UNIVERSITÄTSmedizin. MAINZ

Herz - Focus
Eppstein, 18.1.2017

Geriatrische Behandlung kardiovaskulärer Erkrankungen– Zwischen Evidenz und Bauchgefühl

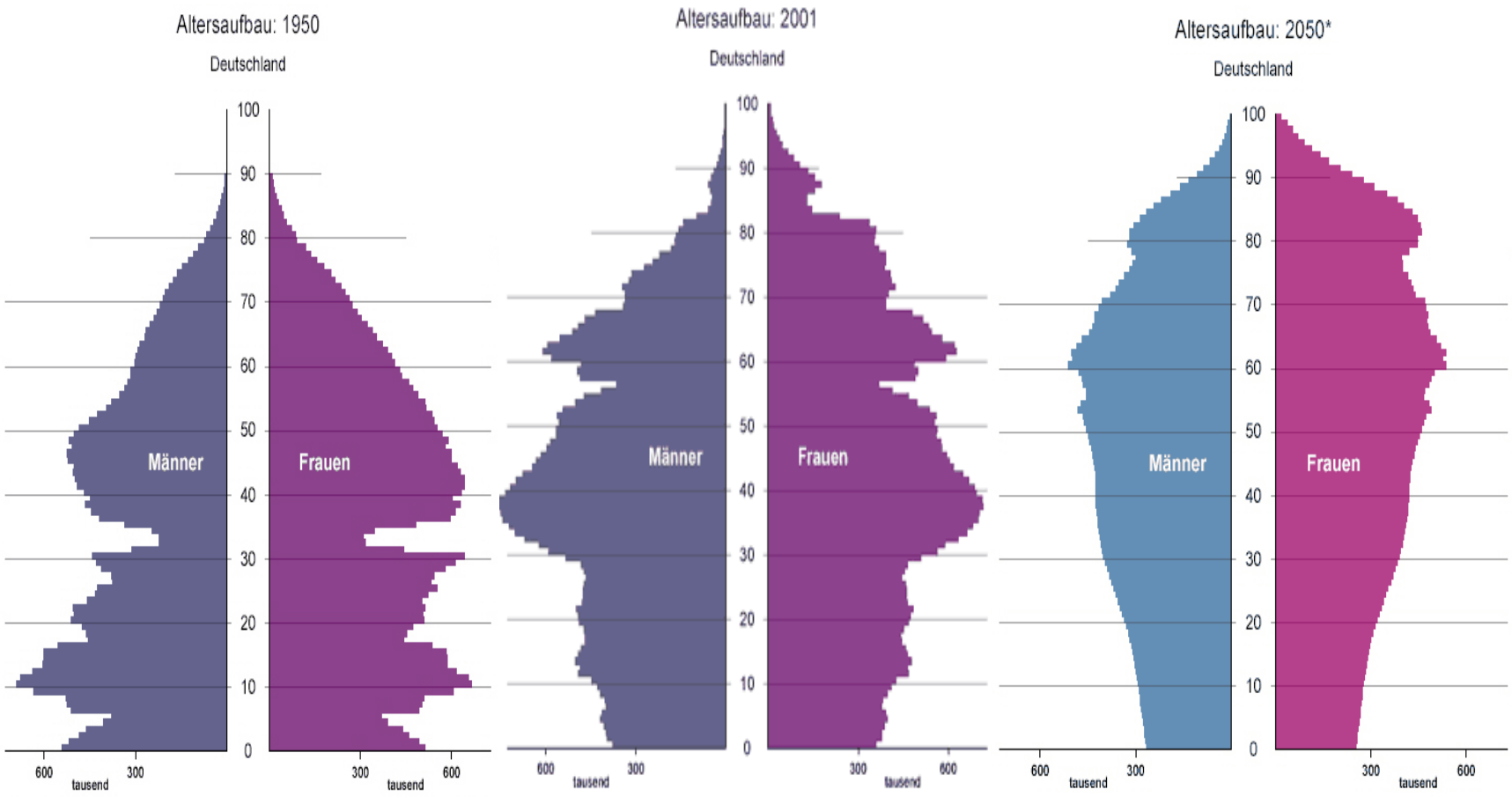
Prof. Dr. Roland Hardt

Zentrum für Allgemeinmedizin und Geriatrie

-Abteilung Geriatrie-

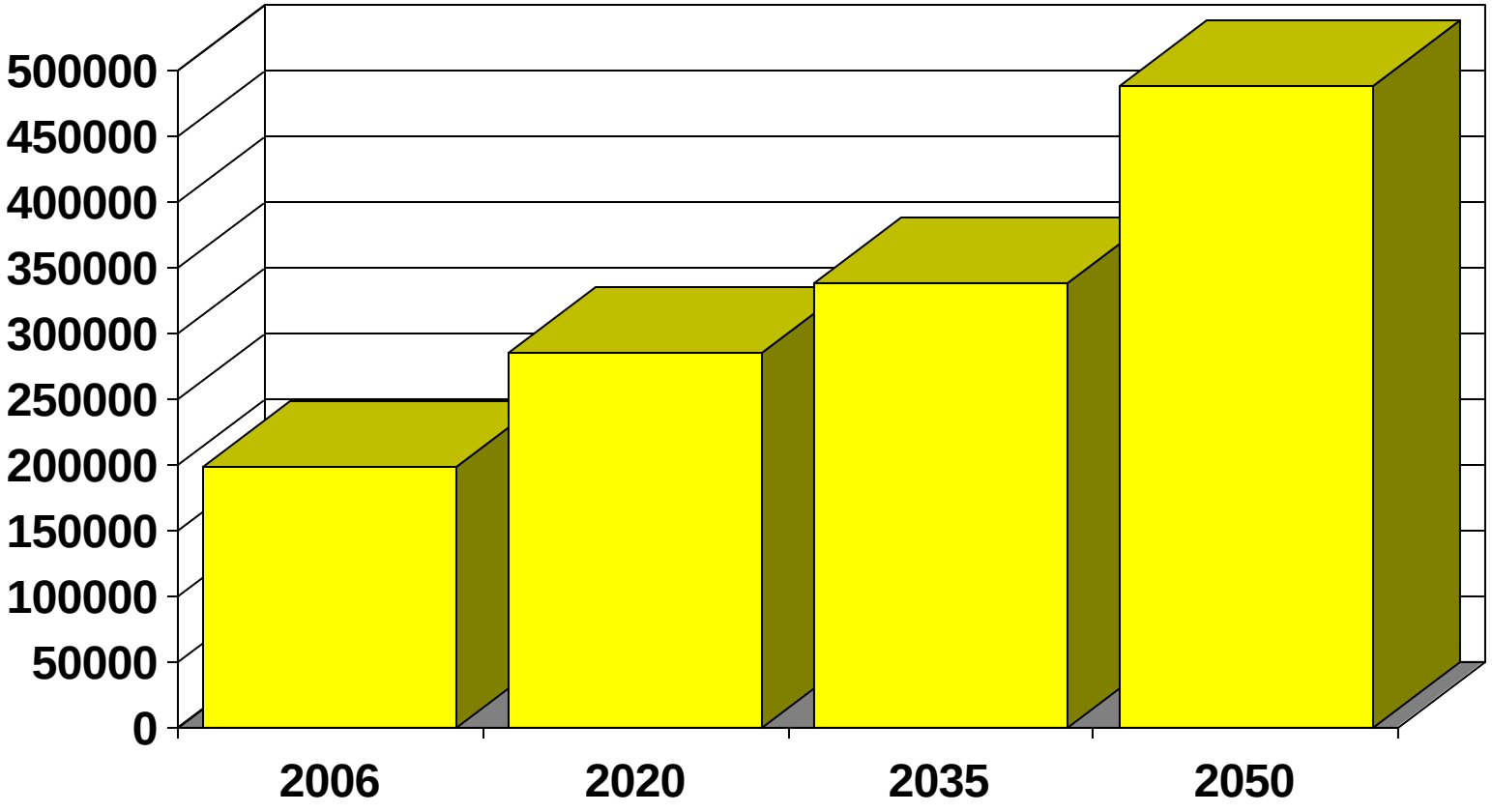
Universitätsmedizin Mainz

Demographischer Wandel
Altersaufbau 1950-2050



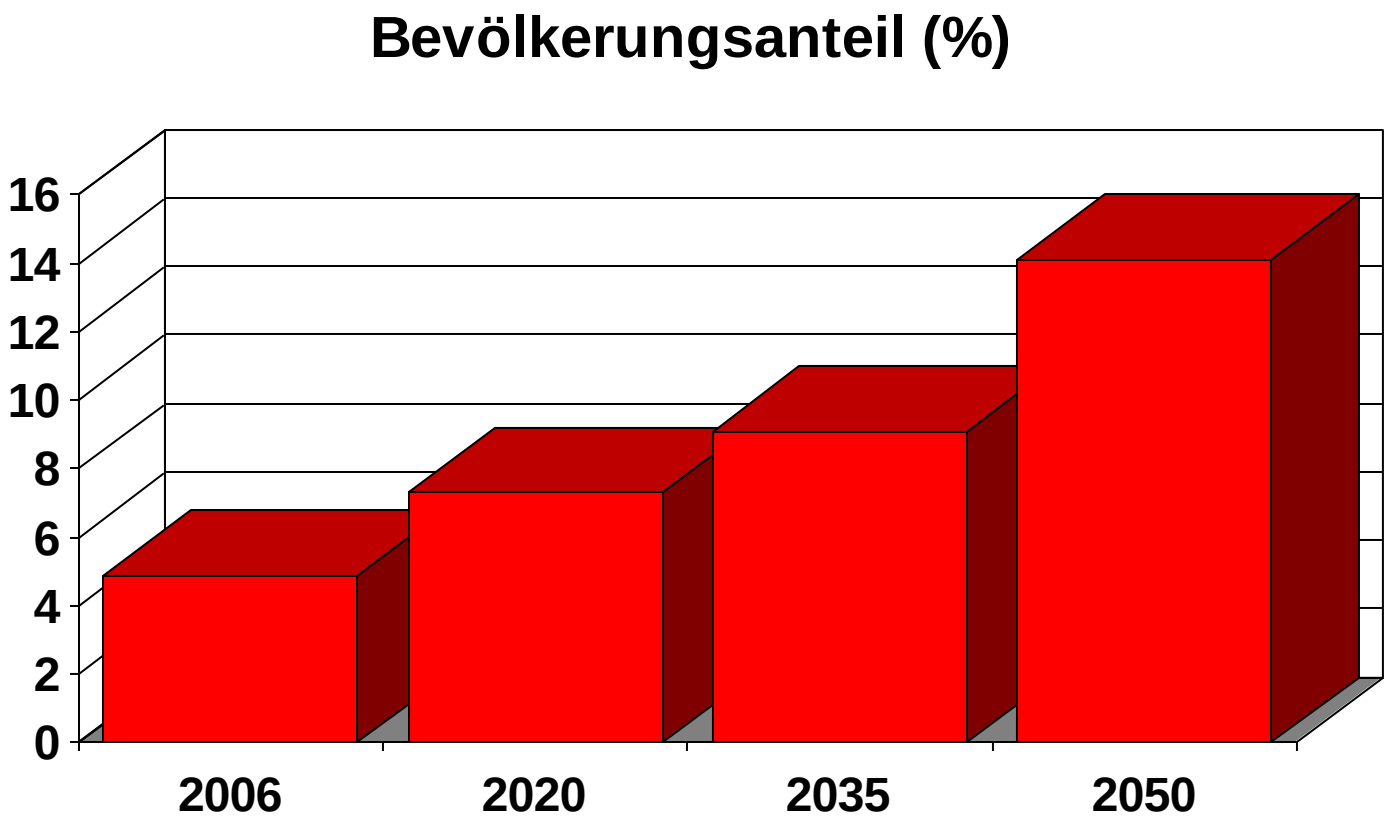
Stat. Bundesamt

Einwohner >80J in Rheinland Pfalz



Stat. Landesamt RLP

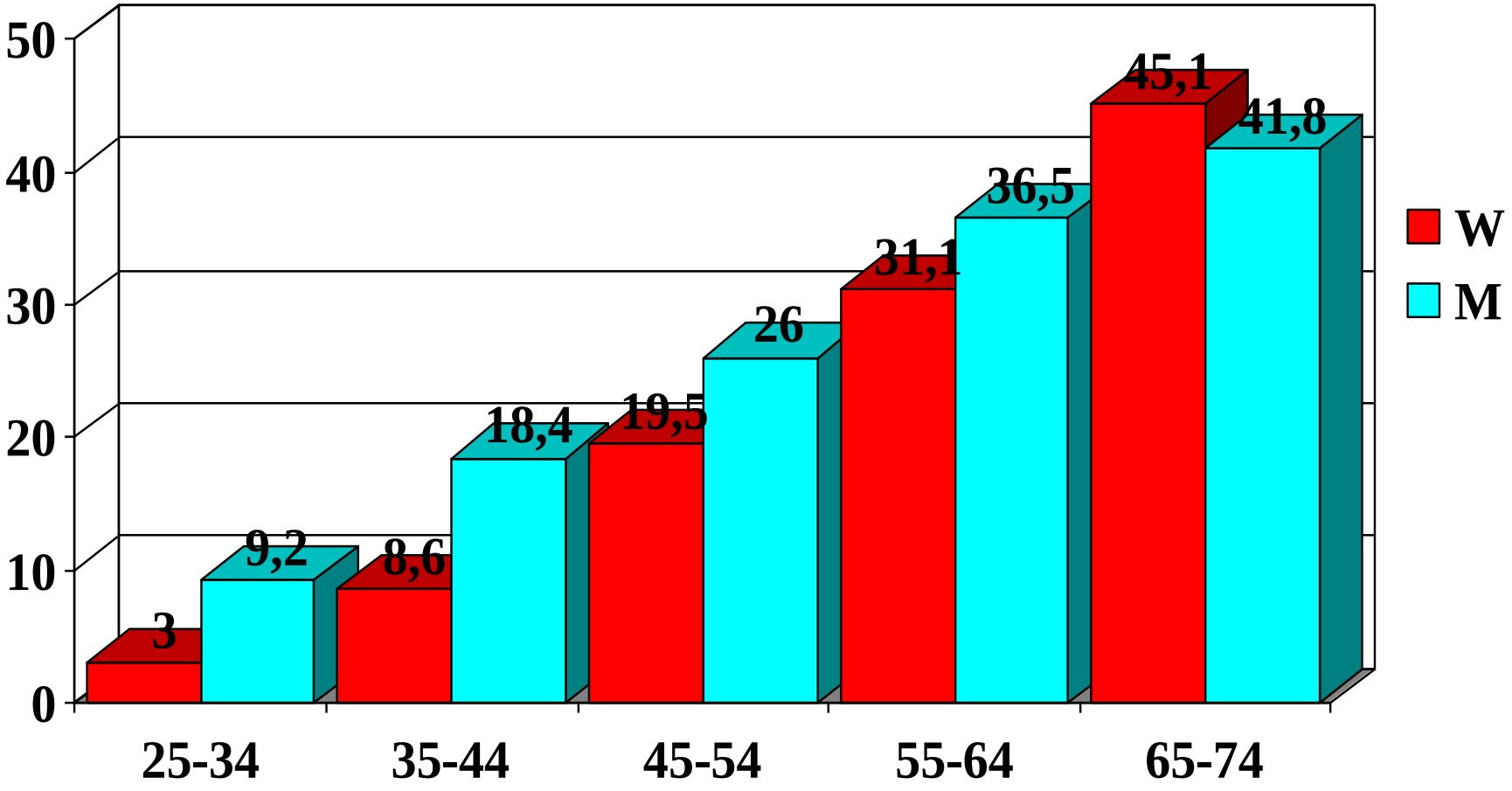
Einwohner >80J in Rheinland Pfalz



Stat. Landesamt RLP

Arterielle Hypertonie

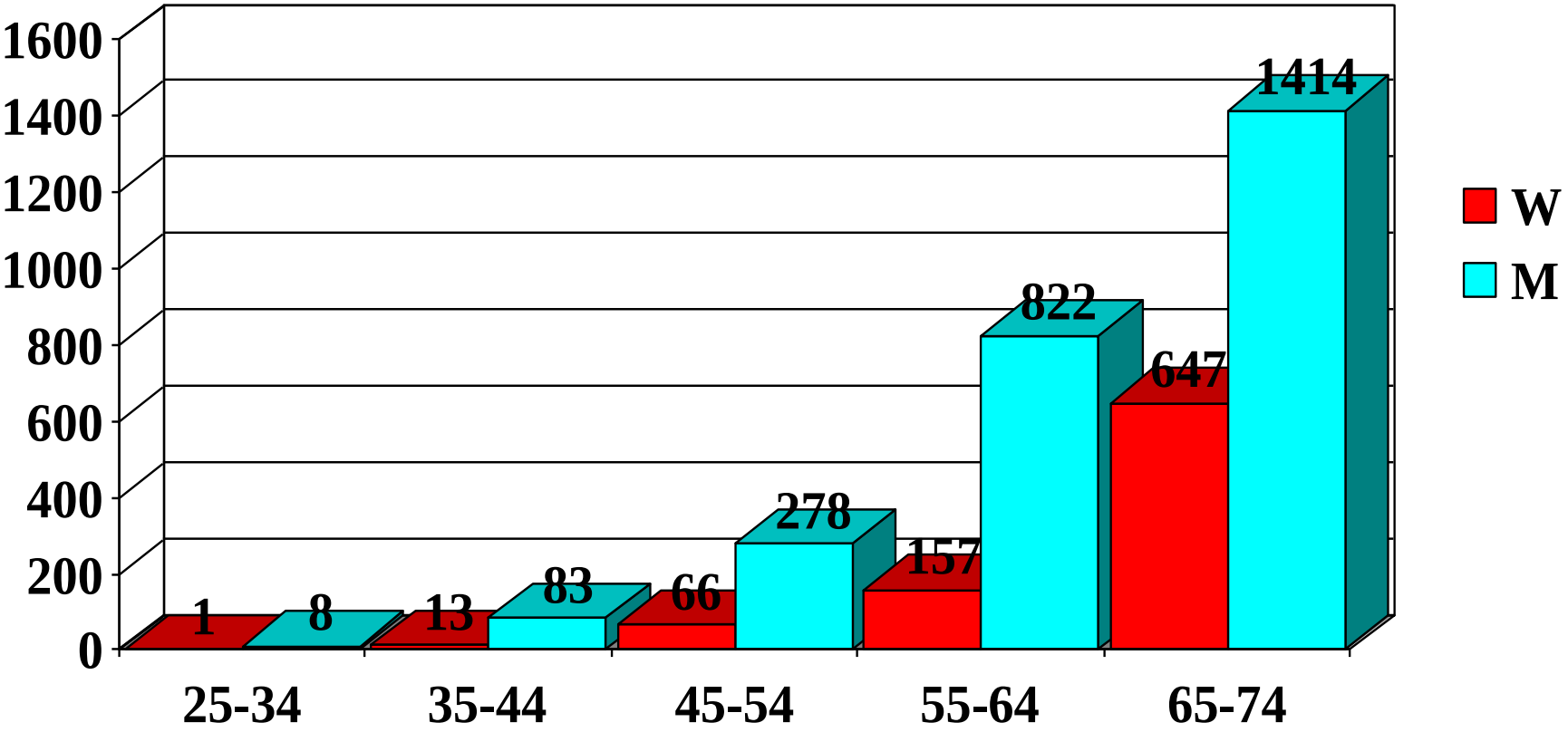
Daten aus dem Monica – Register (Prävalenz in %)



Hense HW.:. Dtsch Med Wschr 2000; 125:1397-1402

Herzinfarkt – Inzidenz

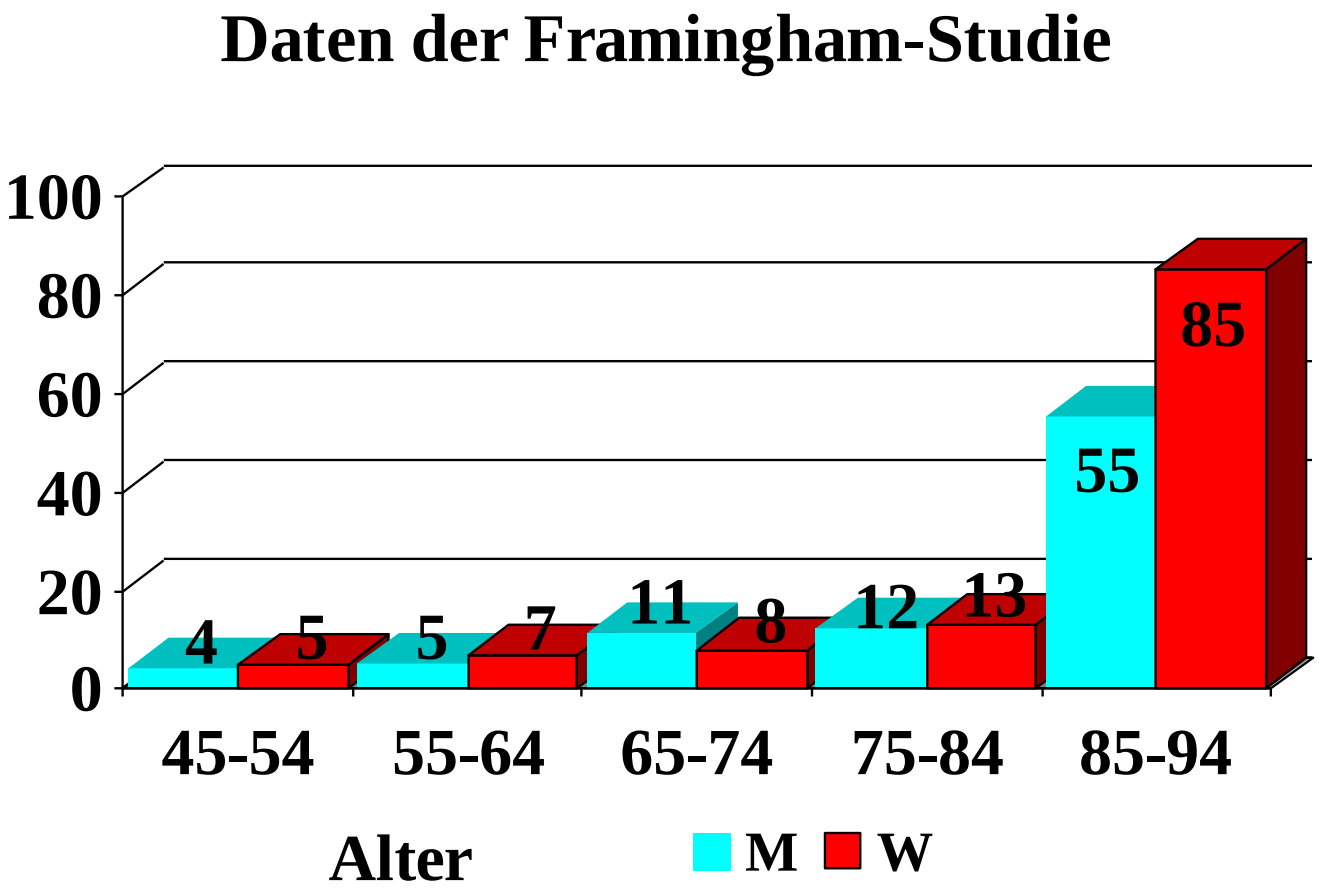
Daten aus dem Monica – Register (Fälle/100000)



