



Paradigmenwechsel in der OAK bei PatientInnen mit Vorhofflimmern

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UpToDate

Häufigste kardiologische Suchbegriffe 2010

1. ***Antithrombotic therapy to prevent embolization in nonvalvular atrial fibrillation***
2. Overview of the management of acute ST elevation MI
3. Diagnosis and evaluation of hypertrophic cardiomyopathy
4. Overview of the therapy of heart failure due to systolic dysfunction
5. Clinical manifestations and diagnosis of ARVD
6. Overview of the management of unstable angina and acute NSTEMI
7. Estimation of cardiac risk prior to noncardiac surgery
8. Indications for valve replacement in aortic stenosis in adults
9.



Agenda

- Allgemeines
- Aspekt der Antikoagulation
 - Risikoabschätzung: Insult, Blutung
- Neue Antikoagulationen



Agenda

- Allgemeines

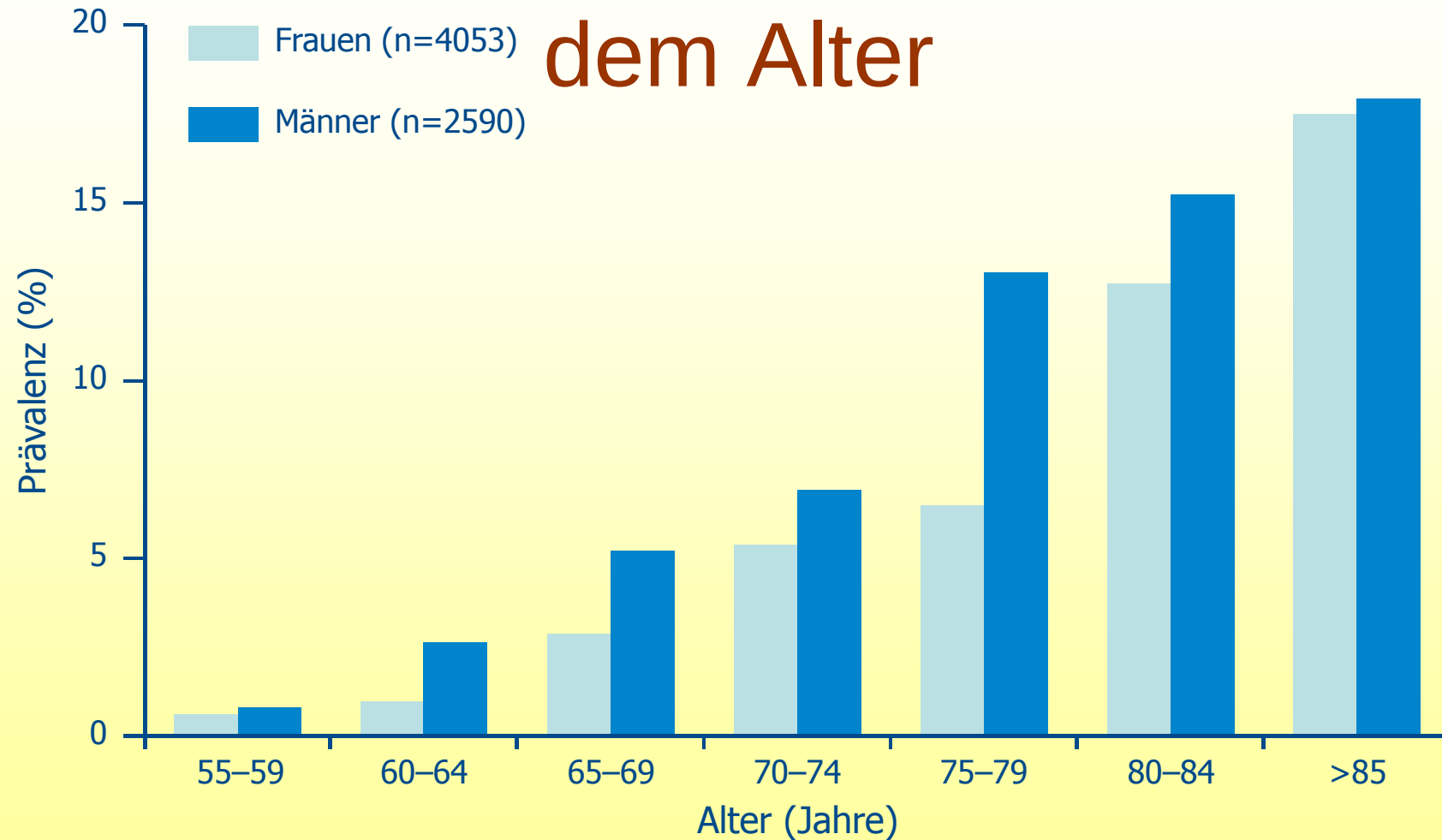


Allgemeines

- Vorhofflimmern ist häufigste Arrhythmie, ca. 2% der Gesamtbevölkerung
- Derzeit ca. 6 Millionen Europäer
- Prävalenz in nächsten 50 Jahren: x2!
- 5x erhöhtes Risiko für alle Formen des Schlaganfalls
- Fast 1/3 der Schlaganfälle durch VHF
- Ohne Prävention wird 1 von 20 einen Insult jedes Jahr erleiden!



VHF-Prävalenz steigt mit dem Alter



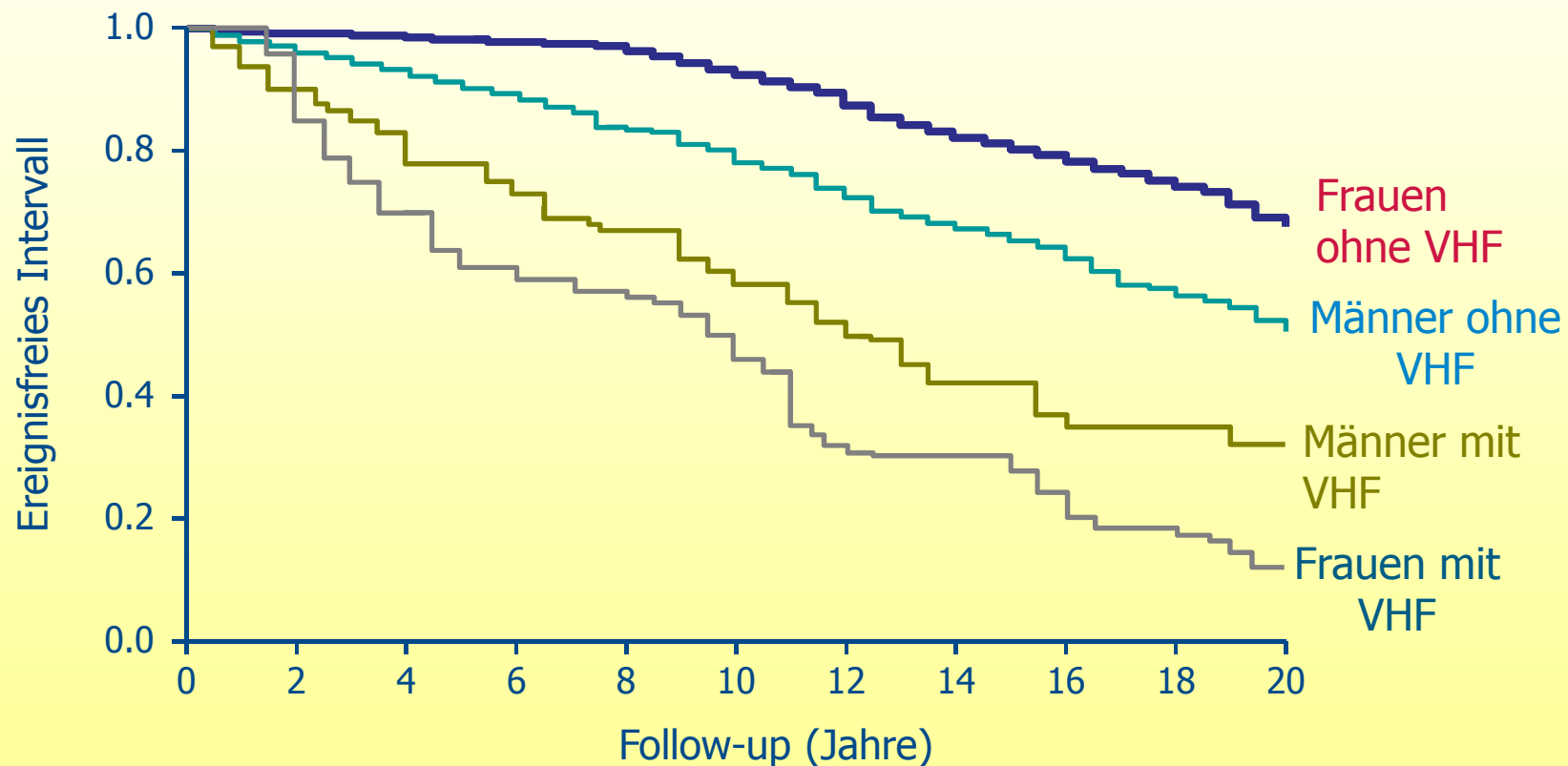
Prävalenz anhand 6808 Teilnehmer in einer europäischen Populationsstudie
Heeringa J et al. Eur Heart J 2006;27:949–53



Vorhofflimmern - Komplikationen

- VHF ist assoziiert mit einer Anzahl an schweren und potentiell lebensbedrohlichen Komplikationen, inklusive Schlaganfall,^{1,2} Herzinsuffizienz² und Tod^{2,3}

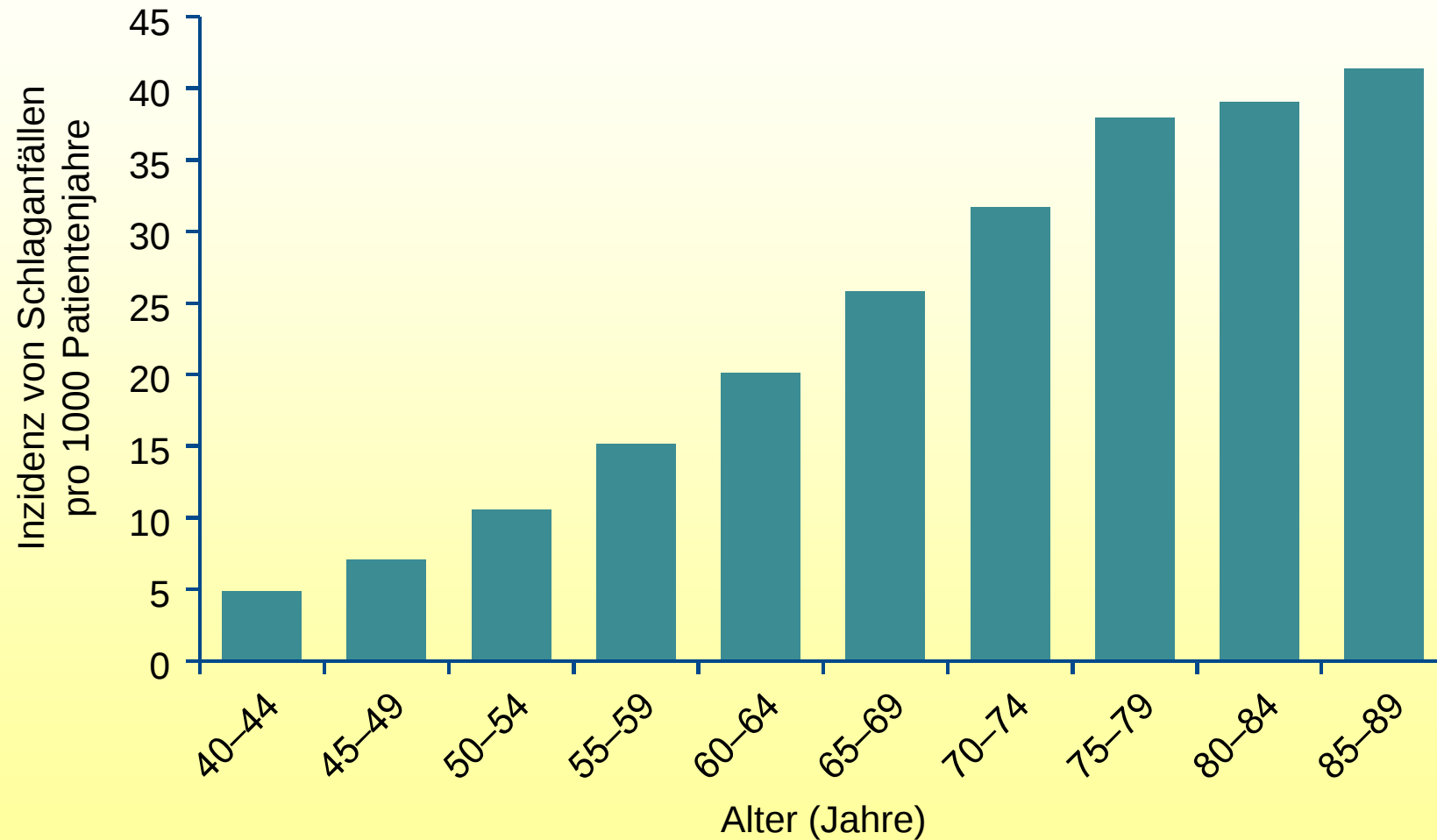
Kardiovaskuläre Hospitalisierungen oder Tod²



