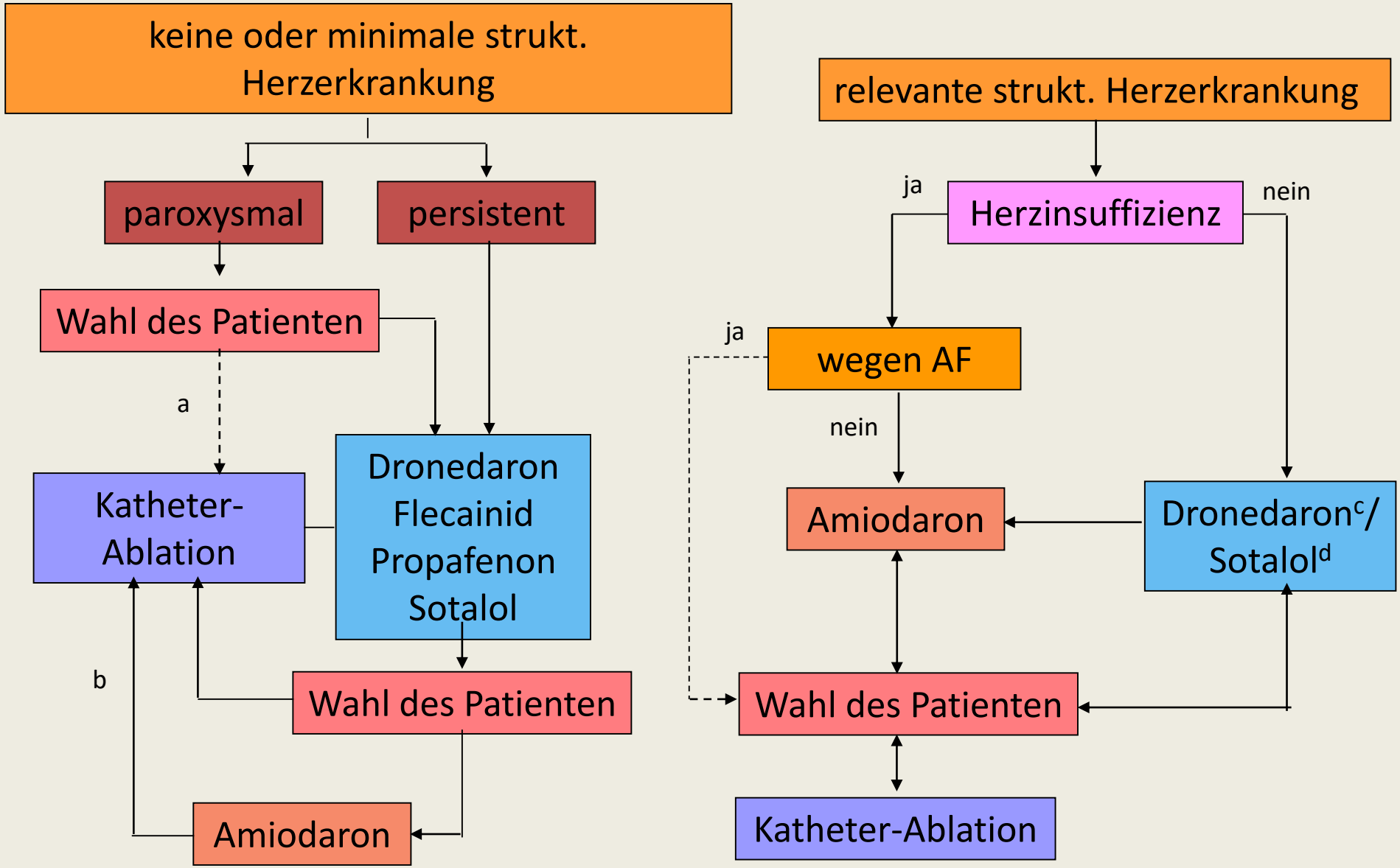
Kardioversion

Ablation

Operation

Triple-Therapie

INDIKATION ZUR ABLATION



a – normalerweise Pulmonalvenen-Isolation; b – umfassendere LA Ablation kann notwendig sein
c – Vorsicht bei KHK d – nicht empfohlen bei LVH

FALL

71jähriger Patient mit Hypertonie und erstmaligem VHF (CHADSVASC=2) seit gestern Abend (~18 Std.). Das VHF geht nicht weg. UND ES STÖRT….

Nach der elektrischen Kardioversion gab es ein symptomatisches Rezidiv.

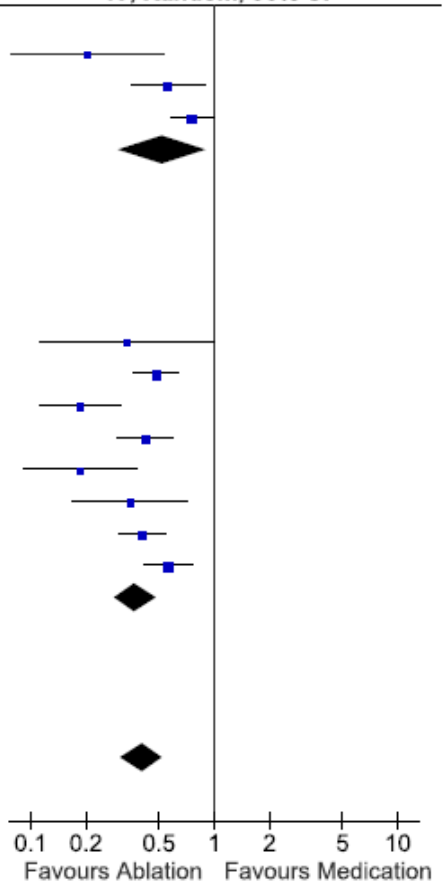
A – Ich kardiovertiere ihn nochmal. Vielleicht hält es ja jetzt.

B – jetzt erfolgt eine Kardioversion unter Rezidivprophylaxe mit Flecainid.

C – Lieber gleich Amiodaron – das hilft wenigstens.

EFFEKTIVITÄT ABLATION VS. MEDIKAMENTE

Study or Subgroup	Catheter Ablation Events	Total	Anti-arrhythmic Drugs Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
2.1.1 Anti-arrhythmic Medication Naive							
Wazni 2005	4	33	22	37	4.8%	0.20 [0.08, 0.53]	2005
Nielsen 2012	22	138	42	148	9.7%	0.56 [0.35, 0.89]	2012
Morillo 2014	36	66	44	61	12.2%	0.76 [0.58, 0.99]	2014
Subtotal (95% CI)		**237**		**246**	**26.6%**	**0.52 [0.30, 0.91]**	
Total events	62		108				
Heterogeneity: Tau² = 0.16; Chi² = 7.24, df = 2 (P = 0.03); I² = 72%							
Test for overall effect: Z = 2.32 (P = 0.02)							
2.1.2 Previous Use of Anti-arrhythmic Medication							
Krittayaphong 2003	3	15	9	15	4.0%	0.33 [0.11, 0.99]	2003
Stabile 2006	30	68	63	69	12.1%	0.48 [0.37, 0.64]	2006
Pappone 2006	14	99	75	99	9.2%	0.19 [0.11, 0.31]	2006
Oral 2006	25	77	53	69	11.2%	0.42 [0.30, 0.60]	2006
Jais 2008	7	53	42	59	6.8%	0.19 [0.09, 0.38]	2008
Forleo 2009	7	35	20	35	6.6%	0.35 [0.17, 0.72]	2009
Wilber 2010	35	103	47	56	11.9%	0.40 [0.30, 0.54]	2010
Mont 2014	39	98	34	48	11.7%	0.56 [0.41, 0.76]	2014
Subtotal (95% CI)		**548**		**450**	**73.4%**	**0.37 [0.29, 0.48]**	
Total events	160		343				
Heterogeneity: Tau² = 0.08; Chi² = 20.22, df = 7 (P = 0.005); I² = 65%							
Test for overall effect: Z = 7.48 (P < 0.00001)							
Total (95% CI)		**785**		**696**	**100.0%**	**0.40 [0.31, 0.52]**	
Total events	222		451				
Heterogeneity: Tau² = 0.12; Chi² = 38.98, df = 10 (P < 0.0001); I² = 74%							
Test for overall effect: Z = 6.93 (P < 0.00001)							
Test for subgroup differences: Chi² = 1.26, df = 1 (P = 0.26), I² = 20.8%							



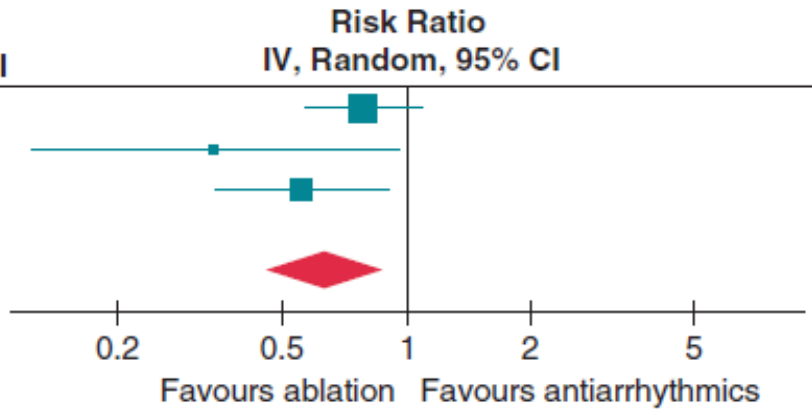
11 randomisierte Studien
zumeist paroxysmales VHF
785 Patienten – Ablation
696 Patienten – Antiarrhythmika
9-24 (zumeist 12) Monate Follow-up