Hense HW.:. Dtsch Med Wschr 2000; 125:1397-1402

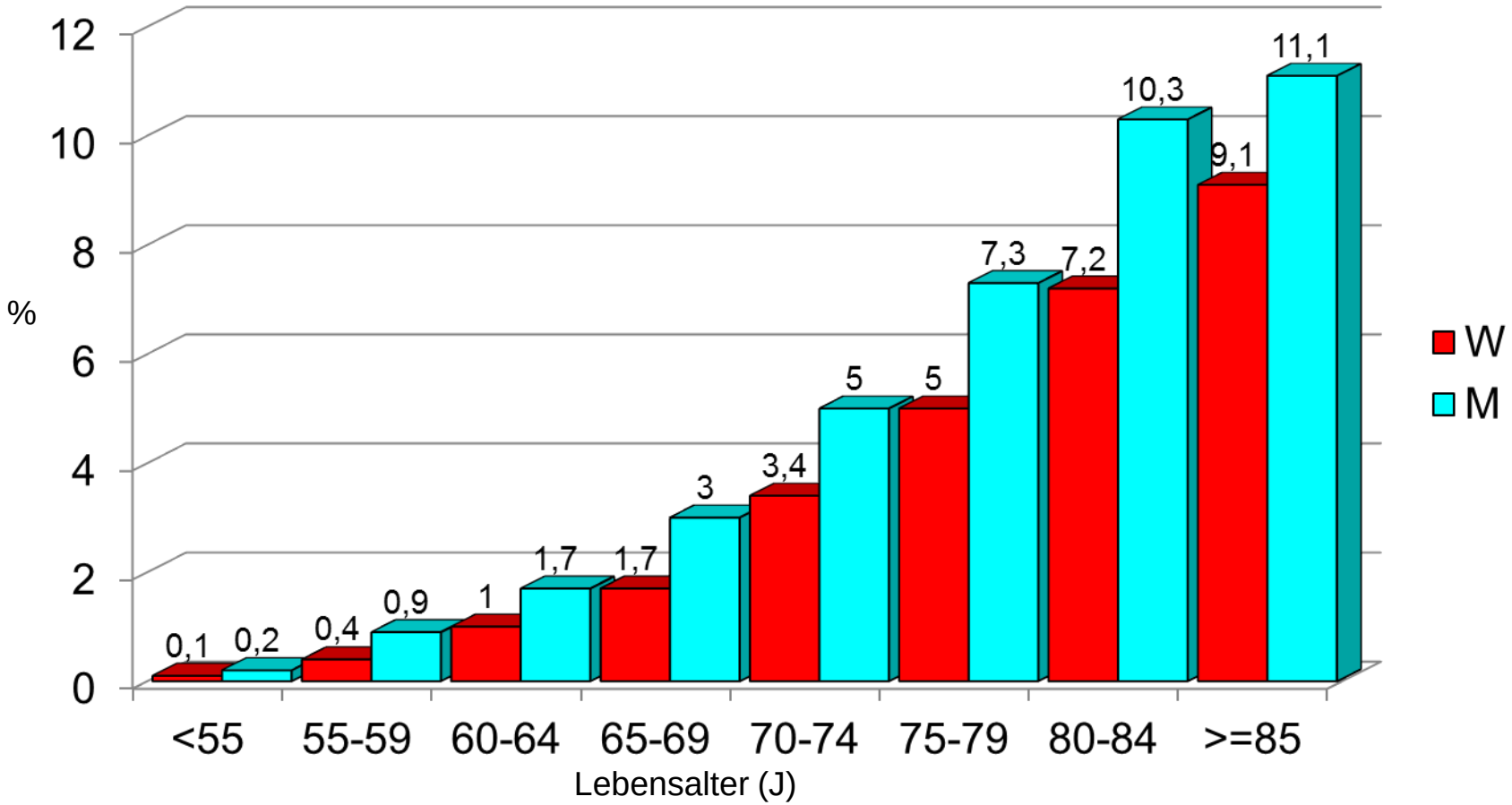
Herzinsuffizienz

Prävalenz nach Alter und Geschlecht (Fälle/1000)



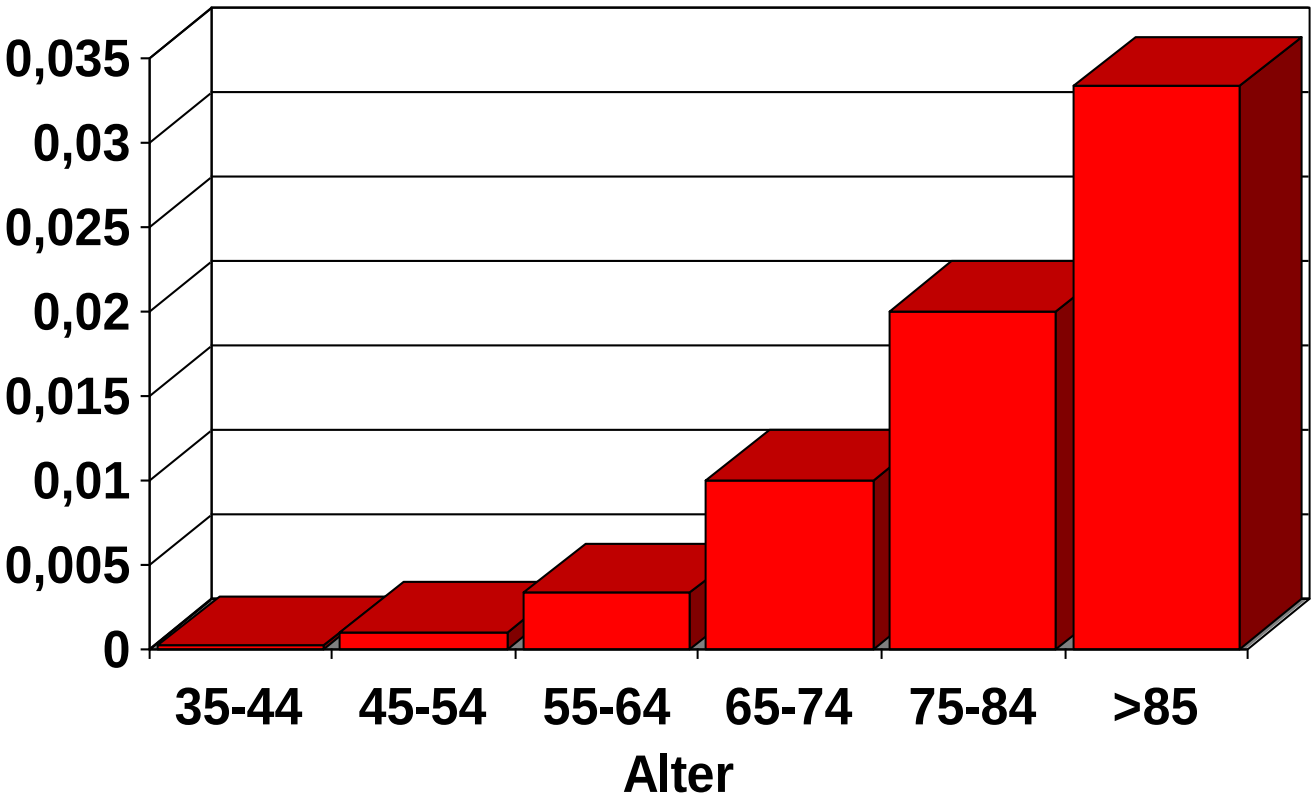
Circulation 2002; 106: 3068-72

Altersabhängige Prävalenz des Vorhofflimmerns



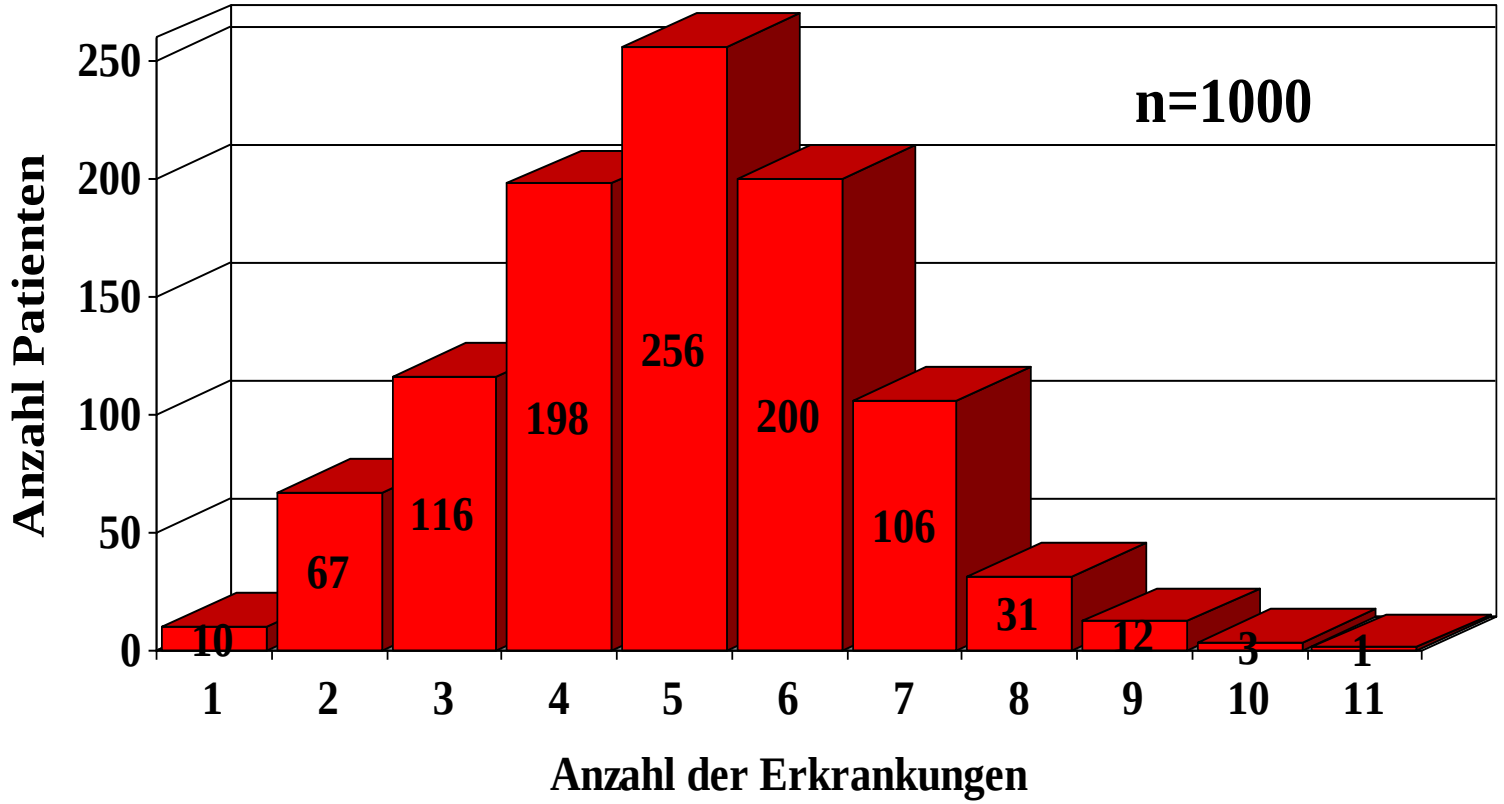
Go, A.S. et al. JAMA 2001;285:2370-2375

Jährliches Schlaganfall-Risiko bei aHT

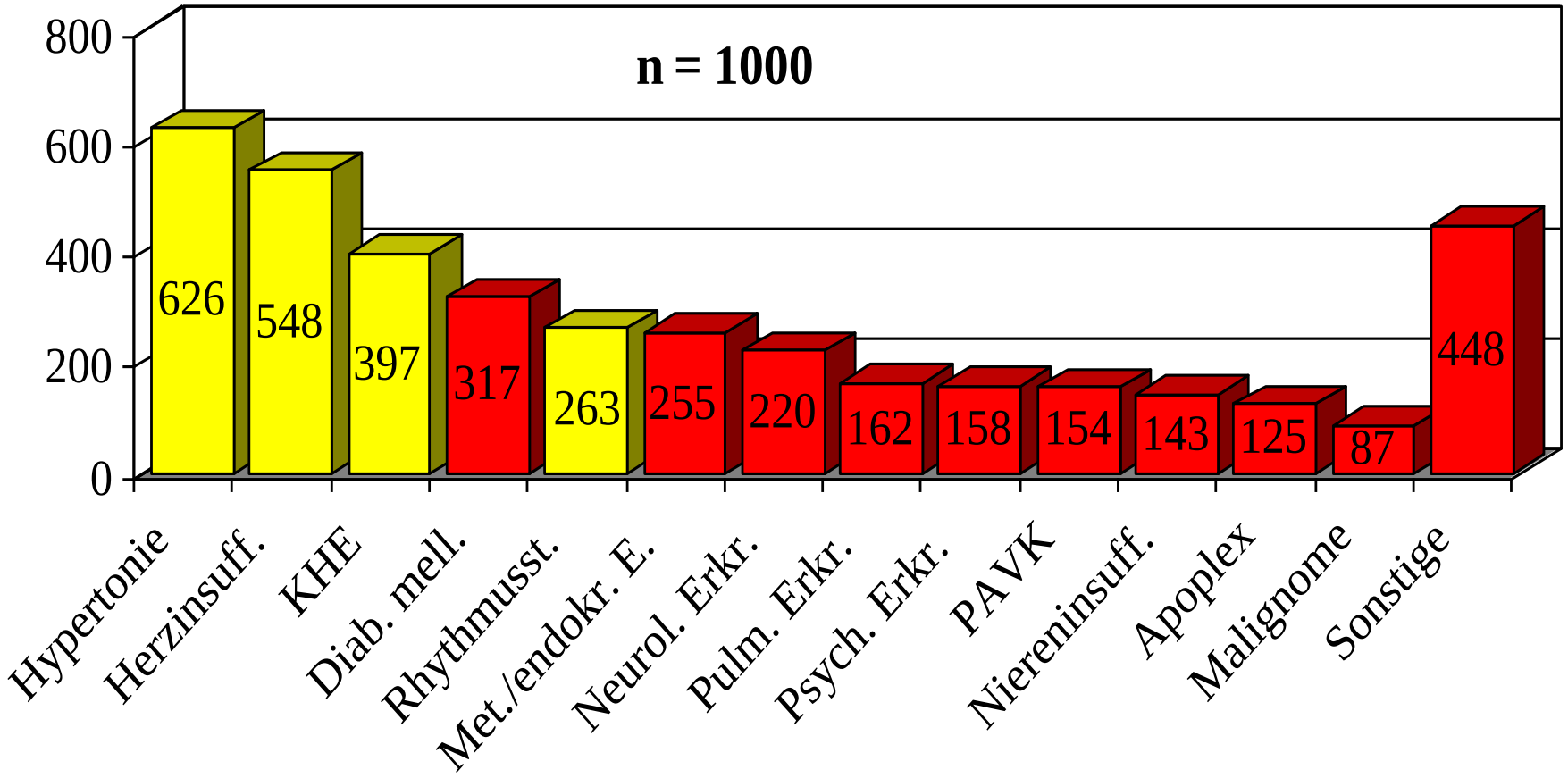


CS Anderson et al. Med J Aust 1993, 188: 80-84

Geriatrie Trier (1995-1997) Multimorbidität

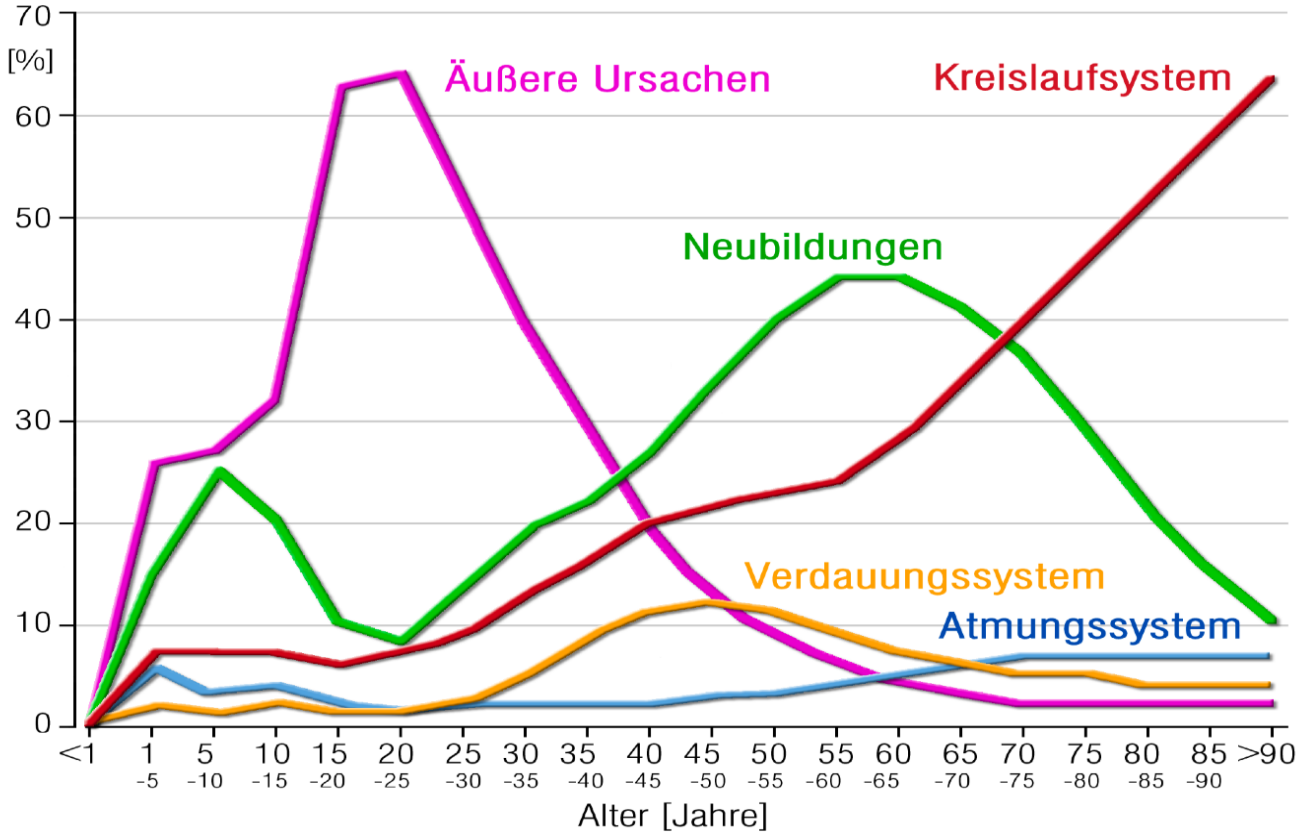


Multimorbidität
Klinisch relevante Erkrankungen



Geriatrie Trier (1995-1997)

Morbiditätsrisiko und Alter



Todesursachenstatistik, Statistisches Bundesamt 2012

Invasive Kardiologie

- Koronarinterventionen Revaskularisation
  - Akutes Koronarsyndrom
  - Stabile AP
- Klappenintervention
  - TAVI
  - Mitraclip
  - Anuloplastie etc.
- Elektrophysiologie
  - Ablation (AF, AFL, AVNRT)
  - Device Therapie
- Risikostratifizierung morbiditätsorintiert, kalend. Alter sekundär
- Gute Datenbasis (Studien, Register) auch für hochaltrige Patienten

→ **Kardiologie goes Geriatrie**

Kardiovaskuläre Erkrankungen in der Geriatrie - Problemfelder

- Prävention:
  - Kardiale Erkrankungen / Ereignisse
  - Thrombembolie / Schlaganfälle
- Therapie
  - Herzinsuffizienz - HFpEF

Prävention der koronaren Herzerkrankung - Risikostratifizierung

10 year risk of fatal CVD in low risk regions of Europe by gender, age, systolic blood pressure, total cholesterol and smoking status

SCORE

15% and over	10-year risk of fatal CVD in populations at low CVD risk
10% - 14%	
5% - 9%	
3% - 4%	
2%	
1%	
< 1%	

Women

Systolic blood pressure (mmHg)	Age	Non-smoker					Smoker				
		4	5	6	7	8	4	5	6	7	8
180	65	4	5	6	6	7	9	9	11	12	14
160	65	3	3	4	4	5	6	6	7	8	10
140	65	2	2	2	3	3	4	4	5	6	7
120	65	1	1	2	2	2	3	3	3	4	4
180	60	3	3	3	4	4	5	5	6	7	8
160	60	2	2	2	2	3	3	4	4	5	5
140	60	1	1	1	2	2	2	2	3	3	4
120	60	1	1	1	1	1	1	2	2	2	3
180	55	1	1	2	2	2	3	3	3	4	4
160	55	1	1	1	1	1	2	2	2	3	3
140	55	1	1	1	1	1	1	1	1	2	2
120	55	0	0	1	1	1	1	1	1	1	1
180	50	1	1	1	1	1	1	1	2	2	2
160	50	0	0	1	1	1	1	1	1	1	1
140	50	0	0	0	0	0	1	1	1	1	1
120	50	0	0	0	0	0	0	0	0	1	1
180	40	0	0	0	0	0	0	0	0	0	0
160	40	0	0	0	0	0	0	0	0	0	0
140	40	0	0	0	0	0	0	0	0	0	0
120	40	0	0	0	0	0	0	0	0	0	0