1. Wolf PA et al. Stroke 1991;22:983–8; 2. Stewart S et al. Am J Med 2002;113:259–64;
3. Benjamin E et al. Circulation 1998;98:946–52



Die Inzidenz von VHF-bedingten Schlaganfällen steigt mit zunehmendem Alter



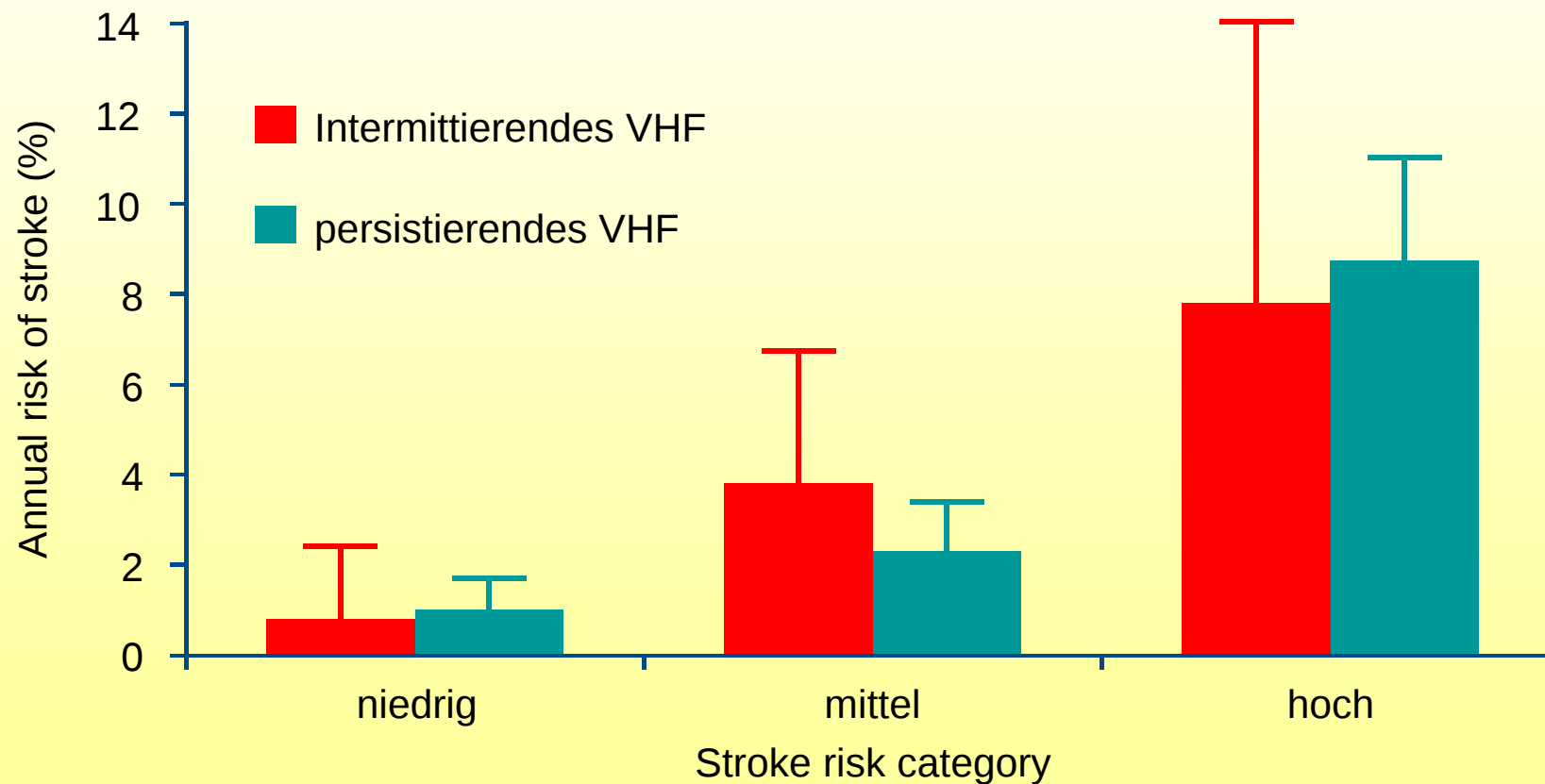
22-year follow-up of 75 126 men in the Danish National Registry of Patients
Frost L et al. Neuroepidemiology 2007;28:109-15



Schlaganfallrisiko besteht auch bei asymptomatischem/paroxysmalem VHF

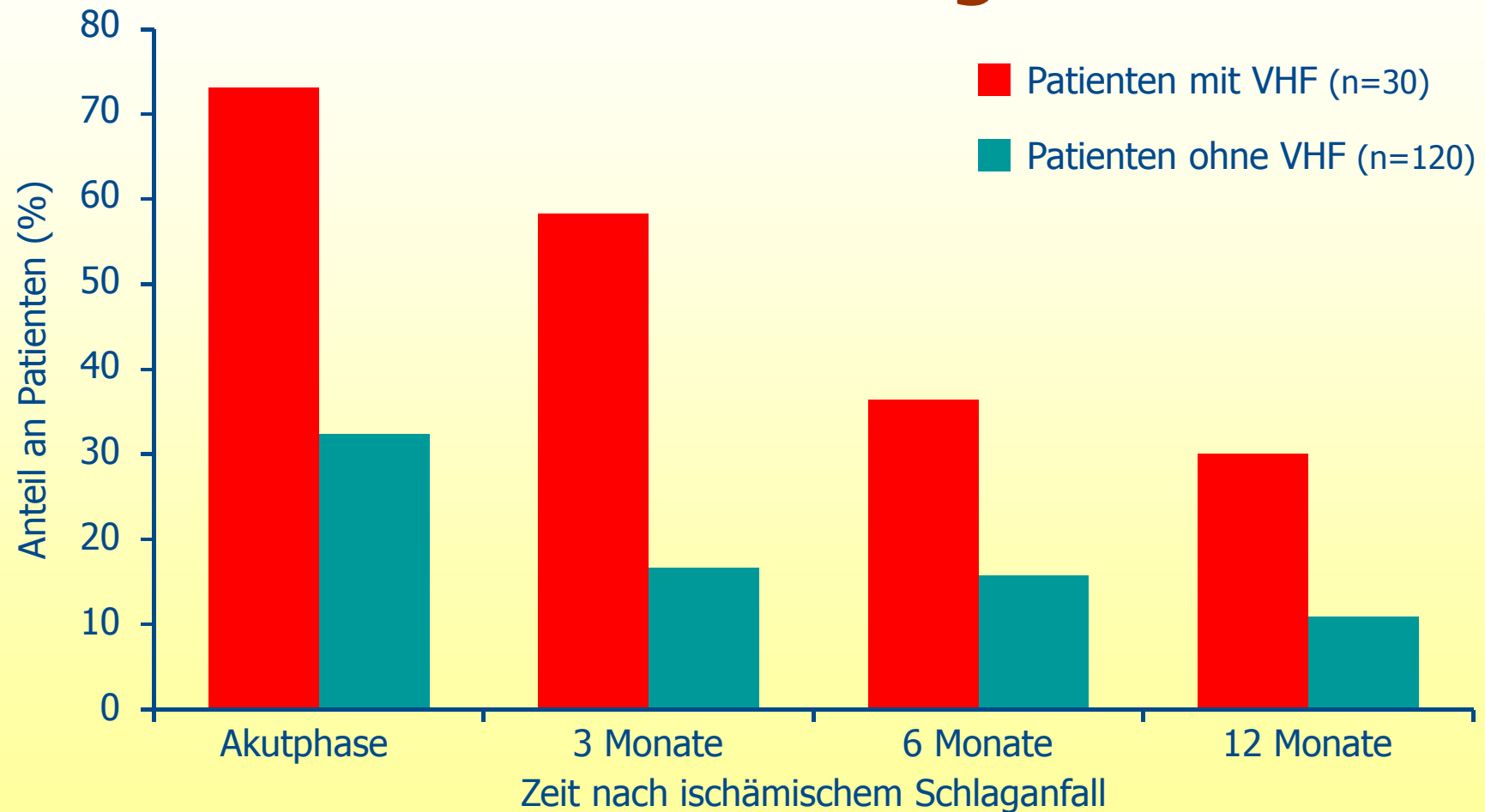
- Das Schlaganfallrisiko unter asymptomatischem oder paroxysmalem VHF ist vergleichbar zu dem unter permanentem VHF^{1,2}

Rate von ischämischen Schlaganfällen¹





Schwere Einschränkung funktioneller Fähigkeiten



>40-year follow-up of 5070 participants in the Framingham study; *Barthel Index
Lin HJ et al. Stroke 1996;27:1760–4



European Heart Journal
doi:10.1093/eurheartj/ehs253

ESC GUIDELINES

ESC GUIDELINES

2012 focused update of the ESC Guidelines for the management of atrial fibrillation

An update of the 2010 ESC Guidelines for the management
of atrial fibrillation
Developed with the special contribution of the European Heart
Rhythm Association

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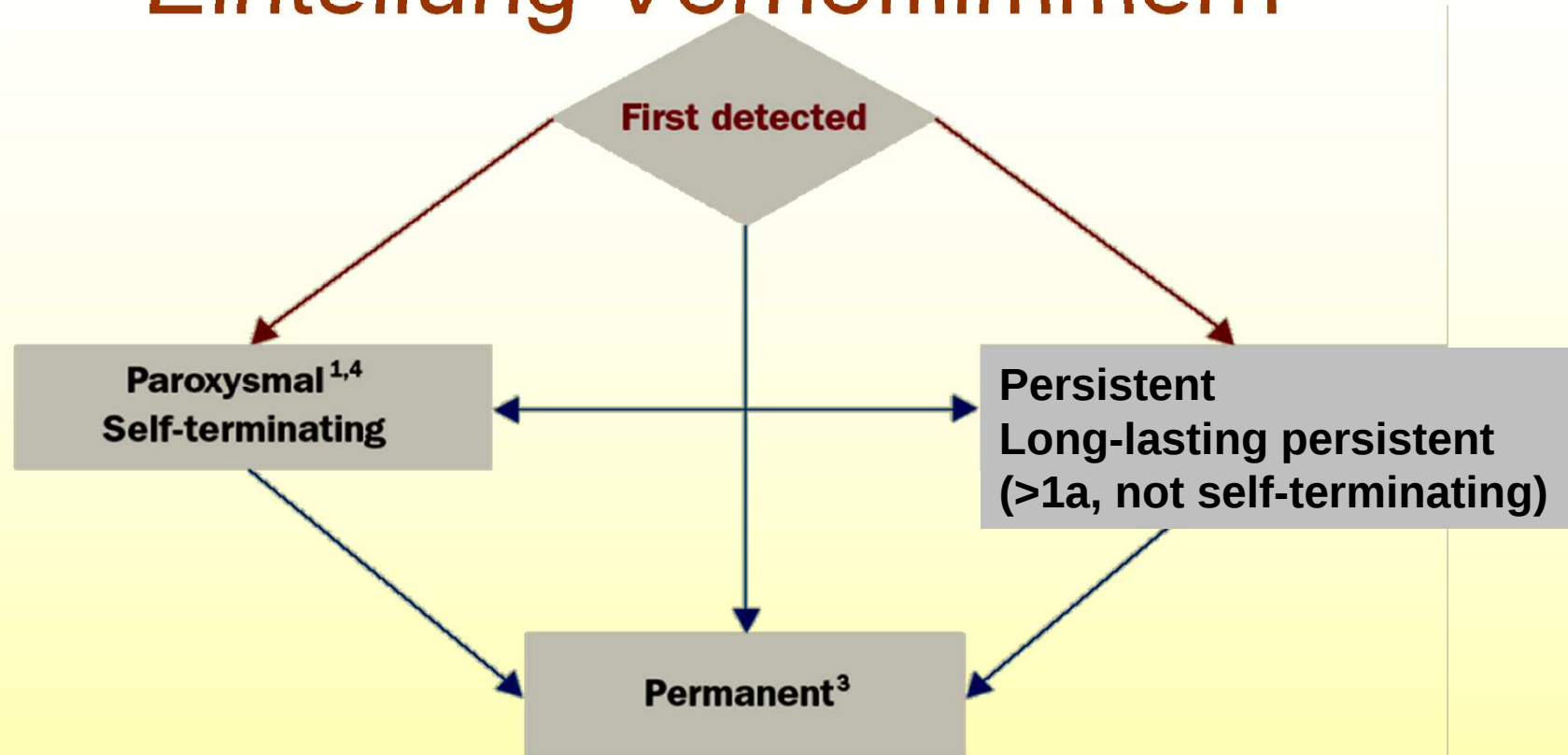
The disclosure forms of the authors and reviewers are available on the ESC website www.escardio.org/guidelines

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Online publication am 24. August 2012



Einteilung Vorhofflimmern



¹ Episodes generally last less than or equal to 7 days (most less than 24 h);

² usually greater than 7 days;

³ cardioversion failed or not attempted;

⁴ either paroxysmal or persistent AF may be recurrent.



