Cholesterinsenkung und Schlaganfall – Gibt es eine Evidenz ?

8. BASIS-Workshop Schlaganfall

Woltersdorf 18. März 2005

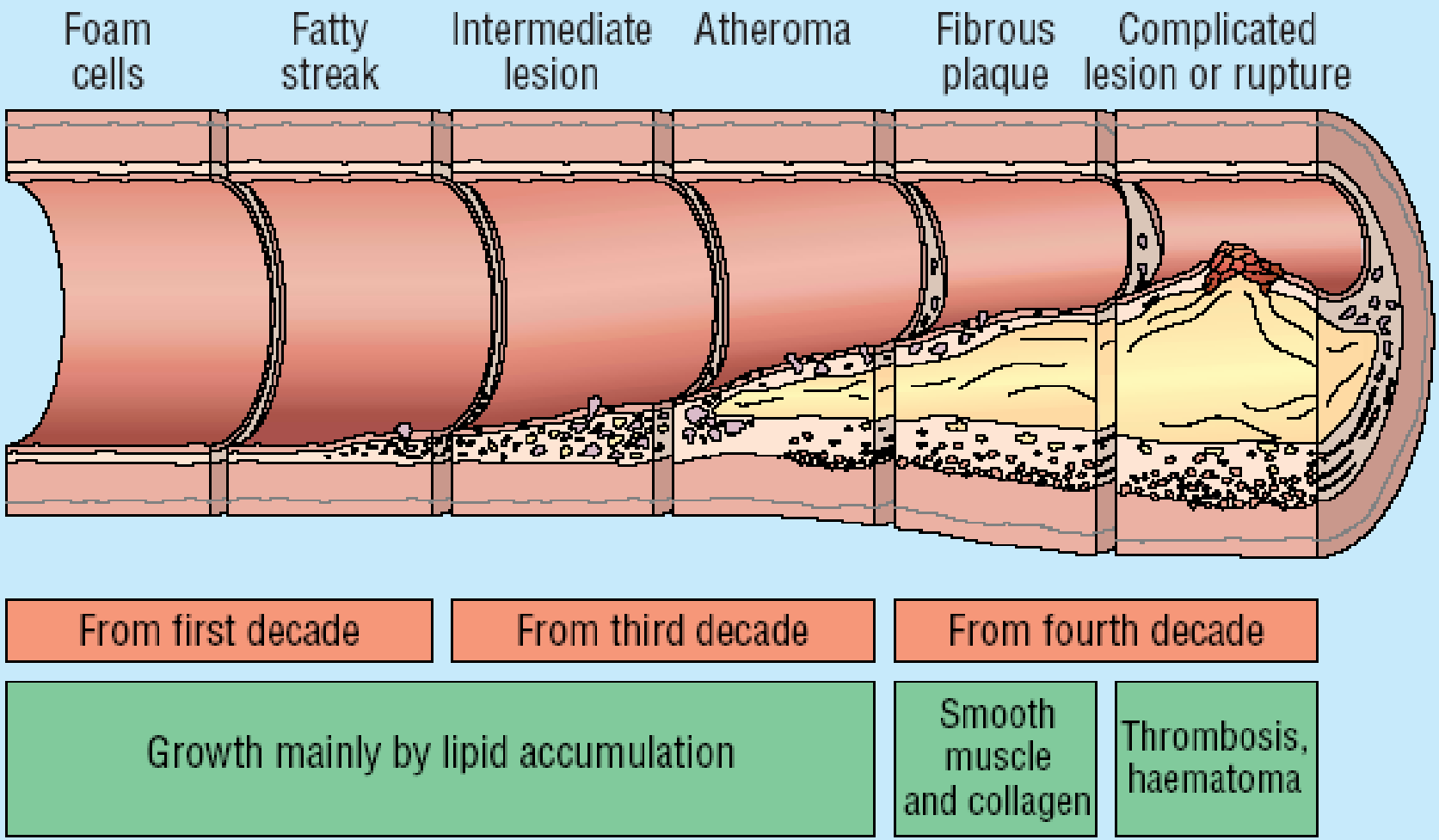
M. Gogol Coppenbrügge

Ateriosklerose

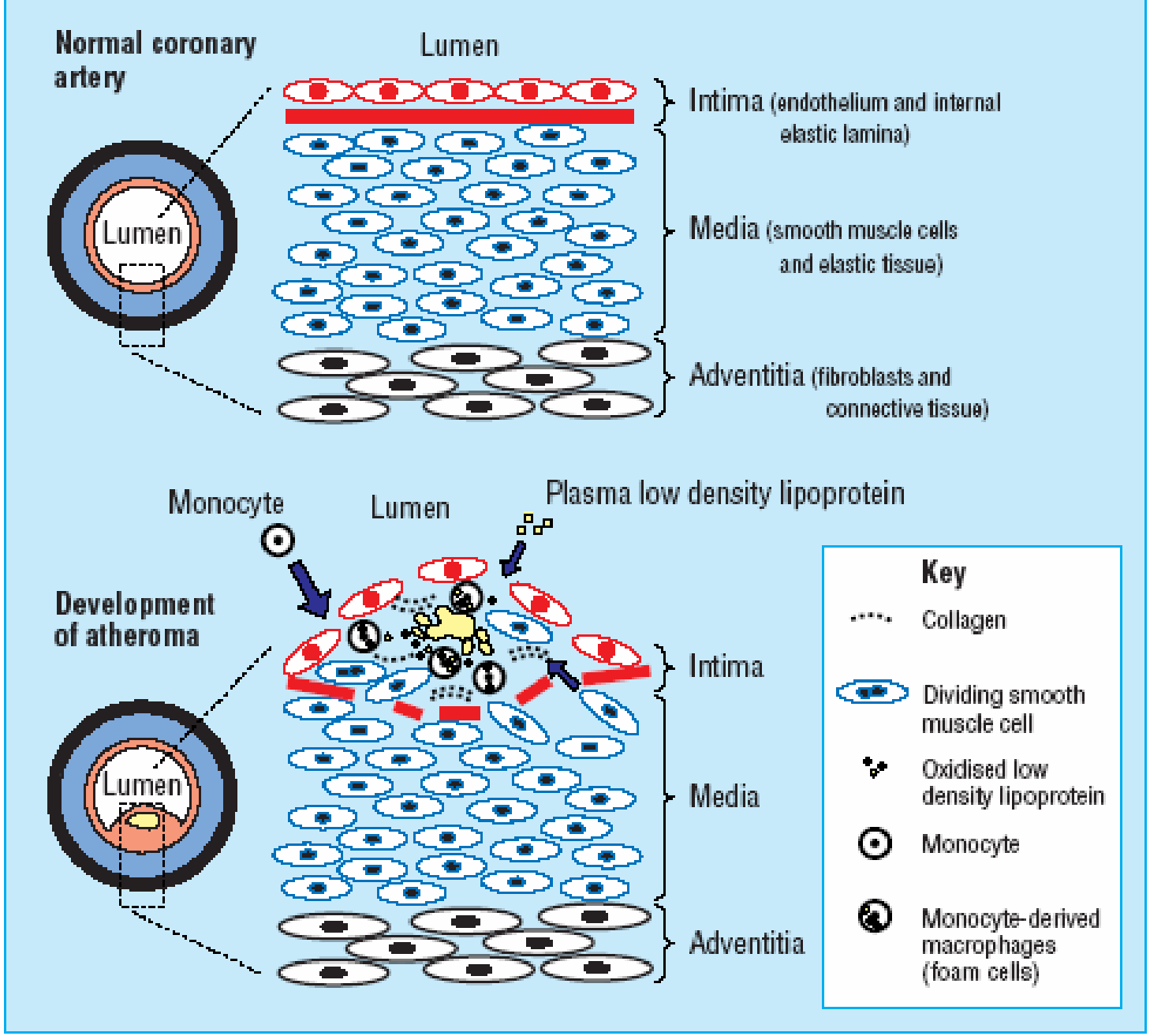
- **Chronisch-inflammatorischer Prozess**
- **Plaqueruptur**

1. Endotheliale Blockade
2. Aggressive LDL-Chol.-Senkung
3. Inhibition der LDL-Oxidation
4. Inhibition entzündl. Zytokinine
5. Thrombozytenfunktionshemmung