Men

Systolic blood pressure (mmHg)	Age	Non-smoker					Smoker				
		4	5	6	7	8	4	5	6	7	8
180	65	8	9	10	12	14	15	17	20	23	26
160	65	5	6	7	8	10	10	12	14	16	19
140	65	4	4	5	6	7	7	8	9	11	13
120	65	2	3	3	4	5	5	5	6	8	9
180	60	5	6	7	8	9	10	11	13	15	18
160	60	3	4	5	5	6	7	8	9	11	13
140	60	2	3	3	4	4	5	5	6	7	9
120	60	2	2	2	3	3	3	4	4	5	6
180	55	3	4	4	5	6	6	7	8	10	12
160	55	2	2	3	3	4	4	5	6	7	8
140	55	1	2	2	2	3	3	3	4	5	6
120	55	1	1	1	2	2	2	2	3	3	4
180	50	2	2	3	3	4	4	4	5	6	7
160	50	1	1	2	2	2	2	3	3	4	5
140	50	1	1	1	1	2	2	2	2	3	3
120	50	1	1	1	1	1	1	1	2	2	2
180	40	0	1	1	1	1	1	1	1	2	2
160	40	0	0	0	1	1	1	1	1	1	1
140	40	0	0	0	0	0	0	1	1	1	1
120	40	0	0	0	0	0	0	0	0	1	1

Cholesterol (mmol/L)

150 200 250 300
mg/dL

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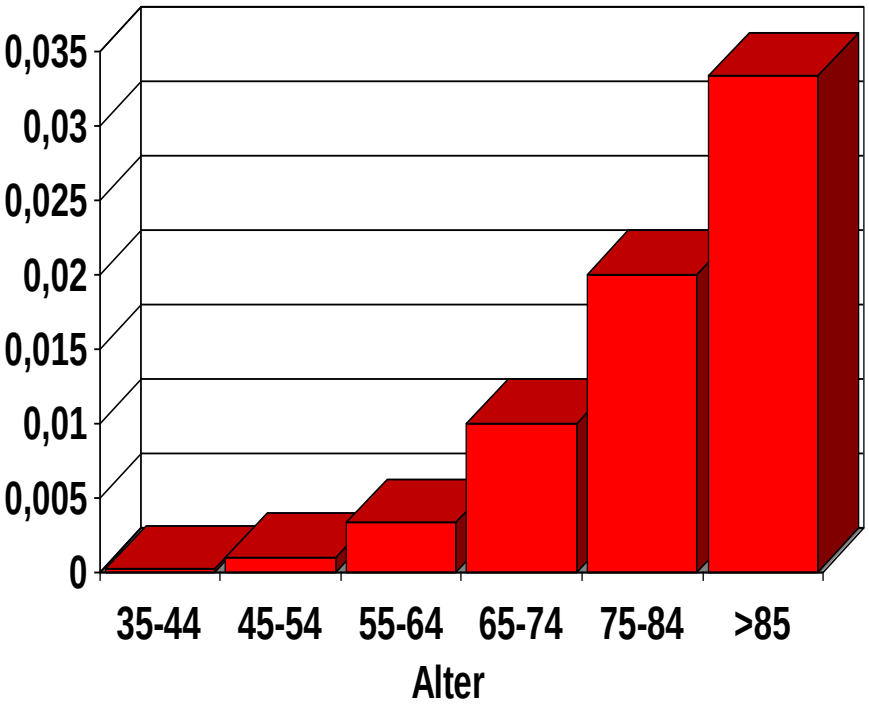
WWW.escardio.org

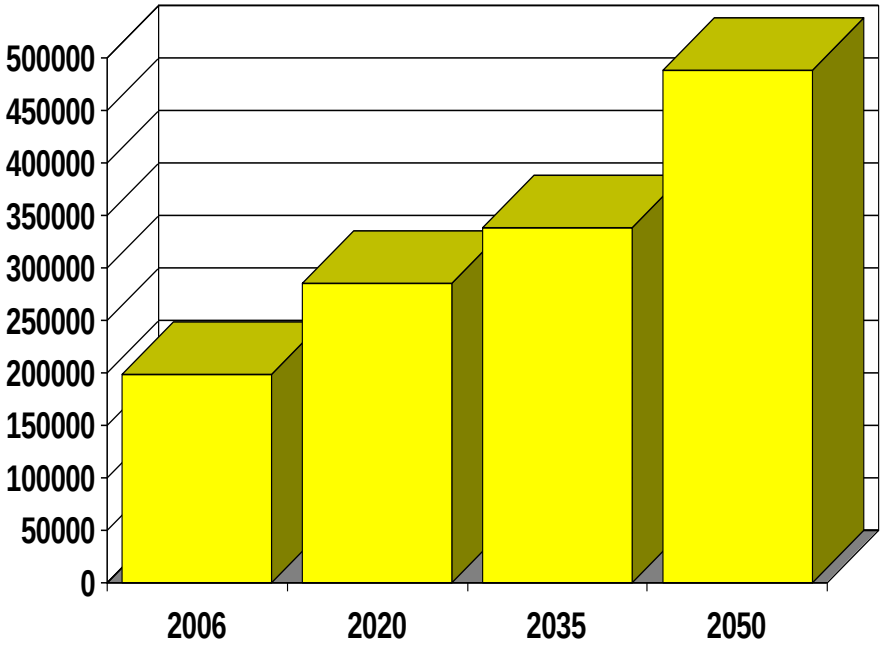
Schlaganfallrisiko und Demographie

Jährliches Schlaganfallrisiko



CS Anderson et al. Med J Aust 1993, 188: 80-84

Einwohner >80J in Rheinland Pfalz

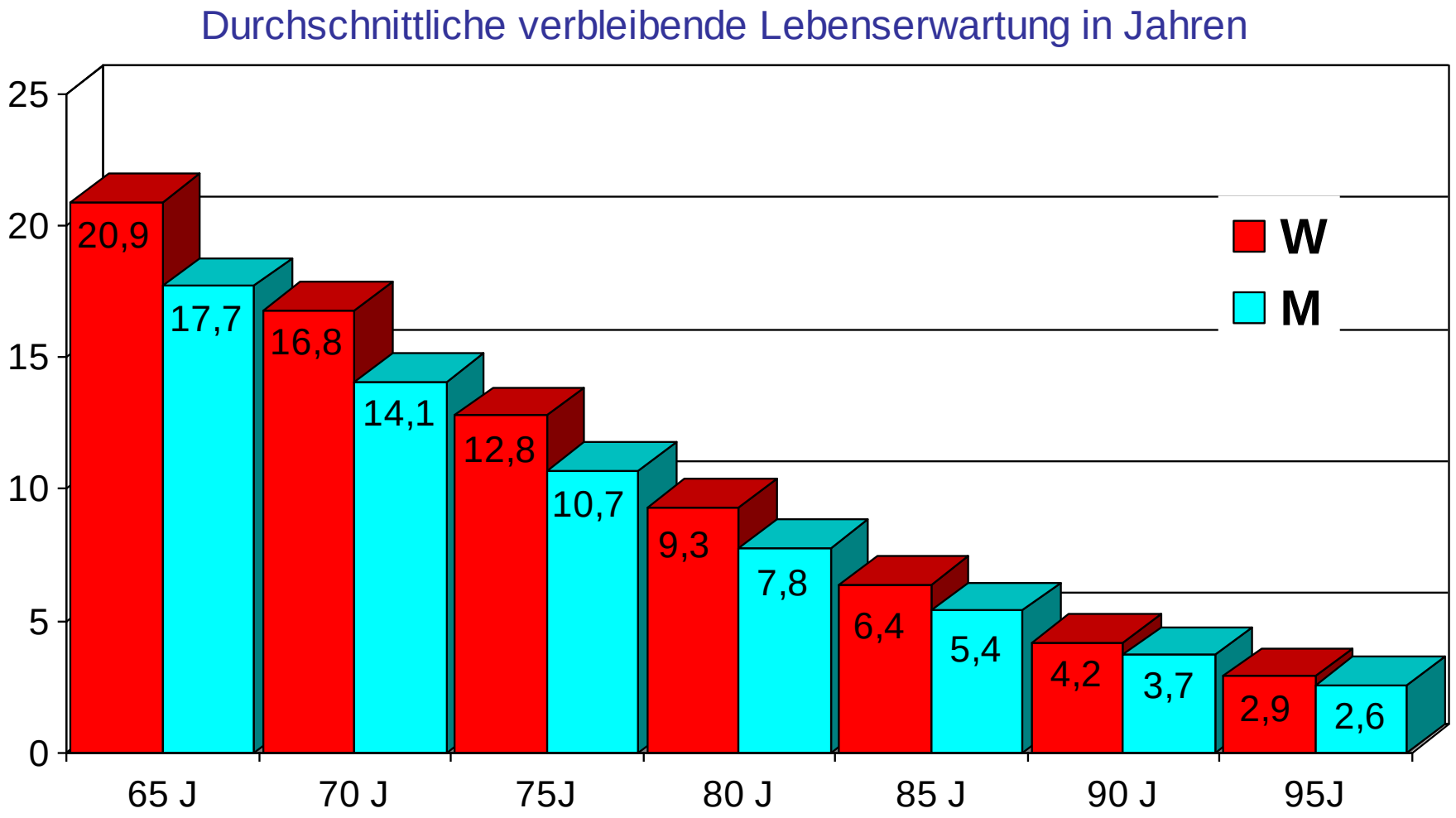


Stat: Landesamt RLP

Pro – Aging:

- Primärprävention: Verhinderung von Neuerkrankungen
- Sekundärprävention: Verhinderung eines wiederkehrenden Ereignisses
- Tertiärprävention: Rehabilitation

Lebenserwartung in Deutschland



Stat. Bundesamt Sterbetafel 2012/2014

Prävention von Herzkreislauferkrankungen

- **Verhalten – Verhaltensänderungen**
  - Nikotinkarenz
  - Bewegung
  - Ernährung – Mediterane Diät „5 a day“
  - Gewichtskontrolle
  - Moderater Alkoholgenuß

Prävention von Herzkreislauferkrankungen

- **Behandlung von Risikofaktoren**
  - **Hypertoniebehandlung**
  - **Antikoagulation bei AF**
  - Diabeteseinstellung (?)
  - Lipidsenker: Statine, Nicotins. Fibrate?
  - Antioxydantien, Vit. E, ASS, Hormonersatz?

Hypertonie: Die großen Drei

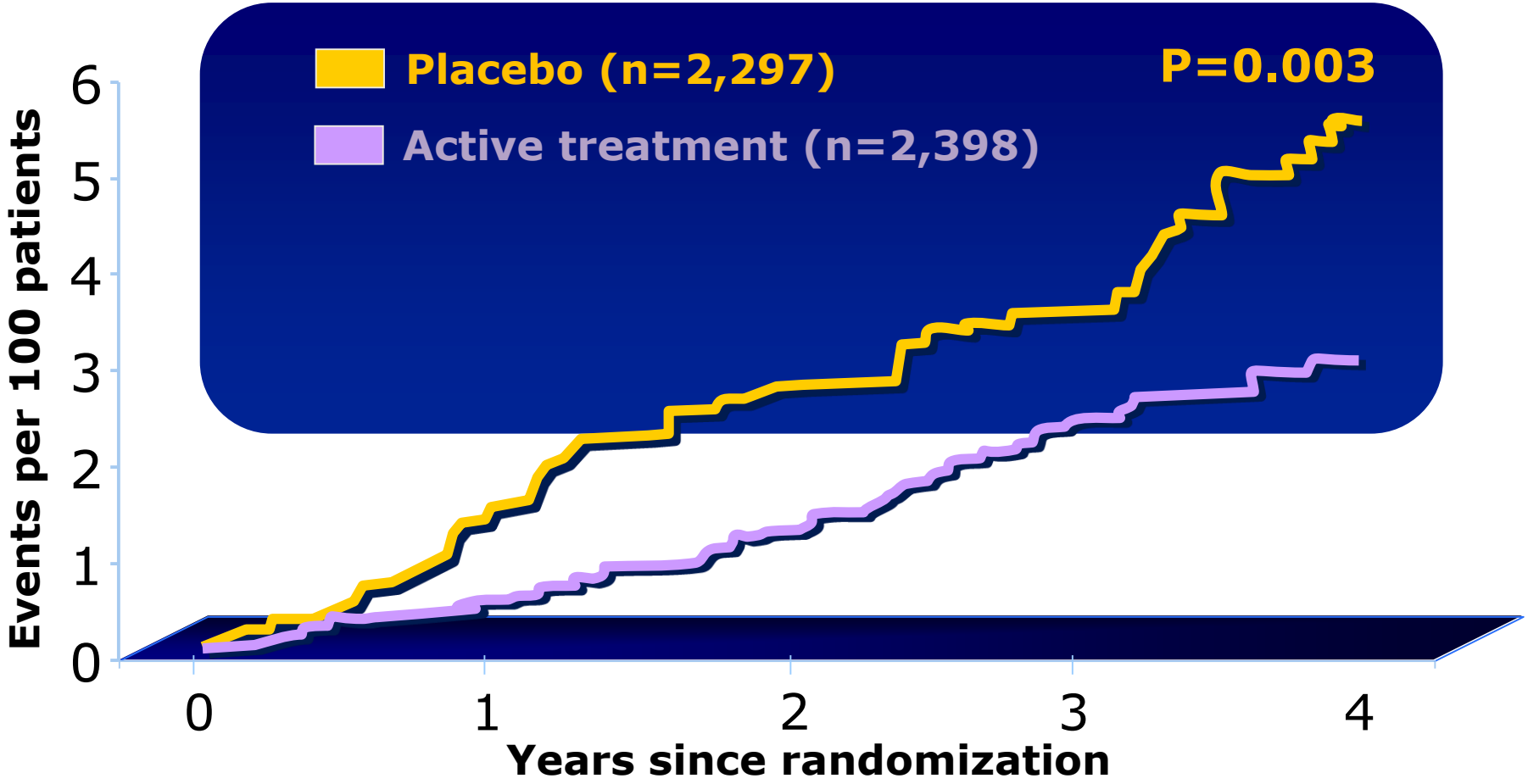
Arterielle Hypertonie - Studien

- **SHEP** Systolic Hypertension in the eldery Program
- **SYST-EUR** Systolic Hypertension Europe
- **STOP-Hypertension** Swedish Trial in Old Patients with Hypertension
- **Stop-Hypertension 2**
- **PROGRESS** Perindopril Protection against Recurrent Stroke Study
- **Treatment of Hypertension in Patients 80 Years of Age or Older** (HYVET – Studie)

Arterielle Hypertonie - Studien

- **SYST-EUR** Systolic Hypertension Europe
  - 4695 Pat. >60J. Follow up 6 J.
  - RR syst. 160-219mmHg, diast. <95mmHg
  - Nitrendipin 10-40mg/d (Enalapril 5-20mg, Hydrochlorothiazid 12,5-25 mg)
  - Rel. Risikoreduktion (Apoplex): **42%,**
  - (Kardiovaskuläre Ereignisse): **31%**

Syst-Eur: Primary Endpoint Fatal and Nonfatal Stroke



Syst-Eur=Systolic Hypertension in Europe Trial

Staessen JA, et al. Lancet. 1997;350:757-764

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Original Article

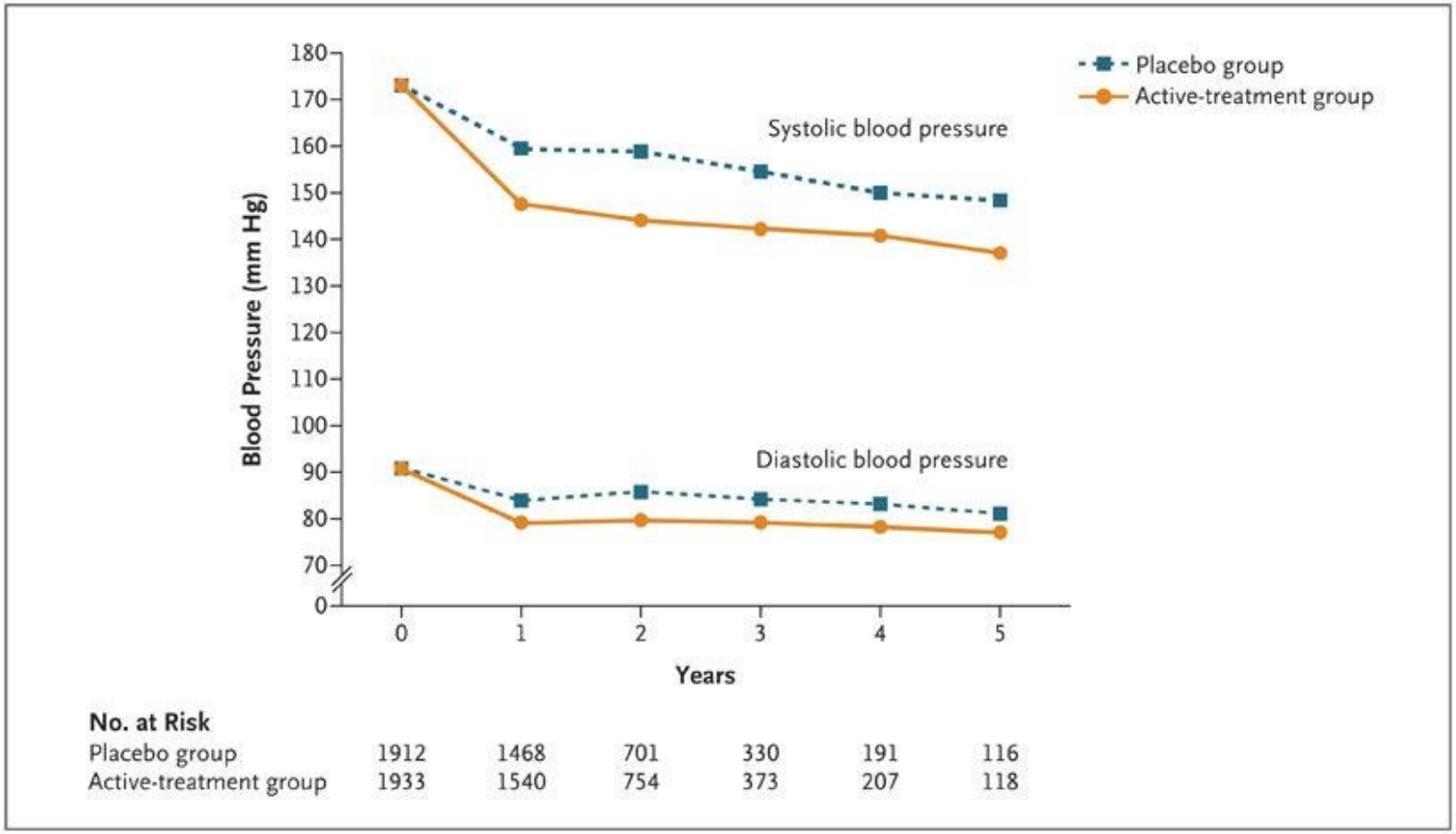
Treatment of Hypertension in Patients 80 Years of Age or Older

Nigel S. Beckett, M.B., Ch.B., Ruth Peters, Ph.D., Astrid E. Fletcher, Ph.D., Jan A. Staessen, M.D., Ph.D., Lisheng Liu, M.D., Dan Dumitrascu, M.D., Vassil Stoyanovsky, M.D., Riitta L. Antikainen, M.D., Ph.D., Yuri Nikitin, M.D., Craig Anderson, M.D., Ph.D., Alli Belhani, M.D., Françoise Forette, M.D., Chakravarthi Rajkumar, M.D., Ph.D., Lutgarde Thijs, M.Sc., Winston Banya, M.Sc., Christopher J. Bulpitt, M.D., for the **HYVET** Study Group

N Engl J Med
Volume 358(18):1887-1898
May 1, 2008

The NEW ENGLAND JOURNAL of MEDICINE

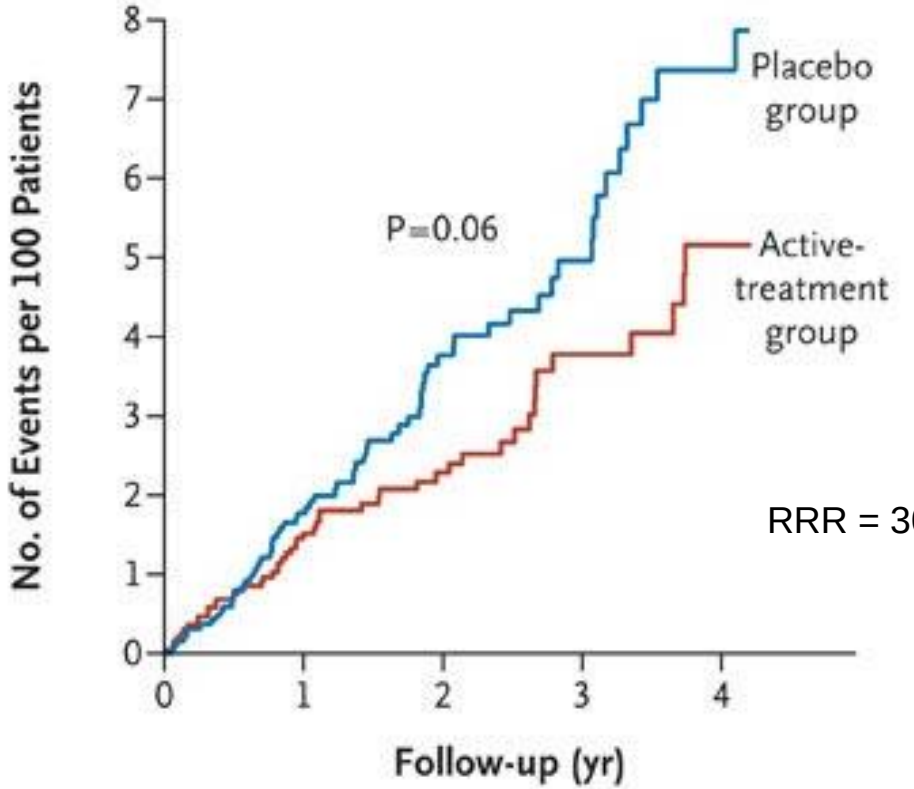
Mean Blood Pressure, Measured while Patients Were Seated, in the Intention-to-Treat Population, According to Study Group