Khan et al Circ Arrhythm Electrophysiol. 2014;7:853-860

ABLATION ALS „1ST LINE“ THERAPIE

Study or subgroup	log(Risk Ratio)	SE	Weight	Risk Ratio IV, Random, 95% CI
MANTRA-PAF 2012	–0.24	0.16	52.9%	0.79 (0.57, 1.08)
RAAFT-1 2005	–1.07	0.52	11.3%	0.34 (0.12, 0.95)
RAAFT-2 2014	–0.58	0.24	35.8%	0.56 (0.35, 0.90)
Total (95% CI)			**100.0%**	**0.63 (0.44, 0.92)**

Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 3.22$, df = 2 ($P = 0.20$); $I^2 = 38\%$
Test for overall effect: $Z = 2.42$ ($P = 0.02$)



3 randomisierte Studien
paroxysmales VHF
245 Patienten – Ablation
246 Patienten – Antiarrhythmika
F/U = 1 Jahr in RAAFT-1,
2 Jahre in RAAFT-2 und MANTRA-PAF

Hakalahti et al Europace (2015) 17, 370–378

INDIKATION ZUR ABLATION

	Geeigneter Patient	Weniger geeigneter Patient
Symptome	Hochsymptomatisch	Wenig symptomatisch
Anti-Arrhythmika versucht	≥1	0
Art des VHF	Paroxysmal	Langanhaltend persistierend
Alter	Jünger (<70 Jahre)	Älter (≥70 Jahre)
Linker Vorhof	Kleiner (<5.0 cm)	Größer (≥5.0 cm)
LV Funktion	Normal	Reduziert
Herzinsuffizienz	Nein	Ja
Andere kardiale Krankheiten	Nein	Ja
Lungenerkrankung	Nein	Ja
Schlafapnoe	Nein	Ja
Übergewicht	Nein	Ja
Z.n. Schlaganfall / TIA	Nein	Ja

Nach Hugh Calkins MD, Heart Rhythm Society

FALL

71jähriger Patient mit Hypertonie und erstmaligem VHF (CHADSVASC=2) seit gestern Abend (~18 Std.). Das VHF geht nicht weg. UND ES STÖRT….

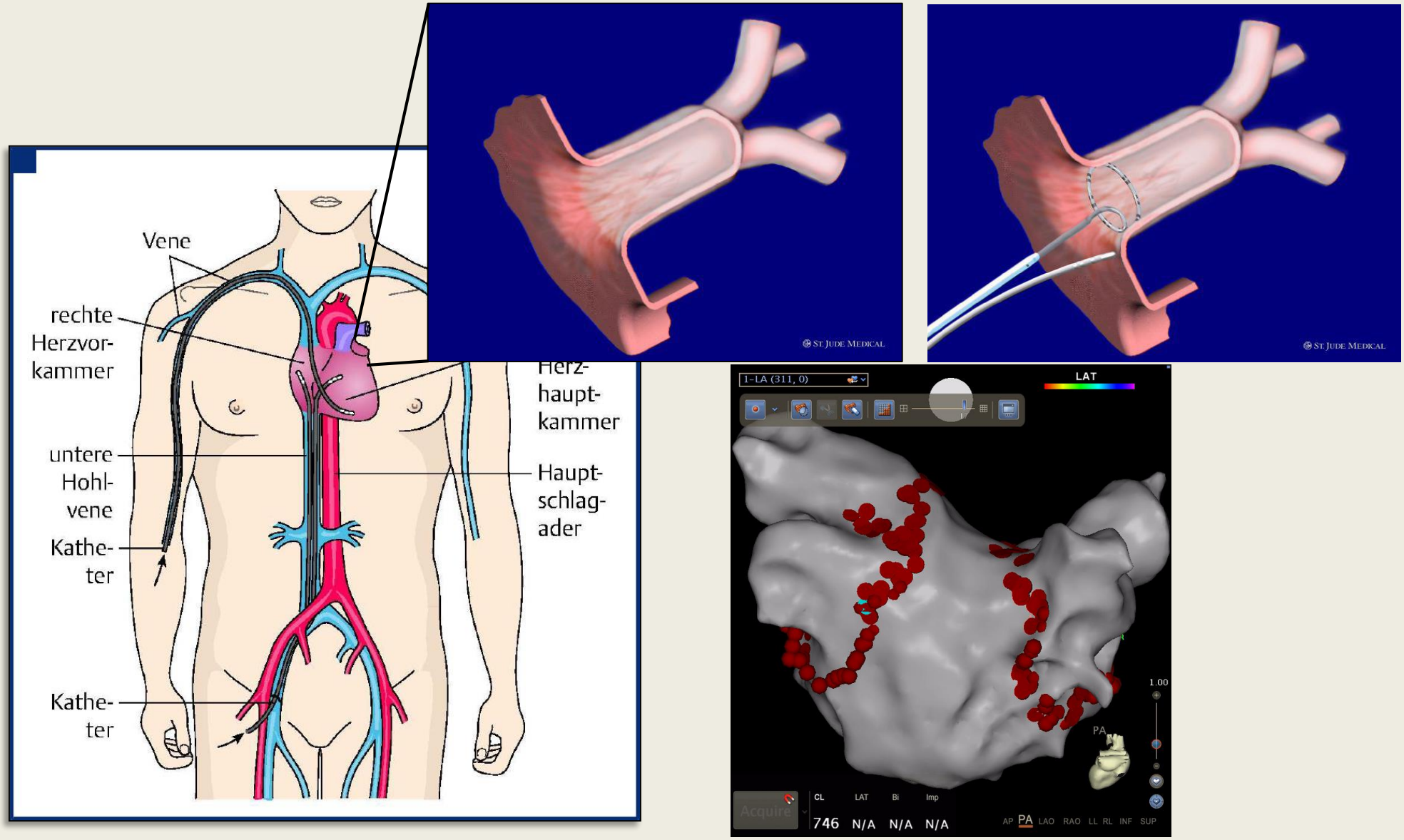
Nach Flecainid und Kardioversion kommt ein neuerliches Rezidiv.

A – Ich schicke den Patienten zu einer Pulmonalvenenisolation.

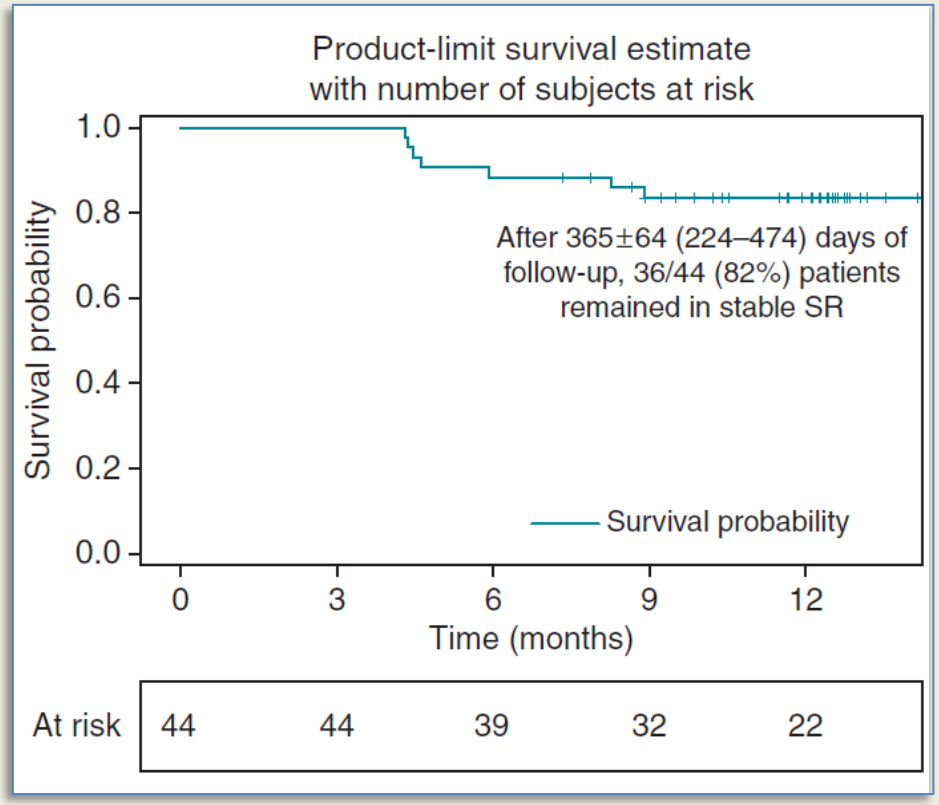
B – ich wechsle jetzt die Strategie – Rhythmuskontrolle ist gescheitert.