Empfehlung für AF-Screening

Recommendations	Class ^a	Level ^b	Ref ^c
Opportunistic screening for AF in patients ≥ 65 years of age using pulse-taking followed by an ECG is recommended to allow timely detection of AF.	I	B	14, 15



Wichtige Fragen

- Herzrhythmus während des Anfalls regulär od. irregulär?
- Auslösende Faktoren (Belastung, Stress, Alkohol)?
- Symptome (EHRA Score)?
- Häufig od. selten, kurz od. lange?
- Begleiterkrankungen (Hypertonie, KHK, HI, PAD, cerebrovask. Erkrankung, Insult, DM, Lungenerkrankung)?
- Alkoholabusus?
- Familiengeschichte für VHF?



European Heart Rhythm Association Score für VHF Symptome

Classification of AF-related symptoms (EHRA score)	
EHRA class	Explanation
EHRA I	'No symptoms'
EHRA II	'Mild symptoms'; normal daily activity not affected
EHRA III	'Severe symptoms'; normal daily activity affected
EHRA IV	'Disabling symptoms'; normal daily activity discontinued



Agenda

- Aspekt der Antikoagulation
 - Risikoabschätzung: Insult, Blutung



RF für Insult/TIA/Embolie bei Patienten mit AF

The Swedish Cohort Atrial Fibrillation Study

	Multivariate hazard ratios (95% CI)
Age (years)	
<65	1.0 (Reference)
65–74	2.97 (2.54–3.48)
≥75	5.28 (4.57–6.09)
Female sex	1.17 (1.11–1.22)
Previous ischaemic stroke	2.81 (2.68–2.95)
Intracranial bleeding	1.49 (1.33–1.67)
Vascular disease (any)	1.14 (1.06–1.23)
• Myocardial infarction	1.09 (1.03–1.15)
• Previous CABG	1.19 (1.06–1.33)
• Peripheral artery disease	1.22 (1.12–1.32)
Hypertension	1.17 (1.11–1.22)
Heart failure (history)	0.98 (0.93–1.03)
Diabetes mellitus	1.19 (1.13–1.26)
Thyroid disease	1.00 (0.92–1.09)
Thyrotoxicosis	1.03 (0.83–1.28)

- Daten robust: >182 000 Patienten mit AF
- SD-Erkrankung bzw. Hyperthyreose, Z.n. Herzinsuff KEINE RF!
- Nur: HF-REF od Dekompensation mit HF-PEF ist RF
- Pat mit NINS erhöhtes AF-Risiko und Komplikationsrisiko inkl Tod

Friberg L, Eur Heart J 2012; 33:1500



CHA₂DS₂-VASc Score

(a) Risk factors for stroke and thrombo-embolism in non-valvular AF

'Major' risk factors

'Clinically relevant non-major' risk factors

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA₂DS₂-VASc

(Note: maximum score is 9 since age may contribute 0, 1, or 2 points)

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease ^a	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	9

(c) Adjusted stroke rate according to CHA₂DS₂-VASc score

CHA ₂ DS ₂ -VASc score	Patients (n = 7329)	Adjusted stroke rate (%/year) ^b
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%



Ziele der Antikoagulation bei Patienten mit AF

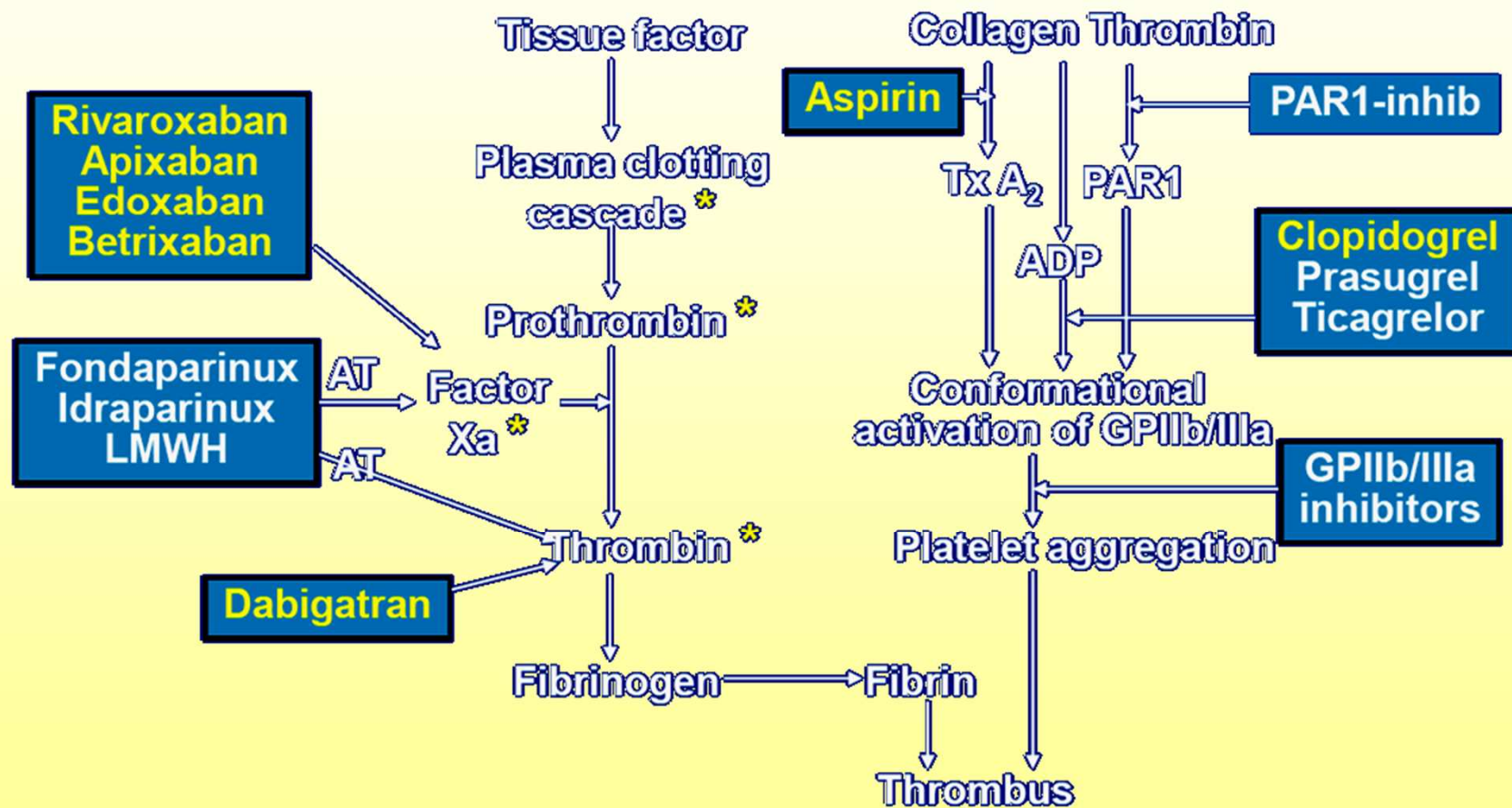
Verhinderung des ischämischen Schlaganfalls

Minimieren der hämorrhagischen Insulte (Risiko reduzieren für ICH)



Ziele für Langzeit-Antithrombotika

Warfarin*





ORIGINAL INVESTIGATION

LESS IS MORE

Risk of Bleeding With Single, Dual, or Triple Therapy With Warfarin, Aspirin, and Clopidogrel in Patients With Atrial Fibrillation

Morten L. Hansen, MD, PhD; Rikke Sørensen, MD; Mette T. Clausen, MSc Pharm;
Marie Louise Fog-Petersen, MSc Pharm; Jakob Raunsø, MD; Niels Gadsbøll, MD, DMSc; Gunnar H. Gislason, MD, PhD;

- Kohortenstudie, Dänemark gesamt
- 1-97 bis 12-06
- 82 854 von 118 606 Pat. hatten eine Verschreibung einer Blutverdünnung
- Dauer mindestens 3a

filled for warfarin, aspirin, or clopidogrel after discharge. During mean (SD) follow-up of 3.3 (2.6) years, 13 573 patients (11.4%) experienced a nonfatal or fatal bleeding. The crude incidence rate for bleeding was high-

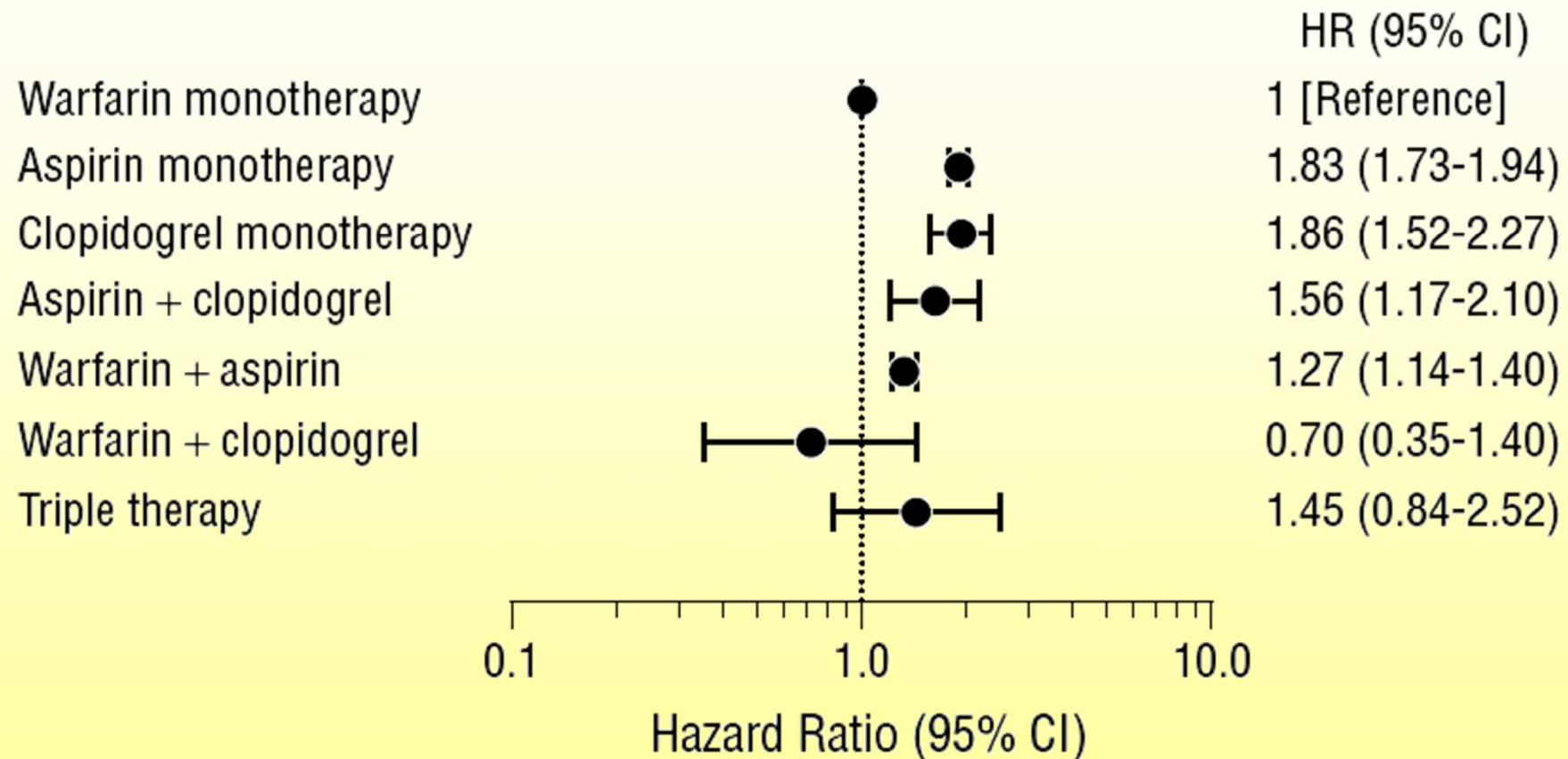
more than 3-fold higher risk than did warfarin monotherapy.