Beckett NS et al. N Engl J Med 2008;358:1887-1898

Kaplan-Meier Estimates of the Rate of End Points, According to Study Group

A Fatal or Nonfatal Stroke



RRR = 30%

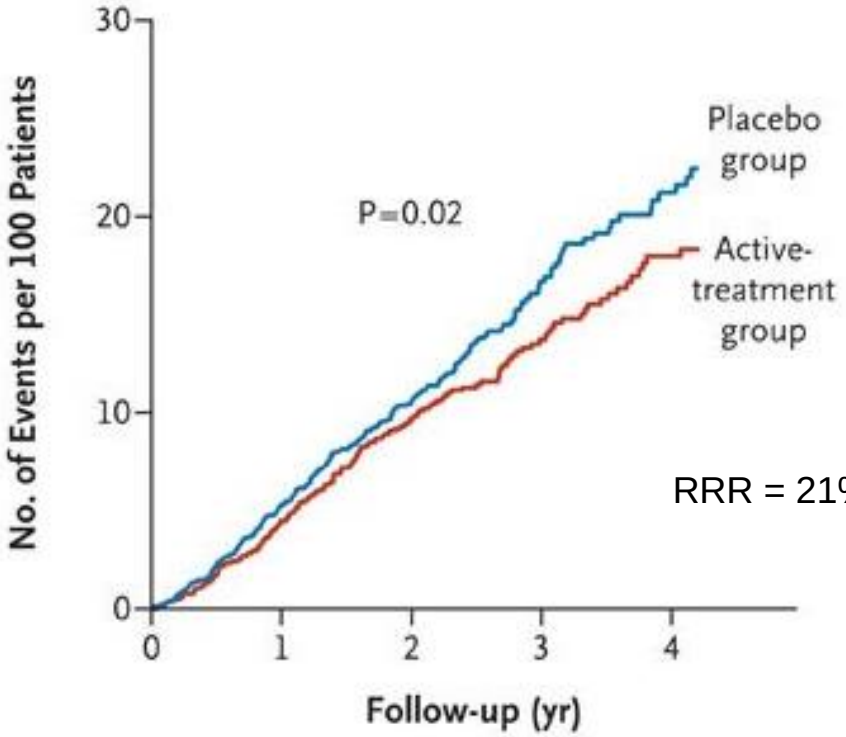
No. at Risk

Placebo group	1912	1484	807	374	194
Active-treatment group	1933	1557	873	417	229

Beckett NS et al. N Engl J Med 2008;358:1887-1898

The NEW ENGLAND JOURNAL of MEDICINE

Kaplan-Meier Estimates of the Rate of End Points, According to Study Group



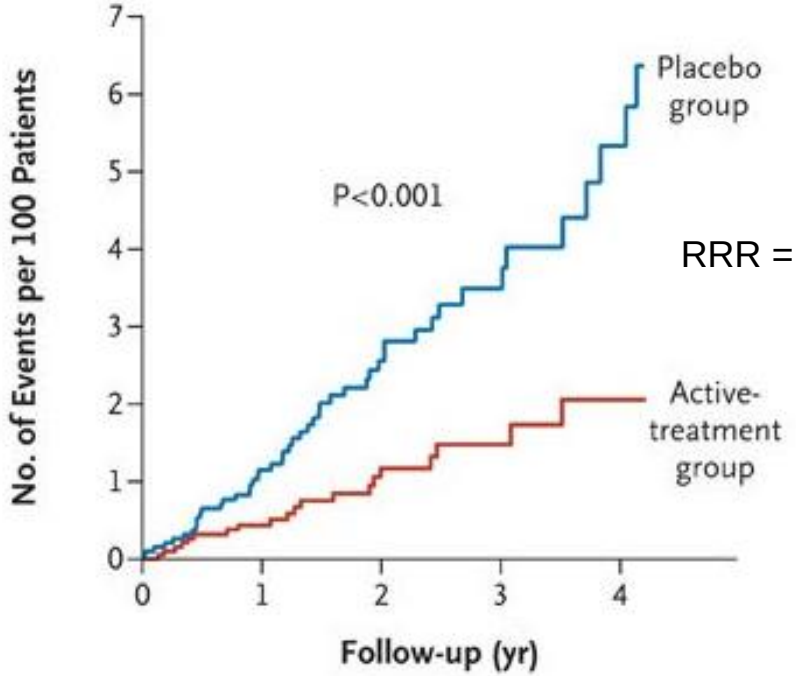
RRR = 21%

No. at Risk					
Placebo group	1912	1492	814	379	202
Active-treatment group	1933	1565	877	420	231

Beckett NS et al. N Engl J Med 2008;358:1887-1898

Kaplan-Meier Estimates of the Rate of End Points, According to Study Group

E Heart Failure



RRR = 64%

No. at Risk					
Placebo group	1912	1480	794	367	188
Active-treatment group	1933	1559	872	416	228

Beckett NS et al. N Engl J Med 2008;358:1887-1898

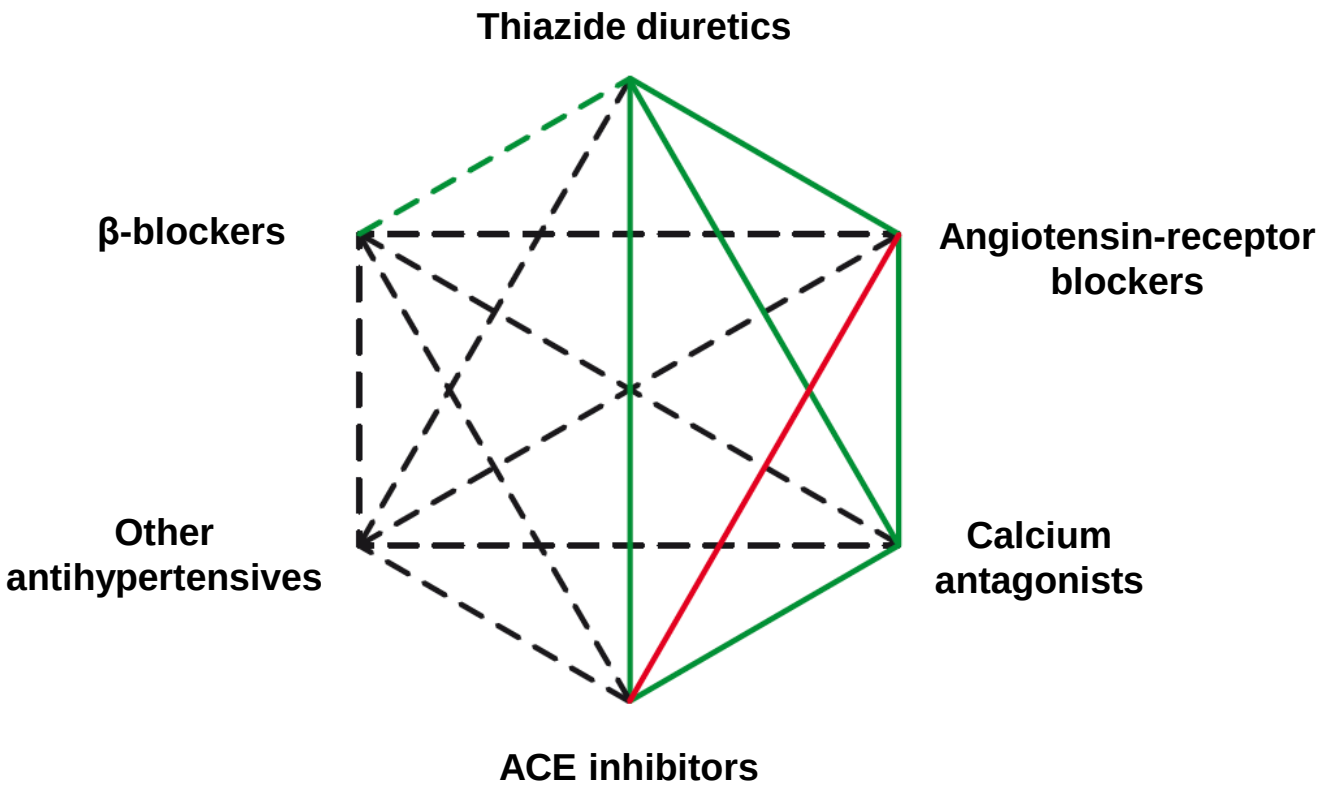
The NEW ENGLAND JOURNAL of MEDICINE

Blood pressure goals in hypertensive patients

Recommendations	
SBP goal for "most" •Patients at low–moderate CV risk •Patients with diabetes •Consider with previous stroke or TIA •Consider with CHD •Consider with diabetic or non-diabetic CKD	**<140 mmHg**
SBP goal for elderly •Ages <80 years •Initial SBP ≥160 mmHg	**140-150 mmHg**
SBP goal for fit elderly Aged <80 years	**<140 mmHg**
SBP goal for elderly >80 years with SBP •≥160 mmHg	**140-150 mmHg**
DBP goal for "most"	**<90 mmHg**
DB goal for patients with diabetes	**<85 mmHg**

SBP, systolic blood pressure; CV, cardiovascular; TIA, transient ischaemic attack; CHD, coronary heart disease; CKD, chronic kidney disease; DBP, diastolic blood pressure.

Possible combinations of classes of antihypertensive drugs



Green continuous lines: preferred combinations; **green dashed line**: useful combination (with some limitations); **black dashed lines**: possible but less well tested combinations; **red continuous line**: not recommended combination. Although verapamil and diltiazem are sometimes used with a beta-blocker to improve ventricular rate control in permanent atrial fibrillation, only dihydropyridine calcium antagonists should normally be combined with beta-blockers.

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Original Article

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The **SPRINT** Research Group

N Engl J Med
Volume 373(22):2103-2116
November 26, 2015

The NEW ENGLAND JOURNAL of MEDICINE

Relative Risiko Reduktion und NNT (Number needed to treat)

„Lohnt sich das eigentlich noch:

Prävention bei 80-jährigen???“

Ein einfaches Rechenexempel….

Hypertonie und Schlaganfallrisiko

35 - 44jährige	1 : 5.000
45 - 54jährige	1 : 1.000
55 - 64jährige	1 : 300
65 - 74jährige	1 : 100
75 - 84jährige	1 : 50
über 85jährige	1 : 30

CS Anderson et al. Med J Aust 1993, 188: 80-84

Relative Risiko Reduktion und NNT

Bei einer Rel. Risiko-Red. von 50% beträgt bei den 40-jährigen die NNT demnach : 1/5000 x ½ :

10000 Patienten müssen ein Jahr lang antihypertensiv behandelt werden, um ein Schlaganfallereignis zu verhindern.

Bei den 80-jährigen und einem Schlaganfallrisiko von 1/50 beträgt die NNT nur noch 1/50 x ½ = 100:

Nur noch **100** Patienten müssen für den gleichen Effekt behandelt werden.

Herzinsuffizienz im Alter

Original Article

Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction

Theophilus E. Owan, M.D., David O. Hodge, M.S., Regina M. Herges, B.S., Steven J. Jacobsen, M.D., Ph.D., Veronique L. Roger, M.D., M.P.H., and Margaret M. Redfield, M.D.

N Engl J Med
Volume 355(3):251-259
July 20, 2006

Characteristics of Patients with Heart Failure and Preserved or Reduced Ejection Fraction

Table 1. Characteristics of Patients with Heart Failure and Preserved or Reduced Ejection Fraction.*

Characteristic	Reduced Ejection Fraction (N=2429)	Preserved Ejection Fraction (N=2167)	P Value	Adjusted P Value†
Age (yr)	71.7±12.1	74.4±14.4	<0.001	NA
Male sex (% of patients)	65.4	44.3	<0.001	<0.001
Body-mass index‡	28.6±7.0	29.7±7.8	0.002	0.17
Obesity (% of patients)‡§	35.5	41.4	0.007	0.002
Serum creatinine on admission (mg/dl)	1.6±1.0	1.6±1.1	0.31	0.30
Hemoglobin on admission (g/dl)	12.5±2.0	11.8±2.1	<0.001	<0.001
Hypertension (% of patients)	48.0	62.7	<0.001	<0.001
Coronary artery disease (% of patients)	63.7	52.9	<0.001	<0.001
Atrial fibrillation (% of patients)	28.5	41.3	<0.001	<0.001
Diabetes (% of patients)	34.3	33.1	0.42	0.61
Substantial valve disease (% of patients)	6.5	2.6	<0.001	0.05
Ejection fraction (%)	29±10	61±7	<0.001	NA

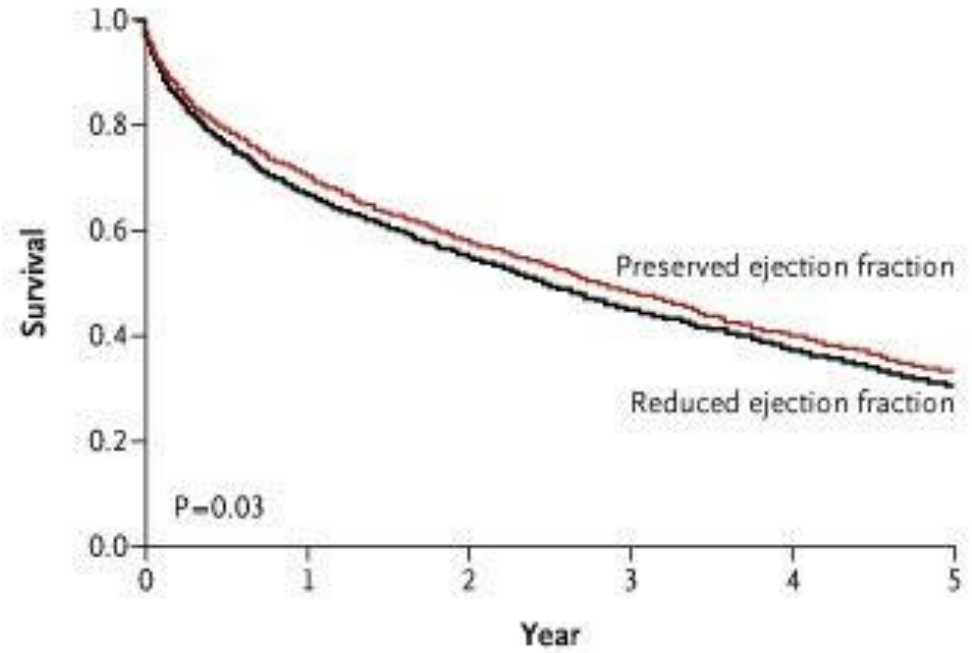
* Continuous variables are expressed as means ±SD. To convert values for creatinine to micromoles per liter, multiply by 88.4.

† The P values are adjusted for age. NA denotes not applicable.

‡ Data on height and weight were not consistently accessible by electronic means over the course of the study; during the three consecutive five-year periods of the study, the data were available for 9 percent, 31 percent, and 83 percent of the study population, respectively. The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Obesity was defined by a body-mass index of 30 or more.

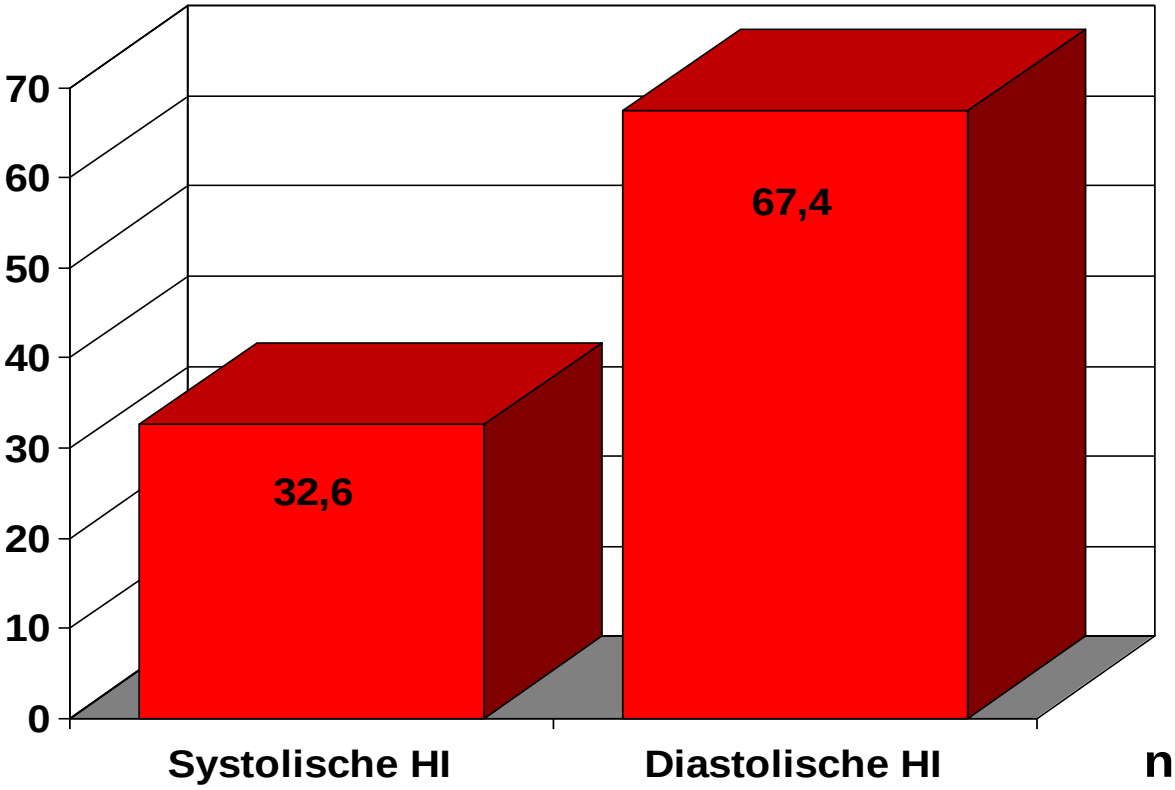
Kaplan-Meier Survival Curves for Patients with Heart Failure and Preserved or Reduced Ejection Fraction



No. at Risk

Reduced ejection fraction	2424	1637	1350	1049	813	604
Preserved ejection fraction	2166	1539	1270	1001	758	574

Herzinsuffizienz in der Geriatrie



n=376

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Diastolische Herzinsuffizienz: I-PRESERVE Studie

Original Article

Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction

Barry M. Massie, M.D., Peter E. Carson, M.D., John J. McMurray, M.D., Michel Komajda, M.D., Robert McKelvie, M.D., Michael R. Zile, M.D., Susan Anderson, M.S., Mark Donovan, Ph.D., Erik Iverson, M.S., Christoph Staiger, M.D., Agata Ptaszynska, M.D., for the I-PRESERVE Investigators

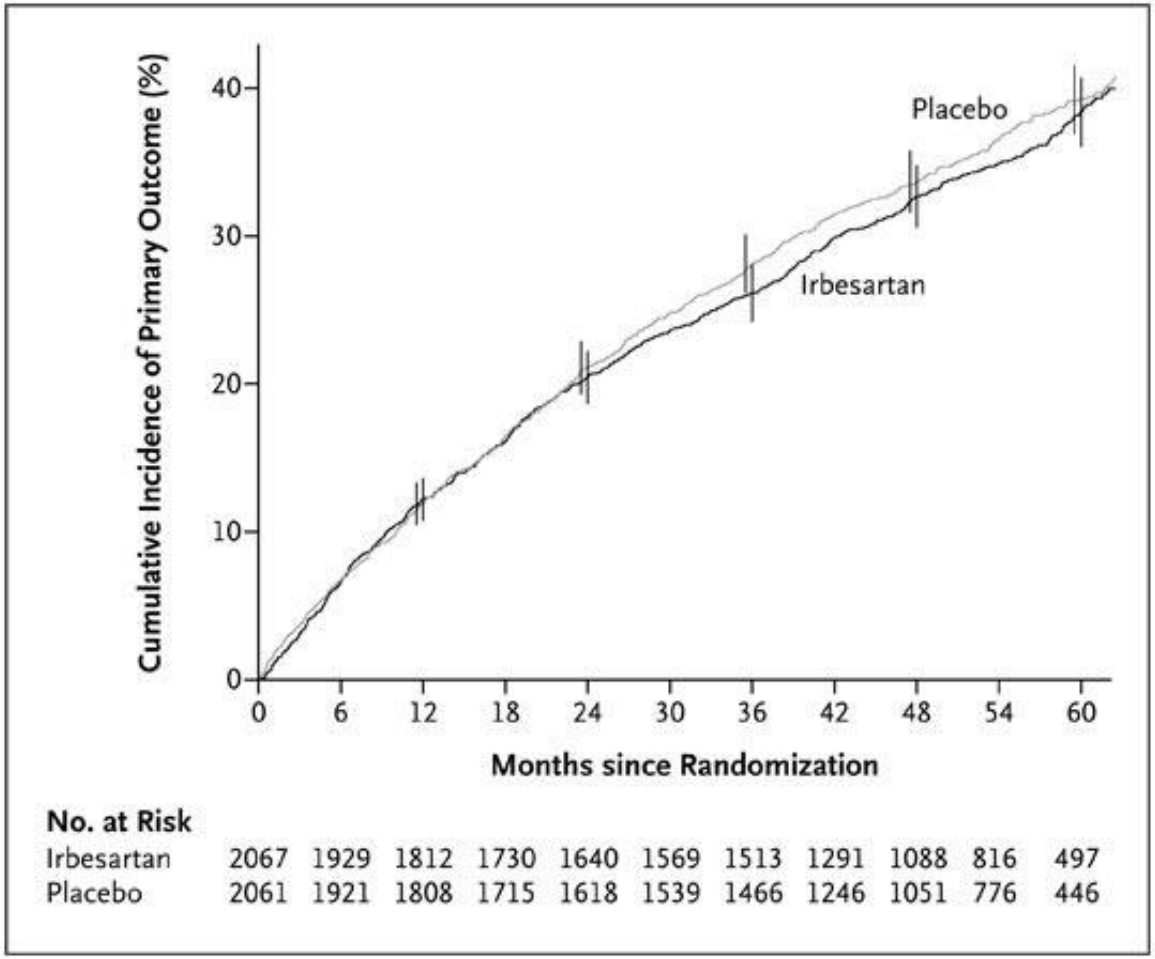
The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 359(23):2456-2467 December 4, 2008

Study Overview

- In a multicenter trial, 4128 patients who had heart failure with a preserved ejection fraction were randomly assigned to receive irbesartan or placebo and were followed for a mean of 49.5 months
- There were no significant differences between the two study groups in the rate of the primary outcome (death or hospitalization for heart failure)

