Cholesterinsenkung im Alter – was ist gesichert ?

20. Bad Nauheimer Gerontologisch/Geriatrisches Symposium

Bad Nauheim 13. November 2004

M. Gogol Coppenbrügge

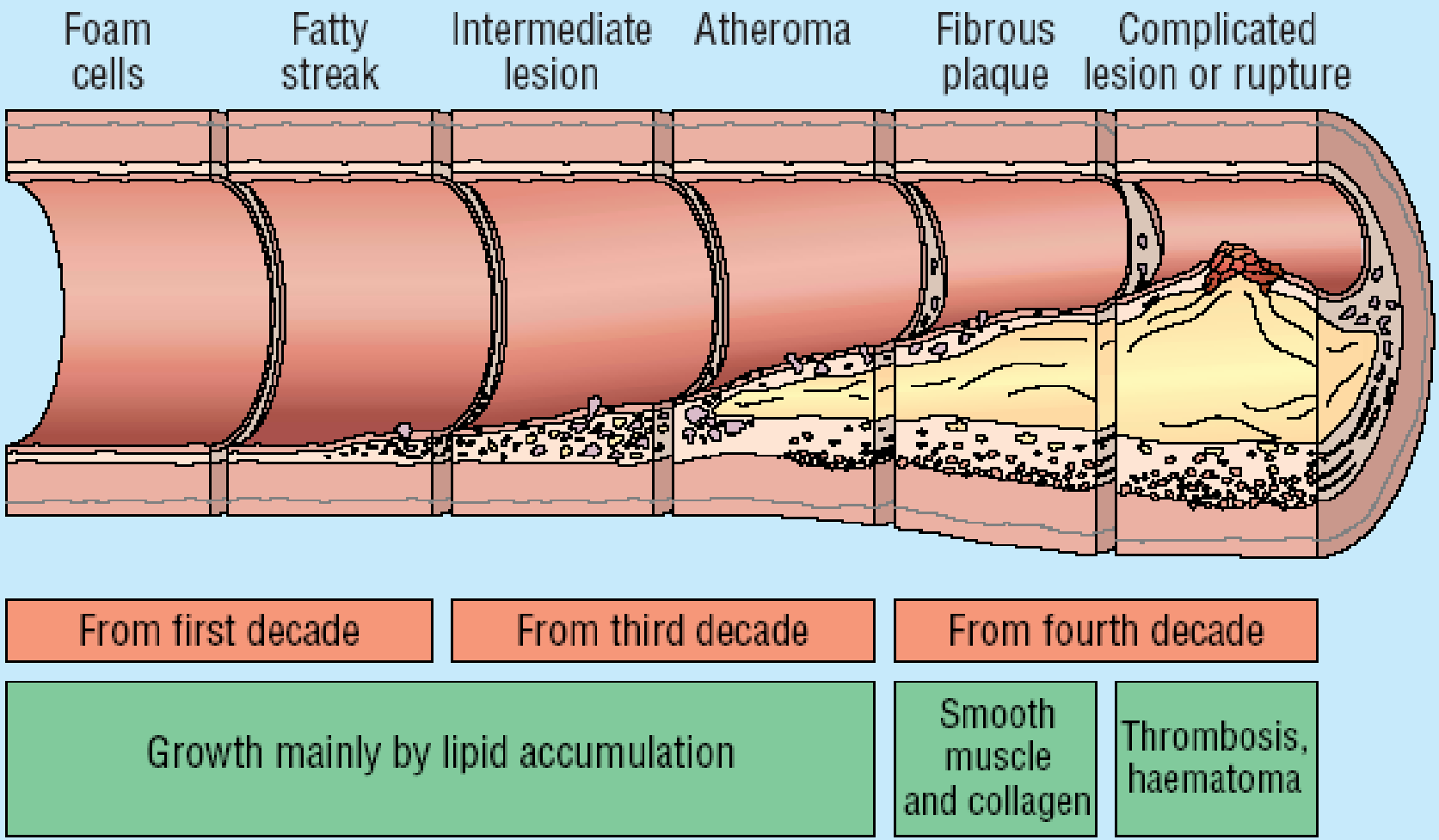
KRANKENHAUS LINDENBRUNN

Ateriosklerose

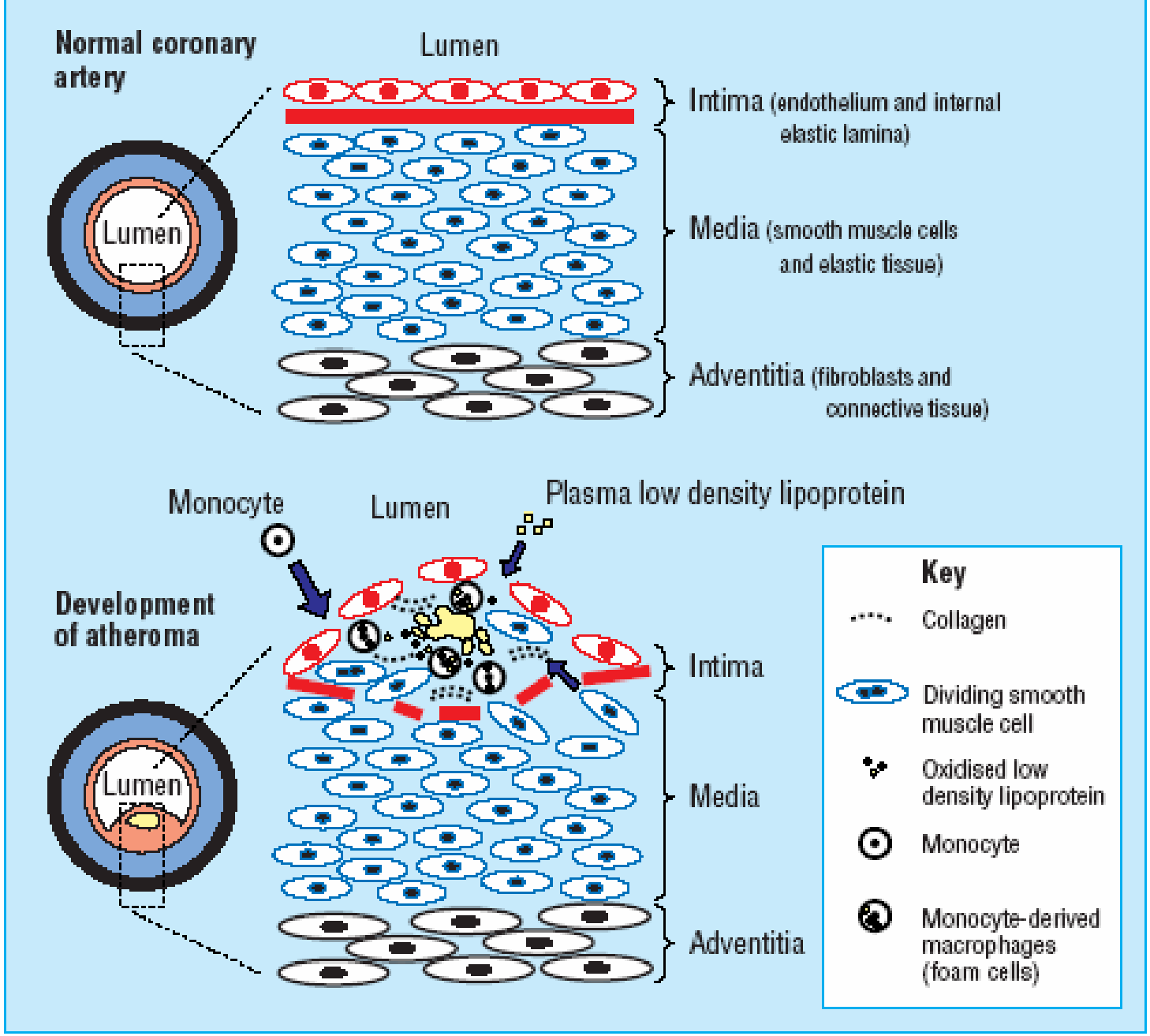
- **Chronisch-inflammatorischer Prozess**
- **Plaqueruptur**