Arch Intern Med. 2010;170(16):1433-1441

Hansen, Arch Int Med 2010; 170: 1433

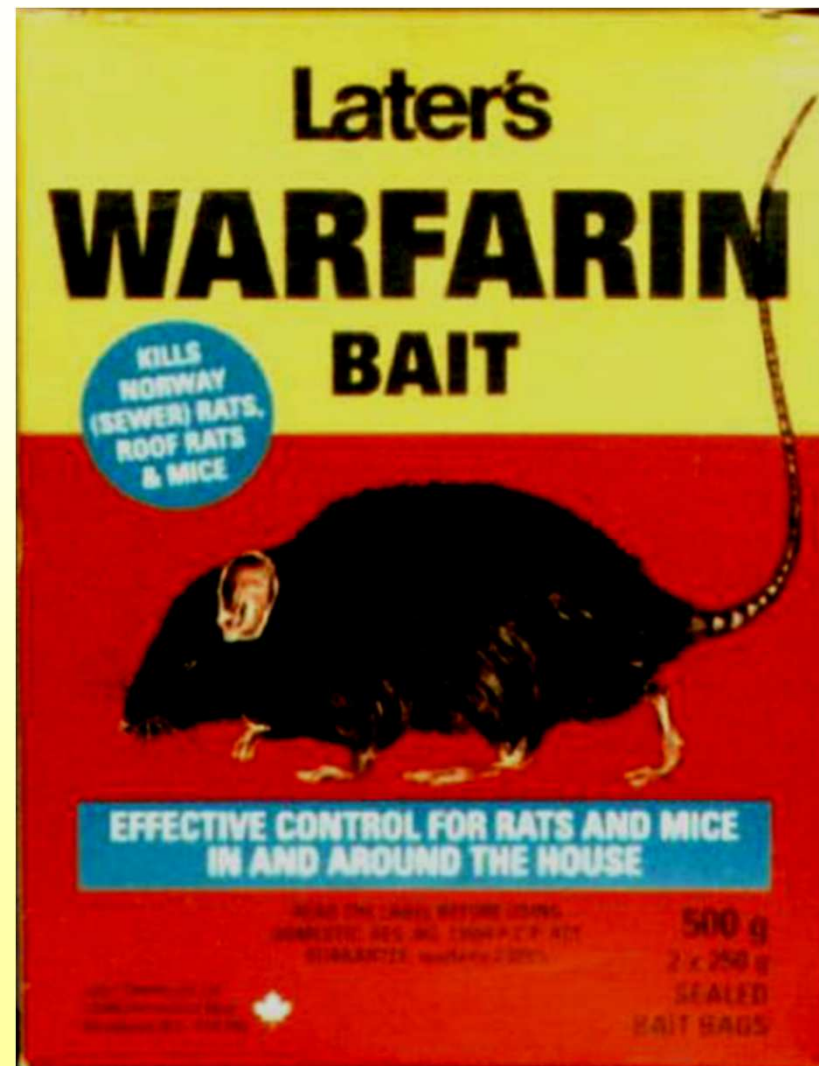


HR für ischämischen Schlaganfall



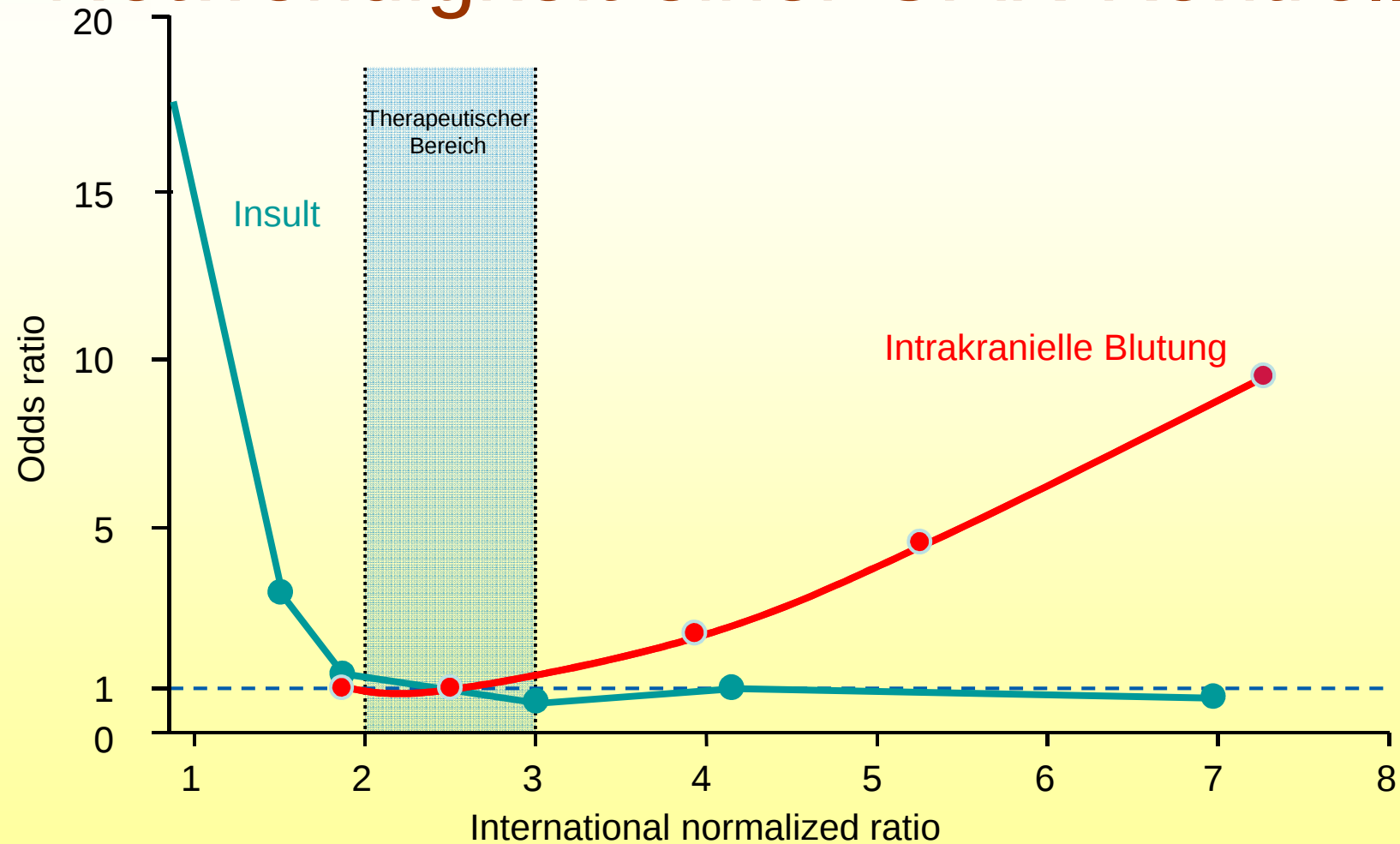
Nicht-fataler Schlaganfall: 9785; fataler Schlaganfall: 3537