Kaplan-Meier Curves for the Primary Outcome



N Engl J Med 359(23):2456-2467 December 4, 2008

Conclusion

- Irbesartan did not improve the outcomes of patients with heart failure and a preserved left ventricular ejection fraction

Diastolische Herzinsuffizienz: Topcat - Studie

UNIVERSITÄTSmedizin. MAINZ

Original Article

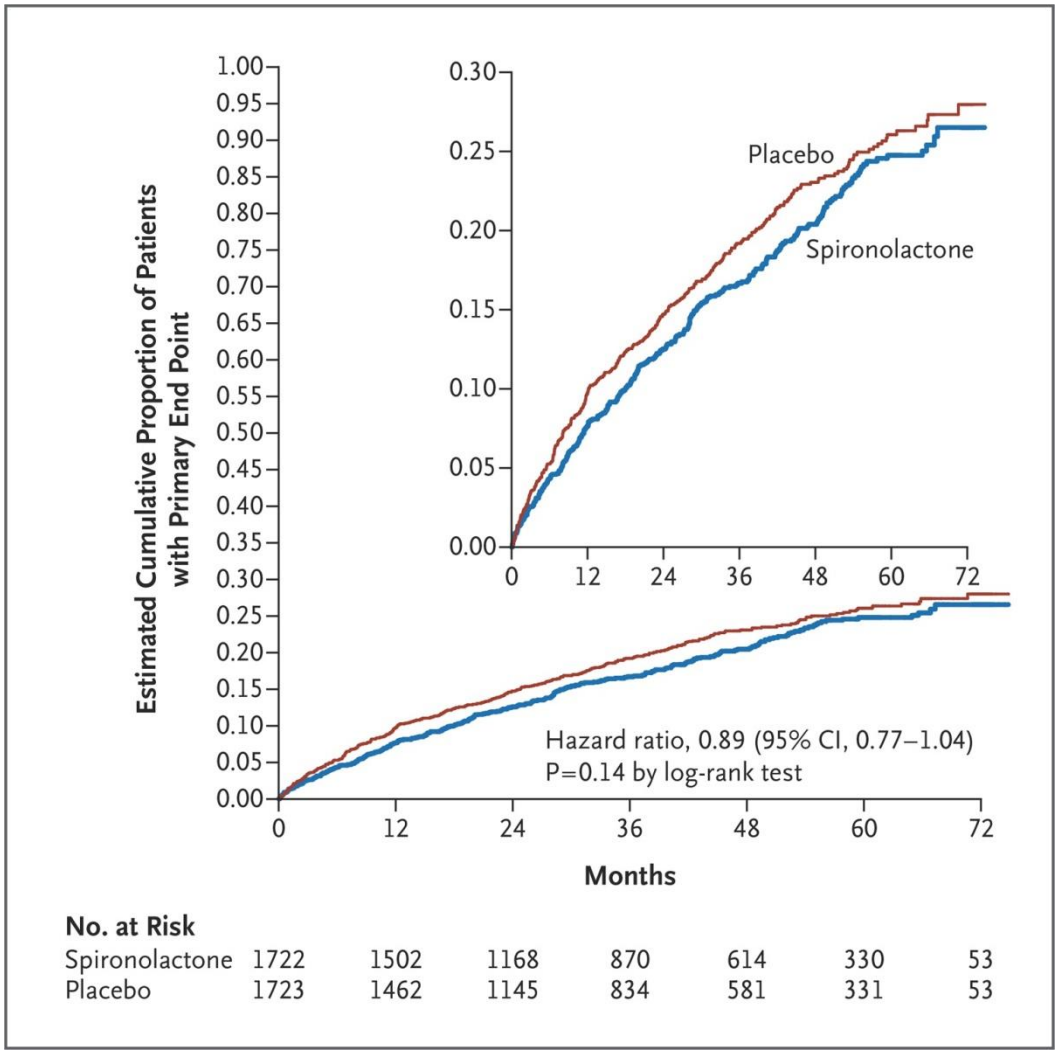
Spironolactone for Heart Failure with Preserved Ejection Fraction

Bertram Pitt, M.D., Marc A. Pfeffer, M.D., Ph.D., Susan F. Assmann, Ph.D., Robin Boineau, M.D., Inder S. Anand, M.D., Brian Claggett, Ph.D., Nadine Clausell, M.D., Ph.D., Akshay S. Desai, M.D., M.P.H., Rafael Diaz, M.D., Jerome L. Fleg, M.D., Ivan Gordeev, M.D., Ph.D., Brian Harty, M.A., John F. Heitner, M.D., Christopher T. Kenwood, M.S., Eldrin F. Lewis, M.D., M.P.H., Eileen O'Meara, M.D., Jeffrey L. Probstfield, M.D., Tamaz Shaburishvili, M.D., Ph.D., Sanjiv J. Shah, M.D., Scott D. Solomon, M.D., Nancy K. Sweitzer, M.D., Ph.D., Song Yang, Ph.D., Sonja M. McKinlay, Ph.D., for the **TOPCAT** Investigators

N Engl J
Volume 370(15):1383-1392
April 10, 2014

The NEW ENGLAND JOURNAL of MEDICINE

Kaplan–Meier Plot of Time to the First Confirmed Primary-Outcome Event.



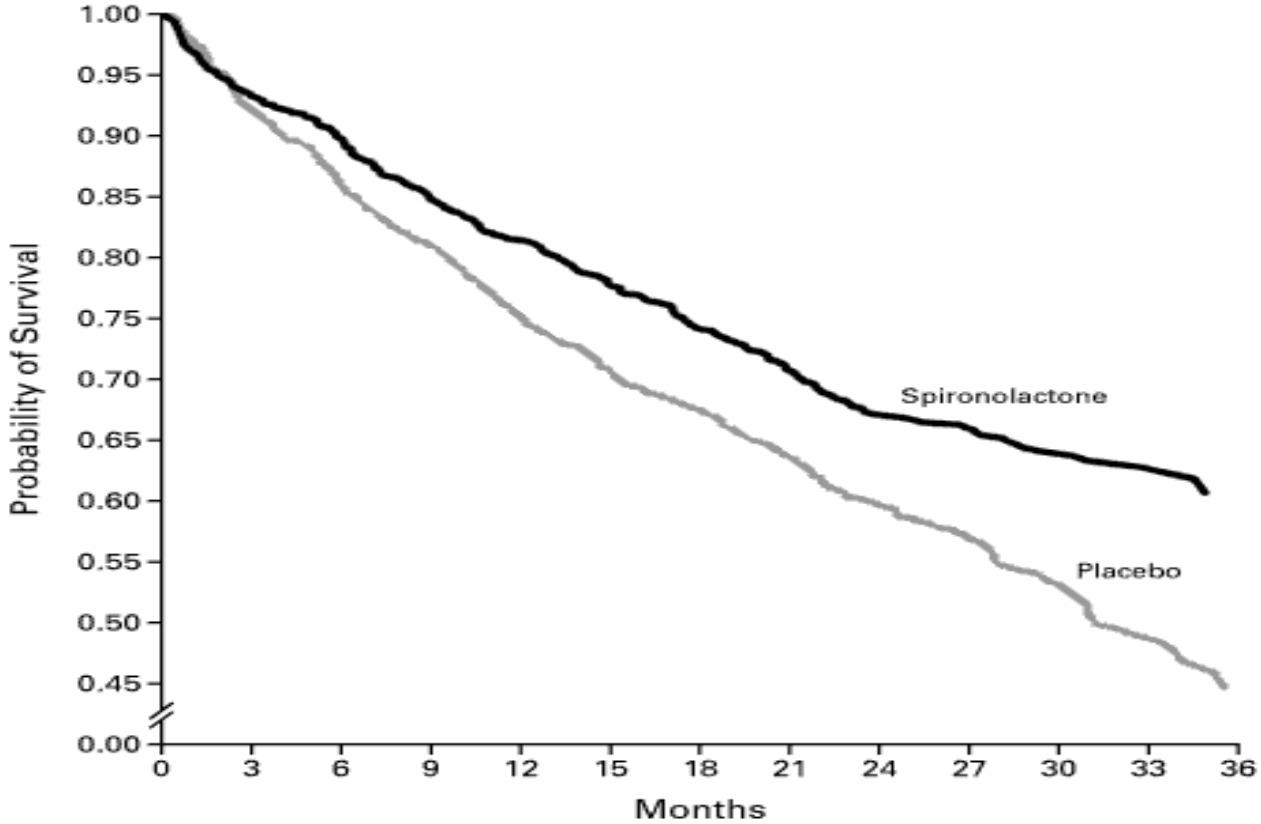
Pitt B et al. N Engl J Med 2014;370:1383-1392

Conclusions

- In patients with heart failure and a preserved ejection fraction, treatment with spironolactone did not significantly reduce the incidence of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure.

RALES und die Folgen

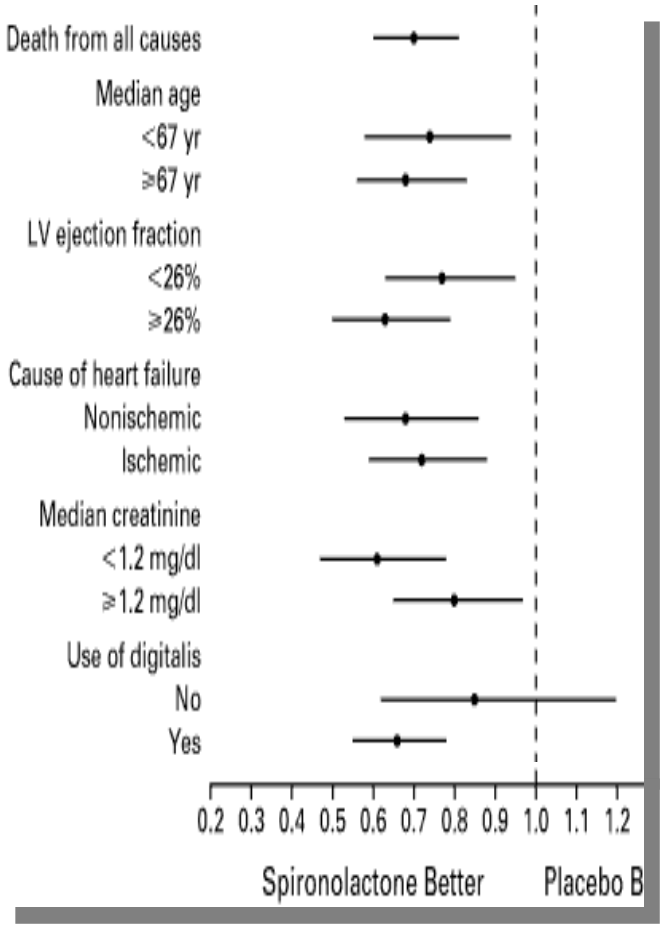
MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE

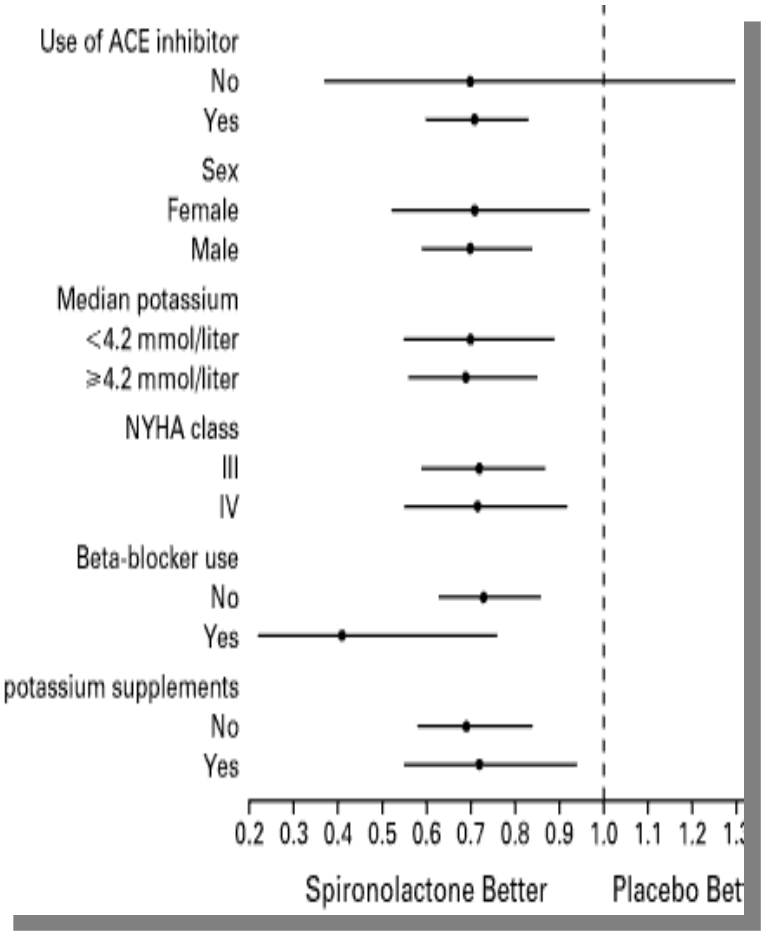


No. at Risk													
Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

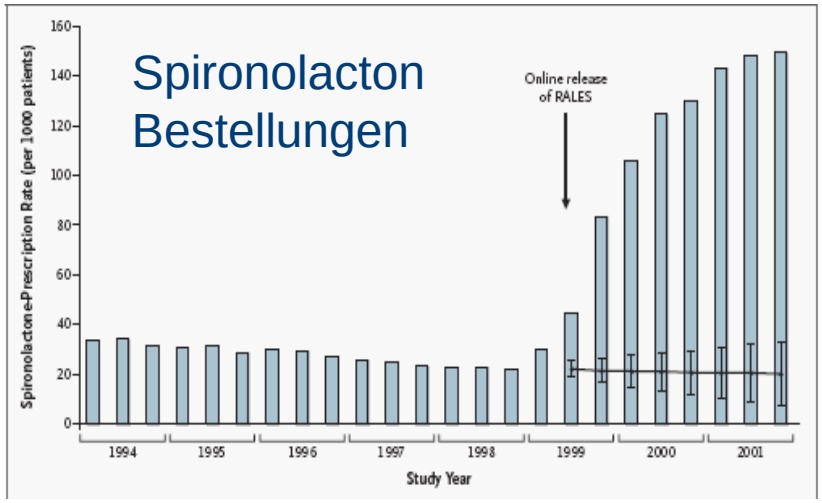
B. PITT et al. (N Engl J Med 1999:341:709-17.)

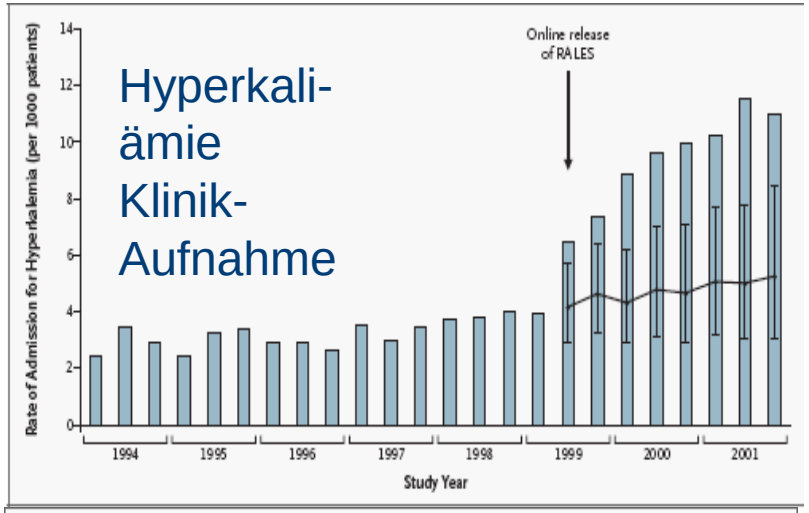
RALES - Subgruppenanalyse

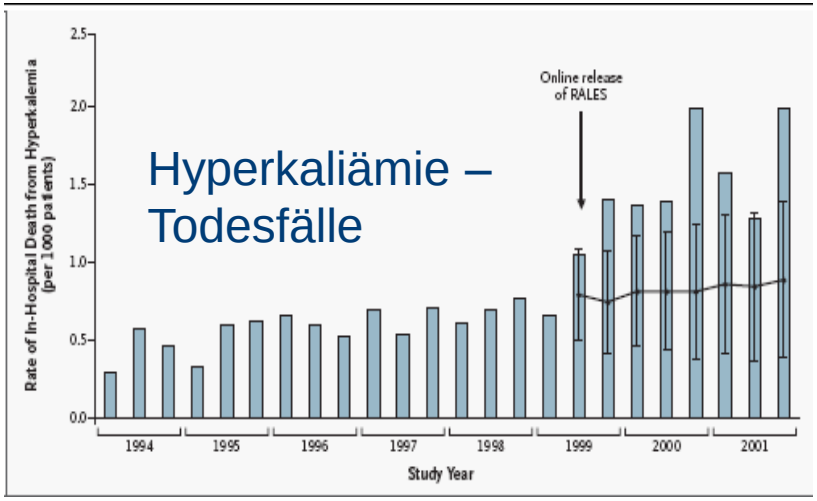


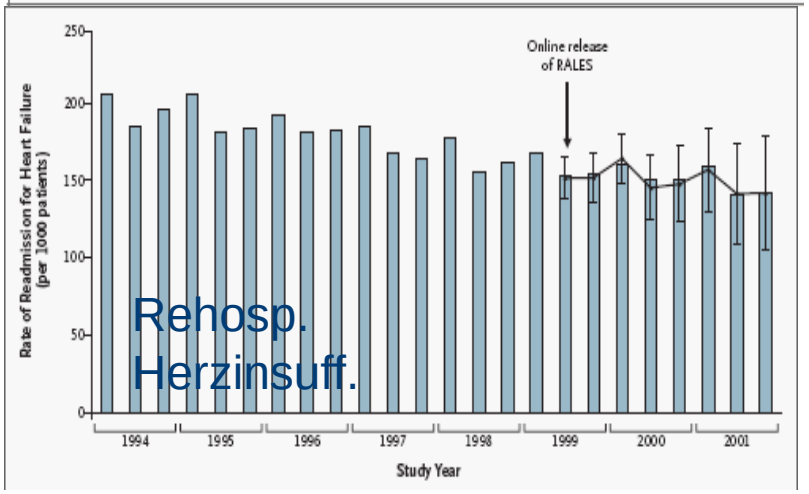


(Ontario Canada) Rates of Hyperkalemia after Publication of the Randomized Aldactone Evaluation Study









David N. Jurlink Engl J Med 2004;351:543-51

RALES und die Folgen

- Studienergebnisse wurden unkritisch auf die Versorgungsebene übertragen
- Während die Studienpopulation vorwiegend aus Männern mit systolischer Herzinsuffizienz bestand, wurden in Kanada vorwiegend Frauen mit (wahrscheinlicher) HFpEF (diastolischer Herzinsuffizienz) behandelt, die im Mittel ca. 10 Jahre älter waren.

Paramount

The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial

Prof Dr Scott D Solomon, MD, Prof Michael Zile, MD, Prof Burkert Pieske, MD, Prof Adriaan Voors, MD, Amil Shah, MD, Elisabeth Kraigher-Krainer, MD, Victor Shi, MD, Toni Bransford, MD, Madoka Takeuchi, MS, Jianjian Gong, PhD, Martin Lefkowitz, MD, Prof Milton Packer, MD, Prof John JV McMurray, MD for the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion **(PARAMOUNT)** Investigators

The Lancet
Volume 380, Issue 9851, Pages 1387-1395 (October 2012)
DOI: 10.1016/S0140-6736(12)61227-6

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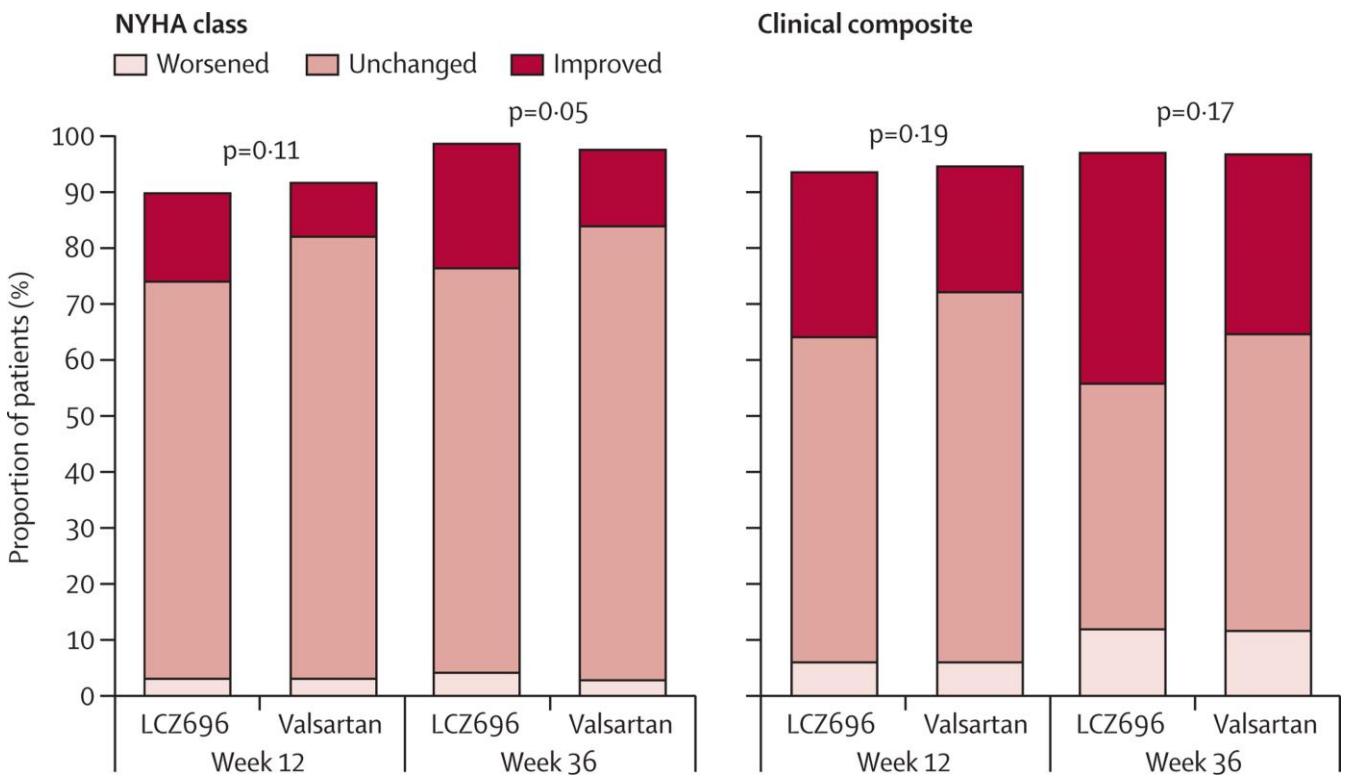
Paramount