C – Jetzt aber Amiodaron – das hilft wenigstens.

INDIKATION ZUR ABLATION

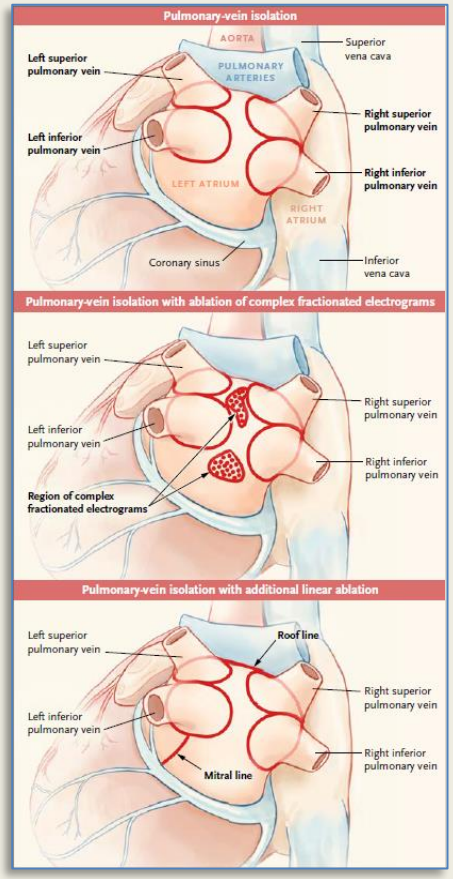


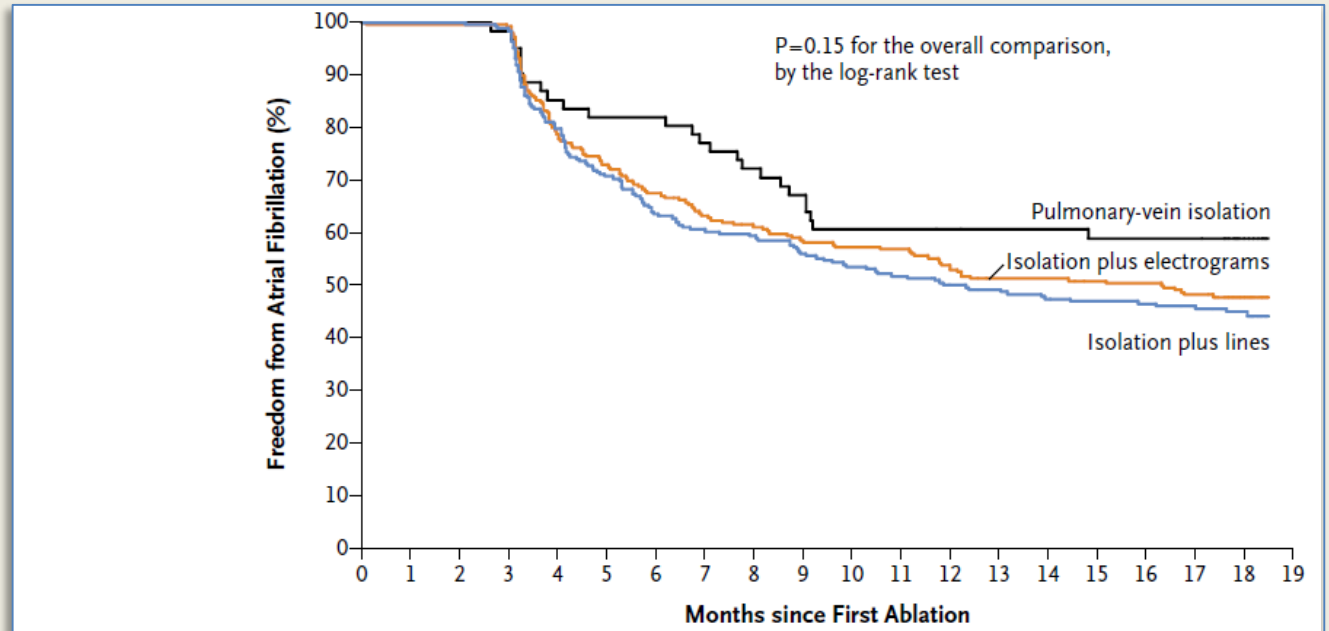
CRYO-ENERGIE



Wissner et al Europace (2015) 17, 1236–1240

PERSISTIERENDES VHF – STAR AF II





No. at Risk

Pulmonary-vein isolation	61	60	50	41	36	23
Isolation plus electrograms	244	242	161	137	124	72
Isolation plus lines	244	240	152	133	115	57

Verma et al N Engl J Med 2015;372:1812-22.

LANGZEIT-ERFOLG DER PVI

Langzeit-Erfolg (frei von VHF oder AT) → 70-90% der Patienten

ohne antiarrhythmische Medikamente

einige Studien haben 7 Jahre Nachbeobachtung

Viele Patienten brauchen >1 Prozedur

Die meisten Rezidive im ersten Jahr

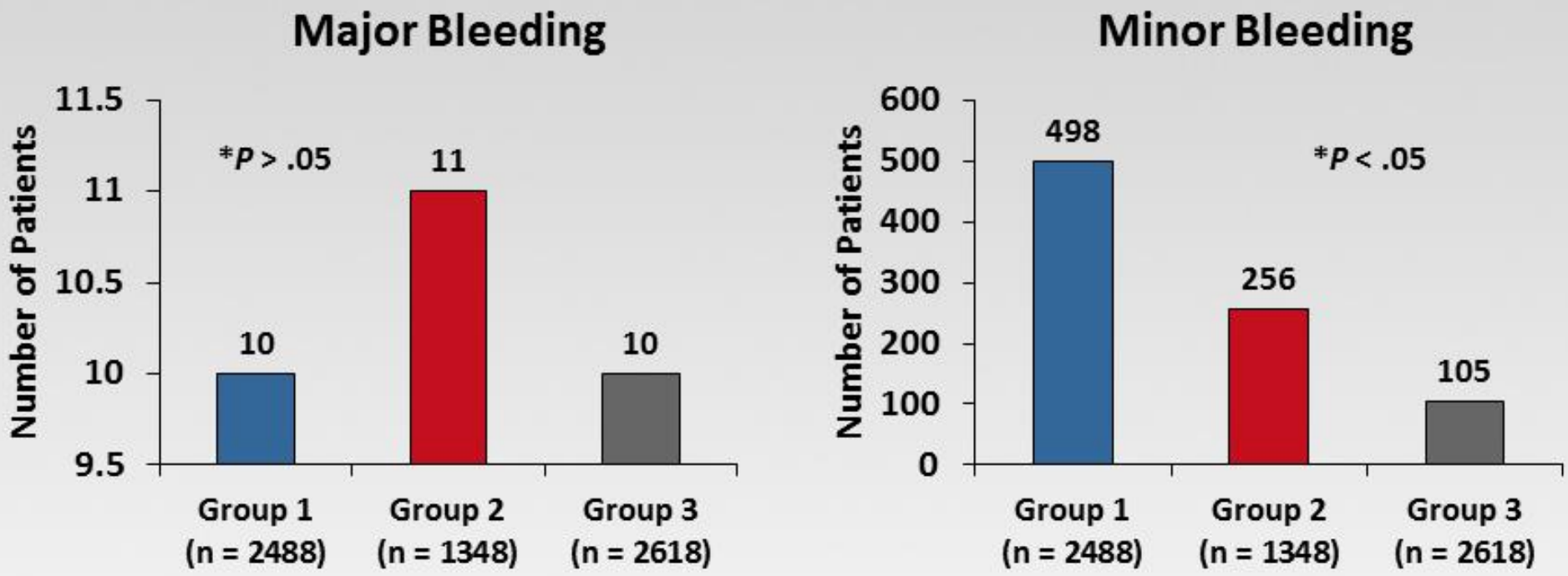
Nach 2-3 Jahren kaum noch Rezidive (nur noch 3%/Jahr)

VHF Rezidive

höchstes Risiko erste Monate nach PVI

Frührezidive sind Prädiktoren für Spätrezidive

MARCUMAR NICHT UNTERBRECHEN BEI PVI



Group 1: ablation with an 8-mm catheter off warfarin
Group 2: ablation with an open irrigated catheter off warfarin
Group 3: ablation with an open irrigated catheter on warfarin