Hansen, Arch Int Med 2010; 170: 1433





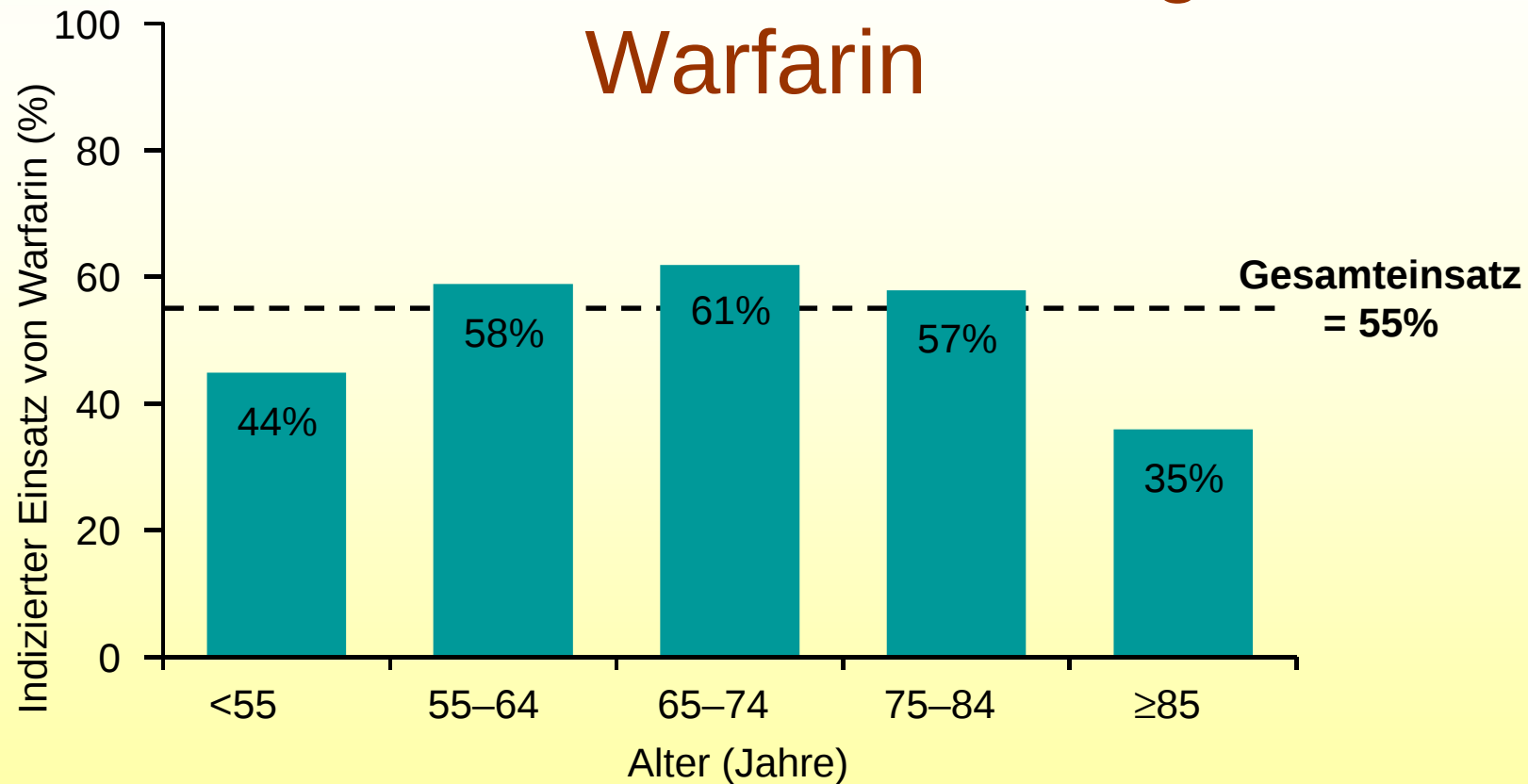
Notwendigkeit einer OAK-Kontrolle



Fuster, Eur Heart J 2007; 27: 1979



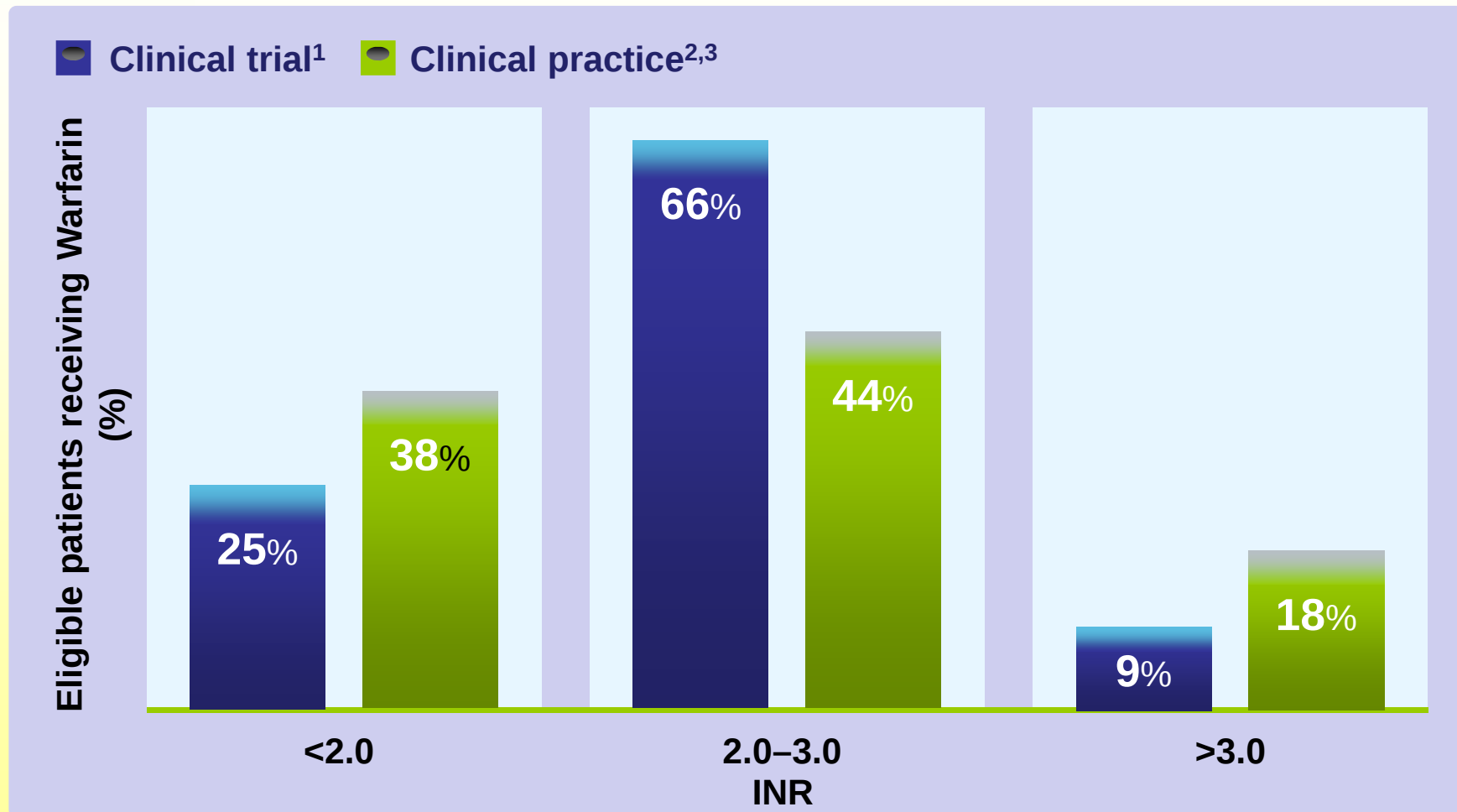
Nur die Hälfte der Patienten mit VHF erhalten den Vitamin-K-Antagonisten Warfarin



- Unzureichender Einsatz bei älteren Patienten mit dem größten Schlaganfallrisiko



Einsatz von Vitamin-K-Antagonisten: klinische Studie vs. klinische Praxis



INR = international normalized ratio ; TTR = time-in-therapeutic-range (INR 2.0–3.0).

1. Kalra L, et al. *BMJ* 2000;320:1236-1239; *Pooled data: up to 83–71% in individualized trials.

2. Samsa GP, et al. *Arch Intern Med* 2000;160:967-973. 3. Matchar DB, et al. *Am J Med* 2002;113:42-51.



Risiko für Blutung bei verschiedenen Therapien

ORIGINAL INVESTIGATION

LESS IS MORE

Risk of Bleeding With Single, Dual, or Triple Therapy With Warfarin, Aspirin, and Clopidogrel in Patients With Atrial Fibrillation

Morten L. Hansen, MD, PhD; Rikke Sørensen, MD; Mette T. Clausen, MSc Pharm;
Marie Louise Fog-Petersen, MSc Pharm; Jakob Raunsø, MD; Niels Gadsbøll, MD, DMSc; Gunnar H. Gislason, MD, PhD;
Fredrik Folke, MD; Søren S. Andersen, MD; Tina K. Schramm, MD; Steen Z. Abildstrøm, MD, PhD;
Henrik E. Poulsen, MD, DMSc; Lars Køber, MD, DMSc; Christian Torp-Pedersen, MD, DMSc

- Wenn Blutung $\Rightarrow$ HR für $\dagger$ 2,45 (2,37-2,57)

Hansen, Arch Int Med 2010; 170: 1433



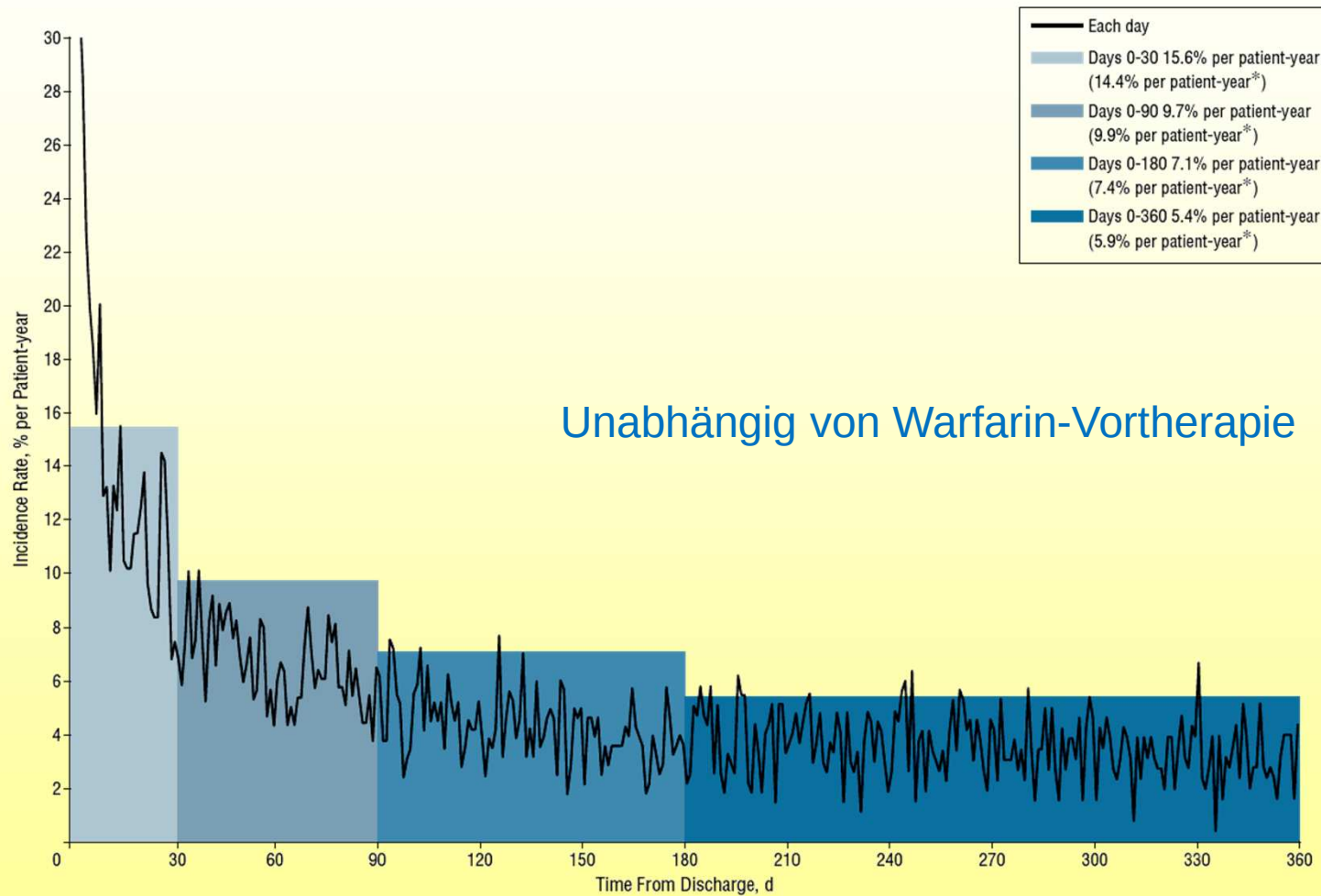
ICH ist die am meisten gefürchtete Komplikation traditioneller Antithrombotika

- ICH ist lebensbedrohlich¹
- Traditionelle Antithrombotika erhöhen das Risiko eines ICH*:¹
 - ASS erhöht Risiko um 40%
 - Warfarin verdoppelt Risiko (INR 2.0–3.0; ➔ 0.3–0.6%/yr)
 - OAK erhöht die Schwere der ICH²





Inzidenzraten für nicht-fatale, fatale Blutungen



Hansen, Arch Int Med 2010; 170: 1433



HR für Blutungen

Keine Therapie

0.83 (0.79-0.86)

HR (95% CI)

Warfarin monotherapy

1 [Reference]

Aspirin monotherapy

0.93 (0.88-0.98)

Clopidogrel monotherapy

1.06 (0.87-1.29)

Aspirin + clopidogrel

1.66 (1.34-2.04)

Warfarin + aspirin

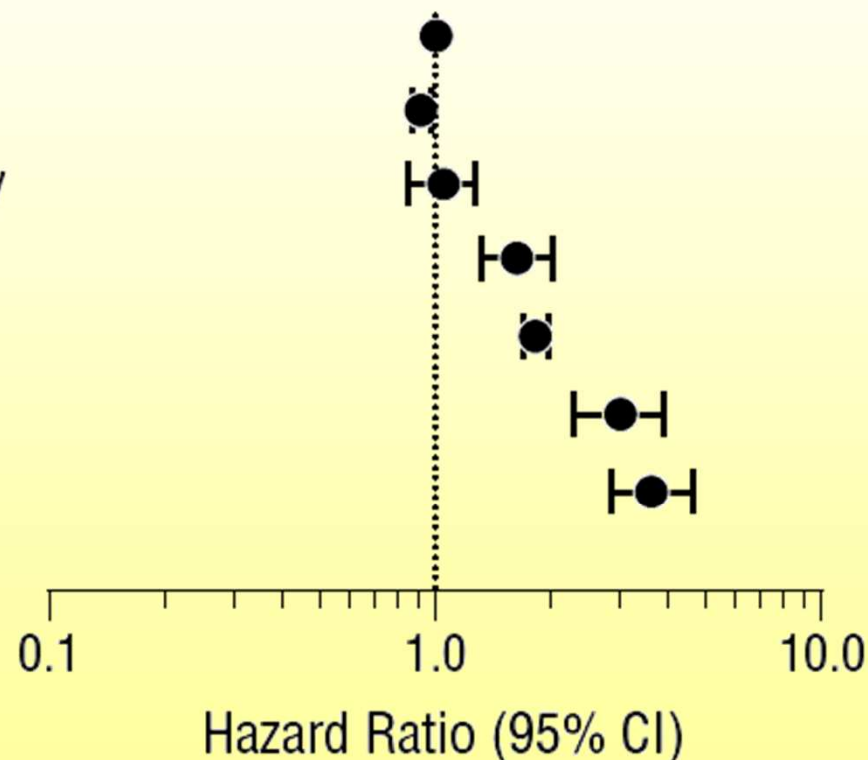
1.83 (1.72-1.96)

Warfarin + clopidogrel

3.08 (2.32-3.91)

Triple therapy

3.70 (2.89-4.76)



Nicht-fatale Blutungen: 12191; fatale Blutungen: 1381

Hansen, Arch Int Med 2010; 170: 1433



HAS-BLED Blutungs-Risikoscore

Letter	Clinical characteristic ^a	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

- **H:** $RR_{syst} > 160$
- **A:** Dialyse, NTX, Crea > 2,26 mg/dl; Cirr hep, Bili > 2x, GOT/GPT/AP > 3x
- **B:** frühere Blutung od Disposition
- **L:** INR $\uparrow$ od. $\downarrow$, < 60%
- **D:** TASS, NSAR, Alkohol-Abusus, etc