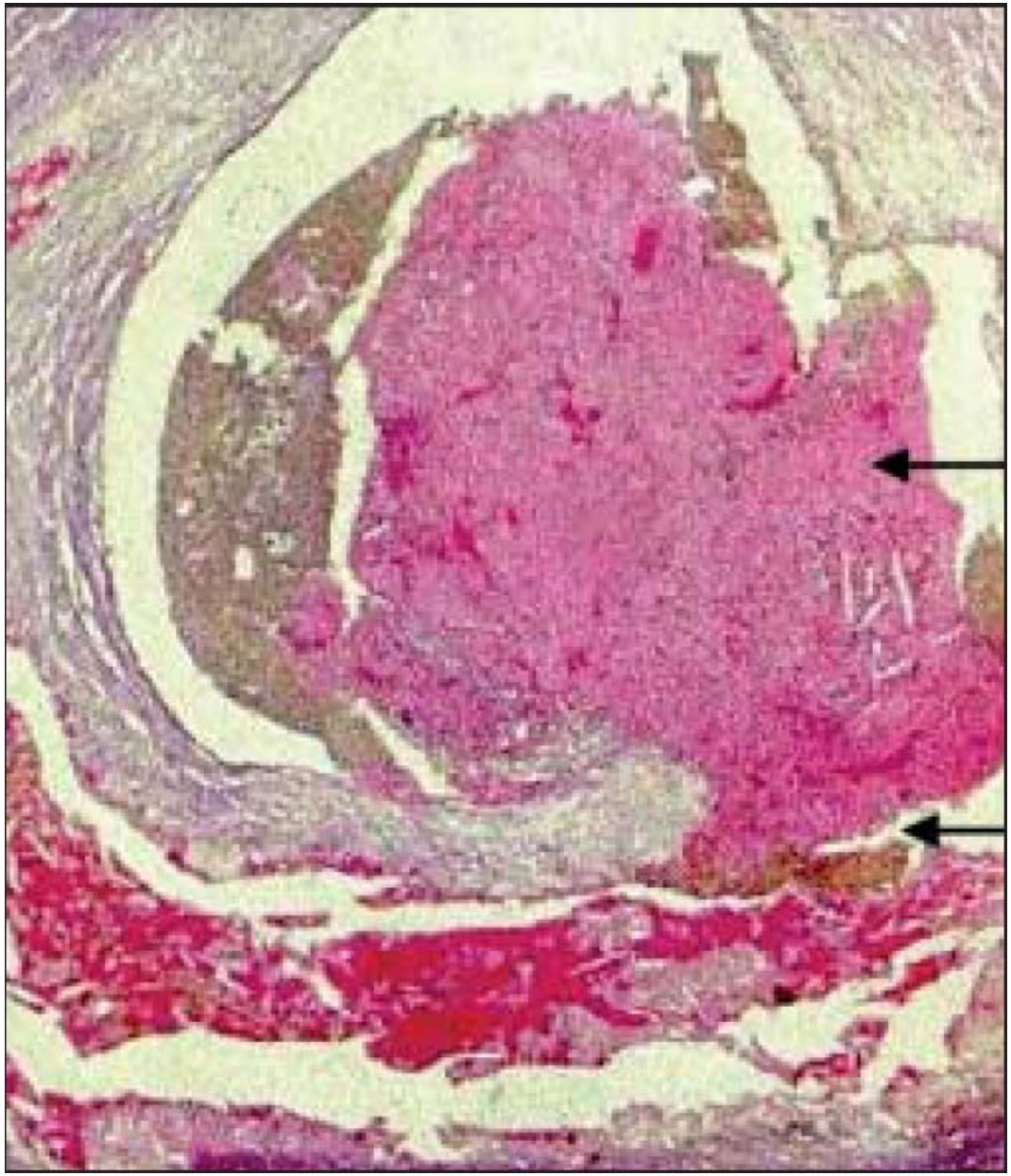
RS Munford *– Statins and the acute-phase response. N Engl J Med 2001;344:2016*
P Libby *– Inflammation in atherosclerosis. Nature 2002;420:868*
JS Forrester *– Prevention of plaque rupture: a new paradigm of therapy. Ann Intern Med 2002;137:823*



ED Grech *– ABC of interventional cardiology: Pathphysiology and investigation of coronary artery disease. BMJ 2003;326:1027*



ED Grech *– ABC of interventional cardiology: Pathphysiology and investigation of coronary artery disease. BMJ 2003;326:1027*



ED Grech et al *– Acute coronary syndrome: ST segment elevation myocardial infarction. BMJ 2003;326:1379*

Metanalyse Statine in RCTs

- 182 primäre Abstracts bzw. Originalarbeiten
- 29 bezüglich der Nutzung von Statinen selektiert, fünf erfüllten die Kriterien :
- die **Scandinavian Simvastatin Survival Study (4S)** **[Simvastatin, Sek.präv.]**
- die **West of Scotland Coronary Prevention Study (WOSCOPS)** **[Pravastatin, Prim.präv]**
- die **Cholesterol and Recurrent Events Trial (CARE)** **[Pravastatin, Sek.präv.]**
- die **Long-term Intervention With Pravastatin in Ischaemic Disease Trial (LIPID)** **[Pravastatin, Sek.präv.]**
- die **Airforce/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)** **[Lovastatin, Prim.präv.]**

- **30.817 Patienten eingeschlossen / mittlere Follow up-Zeit von 5,4 a / mittleres Alter 59 a (WOSCOP: Auschluss Frauen + Alter > 65a)**

JC LaRosa et al. *– Effect of statin on risk of coronary disease: A meta-analysis of randomised controlled trials. JAMA 1999;282:2340*

Statine bei alten Menschen ?

- CSE-Hemmer werden häufig genutzt
- Alle gut validierten, prospektiven RCT´s mit signifikanter Überlegenheit bei
- **Männern, (Frauen), Weisse Rasse, Alter ca. 60 ± 10 a, selektierte Studienpopulation (wenig RF)**

- Bisher unzureichende Datenbasis bei
- Patienten > 75 a generell **?**
- Patienten > 75 a mit Multimorbidität, insbes. dementiellen Syndromen und Frailty-Syndrom **?**

LM Birch – *Unanswered questions: The use of statins in older people to prevent cardiovascular event effects of statins on risk of coronary disease: A meta-analysis of randomized controled trials. J Am Ger Soc 2002;50:391*

Limitationen im Alter / bei Frauen

- 47 RCT`s 1990-2001
- 38 Sek.präv. oder Sek. + Primärpräv.
- 8 (17 %) Ausschluss von Frauen
- 18,6 (11,8-30) % Frauenanteil
- 14 berichten geschlechtskorrelierte Ergebnisse
- 31(66 %) mit Altersausschluss (Median 70 a)
- 13 (28 %) Einschlussalteranteil ≥ 65 a mitgeteilt
- Nur 11 berichten alterskorrelierten Ergebnisse

C Bartlett et al.– *Women, older persons, and ethnic minorities: factors associated with their inclusion in randomised trials of statin 1990 to 2001. Heart 2003;89:327*

Cardiovascular Health Study

- 1250 F + 664 M
- 71 ± 5 a bei Eintritt
- Follow-up 7,3 a
- Keine kardiovaskuläre Erkrankungen

(adj. HR)	CV events	All-Cause Mort.	CV Mort.
Keine Therapie	1,0	1,0	1,0
Statin	0,44 (p 0,001)	0,56 (p 0,01)	0,54 (p 0,08)
No-Statin	0,68 (p 0,14)	0,43 (p 0,02)	0,50 (p 0,18)

RN LeMaitre et al. *– Therapy with hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) and associated risk of incident cardiovascular events in older adults. Arch Intern Med 2002;162:1395*

NCEP Adult Treatment Panel III Guidelines I

Hochrisikopatienten

- Bekannte Cardiovaskuläre Erkrankung plus
- Diabetes mellitus oder
- Schwere / nicht beherrschte RF (z.B. weiteres Rauchen) oder
- Metabolisches Syndrom oder
- Akute Koronarsyndrome (Angina, AMI)

SM Grundy et al. *– Implications of recent clinical trial for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation 2004;110:227*
National Cholesterol Education Program *(NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143*

NCEP Adult Treatment Panel III Guidelines II

- Very High Risk **(< 70 mg/dl)**
- High Risk **(< 100 mg/dl)**
- Moderately High Risk (2 o. >2 RF) **(< 130 mg/dl)**
- Lower Risk (0-1 RF) **(< 160 mg/dl)**

- **KHK:** MI, Angina, Koronarienprozedur
- **Risikoäquivalente Krankeiten:** pAVK, Aortenaneurysma, Carotisstenose, TIA, Diabetes
- **Risikofaktor:** Nikotin, Hypertonie, HDL < 40, positive Familienanamnese, Alter (Männer > 45 a, Frauen > 55 a)

SM Grundy et al. *– Implications of recent clinical trial for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation 2004;110:227*
National Cholesterol Education Program *(NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143*