DiBiase et al. Circulation 2014; 121(23):2550-2556

PVI IN NOAK ZULASSUNGS-STUDIEN

RELY: geplante PVI war Ausschlusskriterium

ROCKET-AF: 79 Pat. abladiert, 321 hatten vorherige Ablation

ARISTOTLE: geplante PVI war Ausschlusskriterium

ENGAGE-AF: alle Prozeduren ausgeschlossen, die VHF eliminieren könnten

BEOBACHTUNGSSTUDIEN ZU NOAK IM RAHMEN VON PVI

Table 3 Comparison of Complications between Rivaroxaban and Warfarin

Complication	Rivaroxaban (N = 321)	Warfarin (N = 321)	Total (N = 642)	p Value
Major bleeding (%)	5 (1.6)	7 (2.2)	12 (1.9)	0.772
Early cardiac tamponade (%)	2 (0.6)	4 (1.2)	6 (0.9)	
Delayed cardiac tamponade (%)	1 (0.3)	0 (0)	1 (0.2)	
≥Moderate access site hematomas (%)	2 (0.6)	3 (0.9)	5 (0.8)	
Minor bleeding complications (%)	16 (5.0)	19 (5.9)	35 (5.5)	0.602
<Moderate access site hematoma (%)	13 (4.0)	18 (5.6)	31 (4.8)	
Insignificant pericardial effusions (%)	3 (0.9)	1 (0.3)	4 (0.6)	
All bleeding complications (%)	21 (6.5)	26 (8.1)	47 (7.3)	0.449
Thromboembolic complications (stroke/TIA) (%)	1 (0.3)	1 (0.3)	2 (0.3)	1.00
TIA (%)	1 (0.3)	1 (0.3)	2 (0.3)	
Stroke	0	0	0	
Bleeding and thromboembolic complications (%)	22 (6.8)	27 (8.4)	49 (7.6)	0.457
Other complications	3 (0.9)	2 (0.6)	5 (0.8)	1.00

Table 3 Warfarin

	Warfarin (n = 145)	Total (N = 290)	p Value
Major bleedin	1 (1)	10 (3)	0.019
Periprocedu	1 (1)	7 (2)	0.12
Late perica	0 (0)	3 (1)	0.25
Minor bleedin	8 (6)	20 (7)	0.35
Groin hema	5 (3)	11 (4)	0.76
Pericardial	4 (3)	10 (3)	0.75
Total bleeding	9 (6)	29 (10)	0.031
Embolic comp	0 (0)	3 (1)	0.25
Composite of	9 (6)	32 (11)	0.009

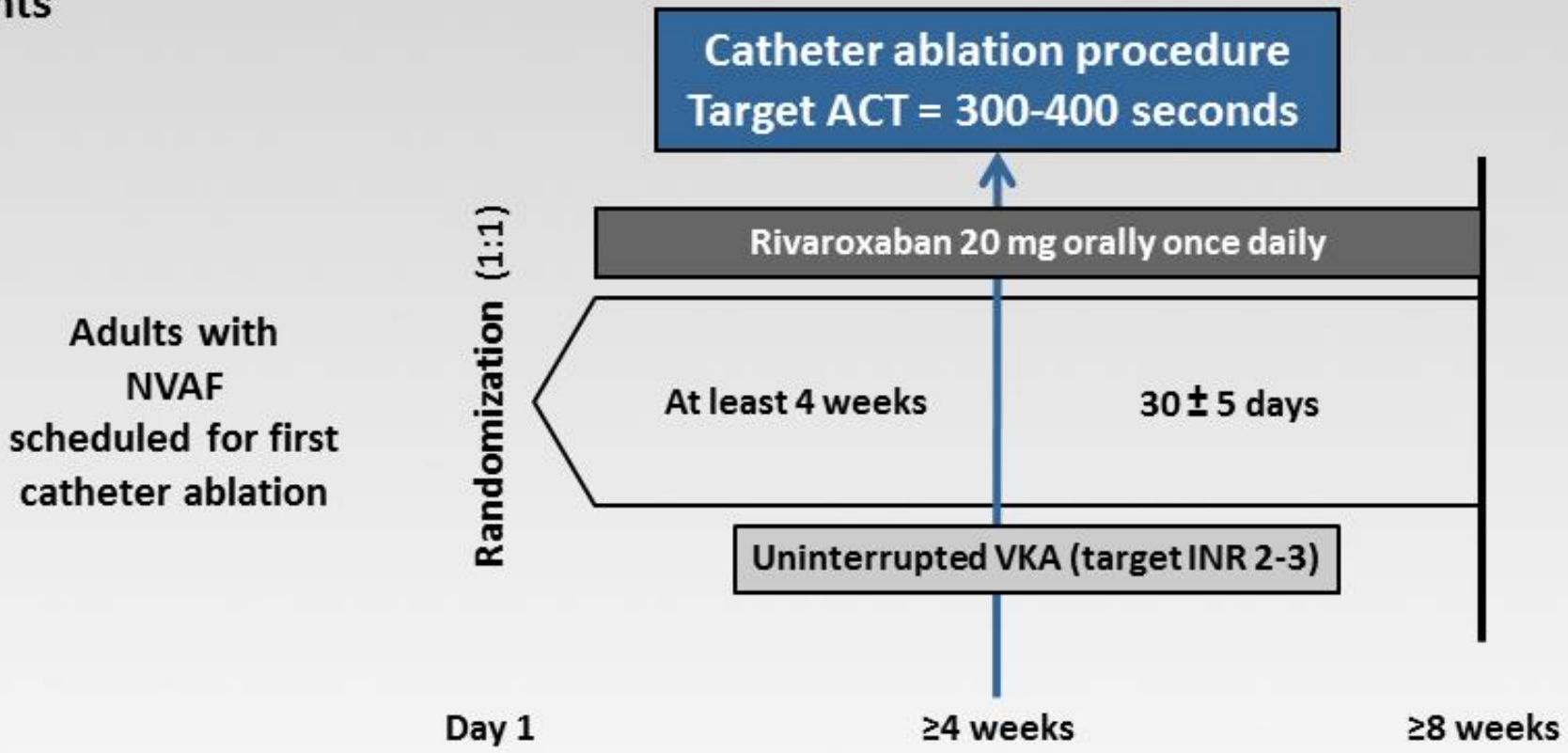
Gruppe >75 Jahre
= erhöhtes Blutungs-Risiko

ivaroxaban abends eingenommen
vs. Warfarin ohne Pause

Lakkireddy et al. J Am Coll Cardiol 2012;59:1168–74
Lakkireddy et al. J Am Coll Cardiol 2014;63:982–8

VENTURE-AF

Primary objective: exploratory study to evaluate safety of rivaroxaban and uninterrupted VKA as measured by postprocedure major bleeding events in 200 patients



Status: Enrolling

ACT = activated clotting time; NVAF = nonvalvular atrial fibrillation

clinicaltrials.gov

PROSPEKTIVE BEOBACHTUNGS-STUDIE

Konsekutive Patienten mit Pulmonalvenenisolation
TEE ~10 Tage nach PVI

Marcumar:	27 Patienten	keine Thromben
Dabigatran:	19 Patienten	keine Thromben
Rivaroxaban:	22 Patienten	keine Thromben
Apixaban:	12 Patienten	keine Thromben

KEINE Perikardtamponade

Feurich et al. submitted for publication

Kardioversion

Ablation

Operation

Triple-Therapie

FALL

71jähriger Patient mit Hypertonie und erstmaligem VHF (CHADSVASC=2) seit gestern Abend (~18 Std.). Das VHF geht nicht weg. UND ES STÖRT….

Nach der PVI hat er nun schon 8 Monate Ruhe. Er nimmt weiter Marcumar und stellt sich vor mit der Frage nach Pause der Antikoagulation wegen einer anstehenden OP.

A – Ich setze Marcumar einfach ab.

B – Marcumar absetzen und „bridging“ mit NMH ab INR < 2.

C – Umsetzen auf ein NOAK und Pause vor der OP entsprechend Risiko.

BRIDGING

34 Beobachtungsstudien, 1 randomisierte Studie, 12278 Patienten

Thrombo-Embolien in 73 von 7118 “gebridgeten” Patienten (0,9%)
32 von 5160 nicht “gebridgeten” Patienten (0,6%)

→ **KEIN UNTERSCHIED !!**

“Bridging” mit therapeutischer Dosierung von NMH führte zu:

5,4-fach mehr Blutungen allgemein
3,6-fach mehr “große” Blutungen

Thrombose-prophylaktische Dosierung von NMH führte zu:

→ Kein Unterschied thrombo-embolischer Ereignisse
ABER: 2,3-fach mehr Blutungen allgemein