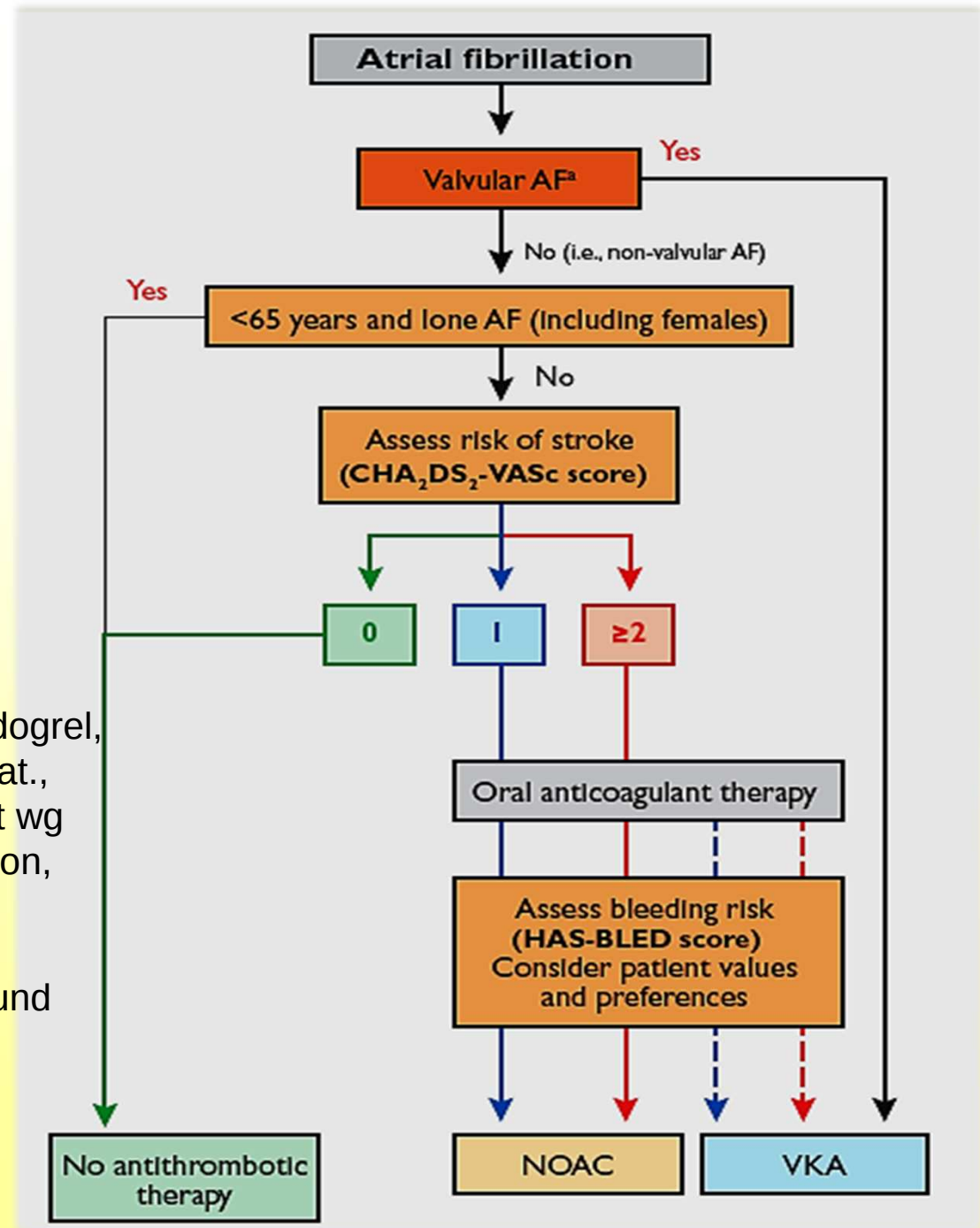
Score $\geq 3 \Rightarrow$ „Hohes Risiko“, Vorsicht und häufigere Kontrollen, bes. nach Einleitung!

Pisters, Chest 2010; March 18 [Epub ahead of print]



Thrombozytenhemmung mit ASS+Clopidogrel, od. weniger wirksam –ASS alleine für Pat., die OAK ablehnen, nicht vertragen (nicht wg Blutung!); bei KI für beides: LAA-Okklusion, oder chir. Entfernung

a: inkludiert rheumatische Klappenerkr. und Künstliche Klappen





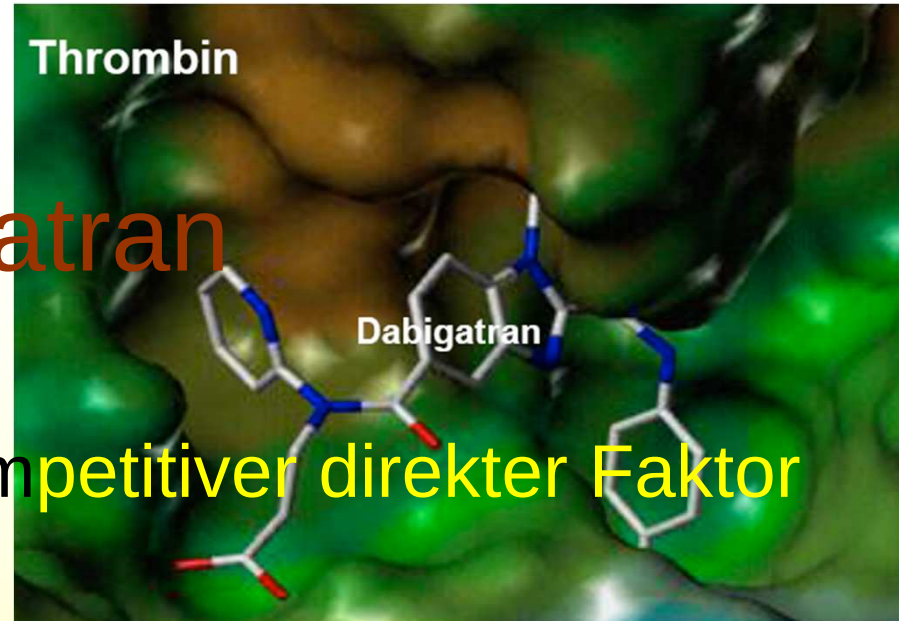
Neue Antikoagulantien bei AF

NOAC

- *Direkte Thrombininhibitoren*
 - *Dabigatran*
- *Direkte Faktor Xa Inhibitoren*
 - *Rivaroxaban*
 - *Apixaban*



Dabigatran



- Spezifisch selektiver kompetitiver direkter Faktor IIa Hemmer
- Hemmt freie und Fibrin-gebundene IIa Aktivität
- Orales Prodrug mit eher schlechter Bioverfügbarkeit – 6,5%
- T_{1/2}: 12-17h (80% renale Ausscheidung)
- Dosierung: 2x täglich
- 1-4h nach Gabe max. Inhibierung des F IIa
- Kein direkter Effekt auf Plättchenaggregation



Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

Randomized **E**valuation of **L**ong term anticoagulant therapy

comparing the efficacy and safety of two blinded doses of dabigatran etexilate with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation:

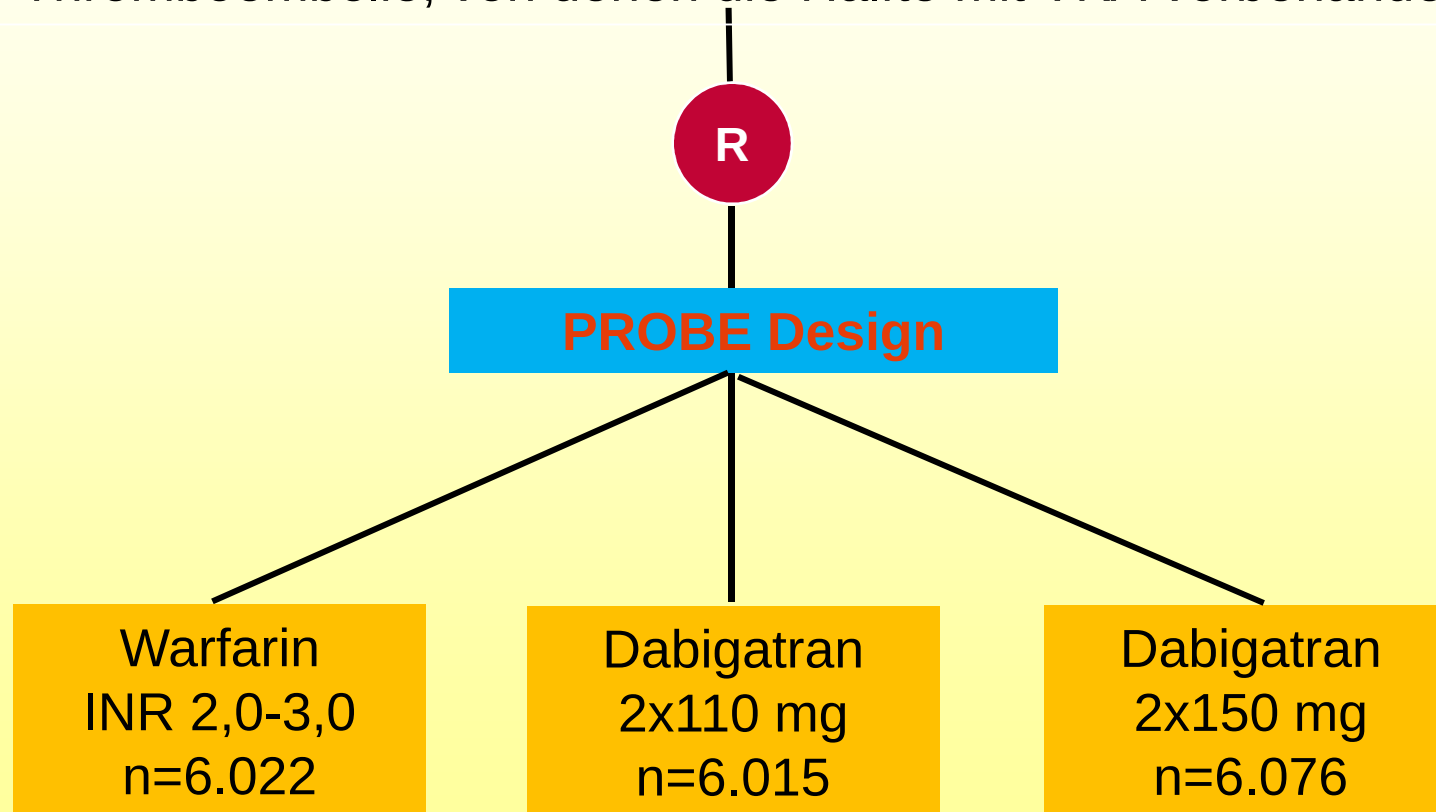
prospective, multi-centre, parallel-group, non-inferiority trial

Connolly, N Engl J Med 2009; 361: 1139



Studiendesign

18.113 Patienten mit nicht-valvulärem Vorhofflimmern und zumindest 1 zusätzlichen Risikofaktor für Insult bzw. systemische Thromboembolie, von denen die Hälfte mit VKA vorbehandelt ist





Datenqualität

- 99.9% komplette Datensätze
 - 20 von 18.113 Patienten “lost to follow-up”
- Time in Therapeutic Range (TTR) im VKA-Arm
 - 67% bei VKA-vorbehandelten Patienten
 - 61% bei VKA-naiven Patienten
- Dauer: 12-28 Monate



Einschluss - Ausschluss

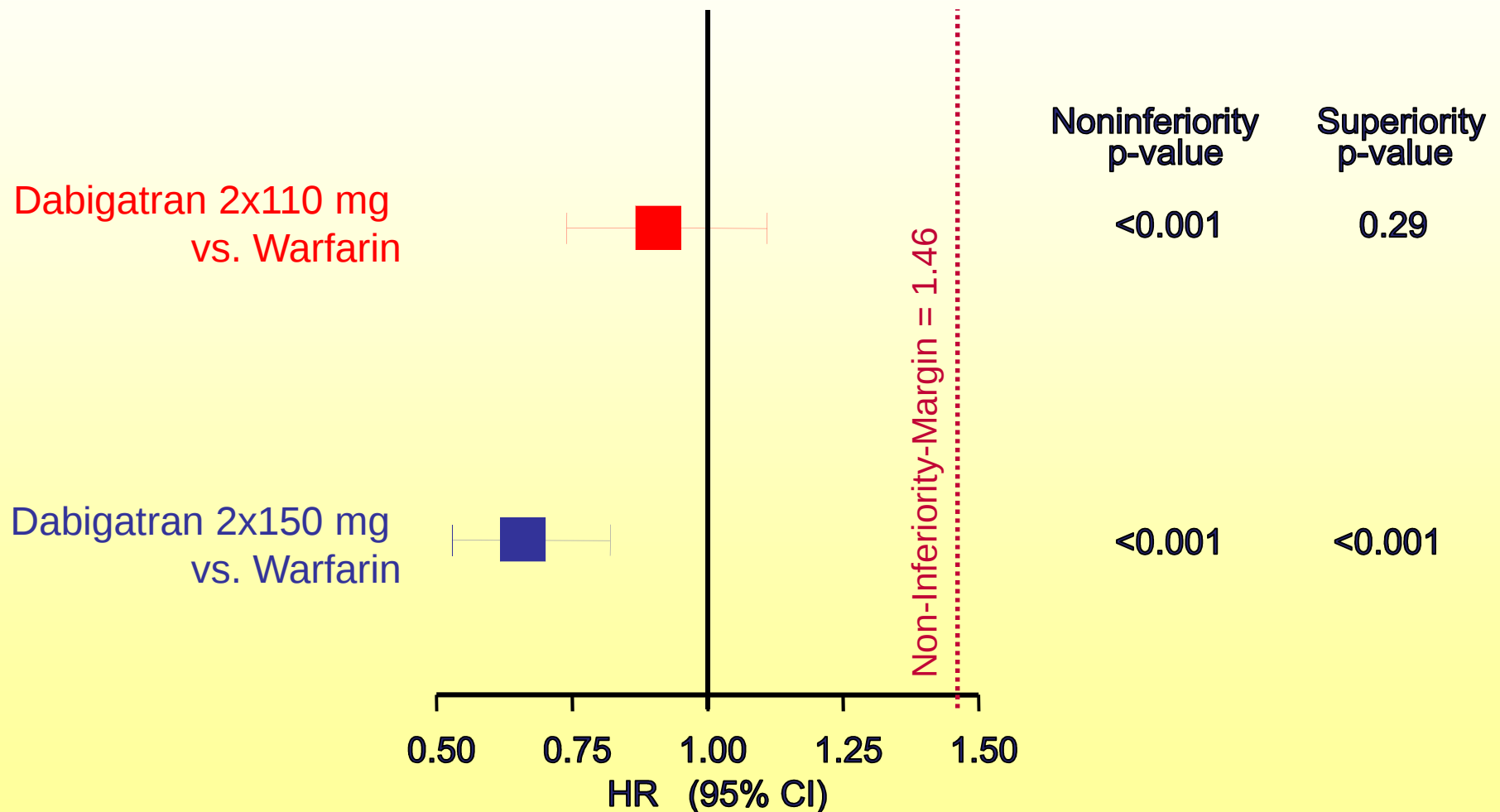
- EKG: Vorhofflimmern
- plus ≥ 1 zusätzlicher Risikofaktor
 - anamnestisch Insult oder TIA
 - LVEF < 40%
 - HI ($\geq$ NYHA II)
 - Alter über 75
 - Alter 65 bis 74
 - plus Diabetes mellitus
 - plus Hypertonie
 - plus koronare Herzkrankheit
- rezenter Insult
- erhöhtes Blutungsrisiko
- Kreatinin-Clearance < 30 ml/min
-