Statine pro I

„All agree that the introduction of … statins … has revolutionized the practise of cardio-vascular medicine. A series of well-known, well-designed, conclusive, and concordant studies has shown that statin therapy can reduce „hard“ end points, including myocardial infarction, stroke, and cardiovascular, and all-cause mortality in a broad variety of populations …“

P Libby, JT Willerson *– Introduction. Circulation 2004;109[suppl II]:II-1*

Statine pro II

M Kaste *– Statins in threatened stroke. Stroke 2003;34:351*

JME Walsh et al. *– Drug treatment of hyperlipidemia in women. JAMA 2004;291:2243*

SE Strauss et al. *– New evidence for stroke prevention. JAMA 2002;288-1388*

SE Strauss et al. *– New evidence for stroke prevention. Clinical applications. JAMA 2002;288:1396*

JF Toole et al. *– Stroke prevention. Optimizing the response to a common threat. JAMA 2004;292:1885*

DF Hanley *– The challenge of stroke prevention. JAMA 2004;291-621*

J-C Corvol et al. *– Differential effects of lipid-lowering therapies on stroke prevention. Arch Intern Med 2003;163:669*

CF Hennekens et al. *– Additive benefits of pravastatin and aspirin to decrease risks of cardiovascular disease. Randomized and observational comparisons of secondary prevention trials and their meta-analyses. Arch Intern Med 2004;164:40*

JP Broderick et al. *– Treatment of acute ischemic stroke. Part II: Neuroprotection and medical management. Circulation 2002;106:1736*

GJ Hankey *– Secondary prevention of recurrent stroke. Stroke 2005;36:218*

J Martí-Fàbregas et al. *– Favorable outcome of ischemic stroke in patients pretreated with statins. Stroke 2004:35:1117*

Statine pro IV

KW Muir *– Secondary prevention for stroke and transient ischaemic attacks. BMJ 2004;328:297*

G Gubitz et al. *– Regular review: Prevention of ischaemic stroke. BMJ 2000;321:1455*

C Warlow et al. *– Stroke. Lancet 2003;362:1211*

P Sandercock *– Statins for stroke prevention ? Lancet 2001;357:1548*

P Durrington *– Dyslipidaemia. Lancet 2003;362:717*

HD White – *Pravastatin therapy and the risk of stroke. NEJM 2000;343:317*

EJ Topol *– Intensive statin therapy – a sea change in cardiovascular prevention. NEJM 350;2004:1562*

LB Goldstein *– Primary prevention of ischemic stroke. A statement for healthcare professionels from the Stroke Council of the American Heart Association. Stroke 2001;32:280*

PB Gorelich *– Stroke prevention therapy beyond antithrombotics: unifying mechanisms in ischemic stroke pathogenesis and implications for therapy. An invited review. Stroke 2002;33:862*

RC Pasternak et al. *– ACC/AHA/NHLBI clinical advisory on the use and safety of statins. Stroke 2002;33:2337*

The Stroke Council *– Statins after ischemic strake and transient ischemic attack. An advisory statement from the Stroke Council, American Heart Association and American Stroke Association. Stroke 2002;35:1023*

L Mosca et al. *– Evidence-based guidelines for cardiovascular disease prevention in woman. Circulation 2004;109:672*

Statine pro III

JY Streifler *– Statins, stroke outcome, and stroke prevention: When should we start treatment? Stroke 2004;35:1121*

JP Broderick *– William M Feinberg Lecture: Stroke therapy in the year 2025. Burden, breakthroughs, and barriers to progress. Stroke 2003;35:205*

SC Fagan et al. *– Targets for vascular protection after acute ischemic stroke. Stroke 2004;35:2220*

B Piechowski-Józwiak et al. *– Cholesterol as a risk factor for stroke. The fugitive? Stroke 2004;35-1523*

P Amarenco et al. *– Statins in stroke prevention and carotid atherosclerosis. Systemativ review and up-to-date meta-analysis. Stroke 2004;35:2902*

U Rauch et al. *– Thrombus formation on atherosclerotic plaques: Pathogenesis and clinical consequences. Ann Intern Med 2001;134:224*

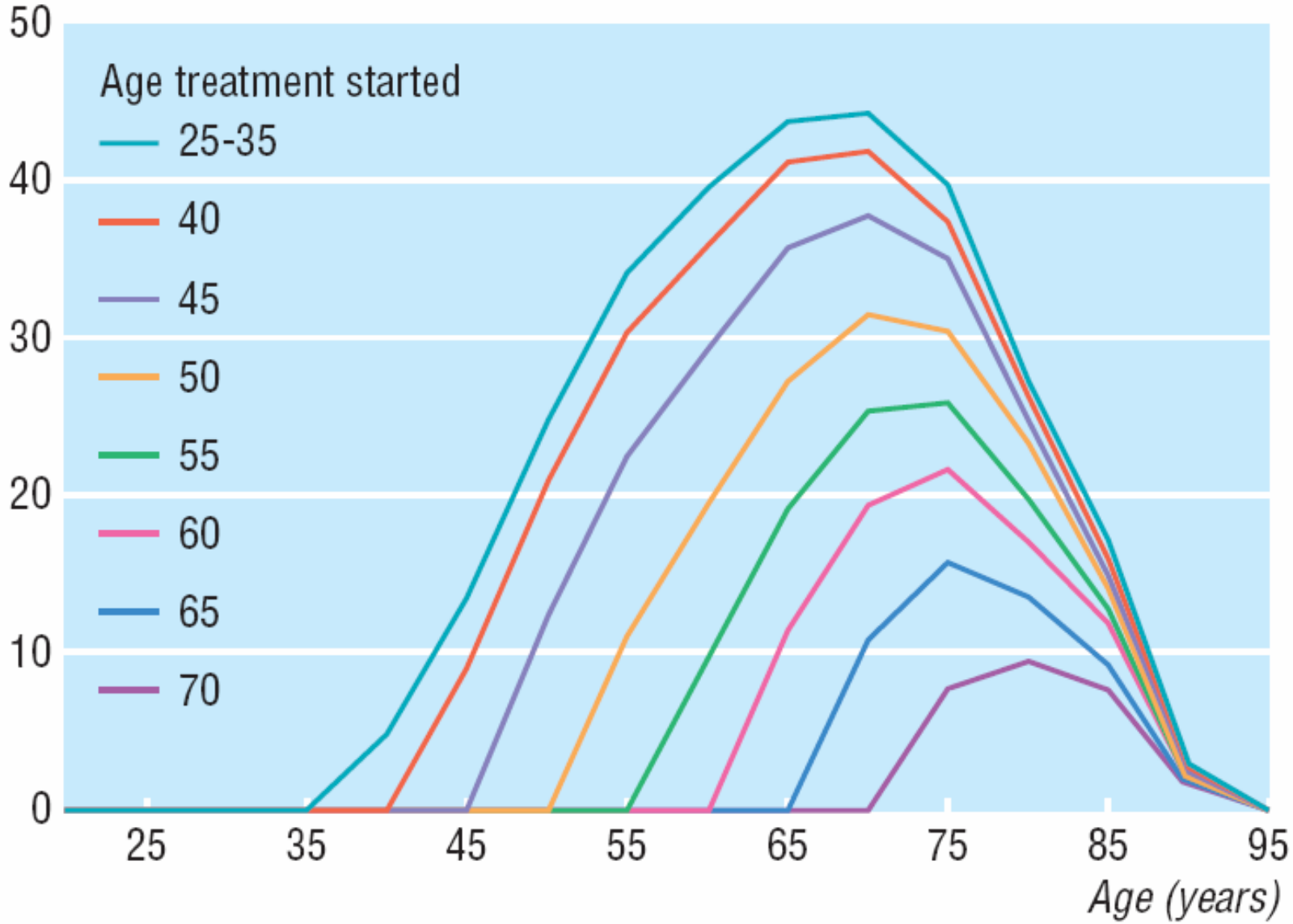
V Snow et al. *– Lipid control in the management of type 2 diabetes mellitus: Aclinical practise guideline from the American College of Physicians. Ann Intern Med 2004;140:644*

S Vijan et al. *– Pharmacologic lipid-lowering therapy in type 2 diabetes mellitus: Background paper for the American College of Physicians. Ann Intern Med 2004;140:650*

