Cholesterinsenkung im Alter – was ist gesichert ?

Vorsymposium der Sektion Geriatrie im BDI

111. Kongress DGIM

Wiesbaden 02. April 2005

M. Gogol Coppenbrügge

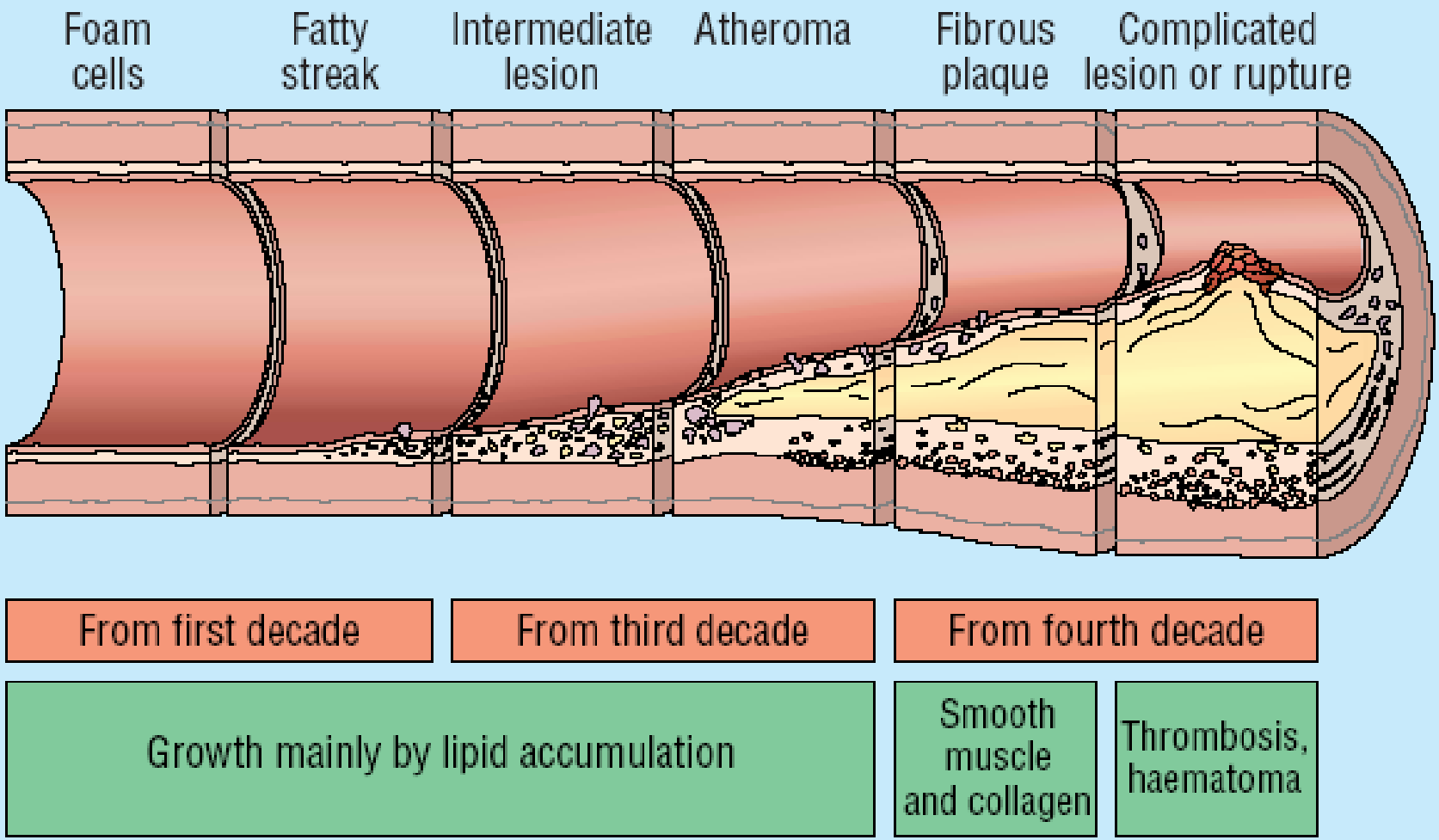
KRANKENHAUS LINDENBRUNN

Ateriosklerose

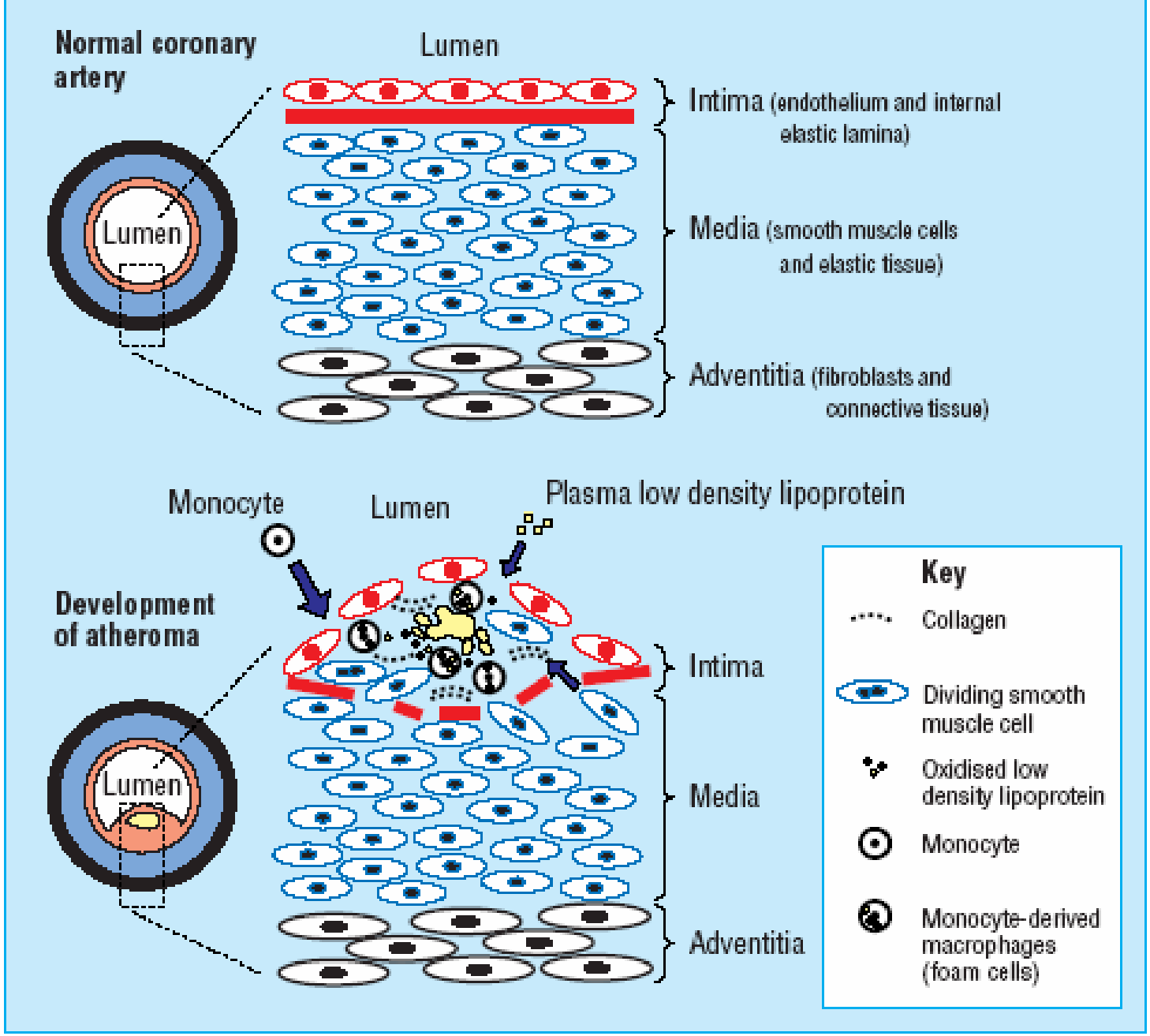
- **Chronisch-inflammatorischer Prozess**
- **Plaqueruptur**

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;344:2016-2018*
P Libby *– Inflammation in atherosclerosis. Nature 2002;420:868-874*
JS Forrester *– Prevention of plaque rupture: a new paradigm of therapy. Ann Intern Med 2002;137:823-833*