CHADS₂-Score im Mittel: 2,2

Connolly, N Engl J Med 2009; 361: 1139



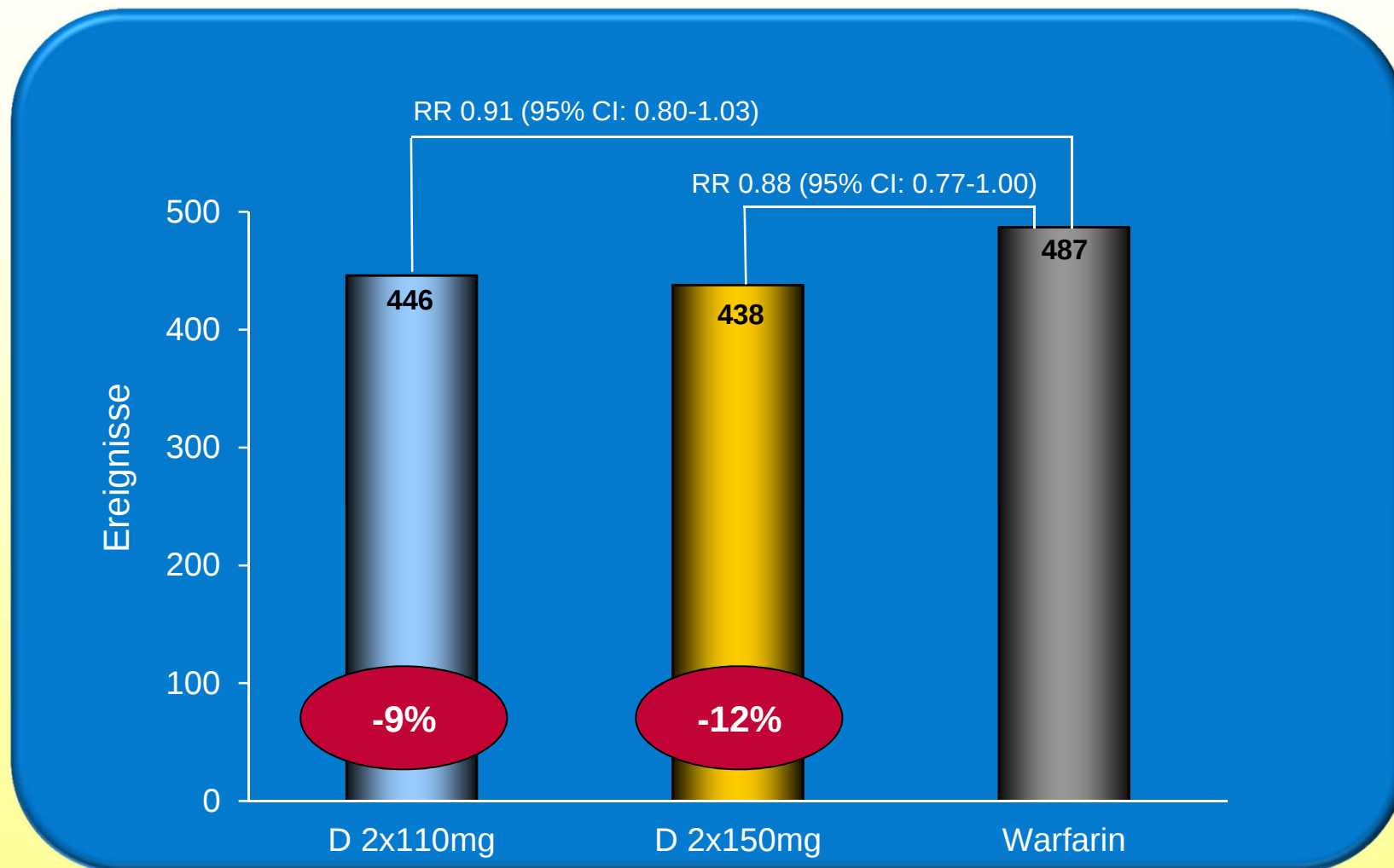
Primärer Endpunkt: Insult / systemische Thromboembolie