Siegal et al, Circulation. 2012;126:1630-1639

BRIDGING

Das Risiko eines perioperativen Schlaganfalles wird evtl. **überschätzt**

10 Tage Unterbrechung:
bei einem Schlaganfallrisiko von 2-10% pro Jahr (abh. von CHADSVASc-Score)

→ **theoretisch 0,012-0,18% Risiko**

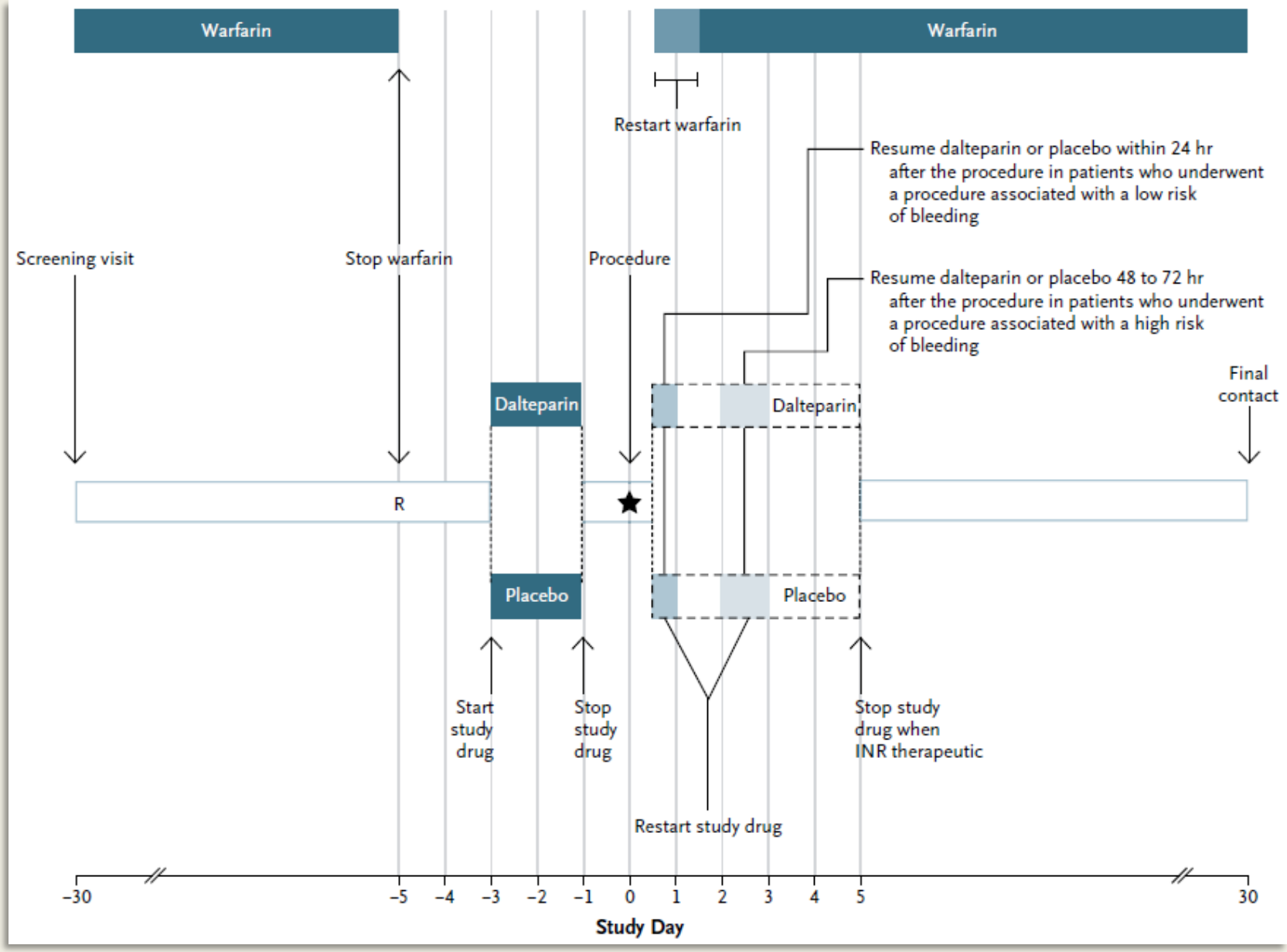
Das Risiko einer postoperativen Blutung wird evtl. **unterschätzt**

durchschnittlich ~3%

→ **steigt durch NMH nach 12-24 Std. auf ~20%**

Douketis, Thromb Hemost 2012;108:210-213
Spyropoulos, Thromb Hemost 2012;108 :213-26

BRIDGE STUDIE



1884 Patienten

Douketis et al, N Engl J Med 2015;373:823-33.

BRIDGE STUDIE

Table 3. Study Outcomes.

Outcome	No Bridging (N=918)	Bridging (N=895)	P Value
	number of patients (percent)		
Primary			
Arterial thromboembolism	4 (0.4)	3 (0.3)	0.01*, 0.73†
Stroke	2 (0.2)	3 (0.3)	
Transient ischemic attack	2 (0.2)	0	
Systemic embolism	0	0	
Major bleeding	12 (1.3)	29 (3.2)	0.005†
Secondary			
Death	5 (0.5)	4 (0.4)	0.88†
Myocardial infarction	7 (0.8)	14 (1.6)	0.10†
Deep-vein thrombosis	0	1 (0.1)	0.25†
Pulmonary embolism	0	1 (0.1)	0.25†
Minor bleeding	110 (12.0)	187 (20.9)	<0.001†

* P value for noninferiority.
† P value for superiority.

Douketis et al, N Engl J Med 2015;373:823-33.

BRIDGING

Vor diagnostischen/operativen/interventionellen Eingriffen sollten niedermolekulare Heparine (NMH) zurückhaltend eingesetzt werden - bei VKA und noch mehr bei NOAK

→ NMH-Bridging nur bei Patienten
mit sehr hohem Schlaganfallrisiko (Z.n. vorheriger Insult)

→ Rücksprache mit dem Operateur

NOAK PAUSE VOR OP

OPs/Eingriffe mit <u>minimalem</u> Blutungsrisiko

Extraktion von 1-3 Zähnen, parodontale Chirurgie, Abszess-Inzision, Katarakt / Glaukom-OP, Endoskopie ohne Intervention, Hautbiopsie, Loop-Recorder Implant

OPs/Eingriffe mit <u>geringem</u> Blutungsrisiko

Endoskopie mit Polypektomie, Prostata-Biopsie, EPU und Ablation, Koronarangiografie, Schrittmacher / ICD Implantation

OPs/Eingriffe mit <u>hohem</u> Blutungsrisiko

spinale oder epidurale Anästhesie, diagn. Lumbalpkt., thorakale/abdominelle Chirurgie, Orthopädie, Leberbiopsie

Heidbuchel et al. Eur Heart J 2013; 34, 2094–2106

NOAK PAUSE VOR OP

	Dabigatran		Apixaban		Edoxaban		Rivaroxaban	
	Low	High	Low	High	Low	High	Low	High
CrCl >80 ml/min	≥24h	≥48h	≥24h	≥48h	≥24h	≥48h	≥24h	≥48h
CrCl 50-80 ml/min	≥36h	≥72h	≥24h	≥48h	≥24h	≥48h	≥24h	≥48h

Modifiziert nach Heidbuchel et al. Eur Heart J 2013; 34, 2094–2106

Kardioversion

Ablation

Operation

Triple-Therapie

REDUKTION KARDIOVASKULÄRER EREIGNISSE

Event prevention	Class[a]	Level[b]
Low-dose aspirin daily is recommended in all SCAD patients	I	A
Clopidogrel is indicated as an alternative in case of aspirin intolerance	I	B
Statins are recommended in all SCAD patients	I	A
It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g. heart failure, hypertension or diabetes)	I	A

Windecker et al. ESC/EACTS guidelines on myocardial revascularization EHJ 2014;35(37):2541-619

ANTITHROMBOZYTÄRE THERAPIE NACH STENT-PCI

Event prevention	Class[a]	Level[b]
DAPT is indicated for at least 1 month after BMS implantation	I	A
DAPT is indicated for 6 months after DES implantation	I	B
Shorter DAPT duration (<6 months) may be considered after DES implantation in patients at high bleeding risk	IIb	A
Life-long single antiplatelet therapy, usually ASA, is recommended	I	A
Instruction of patients about the importance of complying with antiplatelet therapy is recommended	I	C
DAPT may be used for more than 6 months in patients at high ischaemic risk and low bleeding risk	IIb	C

Windecker et al. ESC/EACTS guidelines on myocardial revascularization EHJ 2014;35(37):2541-619