MF Oliver *– Cholesterol and strokes. BMJ 2000;320:459*

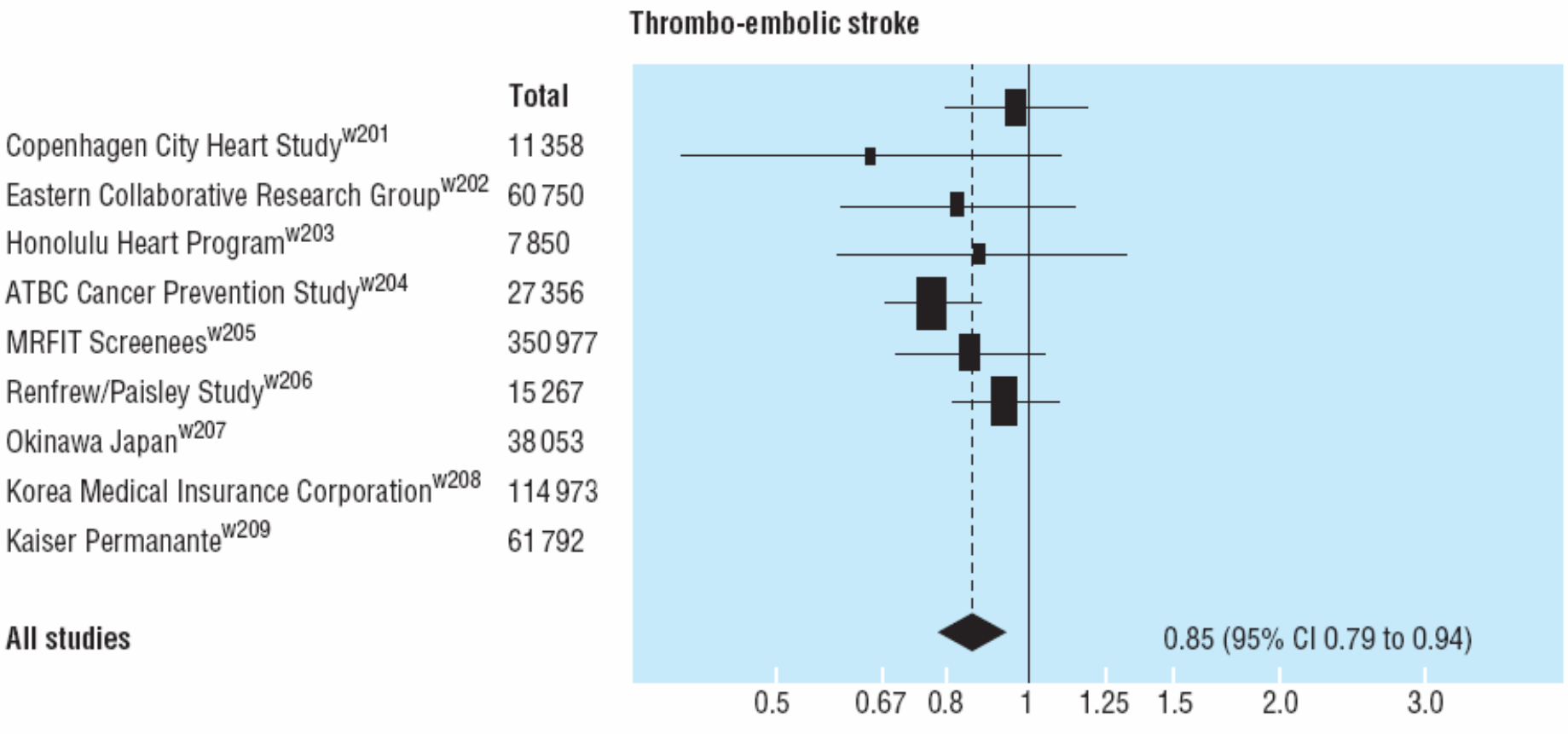
KR Lees et al. *– ABC of arterial and venous disease: Secondary prevention of transient ischaemic attack and stroke. BMJ 2000;320:991*

Total number of life years free of cv events



S Ulrich et al. *– What is the optimal age for starting lipid lowering treatment? A mathematical model. BMJ 2000;320:1134*

Statins and Stroke outcome



MR Law et al. *– Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 2003;326:1423*

PROSPER

Prospective Study of Pravastatin in the Elderly at Risk

- 2.804 M., 3.000 F.
- 75,3 ± 3,4 a
- Follow-up 3,2 a
- RF für cardiovaskuläre Erkrankungen
- 40 mg Pravastatin vs. Placebo
- Prim. EP: KHK Tod, n-fatal MI, fatal o. n-fatal Stroke

J Shepherd et al. *– Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623*

PROSPER – Stroke outcome

	Pravastatin	Placebo
Men	**(n=1396)**	**(n=1408)**
CHD death, non-fatal MI, and fatal or non-fatal stroke	222	279
CHD death, non-fatal MI	167	219
Fatal and non-fatal stroke	65	70
TIA	38	53
Women	**(n=1495)**	**(n=1505)**
CHD death, non-fatal MI, and fatal or non-fatal stroke	186	194
CHD death, non-fatal MI	125	137
Fatal and non-fatal stroke	70	61
TIA	39	49

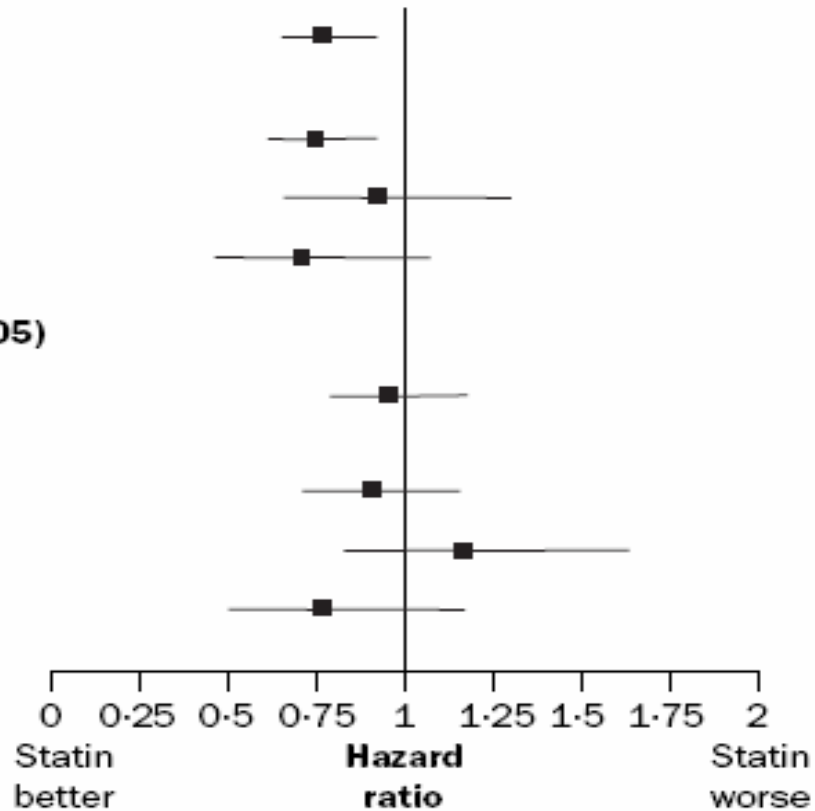


Figure 3: **Major cardiovascular outcomes, according to sex**
CHD=coronary heart disease. MI=myocardial infarction. TIA=transient ischaemic attack. The primary endpoint of the study is reproduced for comparative purposes.

J Shepherd et al. *– Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623*

ALLHAT-LLT

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

- 10.355 Pat., 48 % Frauen
- 66 ± 7,6 a
- LDL mäßig ↑ (129 ± 21 mg%)
- BMI 29 ± 6
- Hypertonie + 1 kardiosvaskulärer RF
- 40 mg Pravastatin vs. Placebo
- Kein Vorteil, da 30 % Statine in der Pl.gr.
- LDL-Senkung 17 vs. 8 %

The ALLHAT officers and coordinators for the ALLHAT collaborative research group.
Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antiihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002;288:2998

ALLHAT-LLT – Stroke outcome

	Pravastatin Event rate % + SD	**Usual care** Event rate % + SD	Relative Risk (95 % CI)
Stroke mortality	2,1 ± 0,3	2,0 ± 0,3	0,95 (0,66 – 1,39)
Stroke ***fatal and non-fatal***	5, 3 ± 0,4	5,8 ± 0,4	0,91 (0,75 – 1,09)

The ALLHAT officers and coordinators for the ALLHAT collaborative research group.
Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antiihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002;288:2998