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



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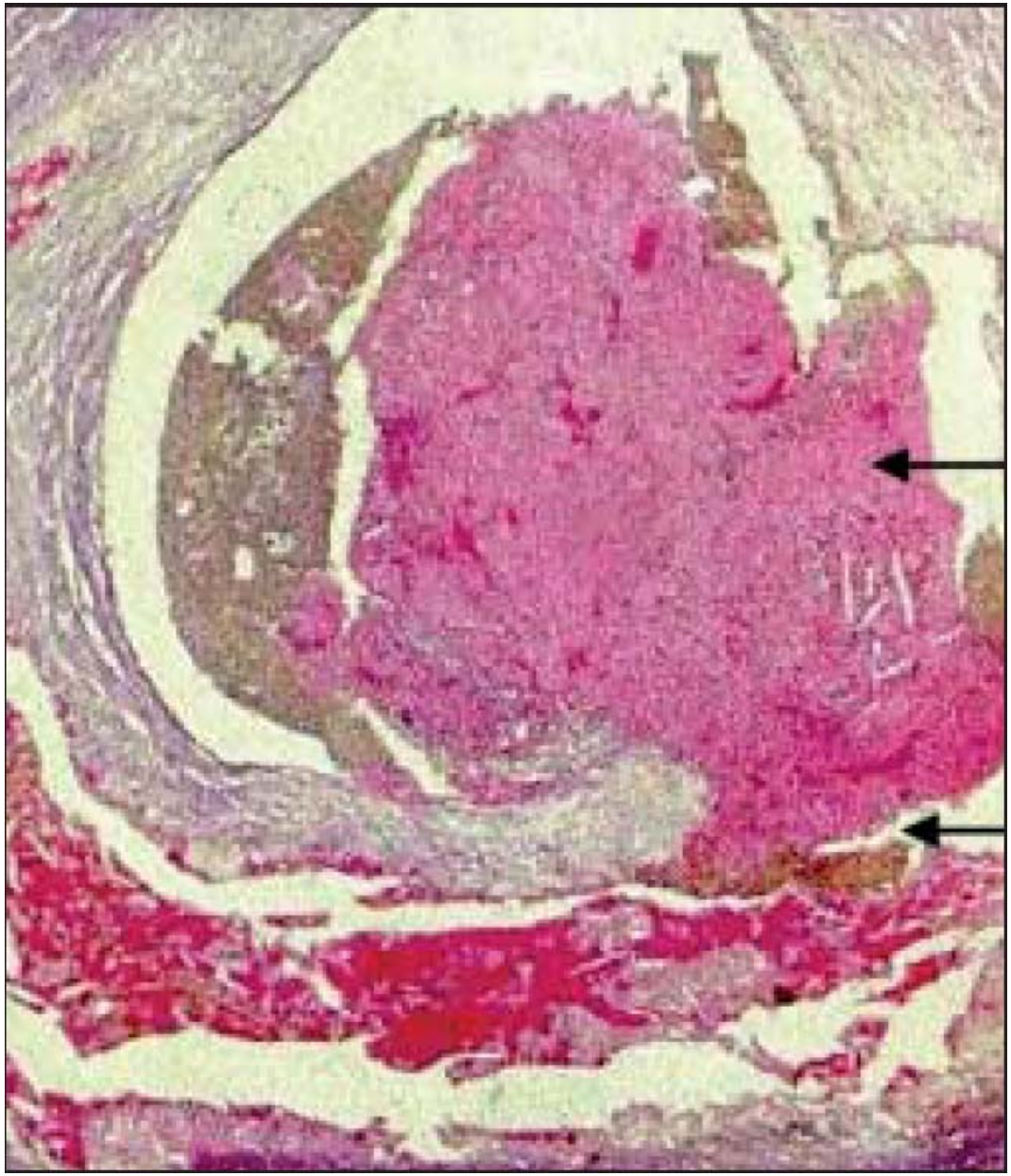


ED Grech et al *– Acute coronary syndrome: ST segment elevation myocardial infarction. BMJ 2003;326:1379*

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 RCTs 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*

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*

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;360:7*

PROSPER I

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 II

Prospective Study of Pravastatin in the Elderly at Risk

- Kombin. Prim. EP ↓ 15 % (p=0,014)
- KHK Tod ↓ 24 % (p=0,043)
- N-fatal MI ↓
- New cancer ↑

- Effekte **NICHT** bei Frauen
- Effekte bei HDL < 1,11 mmol/l und **KEIN** Diabetes
- Primärprävention **NS**
- Sekundärprävention TIA/Stroke **NS**

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

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

Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm II

Sek. / Tert. EP n.s.

- Gesamtmortalität
- Kardiovaskul. Mortalität
- Herzinsuffizienz
- Stummer MI
- Instabile AP
- pAVK
- Diabetes-Entwicklung
- Niereninsuff.-Entwicklung

Subgruppenanalyse n.s.

- Diabetes
- LVH
- Frauen
- Vorbesteh. Gefäßerkrankungen
- Niereninsuffizienz
- Metabol. Syndrom
- Alter ≤ 60 a

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*

PROVE-IT

Pravastatin or Atorvastatin Evaluation and InfectionTherapy

- Akutes Koronarsyndrom
- 4.162 Pat., 58 ± 11 a, 78 % Männer, 90 % Weisse, LDL 106, HDL 39 mg%
- Follow-up 24 (18-36) Monate
- 40 mg Pravastatin vs. 80 mg Atorvastatin
- Atorv. ↓ 16 % LDL ($p < 0{,}005$)
- **NS:** > 65a, Diabetes, vorh. Statintherapie, LDL < 125, HDL </> 40

CP Cannon et al *– Comparison of intensive and moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350;1495*