TRIPLE THERAPIE – WOEST STUDIE

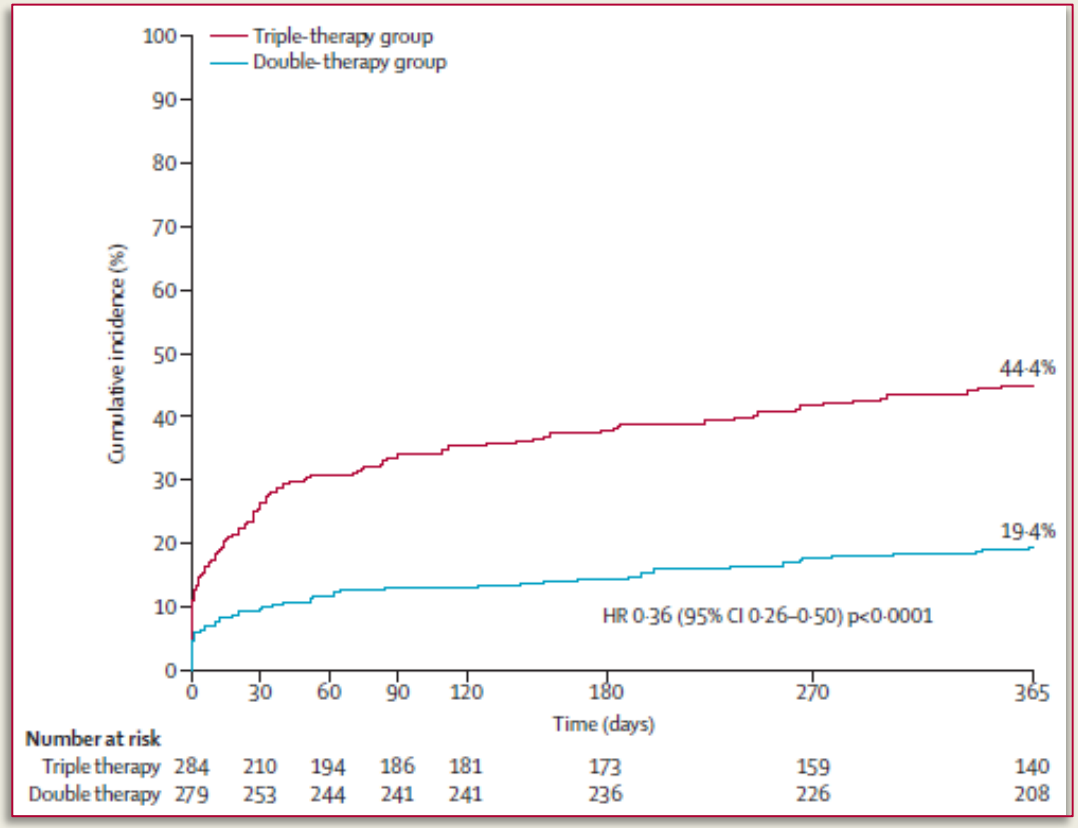
	Double therapy (n=279)	Triple therapy (n=284)
Clinical baseline characteristics		
Mean (SD) age (years)	70·3 (7·0)	69·5 (8·0)
Sex (male/female)	214 (77%)/65 (23%)	234 (82%)/50 (18%)
Risk factors		
Mean (SD) BMI (kg/m²)	27·5 (4·3)	27·9 (4·2)
Diabetes	68 (24%)	72 (25%)
Hypertension	193 (69%)	193 (68%)
Hypercholesterolaemia	191 (68%)	205 (72%)
Current smoker	60 (22%)	42 (15%)
Family history of CAD	116 (42%)	122 (43%)
History of myocardial infarction	96 (34%)	100 (35%)
History of heart failure	71 (25%)	70 (25%)
History of stroke	49 (18%)	50 (18%)
History of PCI	86 (31%)	101 (36%)
History of CABG	56 (20%)	74 (26%)
History of gastrointestinal bleeding	14 (5%)	14 (5%)
History of renal failure	51 (18%)	48 (17%)

	Double therapy (n=279)	Triple therapy (n=284)
(Continued from previous column)		
Indication for oral anticoagulation		
Atrial fibrillation/atrial flutter	164/236 (69%)	162/234 (69%)
Mechanical valve	24/236 (10%)	25/234 (11%)
Other (eg, apical aneurysm, pulmonary embolus, PAD, EF <30%)	48/236 (20%)	47/234 (20%)
Acute coronary syndrome at baseline		
Yes	69 (25%)	86 (30%)
Ejection fraction		
Mean (SD) at baseline (%)	46 (15)	47 (13)
EF <30%	40/190 (21%)	37/206 (18%)

open-label, multicentre, randomised, controlled trial

Dewilde et al. - 2013 Mar 30;381(9872):1107-15.

TRIPLE THERAPIE – WOEST STUDIE



	Double therapy (n=297)	Triple therapy (n=284)	Hazard ratio (95% CI)	p value
Combined secondary endpoint	31 (11·1%)	50 (17·6%)	0·60 (0·38–0·94)	0·035
Death				
All-cause	7 (2·5%)	18 (6·3%)	0·39 (0·16–0·93)	0·027
Cardiac	3 (1·1%)	7 (2·5%)	0·43 (0·11–1·66)	0·207
Non-cardiac	4 (1·4%)	11 (3·9%)	0·36 (0·11–1·13)	0·069
Myocardial infarction				
Any	9 (3·2%)	13 (4·6%)	0·69 (0·29–1·60)	0·382
STEMI	1 (0·4%)	3 (1·1%)	0·34 (0·04–3·25)	0·325
Non-STEMI	8 (2·9%)	10 (3·5%)	0·79 (0·31–2·01)	0·625
Target-vessel revascularisation				
PCI or CABG	20 (7·2%)	19 (6·7%)	1·05 (0·56–1·97)	0·876
PCI	17 (6·1%)	16 (5·6%)	1·06 (0·54–2·10)	0·869
CABG	3 (1·1%)	3 (1·1%)	1·00 (0·20–4·90)	0·998
Stroke				
Any	3 (1·1%)	8 (2·8%)	0·37 (0·10–1·40)	0·128
Ischaemic	2 (0·7%)	8 (2·8%)	0·25 (0·05–1·17)	0·056
Haemorrhagic	1 (0·4%)	0	NA	0·321
Disabling	2 (0·7%)	2 (0·7%)	0·99 (0·14–6·99)	0·988
Non-disabling	1 (0·4%)	7 (2·5%)	0·14 (0·02–1·16)	0·034
Stent thrombosis				
Any	4 (1·4%)	9 (3·2%)	0·44 (0·14–1·44)	0·165
Definite	1 (0·4%)	3 (1·1%)	0·33 (0·03–3·22)	0·319
Probable	0	2 (0·7%)	NA	0·161
Possible	3 (1·1%)	4 (1·4%)	0·75 (0·17–3·30)	0·708

Dewilde et al. - 2013 Mar 30;381(9872):1107-15.

TRIPLE THERAPIE

Patients taking the NOACs may present with an acute coronary syndrome (ACS) and/or undergo percutaneous coronary intervention (PCI). Concomitant use of antiplatelet therapy with the NOACs significantly increases bleeding risk,[96] as is the case with combining any OAC with antiplatelet therapy. In AF patients at risk of stroke, and irrespective of HAS-BLED score, OAC still confers benefit (reduced mortality and major adverse cardiac events) but with more bleeds.[97] In the absence of robust data, in AF patients with an ACS or PCI/stenting, recommendations based on expert consensus on the management of such patients should be followed, as found within the 2010 ESC Guidelines or current European or North American consensus documents.[98–100] Thus, a period of triple therapy is needed (OAC plus aspirin plus clopidogrel), followed by the combination OAC plus single antiplatelet drug and, after one year, management can be with OAC alone in stable patients, where OAC can be adjusted-dose VKA therapy or probably a NOAC. Notably, the only trial where clopidogrel use was not contraindicated was RE-LY, so the data on triple therapy with a NOAC (when given at stroke prevention doses in AF patients) are limited.

A patient taking dabigatran may present with an ACS and, given the non-significant but small numerical increase in MI events with dabigatran compared with warfarin,[71,72] the concerned clinician may consider the use of a VKA or an alternative NOAC (e.g. rivaroxaban or apixaban). There is little evidence to support this, as the relative effects of dabigatran vs. warfarin on myocardial ischaemic events were consistent in patients with or without a baseline history of MI or coronary artery disease. Although twice-daily low-dose rivaroxaban (2.5 mg or 5 mg b.i.d.) has been used with some benefit in ACS,[101] there are no data on ACS relating to the dose of rivaroxaban used for anticoagulation in AF (20 mg o.d.). Apixaban, used in the stroke prevention dose (5 mg b.i.d.) in the ACS setting in combination with aspirin plus clopidogrel, was associated with no reduction in cardiovascular events but an excess of major bleeding.[102] Patients with AF and stable vascular disease (i.e. no acute events or revascularization for >12 months, whether coronary or peripheral artery disease) can be managed with OAC alone, whether as adjusted dose VKA therapy or, probably, a NOAC. In such stable patients, there is no need for concomitant aspirin, which could increase the risk of serious haemorrhage, including intracranial haemorrhage.