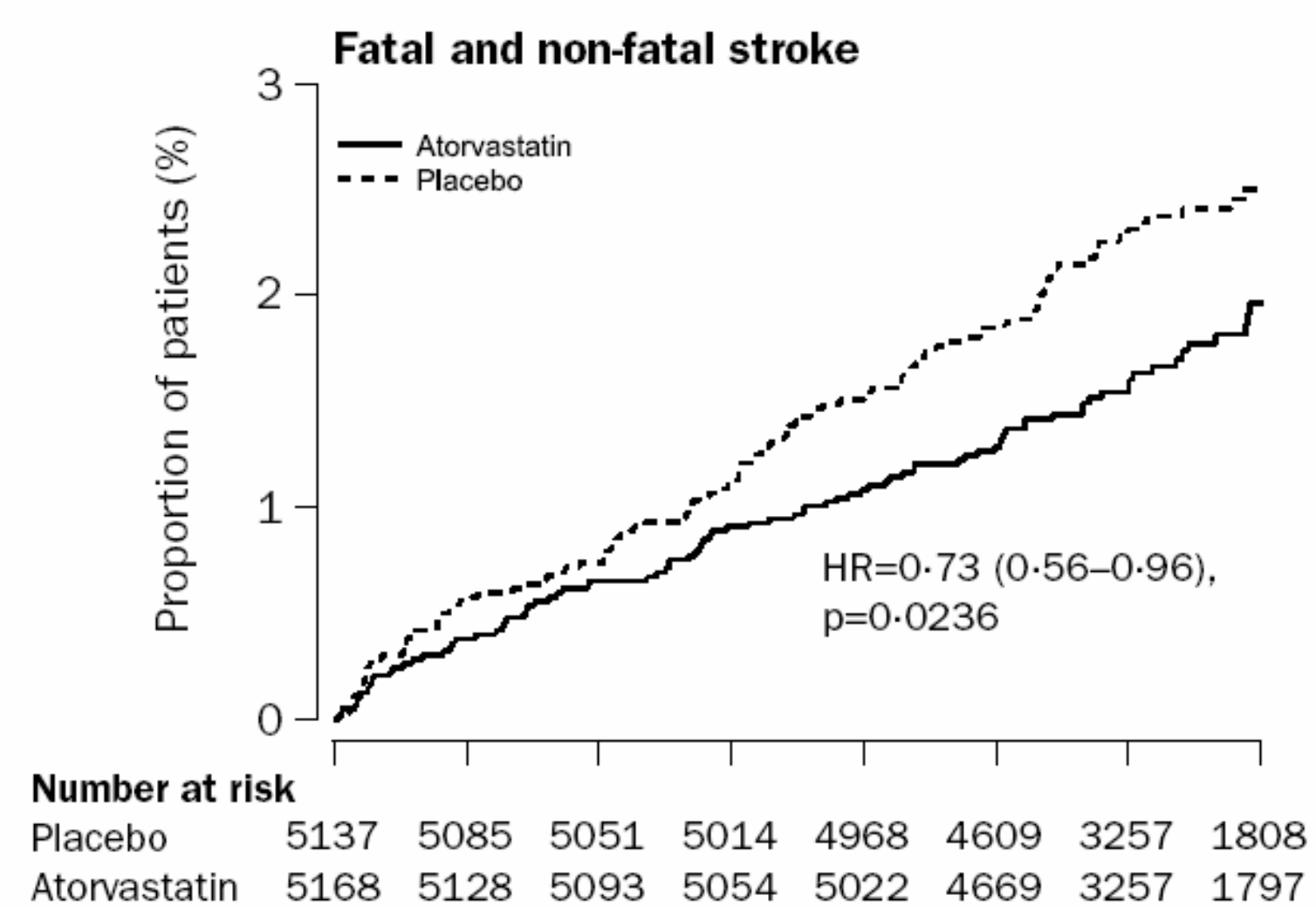
ASCOT-LLA

Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm I

- 10.305 Pat., 63 ± 8,5 a, 19 % Frauen, 95 % weiss, Ges.Chol. ≤ 242 mg%
- Hypertonie + 3 weitere kardiovaskul. RF
- Follow-up 3,3 a
- Prim. EP: n-fatal MI + fatal KHK
- **Signifikanz:** Prim. EP (p 0,0005)
- **Sek. EP:** alle CV-Ereignisse + Prozeduren, alle Koronarereignisse,Stroke
- **Tert.EP:** Chronische KHK

PS Sever et al *– Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentration, in the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA): a multicetre randomised controlled trial. Lancet 2003;361:1149*

ASCOT-LLA – Stroke outcome



PS Sever et al. *– Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentration, in the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA): a multicetre randomised controlled trial. Lancet 2003;361:1149*

CARDS

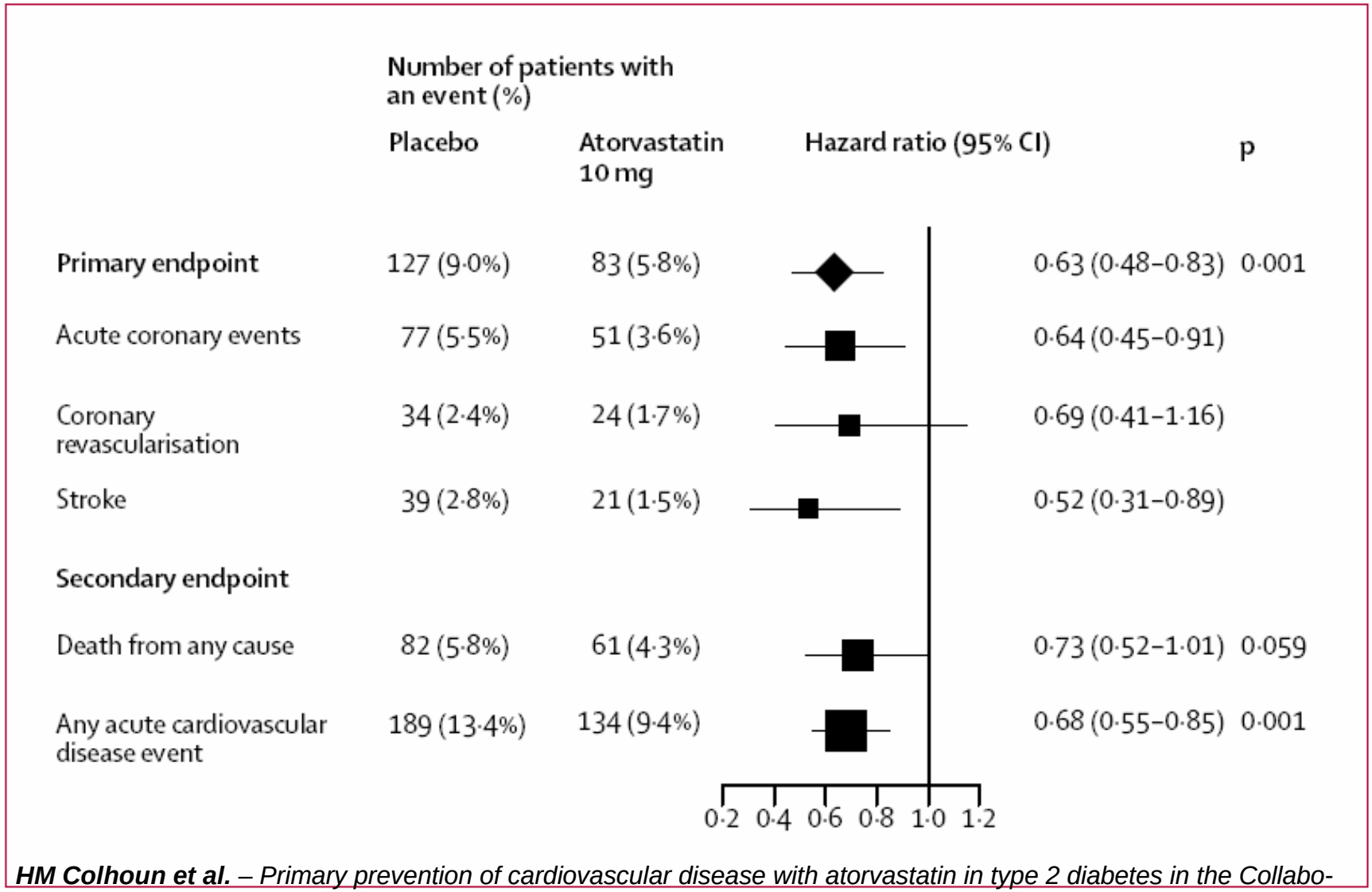
Collaborative Atovastatin Diabetes Study

- 2.838 Pat., 32 % Frauen, 94 % Weisse
- 61 a ± 8 a, 12 % ≥ 70 a, 38 % ≤ 60 a
- Diabetesdauer 7,8 ± 6,3 a, HbA1c 7,8 ± 1,4, BMI 28,8 ± 3,5
- Keine kardiovask. Vorerkrankung, LDL < 4,4, TG < 6,8 mmol/l
- 10 mg Atorvastatin vs. Placebo
- Median follow-up 3,9 a
- Prim. EP: Akute Koronarereignisse, Coronare Revaskularisation, Stroke (p < 0,001)

  Nicht: Revaskularisation, Mortalität p = 0,059
- ALLHAT-LIT + ASCOT-LLA **negativ**
- HPS **positiv**