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Paragon HF

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"
Search for studies: Search
Advanced Search | Help | Studies by Topic | Glossary

Now Available: Final Rule for FDAAA 801 and NIH Policy on Clinical Trial Reporting

Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Study Record Detail

Text Size

Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction (PARAGON-HF)

This study is currently recruiting participants. (see Contacts and Locations)

Verified June 2016 by Novartis

Sponsor:
Novartis Pharmaceuticals

Information provided by (Responsible Party):
Novartis (Novartis Pharmaceuticals)

ClinicalTrials.gov Identifier:
NCT01920711

First received: August 8, 2013
Last updated: June 12, 2016
Last verified: June 2016
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

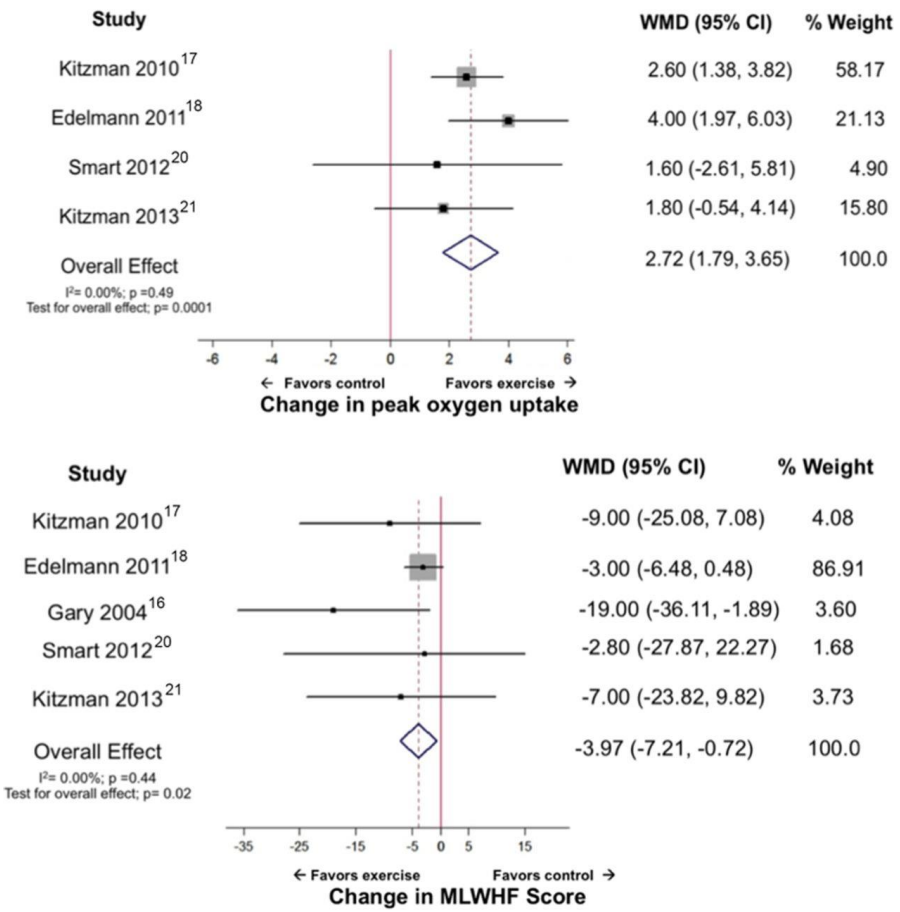
Purpose

The purpose of this study is to evaluate the effect of LCZ696 compared to valsartan in the reduction of cardiovascular death and heart failure(HF) hospitalizations in patients with HF with preserved ejection fraction.

Condition	Intervention	Phase
Heart Failure With Preserved Ejection Fraction	Drug: LCZ696 Drug: Valsartan	Phase 3

Study Type: Interventional

Körperliches Training bei HFpEF



Forest plot showing effect of exercise training on cardiorespiratory fitness, measured as peak oxygen uptake (mL/kg per minute) and quality of life, estimated using Minnesota living with heart failure (MLWHF) score, among participants with heart failure and preserved ejection fraction.

Ambarish Pandey et al. Circ Heart Fail. 2015;8:33-40

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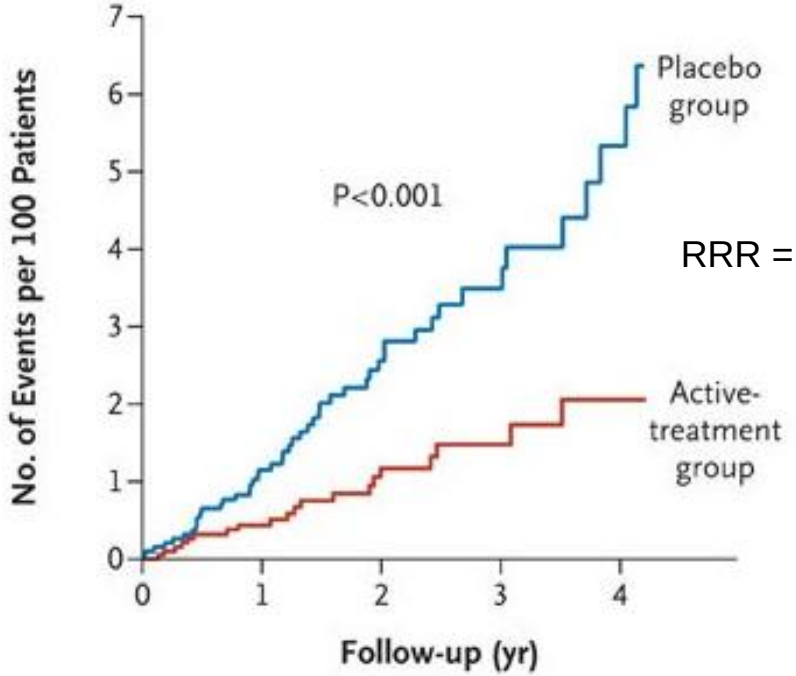
Kaplan-Meier Estimates of the Rate of End Points, According to Study Group

E Heart Failure



RRR = 64%

No. at Risk					
Placebo group	1912	1480	794	367	188
Active-treatment group	1933	1559	872	416	228

Beckett NS et al. N Engl J Med 2008;358:1887-1898

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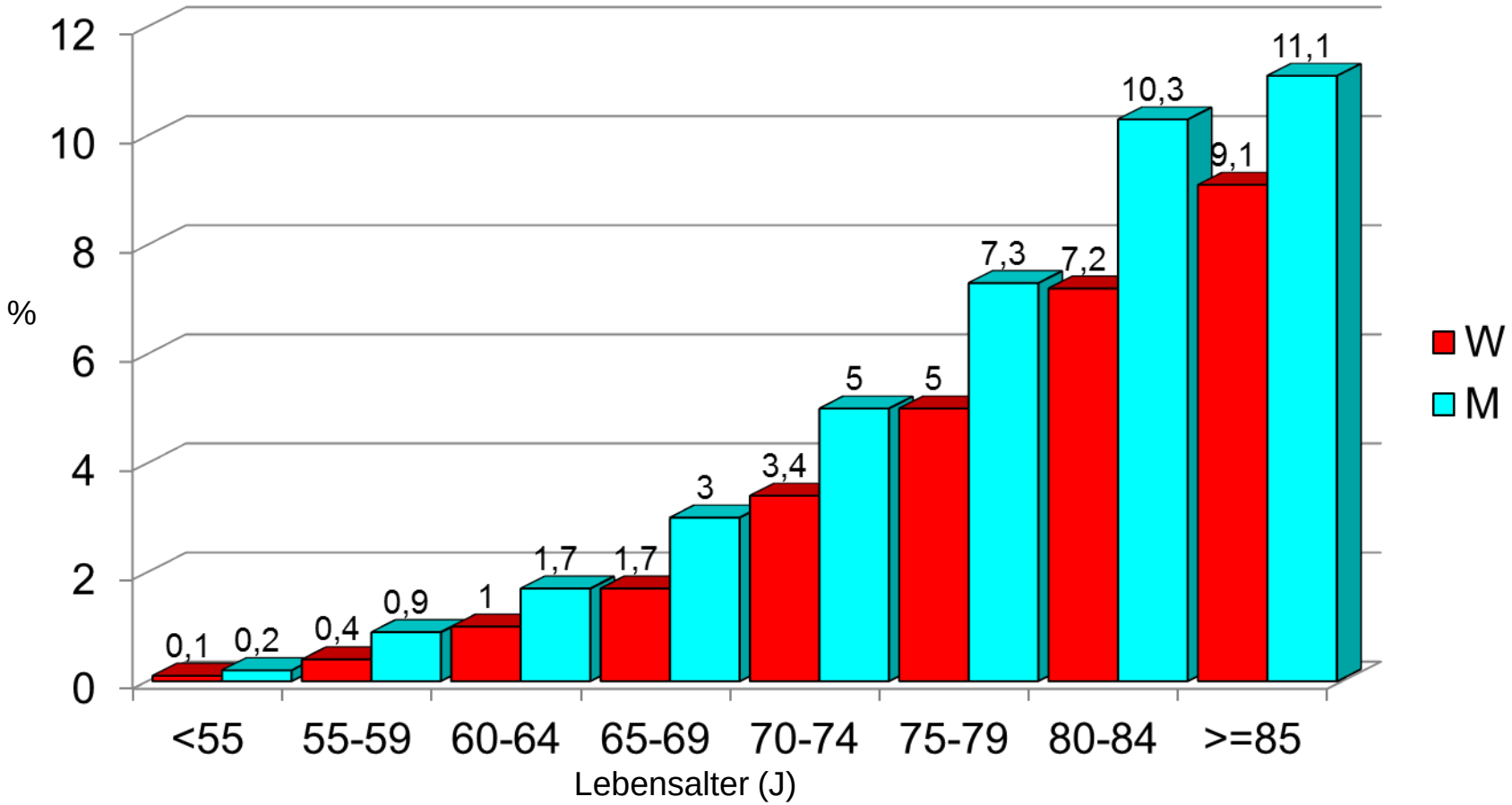
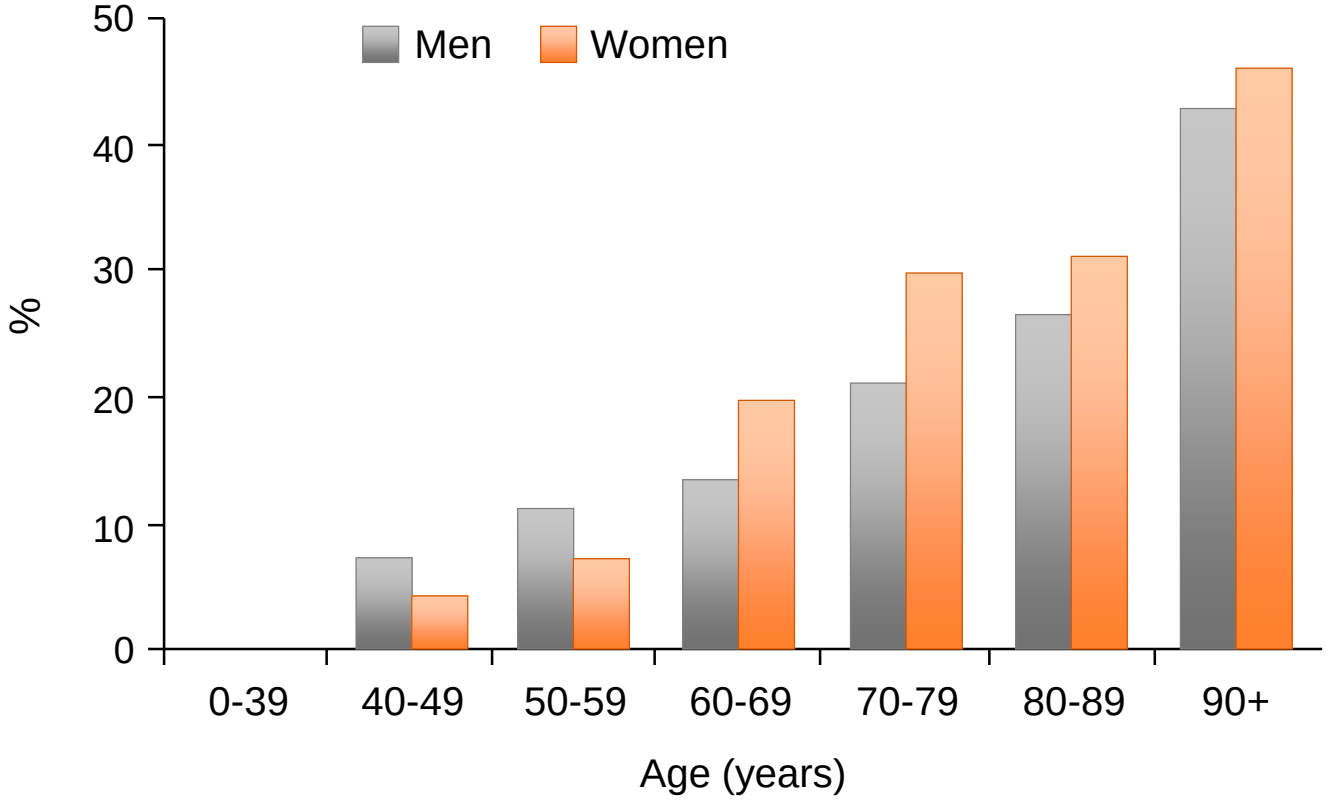
Altersabhängige Prävalenz des Vorhofflimmerns



Go, A.S. et al. JAMA 2001;285:2370-2375

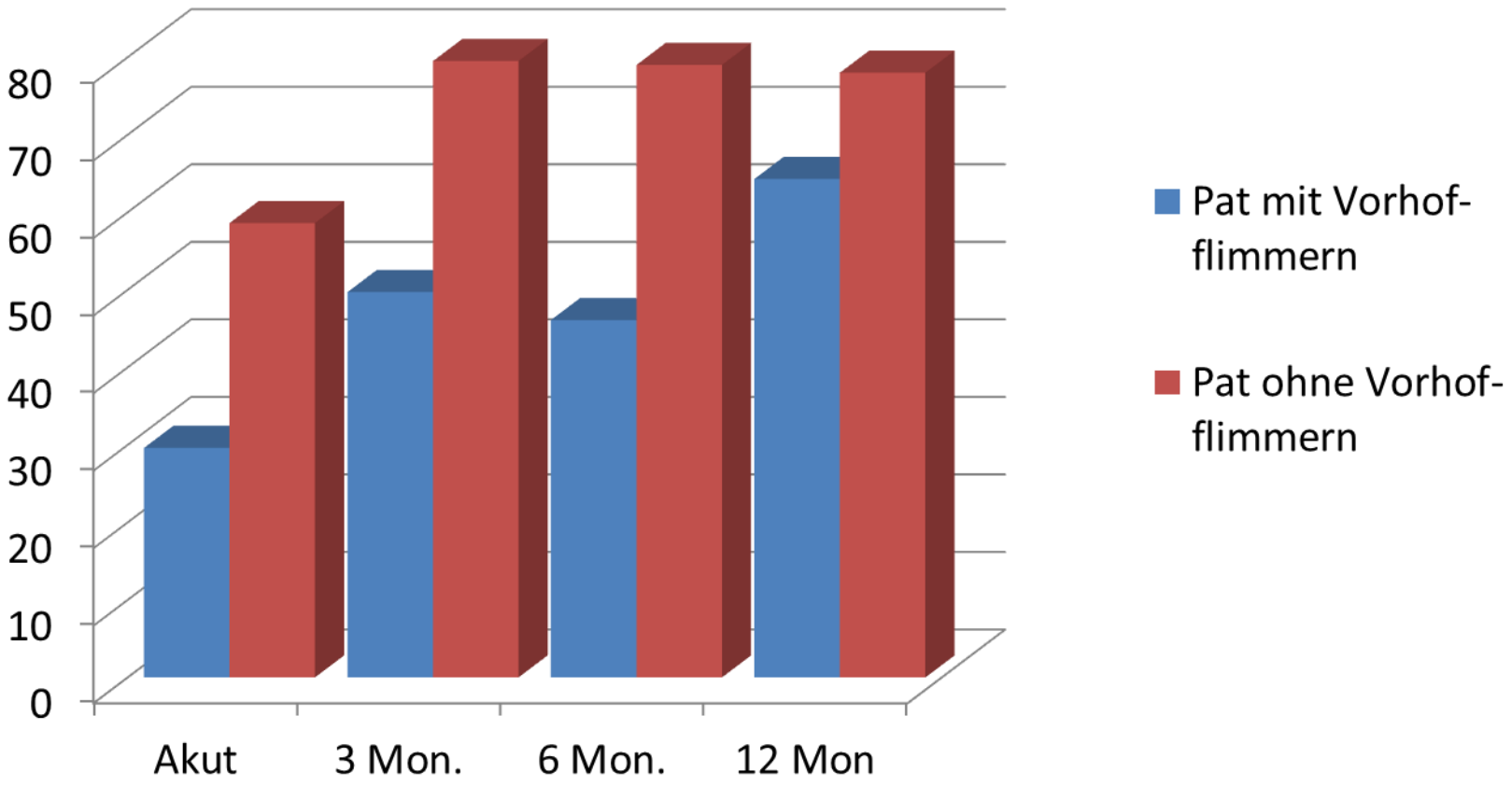
Der Anteil Vofhofflimmern-assoziierter Schlaganfälle steigt mit dem Alter

Größere demografische Veränderungen sind zu erwarten …



Marini C, et al. Stroke 2005;36:1115-9

Barthel-Index bei Patienten mit Schlaganfall



H.J. Lin et al. Stroke 27(1996):1760-4

Schlaganfall bei VHF ist vermeidbar

VKA-Auswirkungen im Vergleich zu Placebo / Kontrolle

Schlaganfall-Reduktion	Tod-Reduktion
67%	26%

Hart RG et al. Ann Intern Med. 2007;146:857-867
Lip GY et al. BJM 2002;325:1022-1025

Orale Antikoagulation bei VHF im höheren Lebensalter

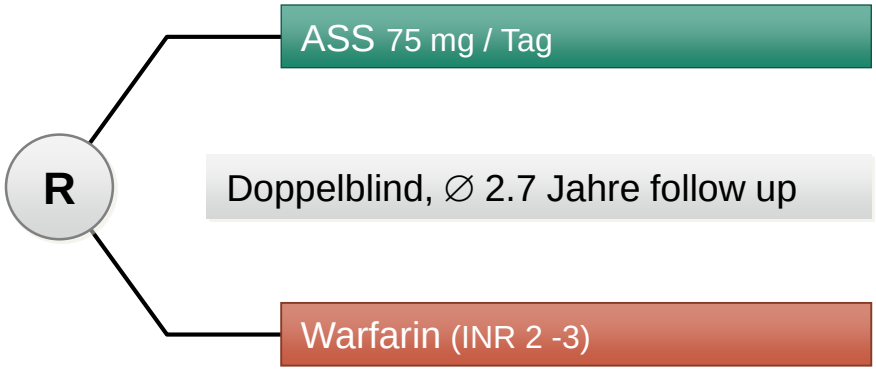
UNIVERSITÄTSmedizin. MAINZ

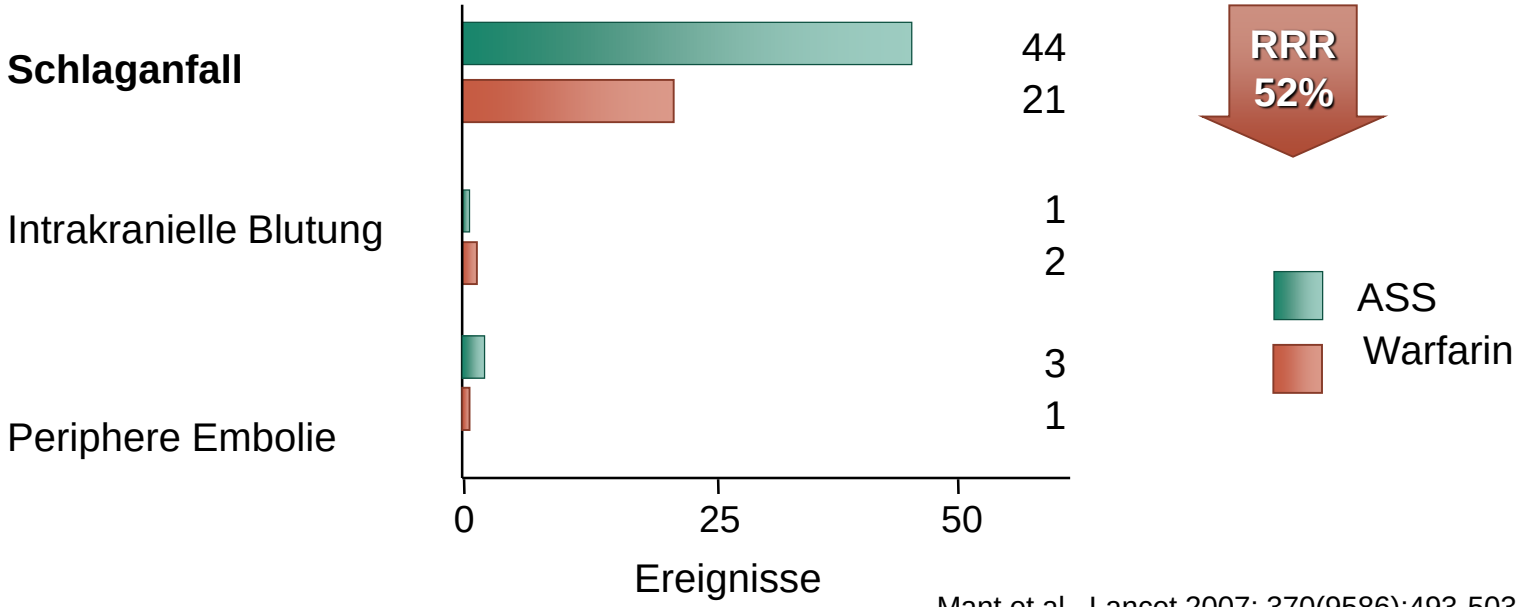
BAFTA

973 Patienten, **> 75 Jahre**

Vorhofflimmern

13 % Sekundärprävention





Mant et al., Lancet 2007; 370(9586):493-503.