Camm et al. Eur Heart J. 2010;31:2369-429

TRIPLE-THERAPIE

Antikoagulanzien und Thrombozyten-Funktionshemmer

ASS oder Clopidogrel

Potentiell erhöhtes Risiko für Blutungskomplikationen

→ Hinzunahme nach individueller Nutzen- Risiko-Abwägung

Nicht-steroidale Antirheumatika (NSAR)

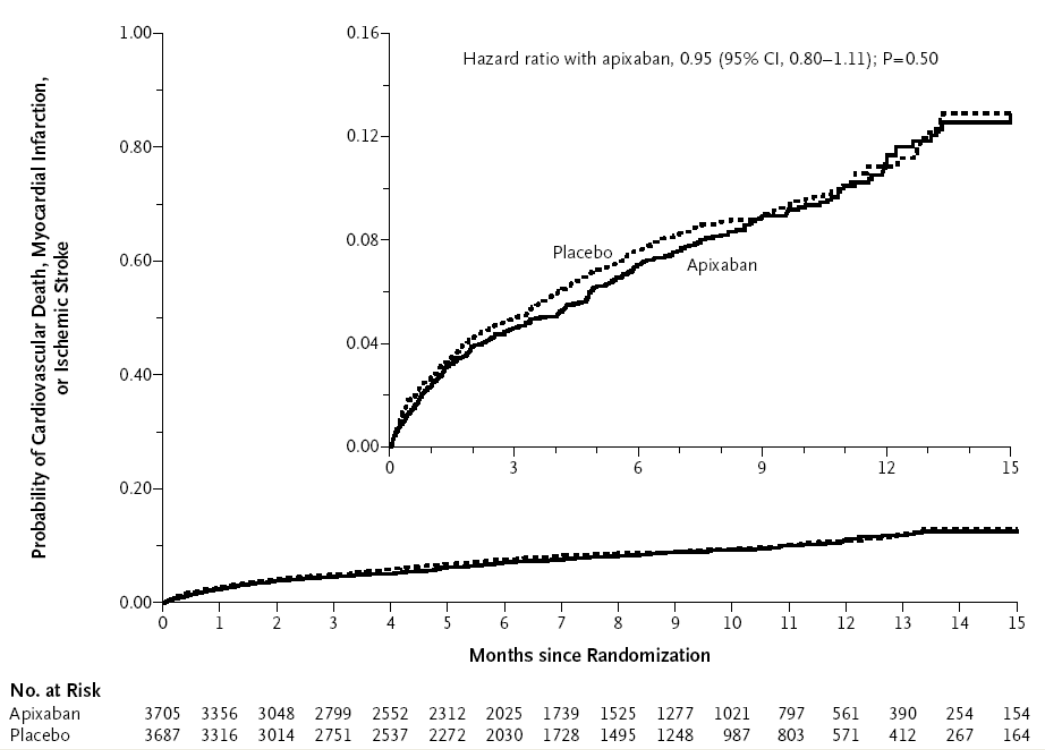
→ OK bei kurzzeitigem Einsatz

Bei Daueranwendung sind engmaschige klinische Kontrollen erforderlich

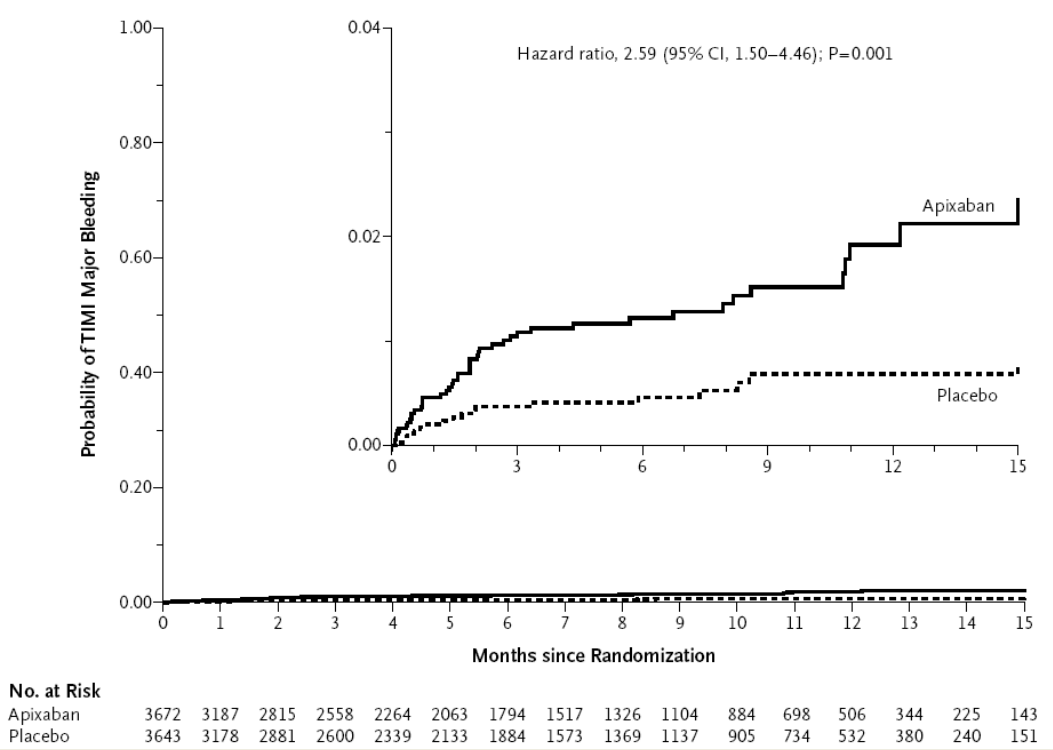
→ Keine Erfahrung hinsichtlich neue antithrombozytäre Therapie und OAK

TRIPLE-THERAPIE

Primärer Endpunkt



TIMI „major“ Blutung



APPRAISE-2

Alexander et al N Engl J Med. 2011 Aug 25;365(8):699-708

TRIPLE-THERAPIE

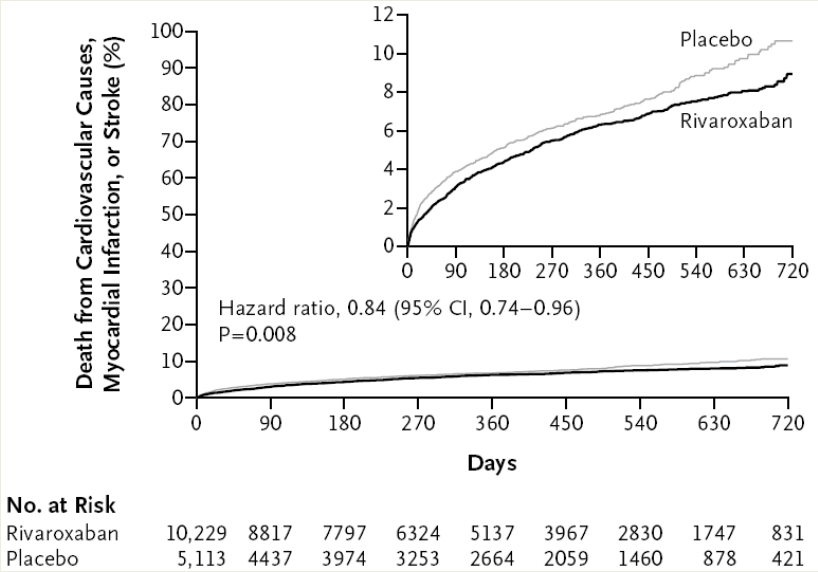


Table 2. Kaplan–Meier Estimates and Hazard Ratios for Efficacy and Safety End Points.*

End Point	Rivaroxaban			Placebo (N=5113)	Rivaroxaban 2.5 mg Twice Daily vs. Placebo			Rivaroxaban 5 mg Twice Daily vs. Placebo			Rivaroxaban Combined vs. Placebo		
	2.5 mg Twice Daily (N=5114)	5 mg Twice Daily (N=5115)	Combined (N=10,229)		Hazard Ratio (95% CI)	P Value		Hazard Ratio (95% CI)	P Value		Hazard Ratio (95% CI)	P Value	
Efficacy						mITT	ITT		mITT	ITT		mITT	ITT
		number (percent)											
Death from cardiovascular causes, myocardial infarction, or stroke — primary end point	313 (9.1)	313 (8.8)	626 (8.9)	376 (10.7)	0.84 (0.72–0.97)	0.02	0.007	0.85 (0.73–0.98)	0.03	0.01	0.84 (0.74–0.96)	0.008	0.002
Death from cardiovascular causes	94 (2.7)	132 (4.0)	226 (3.3)	143 (4.1)	0.66 (0.51–0.86)	0.002	0.005	0.94 (0.75–1.20)	0.63	0.57	0.80 (0.65–0.99)	0.04	0.05
Myocardial infarction	205 (6.1)	179 (4.9)	384 (5.5)	229 (6.6)	0.90 (0.75–1.09)	0.27	0.09	0.79 (0.65–0.97)	0.02	0.008	0.85 (0.72–1.00)	0.047	0.01
Stroke													
Any	46 (1.4)	54 (1.7)	100 (1.6)	41 (1.2)	1.13 (0.74–1.73)	0.56	0.47	1.34 (0.90–2.02)	0.15	0.11	1.24 (0.86–1.78)	0.25	0.19
Ischemic	30 (1.0)	35 (0.9)	65 (0.9)	34 (1.0)	0.89 (0.55–1.45)	0.64	0.82	1.05 (0.65–1.68)	0.84	0.72	0.97 (0.64–1.47)	0.89	0.94
Death from any cause, myocardial infarction, or stroke — secondary end point	320 (9.3)	321 (9.1)	641 (9.2)	386 (11.0)	0.83 (0.72–0.97)	0.02	0.004	0.84 (0.73–0.98)	0.02	0.02	0.84 (0.74–0.95)	0.006	0.002
Death from any cause	103 (2.9)	142 (4.4)	245 (3.7)	153 (4.5)	0.68 (0.53–0.87)	0.002	0.004	0.95 (0.76–1.19)	0.66	0.89	0.81 (0.66–1.00)	0.04	0.08
Stent thrombosis	47 (2.2)	51 (2.3)	98 (2.3)	72 (2.9)	0.65 (0.45–0.94)	0.02	0.02	0.73 (0.51–1.04)	0.08	0.04	0.69 (0.51–0.93)	0.02	0.008
	(N=5115)	(N=5110)	(N=10,225)	(N=5125)									
Safety													
TIMI major bleeding not associated with CABG	65 (1.8)	82 (2.4)	147 (2.1)	19 (0.6)	3.46 (2.08–5.77)	<0.001		4.47 (2.71–7.36)	<0.001		3.96 (2.46–6.38)	<0.001	
TIMI minor bleeding	32 (0.9)	49 (1.6)	81 (1.3)	20 (0.5)	1.62 (0.92–2.82)	0.09		2.52 (1.50–4.24)	<0.001		2.07 (1.27–3.37)	0.003	
TIMI bleeding requiring medical attention	492 (12.9)	637 (16.2)	1129 (14.5)	282 (7.5)	1.79 (1.55–2.07)	<0.001		2.39 (2.08–2.75)	<0.001		2.09 (1.83–2.38)	<0.001	
Intracranial hemorrhage	14 (0.4)	18 (0.7)	32 (0.6)	5 (0.2)	2.83 (1.02–7.86)	0.04		3.74 (1.39–10.07)	0.005		3.28 (1.28–8.42)	0.009	
Fatal bleeding	6 (0.1)	15 (0.4)	21 (0.3)	9 (0.2)	0.67 (0.24–1.89)	0.45		1.72 (0.75–3.92)	0.20		1.19 (0.54–2.59)	0.66	