HM Colhoun et al. *– Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685* ***A Garg*** *– Statins for all patients with type 2 diabetes: not to soon. Lancet 2004;364:641*

CARDS – Stroke outcome



HM Colhoun et al. *– Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685*

Heart Protection Study HPS

- 20.536 Pat.,
- 40-80 a, 24 % > 70 a
- 40 mg Simvastatin vs. Placebo
- LDL ≤ 132 mg%
- Follow-up 5 a
- Ges.Mortalität ↓ 13 % (p=0,0003)
- Non-fatal MI, Koronarer Tod + Stroke ↓ 25 % (p<0,0001)
- Keine Unterschiede i.d. Ergebnissen bei Diabetes, Frauen, Alten (> 70a)
- Placebogruppe : 17 % Statine

MRC/BHF Heart Protection Study *of cholesterol lowering with simvastatin in 20.536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;29:7*

HPS - Stroke outcome I

Type of major vascular event	Simvastatin-allocated (10 269)	Placebo-allocated (10 267)	Event rate ratio (95% CI)
Coronary events			
Non-fatal MI	357 (3·5%)	574 (5·6%)	
Coronary death	587 (5·7%)	707 (6·9%)	
Subtotal: major coronary event	**898 (8·7%)**	**1212 (11·8%)**	**0·73 (0·67–0·79) p<0·0001**
Strokes			
Non-fatal stroke	366 (3·6%)	499 (4·9%)	
Fatal stroke	96 (0·9%)	119 (1·2%)	
Subtotal: any stroke	**444 (4·3%)**	**585 (5·7%)**	**0·75 (0·66–0·85) p<0·0001**
Revascularisations			
Coronary	513 (5·0%)	725 (7·1%)	
Non-coronary	450 (4·4%)	532 (5·2%)	
Subtotal: any revascularisation	**939 (9·1%)**	**1205 (11·7%)**	**0·76 (0·70–0·83) p<0·0001**
ANY MAJOR VASCULAR EVENT	**2033 (19·8%)**	**2585 (25·2%)**	**0·76 (0·72–0·81) p<0·0001**

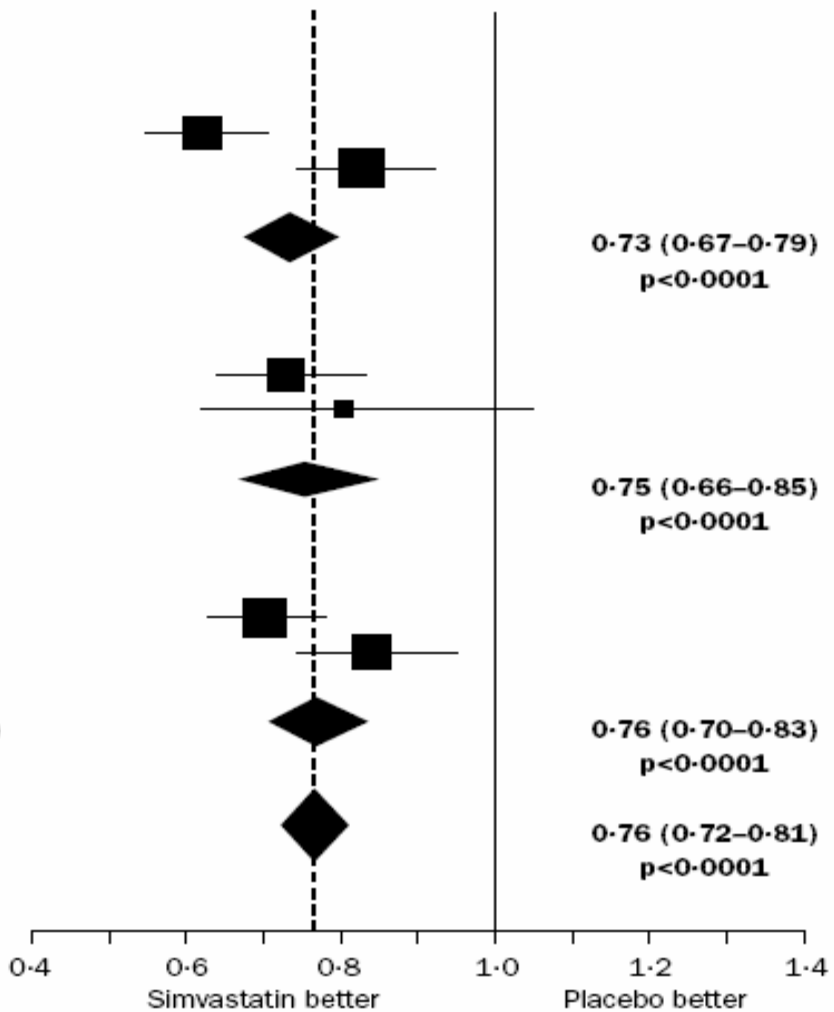


Figure 3: **Effects of simvastatin allocation on first major coronary event, stroke, and revascularisation (defined prospectively as ts")**

MRC/BHF Heart Protection Study *of cholesterol lowering with simvastatin in 20.536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;29:7*

HPS - Stroke outcome II

Type and severity of stroke	Simvastatin-allocated (10 269)	Placebo-allocated (10 267)
Type		
Ischaemic	290 (2·8%)	409 (4·0%)
Haemorrhagic	51 (0·5%)	53 (0·5%)
Not classified	103 (1·0%)	134 (1·3%)
Severity		
Fatal	96 (0·9%)	119 (1·2%)
Severe	42 (0·4%)	51 (0·5%)
Moderate	107 (1·0%)	155 (1·5%)
Mild	138 (1·3%)	189 (1·8%)
Not classified	61 (0·6%)	71 (0·7%)
ANY STROKE	**444 (4·3%)**	**585 (5·7%)**

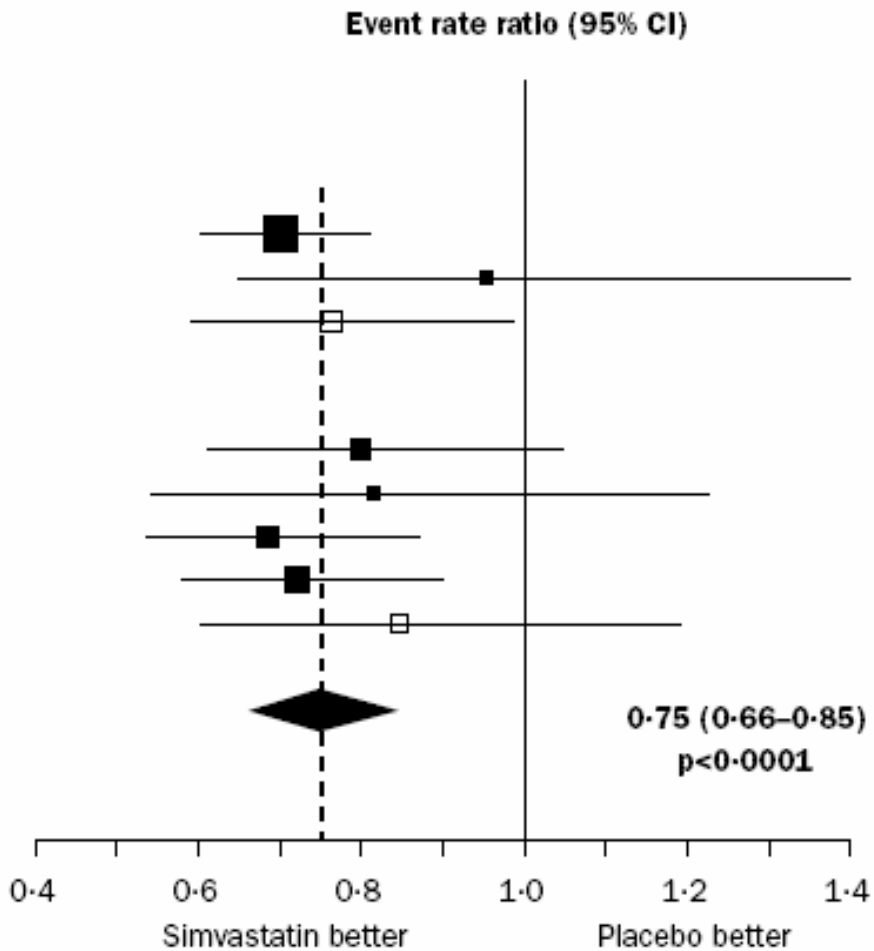


Figure 4: **Effects of simvastatin allocation on first stroke**

MRC/BHF Heart Protection Study *of cholesterol lowering with simvastatin in 20.536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;29:7*

Statine im Alter > 80 a ?