Daten aus der geriatrischen Schlaganfalleinheit

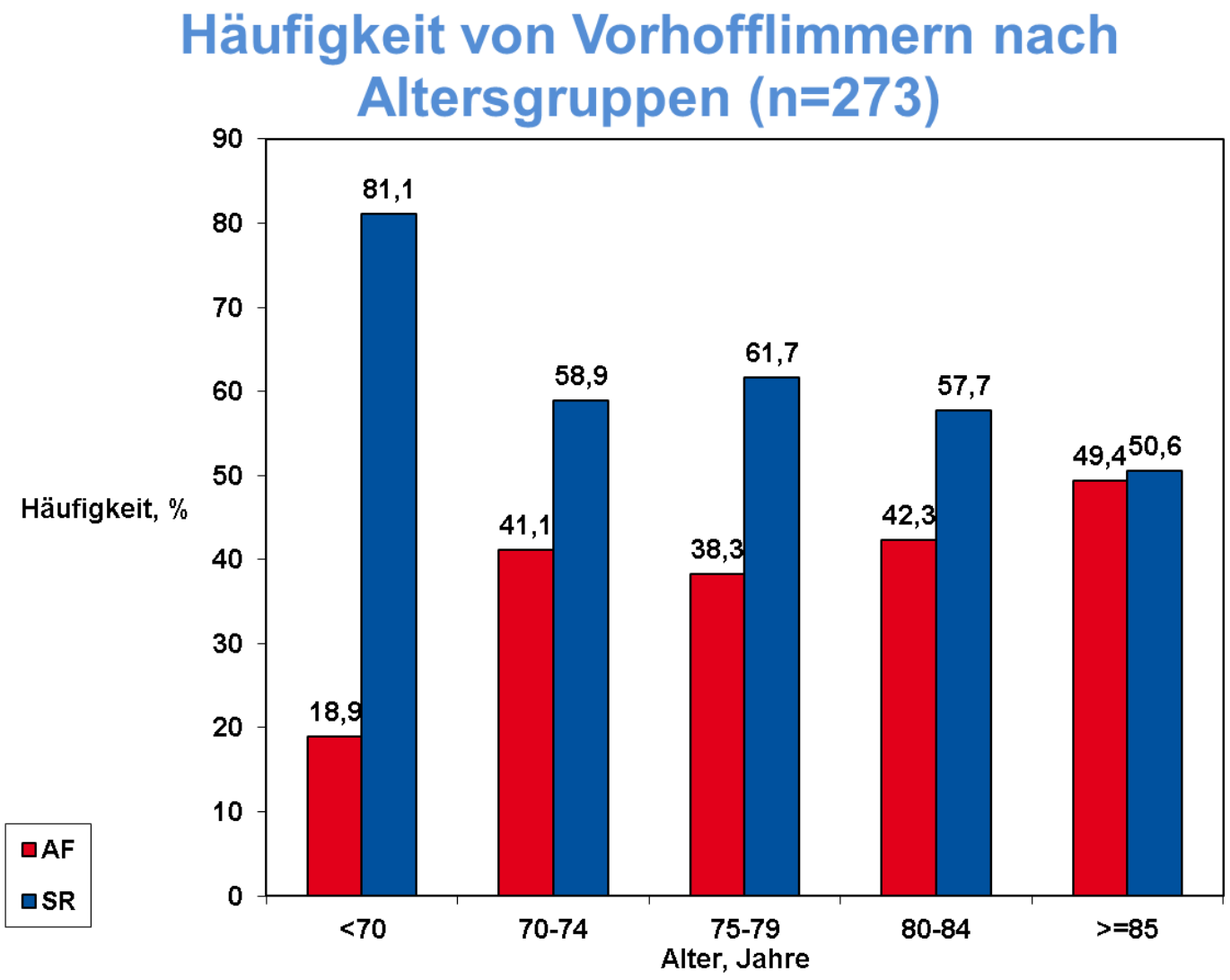
Auswertung von 636 geriatrischen Patienten mit akutem Schlaganfallereignis

Erfassungszeitraum: 01.01.2007 - 31.12.2009

das mittlere Alter der Patienten betrug 82,06 J.

63,1 % der Patienten waren weiblichen Geschlechts

Ergebnisse



A. Lambrecht, 2016

Ergebnisse

Bei 43,1 % der Patienten bestand ein Vorhofflimmern (n = 273)

Bei 63,6 % der Vorhofflimmer-Patienten war die Diagnose bekannt (n = 164), bei 36,4% unbekannt

Ergebnisse

11 von 273 Patienten (≈ 4 %) waren (nach Score) formal ohne Indikation zur oralen Antikoagulation

262 von 273 Patienten (≈ 96 %) waren formal mit Indikation zur oralen Antikoagulation

Von den 164 Patienten mit bekanntem AF bei Aufnahme hatten fast alle (160 Pat.) eine Indikation zur oralen Antikoagulation

A. Lambrecht, 2016

Ergebnisse

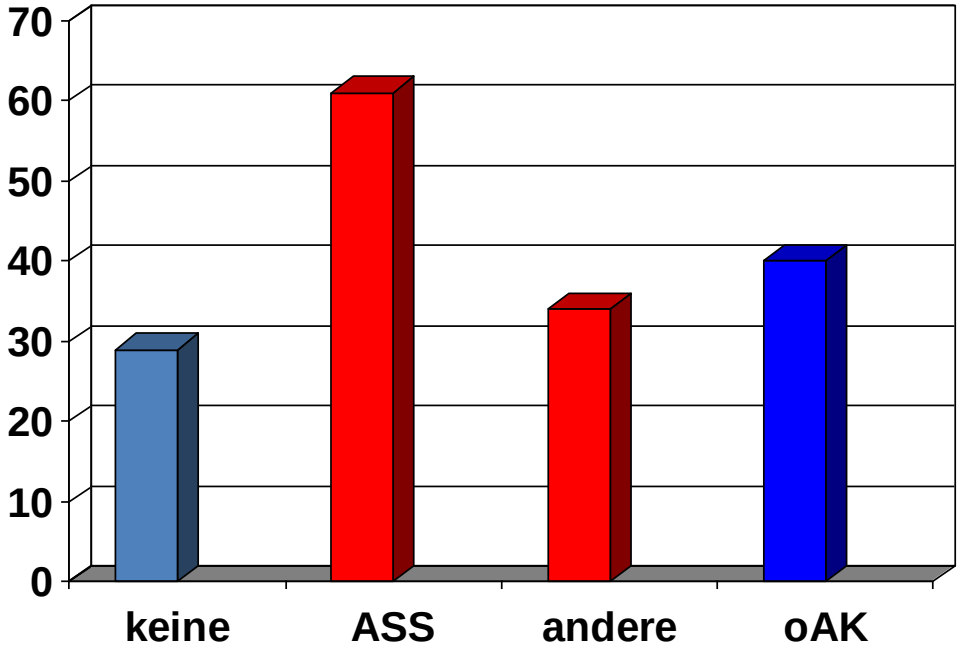
Von 164 Pt. mit **vorbekanntem VHF** erhielten

29 keine Therapie (17,7%)

61 ASS (37,2%)

40 OAK. (24,4%)

34 Pt. in and. Subgruppen



Bei 160 – 40 = 120 Pt.
-> Indikation zur oAK,
2/3 präventive Wirkung angenommen:
⇒80 Schlaganfälle waren verhinderbar!

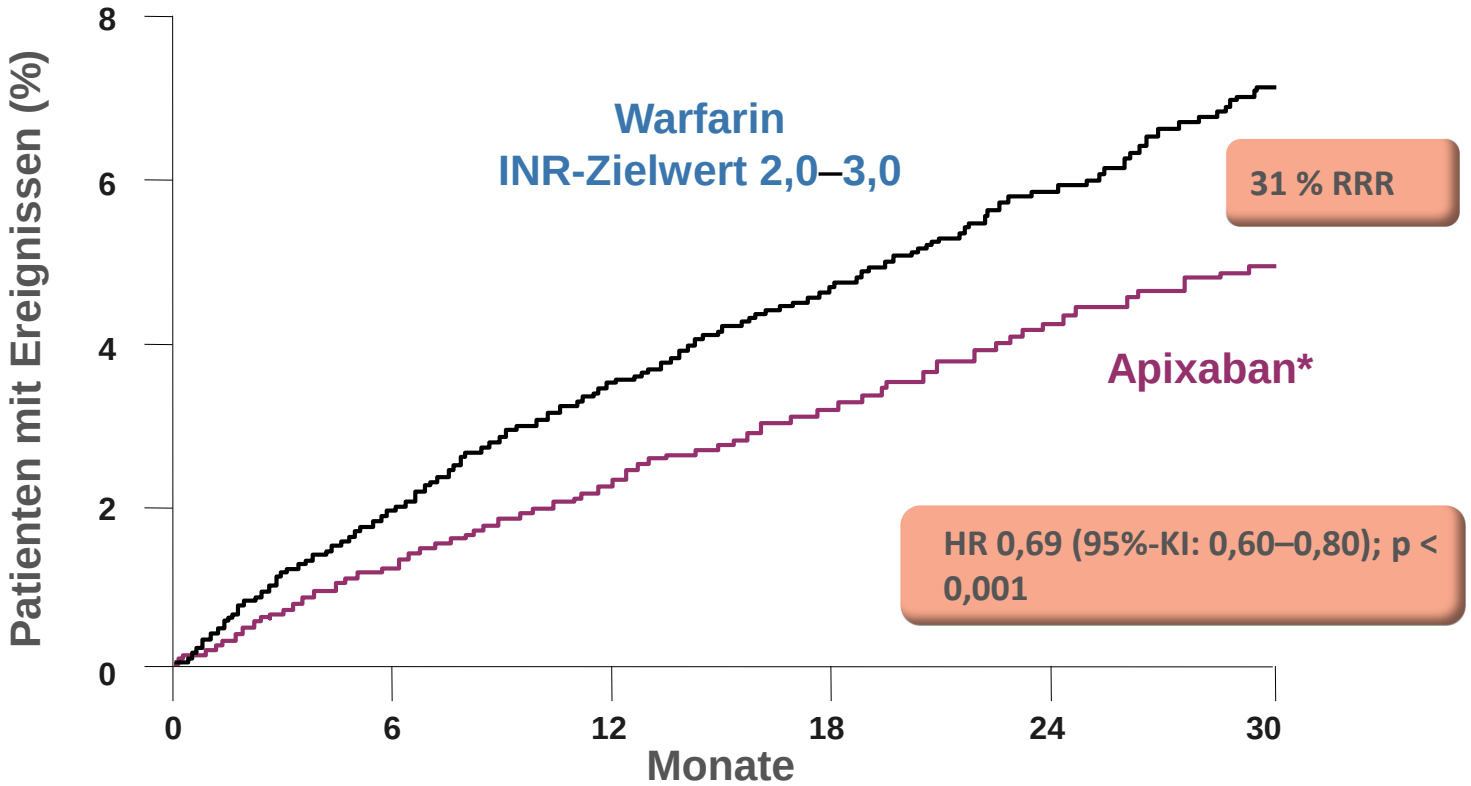
Promotion A. Lambrecht, 2016

NOACs

Synopse aus ESC- Guidelines 2016

	Dabigatran (RE-LY)			Rivaroxaban (ROCKET-AF)		Apixaban (ARISTOTLE)		Edoxaban (ENGAGE AF-TIMI 48)		
Mechanism	Oral direct thrombin inhibitor			Oral direct factor Xa inhibitor		Oral direct factor Xa inhibitor		Oral direct factor Xa inhibitor		
Bioavailability, %	6			66 fasting, 80–100 with food		50		62		
Time to peak levels, hours	3			2–4		3		1–2		
Half-life, hours	12–17			5–13		9–14		10–14		
Excretion	80% renal			66% liver, 33% renal		27% renal		50% renal		
Dose	150 mg twice daily or 110 mg twice daily.			20 mg once daily		5 mg twice daily.		60 mg once daily or 30 mg once daily		
Dose reduction in selected patients				Rivaroxaban 15 mg once daily if CrCl 30-49 mL/min		Apixaban 2.5 mg twice daily. if at least 2 of age ≥80 years, body weight ≤60 kg or serum creatinine level ≥1.5 mg/dL (133 μmol/L)		Edoxaban 60 mg reduced to 30 mg once daily, and edoxaban 30 mg reduced to 15 mg once daily, if any of the following: creatinine clearance of 30–50 mL/min, body weight ≤60 kg, concomitant use of verapamil or quinidine or dronedarone		
Study design	Randomized, open-label			Randomized, double-blind		Randomized, double-blind		Randomized, double-blind		
Number of patients	18 113			14 264		18 201		21 105		
Follow-up period, years	2			1.9		1.8		2.8		
Randomized groups	Dose-adjusted warfarin vs. blinded doses of dabigatran (150 mg twice daily., 110 mg twice daily.)			Dose-adjusted warfarin vs. rivaroxaban 20 mg once daily		Dose-adjusted warfarin vs. apixaban 5 mg twice daily.		Dose-adjusted warfarin vs. edoxaban (60 mg once daily, 30 mg once daily)		
Age, years	71.5 ± 8.7 (mean ± SD)			73 (65–78) [median (interquartile range)]		70 (63–76) [median (interquartile range)]		72 (64–78) [median (interquartile range)]		
Male sex, %	63.6			60.3		64.5		61.9		
$CHADS_2$ score (mean)	2.1			3.5		2.1		2.8		
	Warfarin	Dabigatran 150	Dabigatran 110	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	Edoxaban 60	Edoxaban 30
	n = 6022	*n* = 6076	*n* = 6015	*n* = 7133	*n* = 7131	*n* = 9081	*n* = 9120	*n* = 7036	n = 7035	*n* = 7034
	Event rate, %/year	Event rate, %/year (RR vs. warfarin)	Event rate, %/year (RR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year (HR vs. warfarin)
Stroke/systemic embolism	1.72	1.12 (0.65, 0.52–0.81; *P* for non-inferiority and superiority <0.001)	1.54 (0.89, 0.73–1.09; *P* for non-inferiority <0.001)	2.4	2.1 (0.88, 0.75–1.03; *P* for non-inferiority <0.001, *P* for superiority = 0.12)	1.60	1.27 (0.79, 0.66–0.95; *P* <0.001 for non-inferiority, *P* = 0.01 for superiority)	1.80	1.57 (0.87, 0.73–1.04; *P* <0.001 for non-inferiority, *P* = 0.08 for superiority)	2.04 (1.13, 0.96–1.34; *P* = 0.005 for non-inferiority, *P* = 0.10 for superiority)
Ischaemic stroke	1.22	0.93 (0.76, 0.59–0.97; *P* = 0.03)	1.34 (1.10, 0.88–1.37; *P* = 0.42)	1.42	1.34 (0.94; 0.75–1.17; *P* = 0.581)	1.05	0.97 (0.92, 0.74–1.13; *P* = 0.42)	1.25	1.25 (1.00, 0.83–1.19; *P* = 0.97)	1.77 (1.41, 1.19–1.67; *P* <0.001)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; *P* <0.001)	0.12 (0.31, 0.17–0.56; *P* <0.001)	0.44	0.26 (0.59; 0.37–0.93; *P* = 0.024)	0.47	0.24 (0.51, 0.35–0.75; *P* <0.001)	0.47	0.26 (0.54, 0.38–0.77; *P* <0.001)	0.16 (0.33, 0.22–0.50; *P* <0.001)
Major bleeding	3.61	3.40 (0.94, 0.82–1.08; *P* = 0.41)	2.92 (0.80, 0.70–0.93; *P* = 0.003)	3.45	3.60 (1.04; 0.90-2.30; *P* = 0.58)	3.09	2.13 (0.69, 0.60–0.80; *P* <0.001)	3.43	2.75 (0.80, 0.71–0.91; *P* <0.001)	1.61 (0.47, 0.41–0.55; *P* <0.001)
Intracranial bleeding	0.77	0.32 (0.42, 0.29–0.61; *P* <0.001)	0.23 (0.29 0.19–0.45; *P* <0.001)	0.74	0.49 (0.67; 0.47–0.93; *P* = 0.02)	0.80	0.33 (0.42, 0.30–0.58; *P* <0.001)	0.85	0.39 (0.47, 0.34–0.63; *P* <0.001)	0.26 (0.30, 0.21–0.43; *P* <0.001)
Gastrointestinal major bleeding	1.09	1.60 (1.48, 1.19–1.86; *P* <0.001)	1.13 (1.04, 0.82–1.33; *P* = 0.74)	1.24	2.00 (1.61; 1.30-1.99; *P* < 0.001)	0.86	0.76 (0.89, 0.70–1.15; *P* = 0.37)	1.23	1.51 (1.23, 1.02–1.50; *P* = 0.03)	0.82 (0.67, 0.53–0.83; *P* <0.001)
Myocardial infarction	0.64	0.81 (1.27, 0.94-1.71; *P* = 0.12)	0.82 (1.29, 0.96-1.75; *P* = 0.09)	1.12	0.91 (0.81; 0.63–1.06; *P* = 0.12)	0.61	0.53 (0.88, 0.66–1.17; *P* = 0.37)	0.75	0.70 (0.94, 0.74–1.19; *P* = 0.60)	0.89 (1.19, 0.95–1.49; *P* = 0.13)
Death from any cause	4.13	3.64 (0.88, 0.77–1.00; *P* = 0.051)	3.75 (0.91, 0.80–1.03; *P* = 0.13)	2.21	1.87 (0.85; 0.70–1.02; *P* = 0.07)	3.94	3.52 (0.89, 0.80–0.99; *P* = 0.047)	4.35	3.99 (0.92, 0.83–1.01; *P* = 0.08)	3.80 (0.87, 0.79–0.96; *P* = 0.006)

ARISTOTLE: Apixaban hatte gegenüber Warfarin ein überlegenes Verträglichkeitsprofil bei der Reduktion von schweren Blutungen**



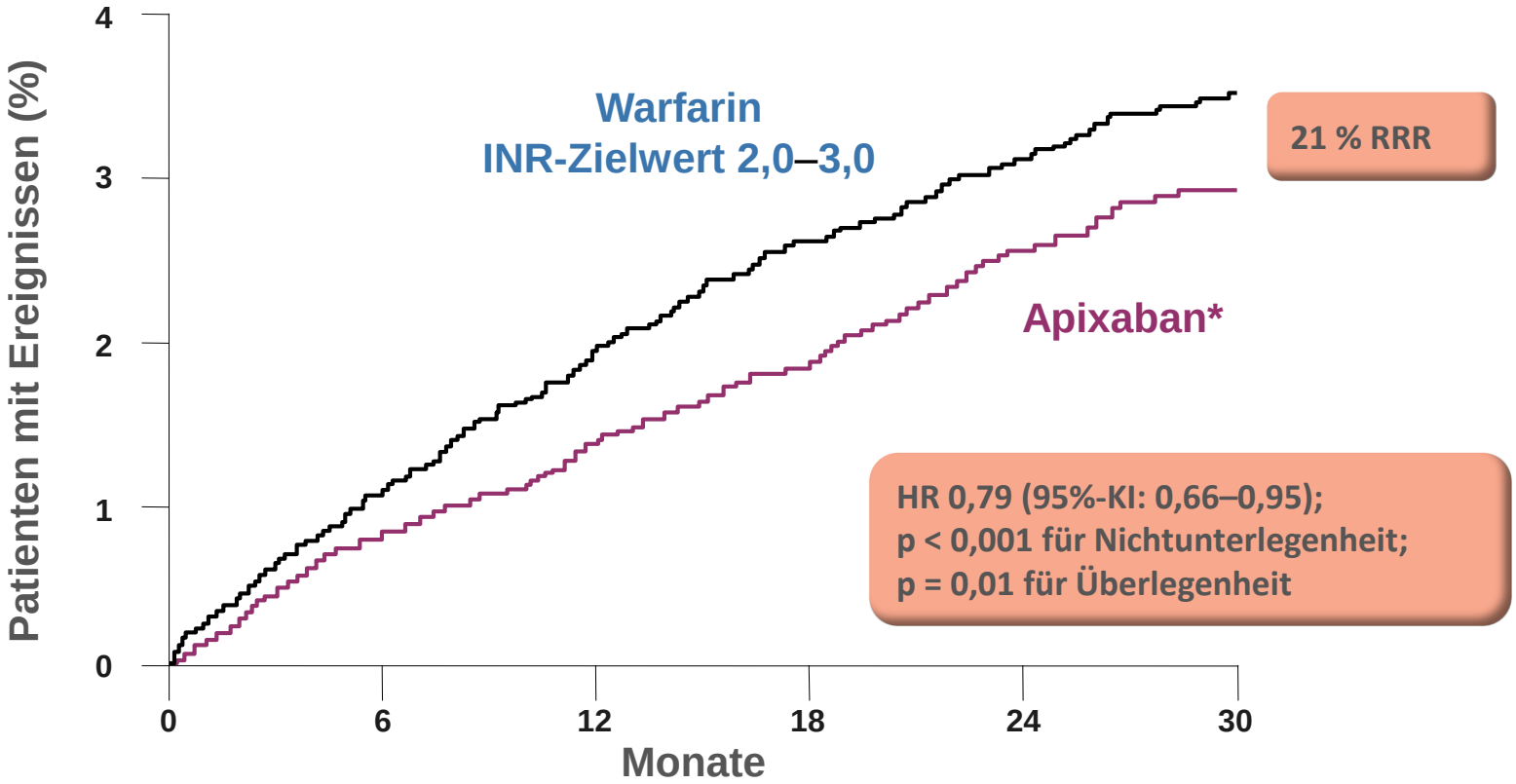
Gefährdete Patienten (n)						
Apixaban	9088	8103	7564	5365	3048	1515
Warfarin	9052	7910	7335	5196	2956	1491

1. Adaptiert nach Granger *et al*. N Engl J Med 2011; 365:981–92. 2. ELIQUIS® Fachinformation, Stand Juli 2014.

* Bei 95,3 % der Patienten wurde ELIQUIS® in einer Dosierung von zweimal täglich 5 mg gegeben. Eine Dosis von zweimal täglich 2,5 mg ELIQUIS® wurde bei Patienten angewendet, die mindestens zwei der folgenden Kriterien erfüllten: Alter von ≥ 80 Jahren, Körpergewicht von ≤ 60 kg oder ein Serumkreatininspiegel von ≥ 1,5 mg/dl (133 µmol/l).