REVERSAL

Reversal of Atherosclerosis with Aggressive Lipid Lowering Trial

- Symptomatische KHK
- Angiographie ≥ 20 % Stenose
- LDL 125-210 mg%
- 654 Pat. (56 ± 9 a, BMI 30,5, 72 % M, 87-90 % weiss)
- 18 Monate Laufzeit
- 80 mg Atorvastin vs. 40 mg Pravastatin
- KH-Progression Atorv. < Pravast. (p 0,02)
- LDL 79 vs. 110 (p < 0,001)
- Klinik: keine Unterschiede
- 25 % lost to follow-up

SE Nissen et al *– Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomised controlled trial.* ***JAMA*** *2004;291:1071-1080*
FM Sacks *– High-intensity statin treatment for coronary heart disease. JAMA 2004:291:1132*

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*
AS Gami et al *– Comment. ACP Journal Club 2005 March/April;142:29*

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*

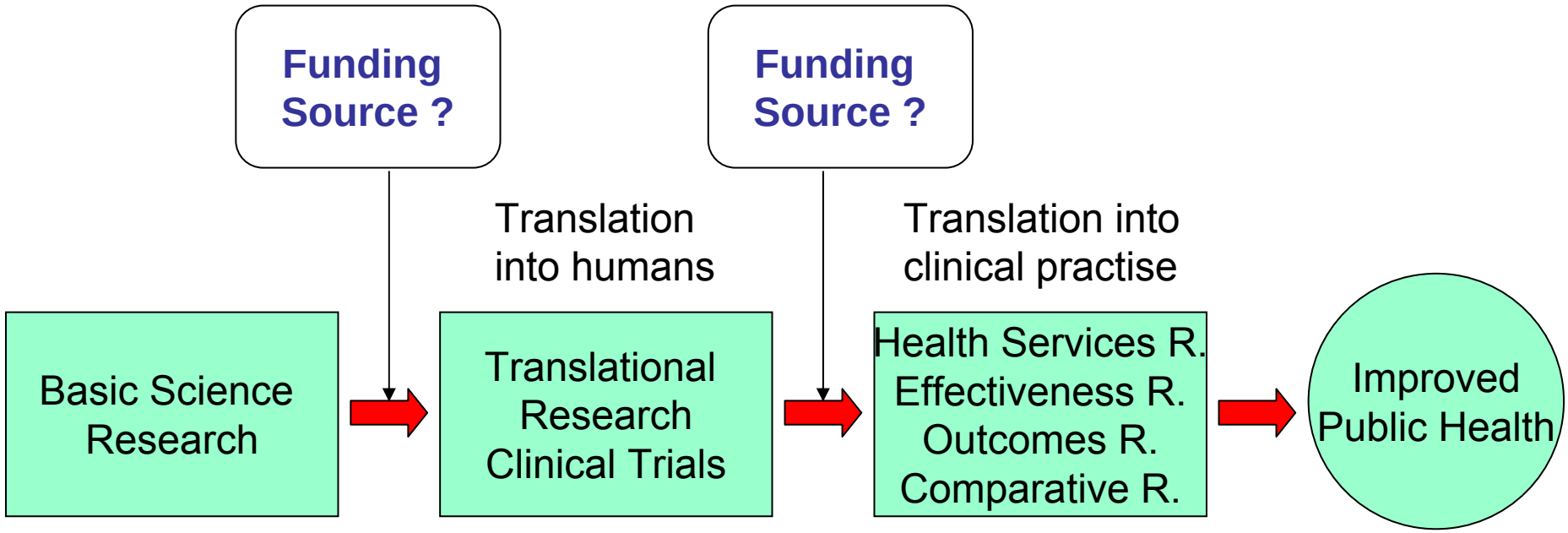
Observationsstudie

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

	Coronar events	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*

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

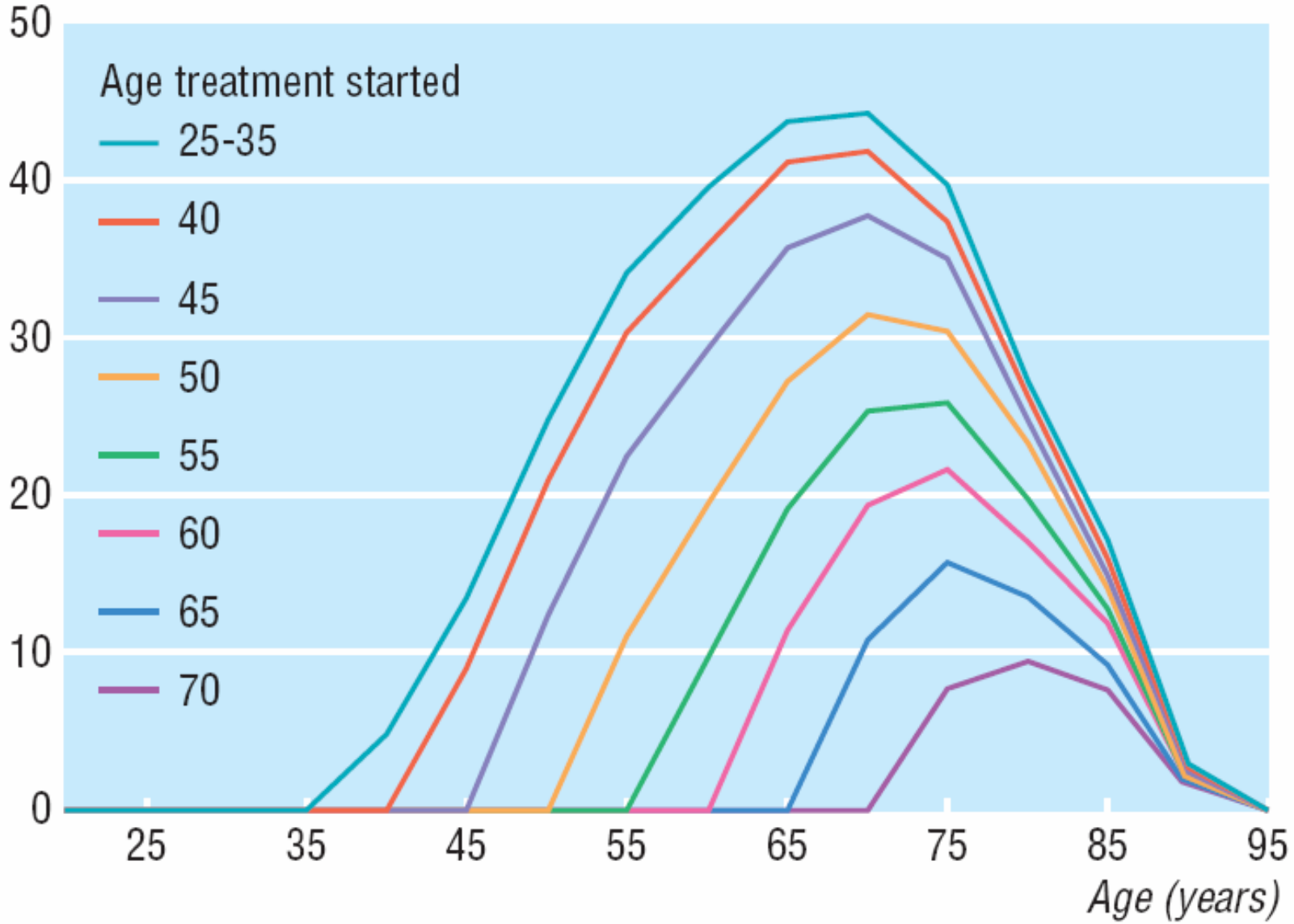
HPS: KA
Prosper: KA
ALLHAT-LLT: 30,3 vs. 31,6 %
ASCOT-LLA: 17,1 vs. 16,9 %
CARDS: 15 %

Statine Pro

„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*

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*

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

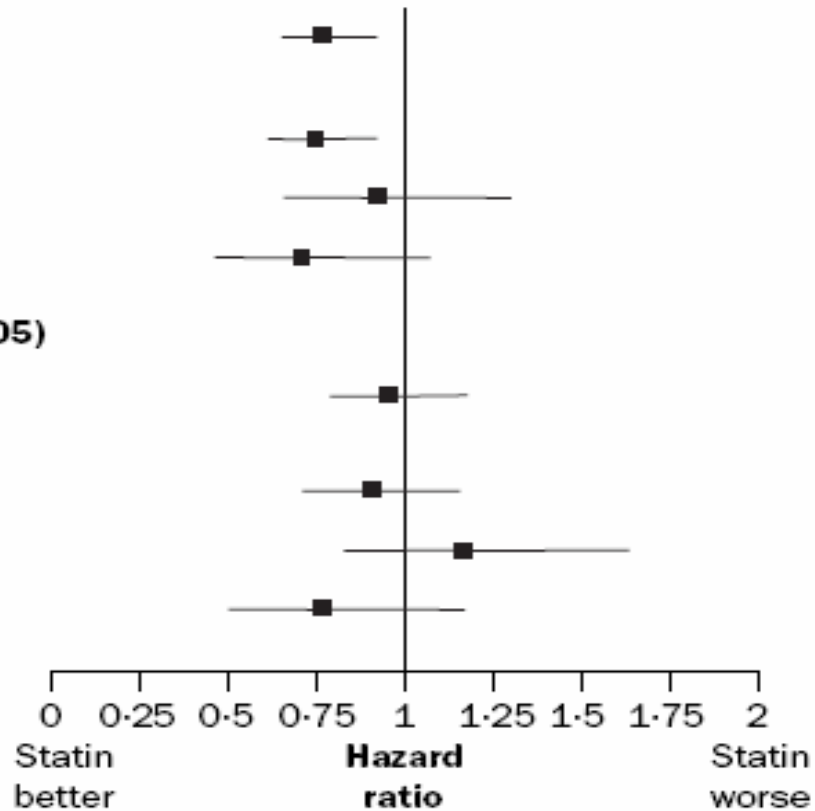


Figure 3: **Major cardiovascular outcomes, according to sex**
CHD=coronary heart disease. MI=myocardial infarction. TIA=transient ischaemic attack. The primary endpoint of the study is reproduced for comparative purposes.