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;326:1027-1030



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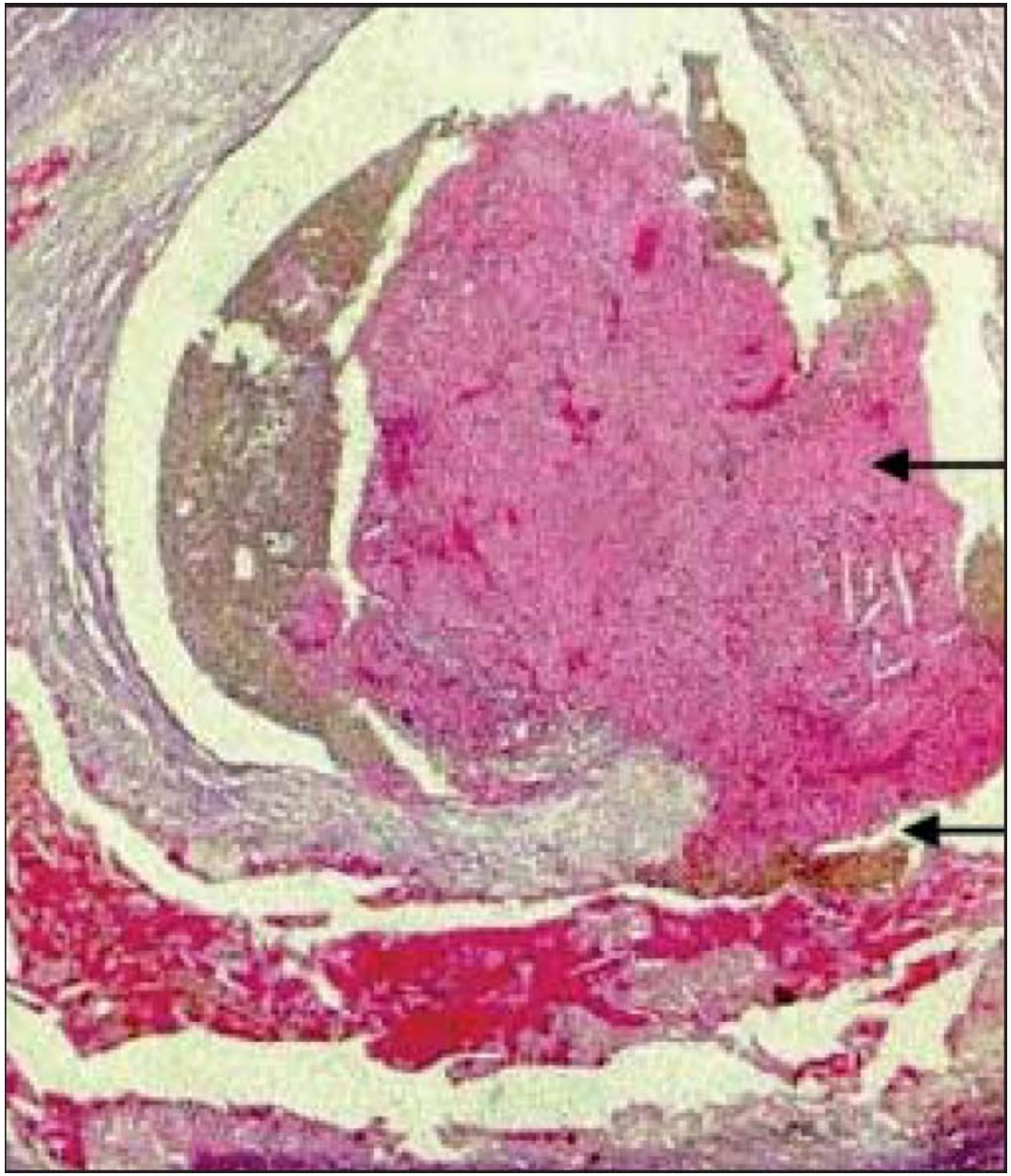


ED Grech et al – Acute coronary syndrome: ST segment elevation myocardial infarction. **BMJ** 2003;326:1379-1381

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;282:2340-6

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;50:391-393

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;89:327-328

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;110:227-239
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;110:227-239
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

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;162:1395-1400

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;29:7-22

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;360:1623-1630

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**

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;288:2998-3007

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;361:1149-1158

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;361:1149-1158

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;1495-1504

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** 2004:291:1132-1134

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;364:685-696

A Garg – Statins for all patients with type 2 diabetes: not to soon. **Lancet** 2004;364:641-642

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;12:351-356
JM Foody, HM Krumholz – Are statins indicated for the primary prevention of CAD in octogenarians? Antagonist viewpoint. **Am J Geriatr Cardiol** 2003;12:357—360

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;89:67-69
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:333-335

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;52:1639-1647

Ezetimibe

- Senkt allein und in Kombination mit Statinen Gesamt- + LDL-Cholesterin (ca. 25 / 17 %) + TG (ca. 15 %)
- Erhöht HDL-Chol. (+ 2 %)
- CRP ↓ ca. 10 %
- Studien in der Altersgruppe 55-65 a, bis 50 % Frauen, BMI > 28, 90 % Weisse