ATLAS investigators. N Engl J Med 2012;366:9-19.

TRIPLE-THERAPIE

Supplemental Table 1: Risk of major bleeding in subgroups of patients who received the combination of aspirin and clopidogrel and those who did not receive the combination of aspirin and clopidogrel

Subgroup	D110 mg bid, n/N (%)	D150 mg bid, n/N (%)	Warfarin, n/N (%)	D110 mg bid vs. warfarin, RR (95% CI)	D150 mg bid vs. warfarin, RR (95% CI)
Aspirin + clopidogrel	29/335 (4.72%)	30/328 (4.66%)	33/339 (5.21%)	0.77 (0.50 to 1.21)	0.81 (0.52 to 1.26)
No aspirin + clopidogrel	313/5677 (2.77%)	369/5747 (3.24%)	388/5681 (3.48%)	0.81 (0.61-0.94)	0.95 (0.82 to 1.10)
P interaction				**0.8727**	**0.5167**

D, dabigatran; CI, confidence interval; RR, relative risk

Triple-Therapie mit Dabigatran 2x110 mg / Tag
Daten aus RELY – keine KHK Studie

Eikelboom et al Circulation 2011;123(21):2363-72

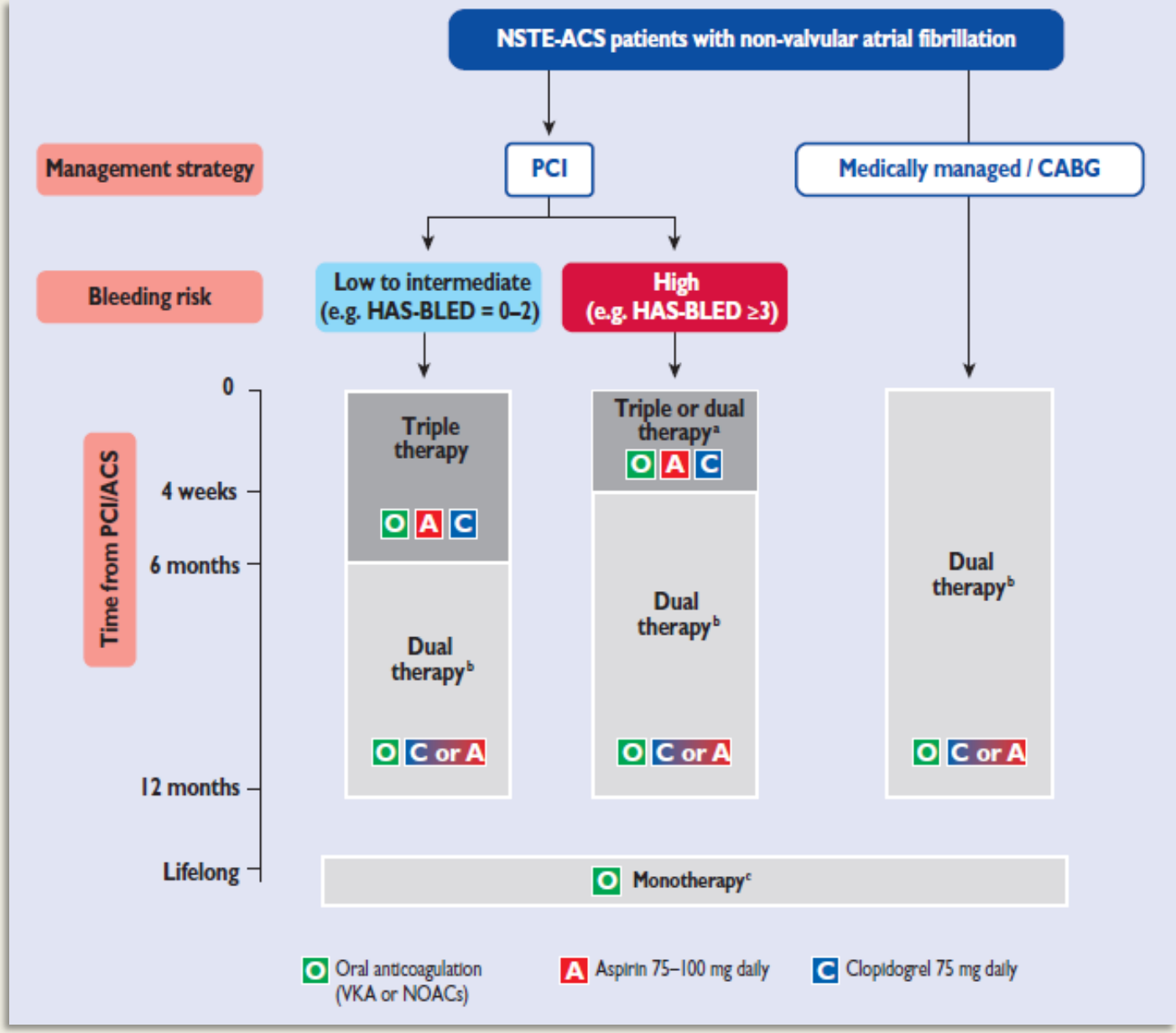
OAK + ANTI-PLÄTTCHENTHERAPIE

Recommendations	Class[a]	Level[b]	Ref.[c]
In patients with a firm indication for OAC (e.g. atrial fibrillation with a CHA_2DS_2-VASc score ≥ 2, recent venous thromboembolism, LV thrombus or mechanical valve prosthesis), OAC is recommended in addition to antiplatelet therapy.	I	C	
An early invasive coronary angiography (within 24 h) should be considered in moderate- to high-risk patients,[d] irrespective of OAC exposure, to expedite treatment allocation (medical vs. PCI vs. CABG) and to determine the optimal antithrombotic regimen.	IIa	C	
Initial dual antiplatelet therapy with aspirin plus a $P2Y_{12}$ inhibitor in addition to OAC before coronary angiography is not recommended.	III	C	

Leitlinie: 2015 NSTEMI

Roffi et al. Eur Heart J 2015 guidelines on non-ST segment elevation myocardial infarction

TRIPLE THERAPIE BEI OAK



Leitlinie: 2015 NSTEMI

Roffi et al. Eur Heart J 2015 guidelines on non-ST segment elevation myocardial infarction

DAPT

Anticoagulation			
During PCI, additional parenteral anticoagulation is recommended, irrespective of the timing of the last dose of all NOACs and if INR is <2.5 in VKA-treated patients.	I	C	
Uninterrupted therapeutic anticoagulation with VKA or NOACs should be considered during the periprocedural phase.	IIa	C	

Antiplatelet treatment			
Following coronary stenting, DAPT including new $P2Y_{12}$ inhibitors should be considered as an alternative to triple therapy for patients with NSTE-ACS and atrial fibrillation with a CHA_2DS_2-VASc score of 1 (in males) or 2 (in females).	IIa	C	
If at low bleeding risk (HAS-BLED ≤2), triple therapy with OAC, aspirin (75–100 mg/day) and clopidogrel 75 mg/day should be considered for 6 months, followed by OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months.	IIa	C	
If at high bleeding risk (HAS-BLED ≥3), triple therapy with OAC, aspirin (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of 1 month, followed by OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months irrespective of the stent type (BMS or new-generation DES).	IIa	C	
Dual therapy with OAC and clopidogrel 75 mg/day may be considered as an alternative to triple antithrombotic therapy in selected patients (HAS-BLED ≥3 and low risk of stent thrombosis).	IIb	B	246, 248
The use of ticagrelor or prasugrel as part of triple therapy is not recommended.	III	C	

Leitlinie: 2015 NSTEMI

Roffi et al. Eur Heart J 2015 guidelines on non-ST segment elevation myocardial infarction

DANKE