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

ALLHAT-LLT – 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)

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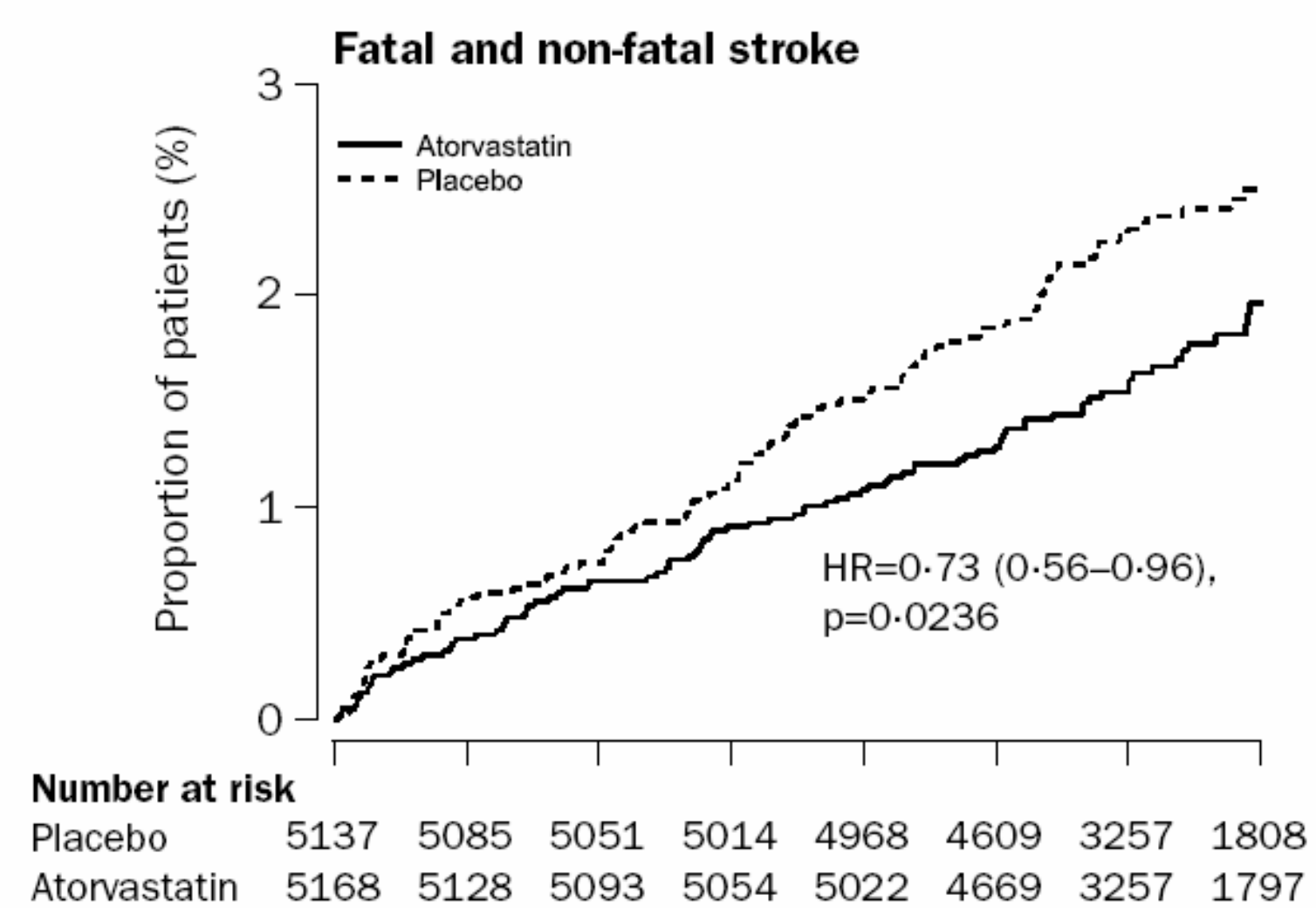
Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antiihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002;288:2998