PRO

- Statine sind effektiv + sicher
- Benefit für Hochrisikopatienten
- HDL ↓
- CRP ↑
- Manifester kardiovaskulärer KH

CONTRA

- Nutzen > 65 a unsicher
- Cholesterin ausser bei KHK nicht assoziiert
- Nutzen > 80 a nicht belegt
- Risiken (Myositis, Rhabdomyolyse, Krebs)
- Behandlung im Einzelfall mit Pat. besprechen

NJ Stone *– Are statins indicated for the primary prevention of coronary heart disease in octogenarians? Protagonist viewpoint. Am J Geriatr Cardiol 2003;12:351*
JM Foody, HM Krumholz *– Are statins indicated for the primary prevention of CAD in octogenarians? Antagonist viewpoint. Am J Geriatr Cardiol 2003;12:357*

Observationsstudie

- 488 M + 922 F
- 81 ± 9 a
- LDL-Cholesterin > 125 mg%
- Follow-up 36 ± 21 Monate

	Coronar events by age	New brain infarction
60 – 70 a:	36 vs 51 % (p 0,038)	13 vs 28 % (p 0,005)
71 – 80 a:	43 vs 75 % (p <0,0001)	16 vs 33 % (p 0,0001)
81 – 90 a:	49 vs 74 % (p <0,0001)	14 vs 24 % (p 0,002)
91 – 100 a:	56 vs 81 % (p <0,0004)	14 vs 20 % (p 0,323)

WS Aronow et al. *– Incidence of new coronary events in older persons with prior myocardial infarction and serum low-density lipoprotein cholesterol > 125 mg/dl treated with statins versus no lipid-lowering drug. Am J Cardiol 2002;89:67*
WS Aronow et al. *– Incidence of new atherothrombotic brain infarction in older persons with prior myocardial infarction and serum low-density lipoprotein cholesterol > 125 md/dl treated with statins versus no lipid-lowering drug. J Gerontol 2002;57A:333*

Cardiovascular Health Study II

Ges.-Chol. / LDL-Chol./ HDL-Chol. / Triglyc.

Adjusted model for age, sex, diabetes, smoking status, cardiovascular disease, systolic blood pressure

MI	HDL-Chol.	p = 0,006
Hem. Stroke	./.	
Isch. Stroke	LDL-Chol.	p = 0,038
	Ges.-Chol.	p = 0,031
Tod	./.	

BM Psaty et al. *– The association between lipid levels and the risks of incident myocardial infarction, stroke, and total mortality: The Cardiovascular Health Study. J Am Geriatr Soc 2004;52:1639*

Statine contra

- Epidemiologische Daten belegen Zusammenhang Stroke und Hypercholesterinämie nicht
- Cholesterinsenkung ist ohne nachweisbaren Nutzen
- Kosten-Nutzen-Effektivität ?
- Keine Daten für geriatrische Patienten > (75) 80 a
- Studiendaten sind widersprüchlich

TS Bowman et al. *– Cholesterol and the risk of stroke. Stroke 2003;34:2930*

GJ Hankey et al. *– Treatment and secondary prevention of stroke: evidence, costs, and effects on individuals and populations. Lancet 1999;354:1457*

B Manktelow et al. *– Interventions in the management of serum lipids for preventing stroke recurrence. The Cochrane Data Basis of Systemativ Reviews 2002, Issue 3*

TA Jacobson *– „The lower the better" in hypercholesterolemia therapy: A reliable clinical guideline? Ann Intern Med 2000;133:549*

P Amarenco *– Statins for stroke prevention. Disappointment and hope. Circulation 2004;109[suppl III]:III-44*

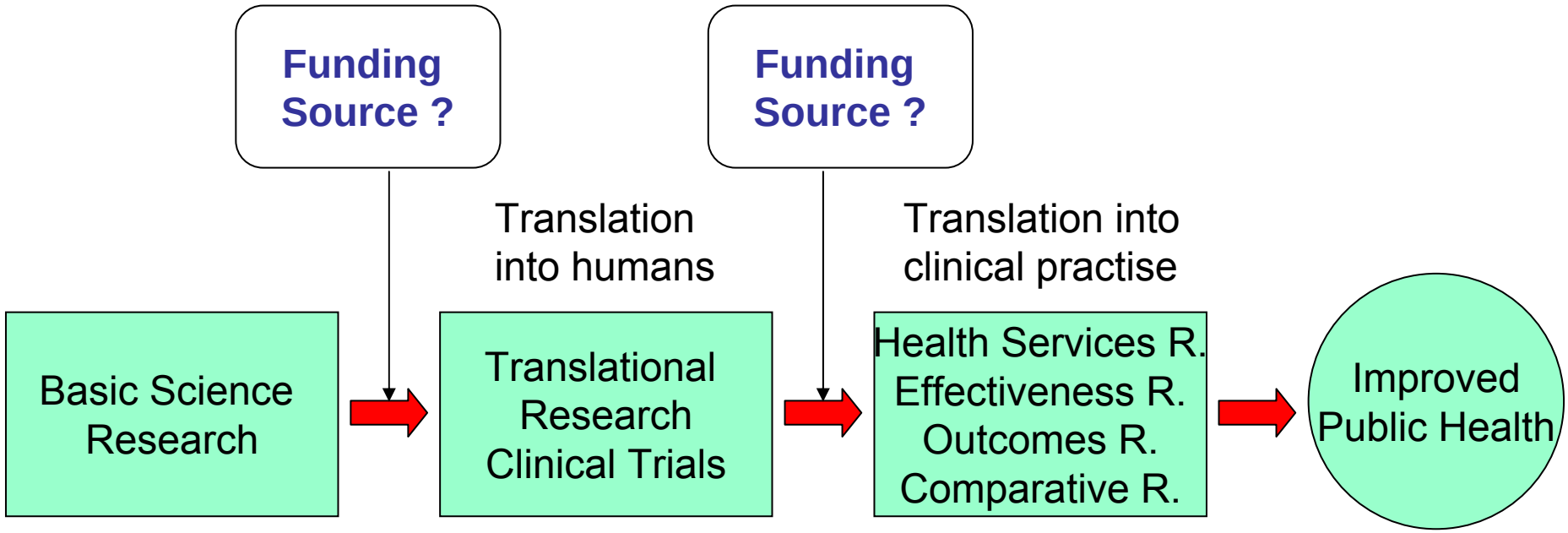
AG Thrift *– Cholesterol is associated with stroke, but is not a risk factor. Stroke 2004;35:1524*

GA Donnan et al. *– Stroke and cholsterol. Weakness of risk versus strength of therapy. Stroke 2004;35:1526*

JG Ray et al. *– Statin use and survival outcomes in elderly patients with heart failure. Arch Intern Med 2005;165:62*

J-C Corvol et al.*– Differential effects of lipid-lowering therapies on stroke prevention. A meta-analysis of randomized trials. Arch Intern Med 2003;163:669-676*

Quo vadis I ?



WP Crowley et al *– Clinical research in the United States at a crossroad. JAMA 2004;291:1120*

Quo vadis II ?

Randomisierungsrate

HPS: von 63.603 Pat. → 20.536 (32 %)
PROSPER: von 23.770 Pat. → 5.804 (25 %)
ALLHAT-LLT: von 42.418 Pat. → 10.355 (25 %)
ASCOT-LLA: von 19.342 Pat. → 10.305 (52 %)
PROVE-IT: k.A.
REVERSAL: von 2.163 Pat. → 657 (30 %)
CARDS: von 4.053 Pat. → 2.841 (70 %)

Thrombozytenaggregationshemmer

HPS: KA
Prosper: KA
ALLHAT-LLT: 30,3 vs. 31,6 %
ASCOT-LLA: 17,1 vs. 16,9 %
CARDS: 15 %

Pleiotrope Funktion von Statinen

- Entzündliche Prozesse
- Oxidative Prozesse
- Thrombotische Prozesse

JT Willerson et al. *– Inflammation as a cardiovascular risk factor. Circulation 2004;109 [suppl II]:II-2*
F Mach *– Statins as immunomodulatory agents. Circulation 2004;109 [suppl II]:II-15*
U Schönbeck et al. *– Inflammation, Immunity, and HMG-CoA reductase inhibitors. Statins as antiinflammatory agents? Circulation 2004;109[suppl II]:18*
U Landmesser et al. *– Endothelial function. A critical determinant in arteriosclerosis? Circulation 2004;109[suppl II]:II-27*
PR Mason et al. *– Effects of HMG-CoA reductase inhibitors on endethelial function. Role of microdomains and oxidative stress. Circulation 2004;109[suppl II]:II-34*
JPJ Halcox et al. *– Beyond the Laboratory. Clinical implications for statin pleiotropy. Circulation 2004;109[suppl II]:II-42*
M Endres et al. *– Effects of statins on endothelium and signaling mechanism. Stroke 2004;35[suppl I]:2708*
TJ DeGraba *– Immunogenetic susceptibility of atherosclerotic stroke. Implications on current and future treatment of vascular inflammation. Stroke 2004;35[suppl I]:2712*
K Becker et al. *– Role of statins in the treatment and prevention of stroke. Introduction. Stroke 2004;35[suppl I]:2706*
M Igel et al. *– Nichtlipidsenkende Effekte von Statinen. DÄ 2004;101:A352*