Connolly, N Engl J Med 2009; 361: 1139



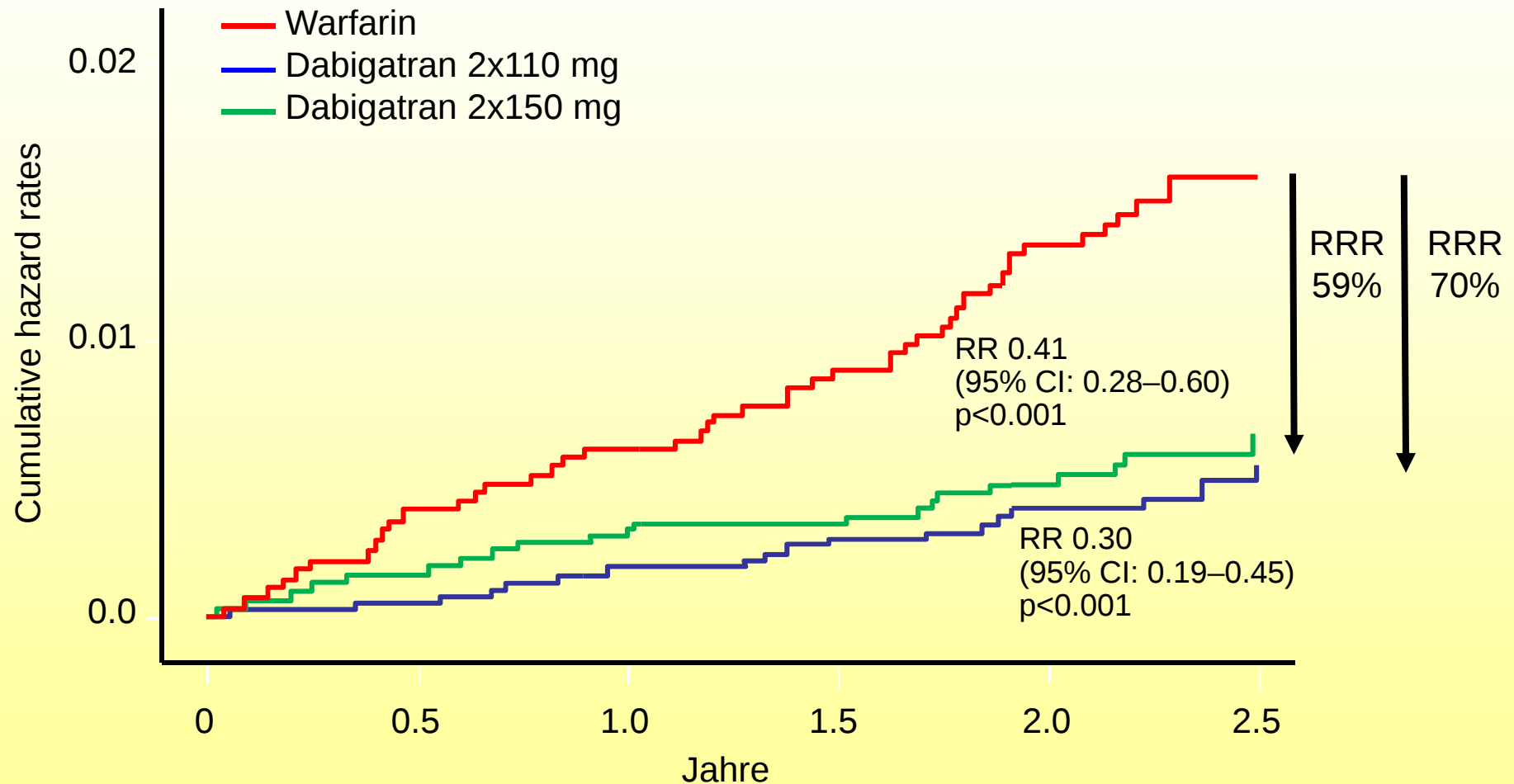
Mortalität



Connolly, N Engl J Med 2009; 361: 1139



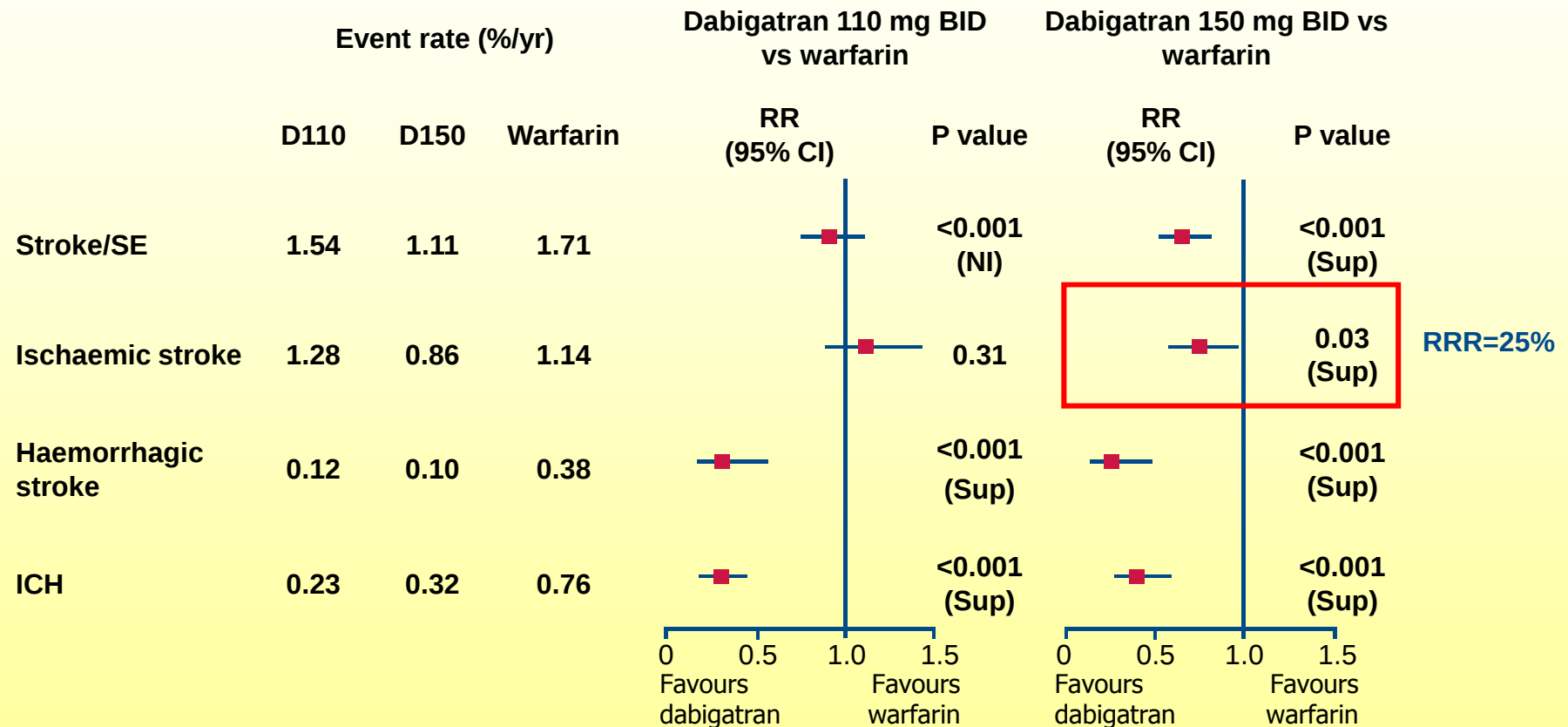
Intrakranielle Blutungen



Connolly, N Engl J Med 2009; 361: 1139



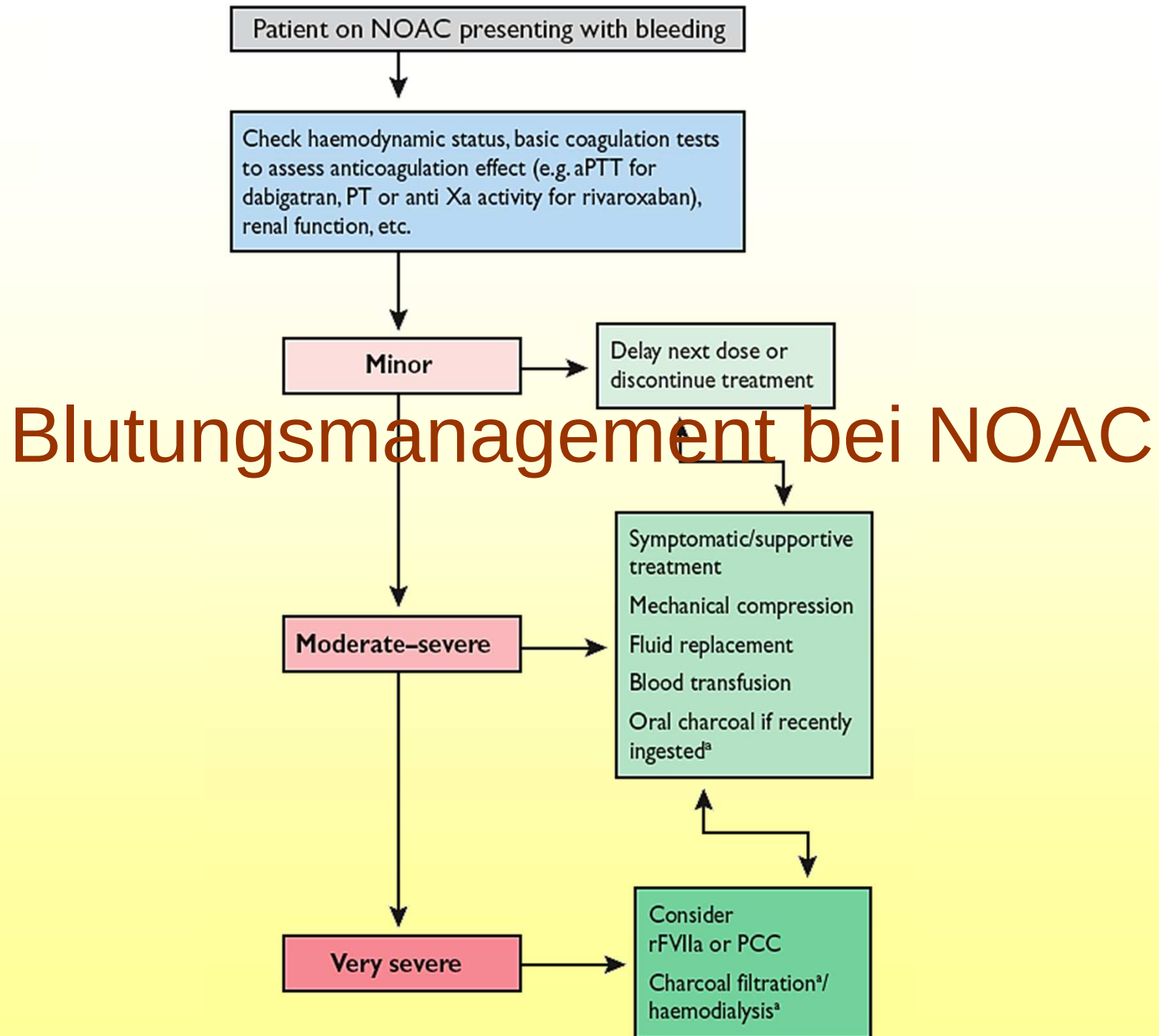
Dabigatran reduziert neben Blutungen AUCH Risiko eines ischämischen Schlaganfalls gegenüber OAK



ICH = intracranial haemorrhage; NI = non-inferiority;

RR = relative risk; RRR = relative risk reduction; SE = systemic embolism; Sup = superiority

Connolly SJ et al. N Engl J Med 2010;363:1875–6





Perioperative Guidelines für Dabigatran

Renal Function Impairment (CrCL mL/min)	Estimated Half-Life, h (Range)	Stopping Dabigatran Before Surgery/Procedure	
		High Risk for Bleeding	Standard Risk for Bleeding
Mild: ≥ 50 to 80	15 (12–18)	2–3 d*	24 h (2 doses)*
Moderate: ≥ 30 to < 50	18 (18–24)	4 d	At least 2 d (48 h)
Severe: < 30	27 (> 24)	> 5 d	2–4 d



2011 ACCF/AHA/HRS Guidelines: Update on Dabigatran

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart
Association® 
Learn and Live™

2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Update on Dabigatran): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

L. Samuel Wann, Anne B. Curtis, Kenneth A. Ellenbogen, N.A. Mark Estes, III, Michael D. Ezekowitz, Warren M. Jackman, Craig T. January, James E. Lowe, Richard L. Page, David J. Slotwiner, William G. Stevenson and Cynthia M. Tracy
Circulation published online Feb 14, 2011;

"Dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization."

(Class I, Level of Evidence: B)



2010 Canadian Stroke Care Guidelines

CANADIAN BEST PRACTICE RECOMMENDATIONS FOR STROKE CARE

UPDATE 2010

“ Patients with atrial fibrillation at low risk of stroke ($\text{CHADS}_2 = 1$) should receive either warfarin or dabigatran.

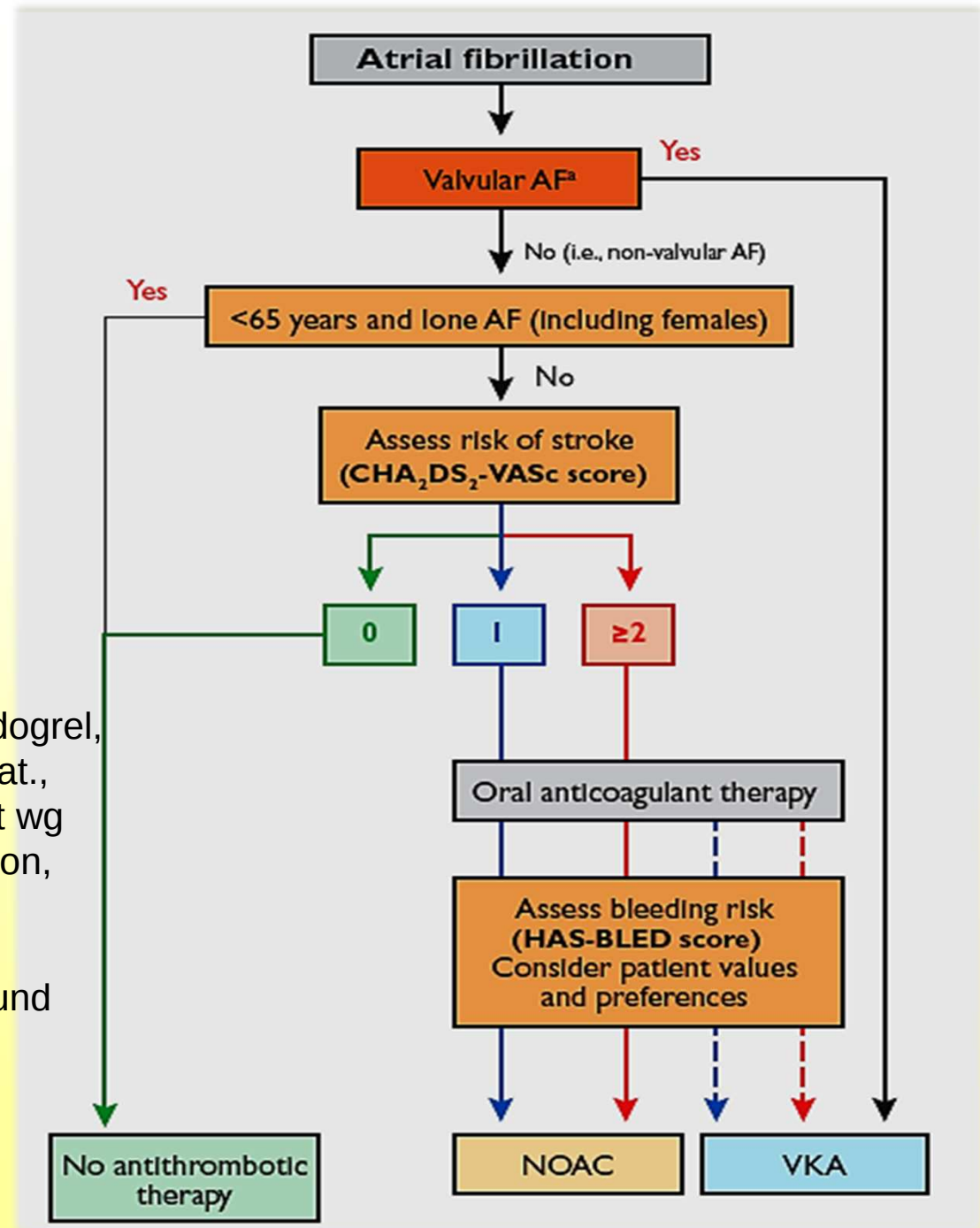
Patients with atrial fibrillation at moderate to high risk of stroke ($\text{CHADS}_2 \geq 2$) should receive either warfarin or dabigatran.

Dabigatran is preferred over warfarin for patients with atrial fibrillation who meet the inclusion criteria for the RE-LY trial. “



Thrombozytenhemmung mit ASS+Clopidogrel, od. weniger wirksam –ASS alleine für Pat., die OAK ablehnen, nicht vertragen (nicht wg Blutung!); bei KI für beides: LAA-Okklusion, oder chir. Entfernung

a: inkludiert rheumatische Klappenerkr. und Künstliche Klappen





Empfehlungen – NOAC I

Recommendations for prevention of thromboembolism in non-valvular AF—NOACs

When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either:

- a direct thrombin inhibitor (dabigatran); or
 - an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)^d
- ... is recommended

I

B

Where OAC is recommended, one of the NOACs, either:

- a direct thrombin inhibitor (dabigatran); or
- an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)^d

... should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit.

IIa

A

Where dabigatran is prescribed, a dose of 150 mg b.i.d. should be considered for most patients in preference to 110 mg b.i.d., with the latter dose recommended in:

- elderly patients, age ≥ 80
- concomitant use of interacting drugs (e.g. verapamil)
- high bleeding risk (HAS-BLED score ≥ 3)
- moderate renal impairment (CrCl 30–49 mL/min).

IIa

B



Empfehlungen – NOAC II

Baseline and subsequent regular assessment of renal function (by CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2–3 times per year.	IIa	B
NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min).	III	A
Recommendations for prevention of thromboembolism in non-valvular AF—bleeding		
Assessment of the risk of bleeding is recommended when prescribing antithrombotic therapy (whether with VKA, NOAC, aspirin/clopidogrel, or aspirin).	I	A
The risk of major bleeding with antiplatelet therapy (with aspirin–clopidogrel combination therapy and – especially in the elderly – also with aspirin monotherapy) should be considered as being similar to OAC.	IIa	B
Recommendations for prevention of thromboembolism in non-valvular AF—peri-cardioversion		
For patients with AF of ≥ 48 h duration, or when the duration of AF is unknown, OAC therapy (e.g. 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/i.v. 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



Zusammenfassung

- **Allgemeines**
 - Häufigste HRST, zunehmend, Insult, † höher, neue ESC-Guidelines
- **Aspekt der Antikoagulation**
 - CHA₂DS₂-VASc Score, HAS-BLED Score, NOAC auf dem Vormarsch!
- **Dabigatran**
 - 150mg: weniger ischämische Ereignisse mit ähnlicher Blutungshäufigkeit
 - 110mg: weniger Blutungen mit ähnlicher Wirkung