** Schwere Blutungen entsprechend den ISTH-Kriterien; wichtiger sekundärer Endpunkt. ISTH: International Society on Thrombosis and Haemostasis; KI: Konfidenzintervall; HR: Hazard Ratio; RRR: Relative Risikoreduktion; INR: International Normalised Ratio.

ARISTOTLE: Schlaganfälle/Systemische Embolien (primärer Endpunkt)



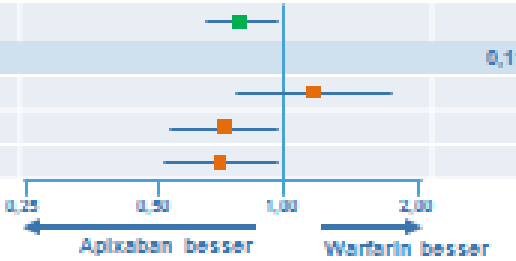
Gefährdete Patienten (n)						
Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

1. Adaptiert nach Granger *et al*. N Engl J Med 2011; 365:981–92. 2. ELIQUIS® Fachinformation, Stand Juli 2014.
KI: Konfidenzintervall; HR: Hazard Ratio; RRR: Relative Risikoreduktion; SE: systemische Embolien; INR: International Normalised Ratio
* Bei 95,3 % der Patienten wurde ELIQUIS® in einer Dosierung von zweimal täglich 5 mg gegeben. Eine Dosis von zweimal täglich 2,5 mg ELIQUIS® wurde bei Patienten angewendet, die mindestens zwei der folgenden Kriterien erfüllten: Alter von ≥ 80 Jahren, Körpergewicht von ≤ 60 kg oder ein Serumkreatininspiegel von ≥ 1,5 mg/dl (133 µmol/l).

ARISTOTLE: Wirksamkeits- und Sicherheitsdaten nach Alter

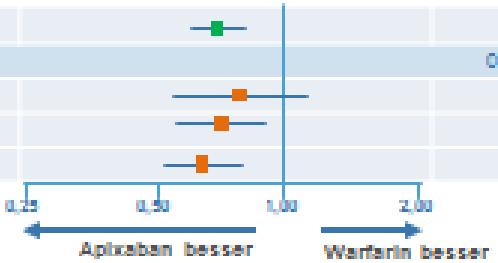
A. Primärer Wirksamkeitsendpunkt: Schlaganfall oder systemische Embolie

Untergruppe	Anzahl der Patienten	Apixaban	Warfarin	Hazard Ratio (95%-KI)	p-Wert für Interaktion
		Anzahl der Ereignisse (%/J.)			
Alle Patienten	18 201	212 (1,27)	265 (1,60)		
Alter					0,11*
< 65 J.	6471	61 (1,00)	44 (0,88)		
65 bis < 75 J.	7052	82 (1,26)	112 (1,73)		
≥ 75 J.	6678	79 (1,68)	109 (2,16)		



B. Schwere Blutungen**

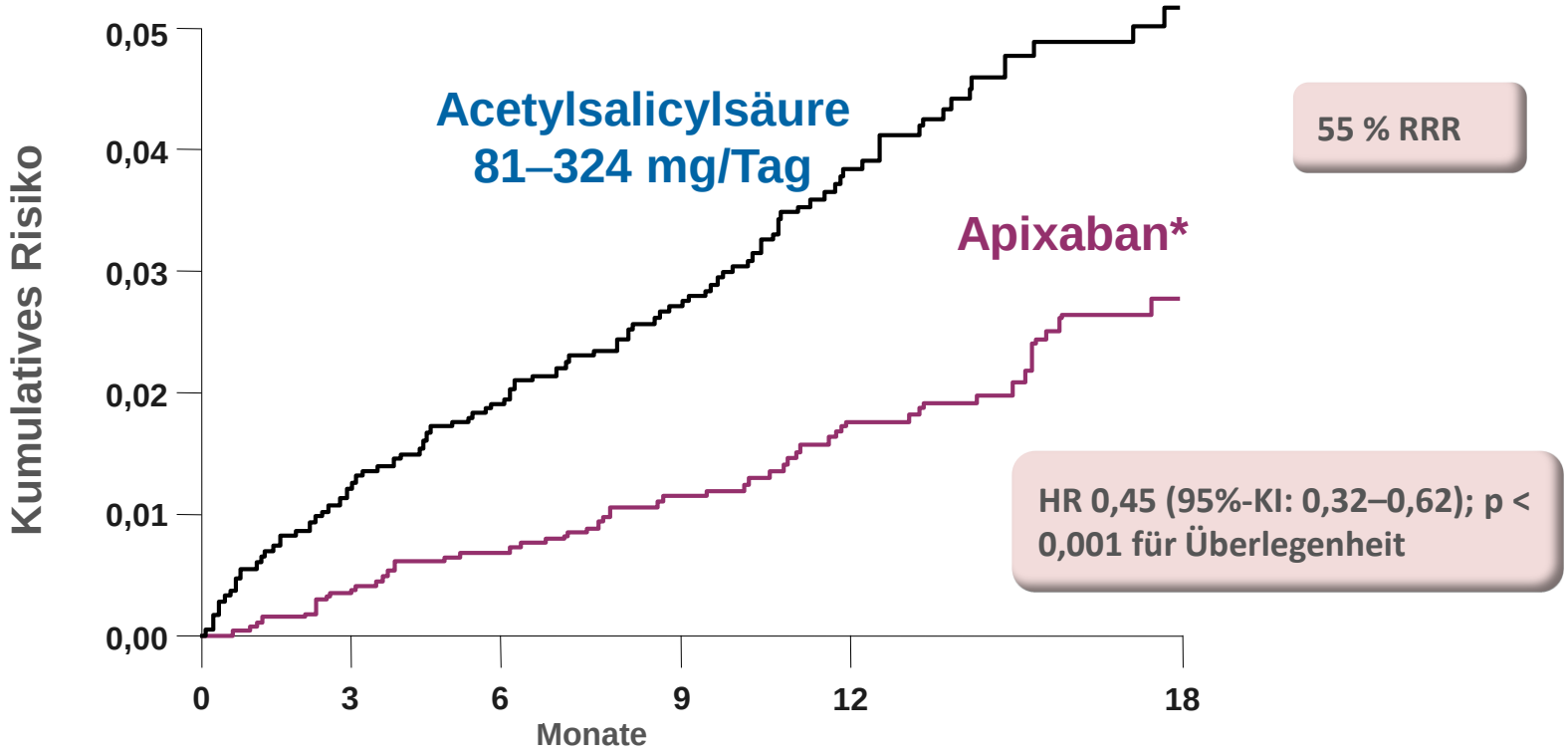
Untergruppe	Anzahl der Patienten	Apixaban	Warfarin	Hazard Ratio (95%-KI)	p-Wert für Interaktion
		Anzahl der Ereignisse (%/J.)			
Alle Patienten	18 140	327 (2,13)	462 (3,09)		
Alter					0,63*
< 65 J.	6455	68 (1,17)	72 (1,51)		
65 bis < 75 J.	7030	120 (1,99)	188 (2,82)		
≥ 75 J.	6855	151 (3,33)	224 (5,18)		



* p-Wert für Interaktion (Alter als kontinuierliche Variable);
** Wichtiger sekundärer Endpunkt

1. Halvorsen et al. Eur Heart J 2014; 35:1864-72

AVERROES: Apixaban reduzierte das Risiko für Schlaganfälle oder SE gegenüber Acetylsalicylsäure signifikant



Gefährdete Patienten (n)						
Apixaban	2808	2758	2566	2125	1522	615
ASS	2791	2716	2530	2112	1543	628

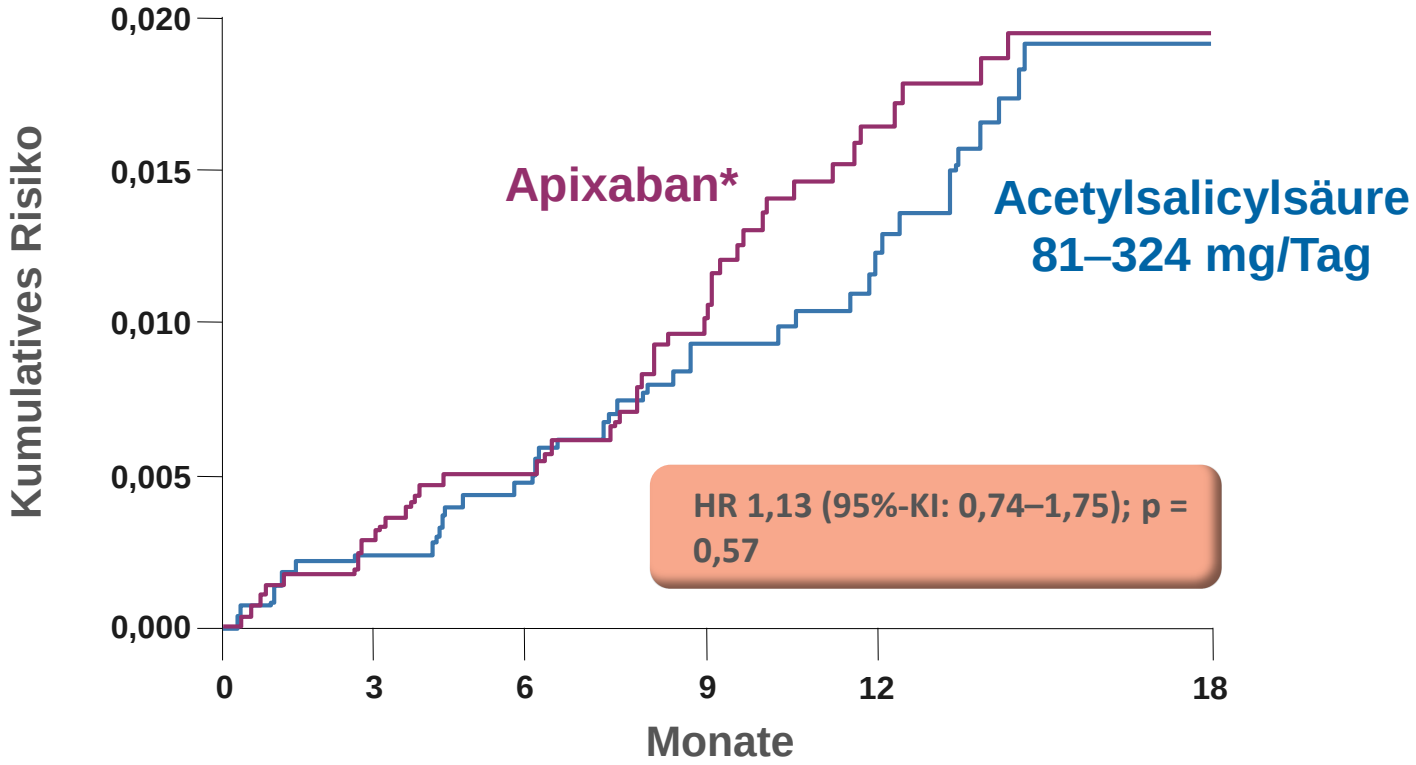
** Primärer Wirksamkeitsendpunkt

* 94 % der ELIQUIS®-Patienten erhielten zweimal täglich 5 mg. Eine Dosis von zweimal täglich 2,5 mg ELIQUIS® wurde bei einer Untergruppe (6 %) der Patienten angewendet, die mindestens zwei der folgenden Kriterien erfüllte:Alter von mindestens 80 Jahren, Körpergewicht von maximal 60 kg oder ein Serumkreatininspiegel von 1,5 mg/dl (133 µmol/l) oder mehr.

Weitere Informationen sind der aktuellen Fachinformation von ELIQUIS® zu entnehmen.[2]

1. Adaptiert nach Connolly *et al*. N Engl J Med 2011; 364:806–17. 2. ELIQUIS® Fachinformation, Stand Juli 2014;
KI: Konfidenzintervall; HR: Hazard Ratio; RRR: Relative Risikoreduktion; ASS: Acetylsalicylsäure; SE: systemische Embolien

AVERROES: Das Risiko für schwere Blutungen** unter Apixaban und Acetylsalicylsäure war vergleichbar



Gefährdete Patienten (n)						
Apixaban	2808	2759	2566	2120	1521	622
ASS	2791	2738	2557	2140	1571	642

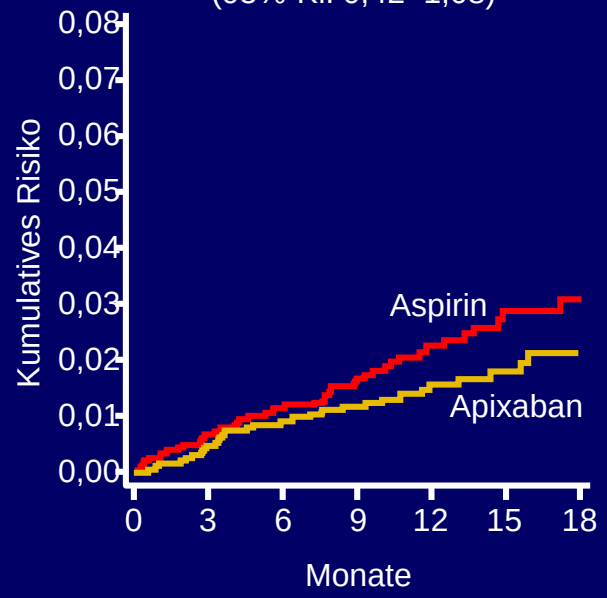
* 94 % der ELIQUIS®-Patienten erhielten zweimal täglich 5 mg. Eine Dosis von zweimal täglich 2,5 mg ELIQUIS® wurde bei einer Untergruppe (6 %) der Patienten angewendet, die mindestens zwei der folgenden Kriterien erfüllte:Alter von mindestens 80 Jahren, Körpergewicht von maximal 60 kg oder ein Serumkreatininspiegel von 1,5 mg/dl (133 µmol/l) oder mehr.
** wichtiger sekundärer Endpunkt

Weitere Informationen sind der aktuellen Fachinformation von ELIQUIS® zu entnehmen.[2]

1. Adaptiert nach Connolly *et al*. N Engl J Med 2011; 364:806–17. 2. ELIQUIS® Fachinformation Stand Juli 2014.
KI: Konfidenzintervall; HR: Hazard Ratio; ASS: Acetylsalicylsäure

Kumulative Ereignisraten für Schlaganfall nach Behandlung und Alter < 75 oder ≥ 75 Jahre

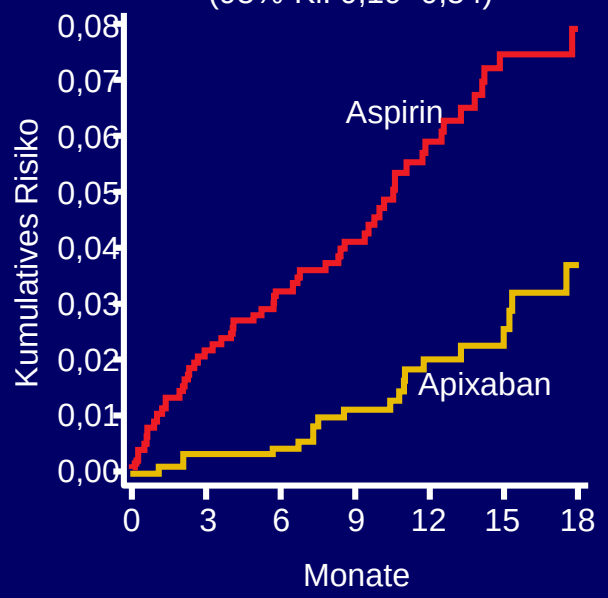
Alter < 75 Jahre
HR bei Apixaban: 0,68
(95%-KI: 0,42–1,08)



Gefährdete Patienten (n)

Aspirin	1.799	1.766	1.643	1.384	1.009	675	402
Apixaban	1.901	1.869	1.745	1.455	1.037	722	419

Alter ≥ 75 Jahre
HR bei Apixaban: 0,33
(95%-KI: 0,19–0,54)



Gefährdete Patienten (n)

Aspirin	992	951	885	730	536	375	229
Apixaban	906	887	820	651	479	327	196

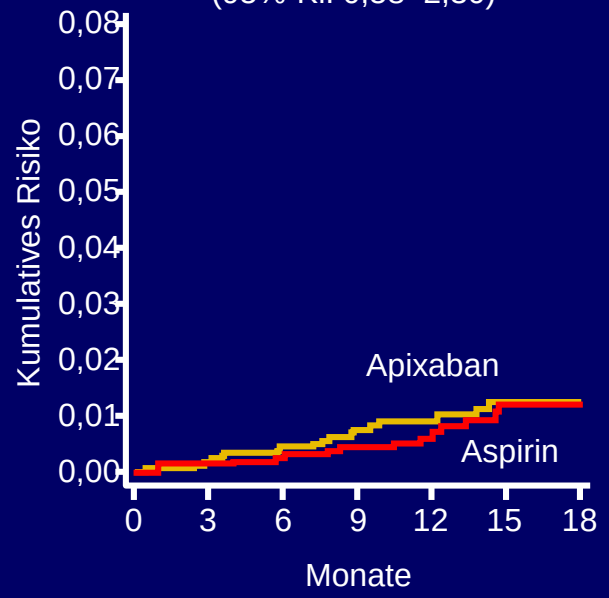
KI = Konfidenzintervall; HR = Hazard Ratio.

Ng KH, et al. *Age Ageing*. 2016;45:77-83.

Für den werbungsfreien reaktiven Gebrauch

Kumulative Ereignisraten für schwere Blutungen nach Behandlung und Alter < 75 oder ≥ 75 Jahre

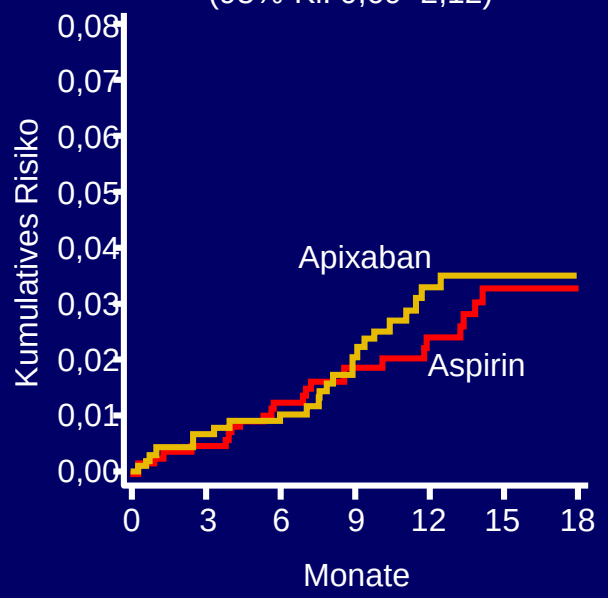
Alter < 75 Jahre
HR bei Apixaban: 1,14
(95%-KI: 0,58–2,30)



Gefährdete Patienten (n)

Aspirin	1.799	1.776	1.654	1.397	1.019	682	407
Apixaban	1.901	1.872	1.748	1.455	1.040	724	424

Alter ≥ 75 Jahre
HR bei Apixaban: 1,21
(95%-KI: 0,69–2,12)



Gefährdete Patienten (n)

Aspirin	992	960	896	740	548	382	233
Apixaban	906	885	816	645	474	321	195

KI = Konfidenzintervall; HR = Hazard Ratio.

Ng KH, et al. *Age Ageing*. 2016;45:77-83.

Für den werbungsfreien reaktiven Gebrauch

Score Systeme - im Alter sinnvoll?

CHA_2DS_2-VASc	Score	HAS-BLED	Score
Congestive heart failure	1	Hypertension (systolic blood pressure >160 mm Hg)	1
Hypertension	1	Abnormal renal and liver function* (1 point each)	1 or 2
Age ≥75 y	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency/predisposition*	1
Stroke/TIA/TE	2	Labile INRs (if on warfarin)*	1
Vascular disease (prior MI, PAD, or aortic plaque)	1	Elderly (eg, age >65 y)	1
		Drugs or alcohol (1 point each)*	1 or 2
Aged 65 to 74 y	1		
Sex category (ie, female sex)	1		
Maximum score	9	Maximum score	9

Circulation. 110, Nr. 16, 2004, S. 2287–92.

Chest. 2010; 138: 1093–1100.

ESC – Guidelines 2016

Recommendations for stroke prevention in AF			
The CHA_2DS_2-VASc score is recommended for stroke risk prediction in patients with AF.	I	A	
Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA_2DS_2-VASc score of 2 or more.	I	A	
Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA_2DS_2-VASc score of 3 or more.	I	A	
When oral anticoagulation is initiated in a patient with AF who is eligible for a non vitamin-K-antagonist oral anticoagulant (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist.	I	A	
Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves.	I	B	
NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C).	III (harm)	B	C
When patients are treated with a vitamin K antagonist, time in therapeutic range (TTR) should be kept as high as possible and closely monitored.	I	A	
Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition.	III (harm)	B	
In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention.	III (harm)	B	
Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk.	III (harm)	A	

Vorhofflimmern im Alter und Antikoagulation

- Die Prävalenz des Vorhofflimmerns steigt mit dem Alter exponentiell an.
- Aufgrund des Alters und der Komorbidität besteht nahezu durgängig eine Indikation zur Antikoagulation, wobei das Risiko für kardioembolische Ereignisse besonders hoch ist.
- Das Blutungsrisiko ist ebenfalls erhöht, wird jedoch vom Benefit der Antikoagulation mehr als aufgewogen. Auf eine Dosisanpassung der NOACs bei alten und untergewichtigen Patienten und/oder eingeschränkter Nierenfunktion ist entsprechend der jeweiligen Gebrauchsinformation zu achten.

Vorhofflimmern im Alter und Antikoagulation

- Wenn sie der Meinung sind, ihr alter Patient mit Vorhofflimmern könnte ASS vertragen…..
- Machen Sie es doch gleich richtig!

Life is not so bad –
if you consider the alternative

(Woody Allen)