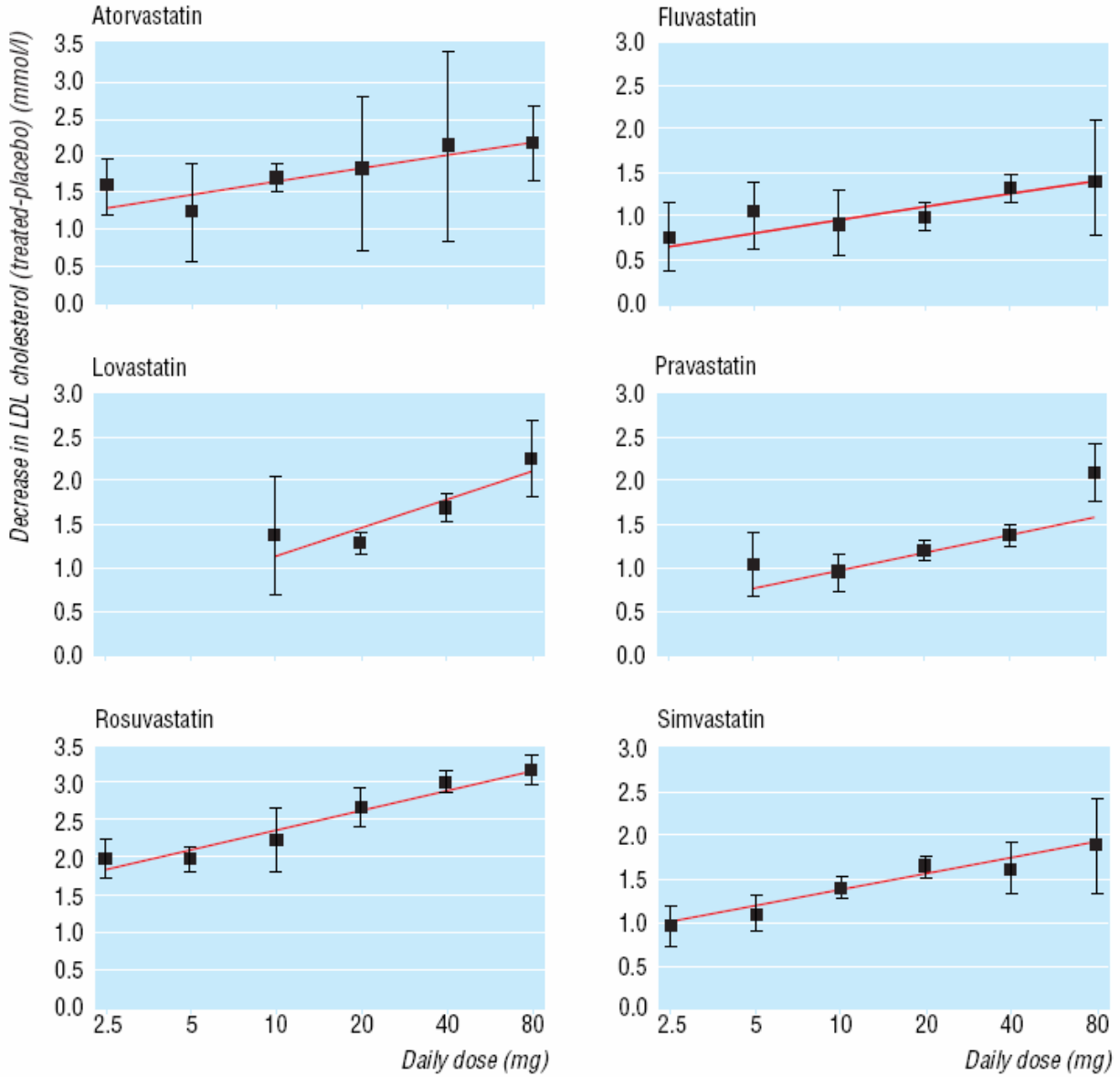


Fig 1 Average reductions in LDL cholesterol concentration (95% confidence intervals) in the 164 trials according to statin and dose (not standardised to pretreatment serum cholesterol concentration)

MR Law et al. *– Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 2003;326:1423*

Take Home Message

- ✓ **Evidenz für KHK mit erhöhten LDL-Cholesterin bis 80 a**
- Zielgrösse der LDL-Senkung unklar
- Evidenz für Stroke, Diabetes etc. unklar
- RCT´s mit Patienten > 80 a nicht existent
- Im Einzelfall diskutieren
- Cave Multipharmakotherapie
- Evidenz einzelne Substanz vs. Klasseneffekt unklar
- Evidenz für Kombinationstherapie im hohen Lebensalter unklar
- Evidenz bei Multimorbidität unklar
- Evidenz bei vaskulärer und Alzheimer-Demenz unklar
- Lifestyle-Intervention generell empfohlen

Das Polypill-Konzept

Table 1 Effects of the Polypill on the risks of ischaemic heart disease (IHD) and stroke after two years of treatment at age 55-64

Risk factor	Agent	Reduction in risk factor	% reduction in risk (95% CI)*		Source of evidence
			IHD event	Stroke	
LDL cholesterol *	Statin†	1.8 mmol/l (70 mg/dl) reduction in LDL cholesterol	61 (51 to 71)	17 (9 to 25)	Law et al[1]
Blood pressure	Three classes of drug at half standard dose	11 mm Hg diastolic	46 (39 to 53)	63 (55 to 70)	Law et al[16]
Serum homocysteine	Folic acid (0.8 mg/day)	3 µmol/l	16 (11 to 20)	24 (15 to 33)	Wald et al[9]
Platelet function	Aspirin (75 mg/day)	Not quantified	32 (23 to 40)	16 (7 to 25)	Table A on bmj.com
Combined effect	All		88 (84 to 91)	80 (71 to 87)	

* *Thiazid, ß-Blocker und ACE-Hemmer*

Table 2 Expected benefits in 100 men and 100 women without a known vascular disease who start taking the Polypill at age 55. Calculations are based on a Markov model and allow for other causes of death

Age (years)	Men		Women	
	No who benefit*	Years gained†	No who benefit*	Years gained†
Up to 65	7	21	3	24
Up to 75	18	16	11	18
Up to 85	30	13	24	14
Up to any age	36	12	35	11

NJ Wald, MR Law *– A strategy to reduce cardiovascular disease by more than 80 %. BMJ 2003;326:1419*

Das Polymeal-Konzept

Table 1 Effect of ingredients of Polymeal in reducing risk of cardiovascular disease

Ingredients	Percentage reduction (95% CI) in risk of CVD	Source
Wine (150 ml/day)	32 (23 to 41)	Di Castelnuovo et al (MA)[6]
Fish (114 g four times/week)	14 (8 to 19)	Whelton et al (MA)[7]
Dark chocolate (100 g/day)	21 (14 to 27)	Taubert et al (RCT)[8]
Fruit and vegetables (400 g/day)	21 (14 to 27)	John et al (RCT)[10]
Garlic (2.7 g/day)	25 (21 to 27)	Ackermann et al (MA)[11]
Almonds (68 g/day)	12.5 (10.5 to 13.5)	Jenkins et al (RCT),[15] Sabate et al (RCT)[16]
Combined effect	76 (63 to 84)	

CVD=cardiovascular disease; MA=meta-analysis; RCT=randomised controlled trial.

OH Franco et al. *– The Polymeal: a more natural, safer, and probably tastier (than the Polypill) strategy to reduce Cardiovascular disease by more than 75 %.*
BMJ 2004;329:1447

Table 2 Lifetime effect (years) of Polymeal at age 50, stratified by sex

Intervention	Total life expectancy		Life expectancy free from CVD		Life expectancy with CVD	
	Effect	Difference	Effect	Difference	Effect	Difference
Men:						
None (overall)	28.7	Ref	21.0	Ref	7.7	Ref
Polymeal	35.2	6.6	30.0	9.0	5.3	–2.4
Women:						
None (overall)	34.2	Ref	26.9	Ref	7.3	Ref
Polymeal	39.0	4.8	35.0	8.1	4.0	–3.3

CVD=cardiovascular disease; Ref=reference value.