ASCOT-LLA – Stroke outcome



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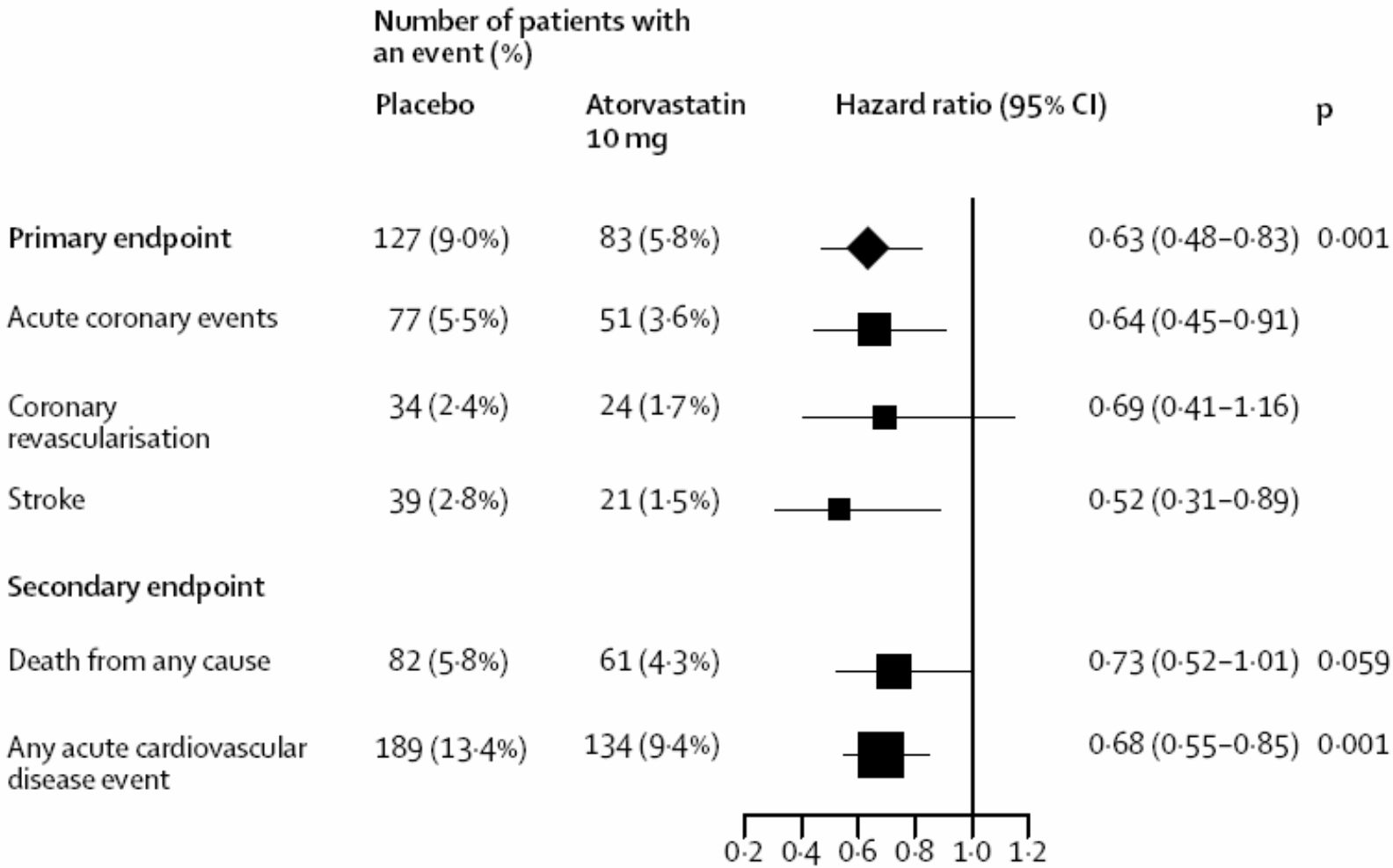
CARDS – Stroke outcome



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*

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**

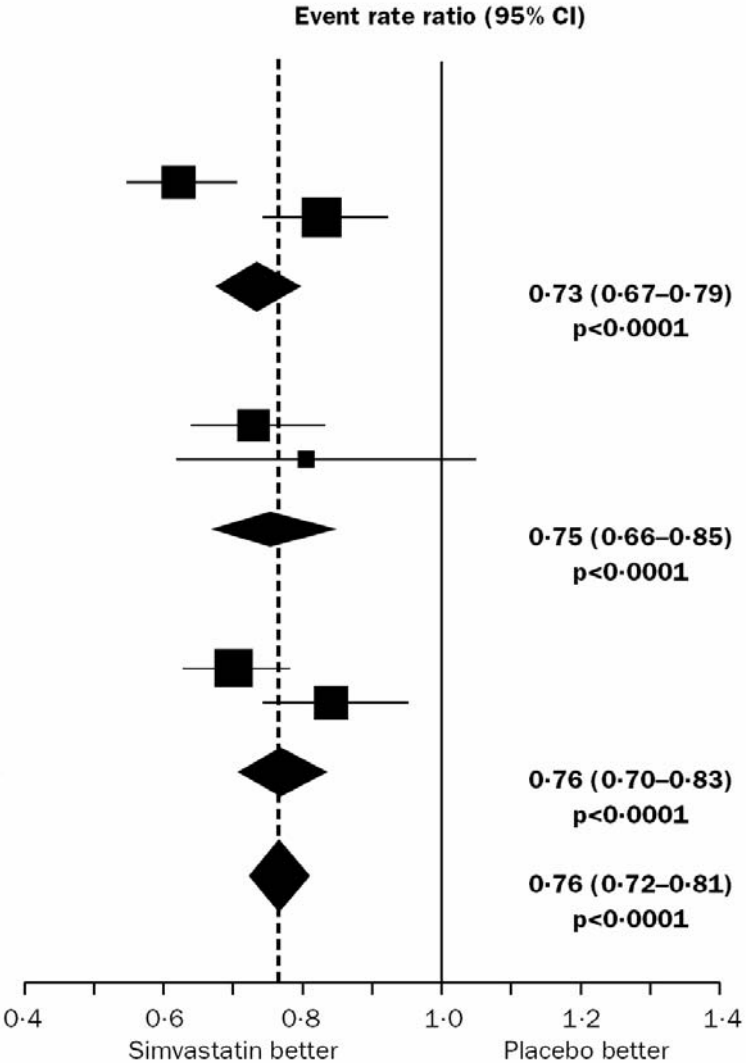


Figure 3: **Effects of simvastatin allocation on first major coronary event, stroke, and revascularisation (defined prospectively as "major vascular events")**

MRC/BHF Heart Protection Study *of cholesterol lowering with simvastatin in 20.536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7*

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%)**

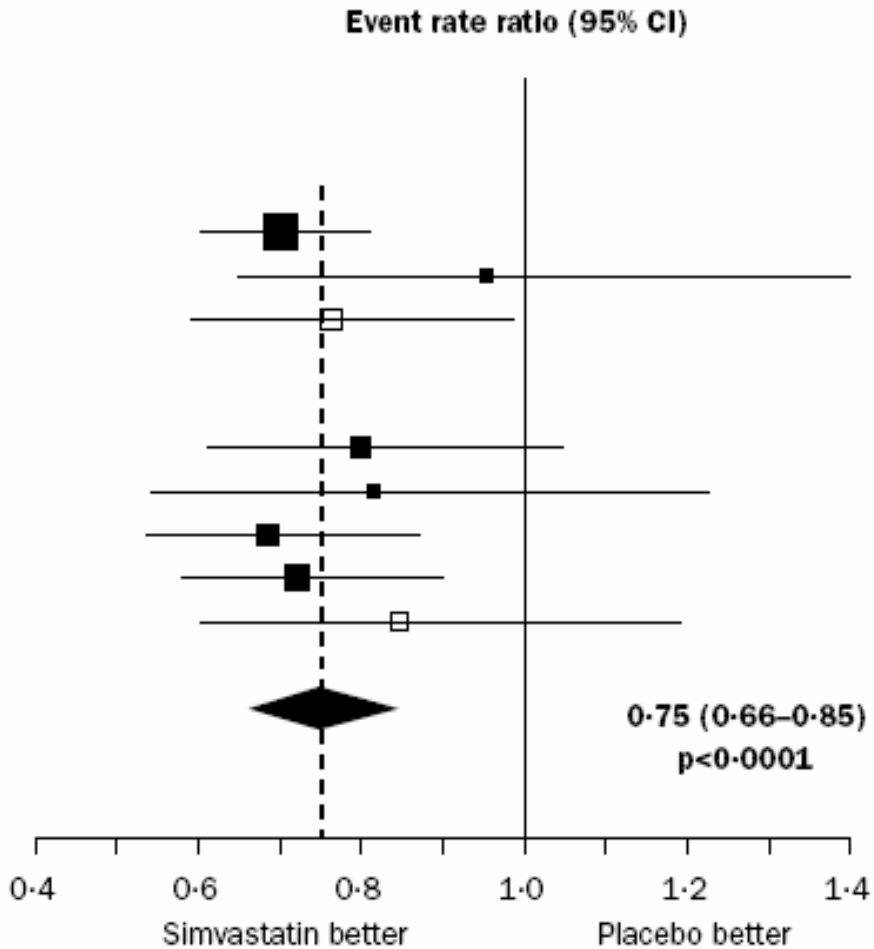


Figure 4: **Effects of simvastatin allocation on first stroke**

MRC/BHF Heart Protection Study *of cholesterol lowering with simvastatin in 20.536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7*


Evidence b(i)ased
BMJ 30.10.2004

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