C Gagné et al – Efficacy and safety of Ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. **Am J Cardiol** 2002;90:1084-1091
CA Dujovne et al – Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. **Am J Cardiol** 2002;90:1092-1097
T Feldmann et al – Treatment of high-risk patients with ezetimibe plus simvastatin co-administration versus simvastatin alone to attain national cholesterol education program adult treatment panel III low-density lipoprotein cholesterol goals. **Am J Cardiol** 2004;93, 1481-1486
CM Ballantyne et al – Efficacy and safety of ezitimibe co-administered with simvastatin compared with atorvastatin in adults with Hypercholesterolemia. **Am J Cardiol** 2004;93:1487-1494

Statineffekte

➢ Reduktion von Frakturen ?

DC Bauer et al – Use of statins and fracture. **Arch Intern Med** 2004;164:146-152

➢ Reduktion von Demenz ?

BA Golom et al – Conceptual foundations of the UCSD statin study. **Arch Intern Med** 2004;164:153-162

HD Scott, K Laake – Statins for the prevention of Alzheimer´s disease (Cochrane Review).In: **The Cochrane Library**, Issue 3,2004

MP Mattson – Pathways towards and away from Alzheimer´s disease. **Nature** 2004;430:631-639

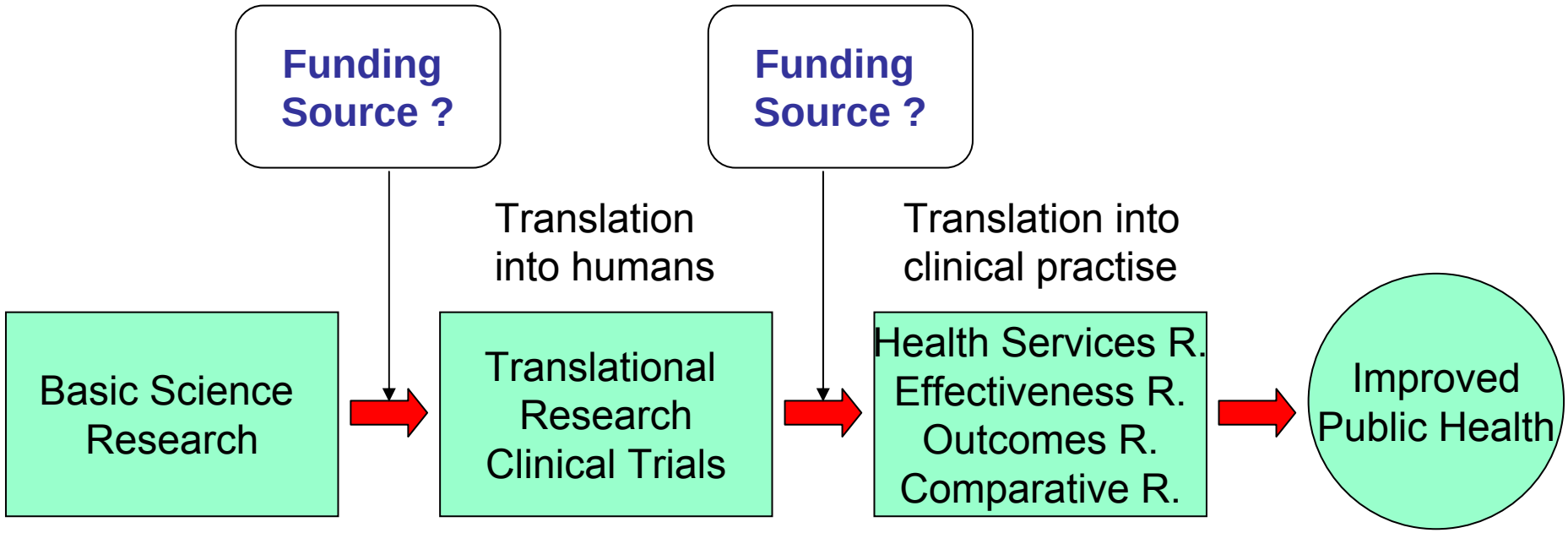
G Atzmon et al – Plasma HDL levels highly correlate with cognitive function in exceptional longevity. **J Gerontol** 2002;57A:M712-M715

➢ Reduktion von Stroke ?

B Manktelow, C Gillies, JF Potter – Interventions in the management of serum lipids for preventing stroke recurrence (Cochrane Review).In: **The Cochrane Library**, Issue 3,2004

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;291:1120-1126

Quo vadis II ?

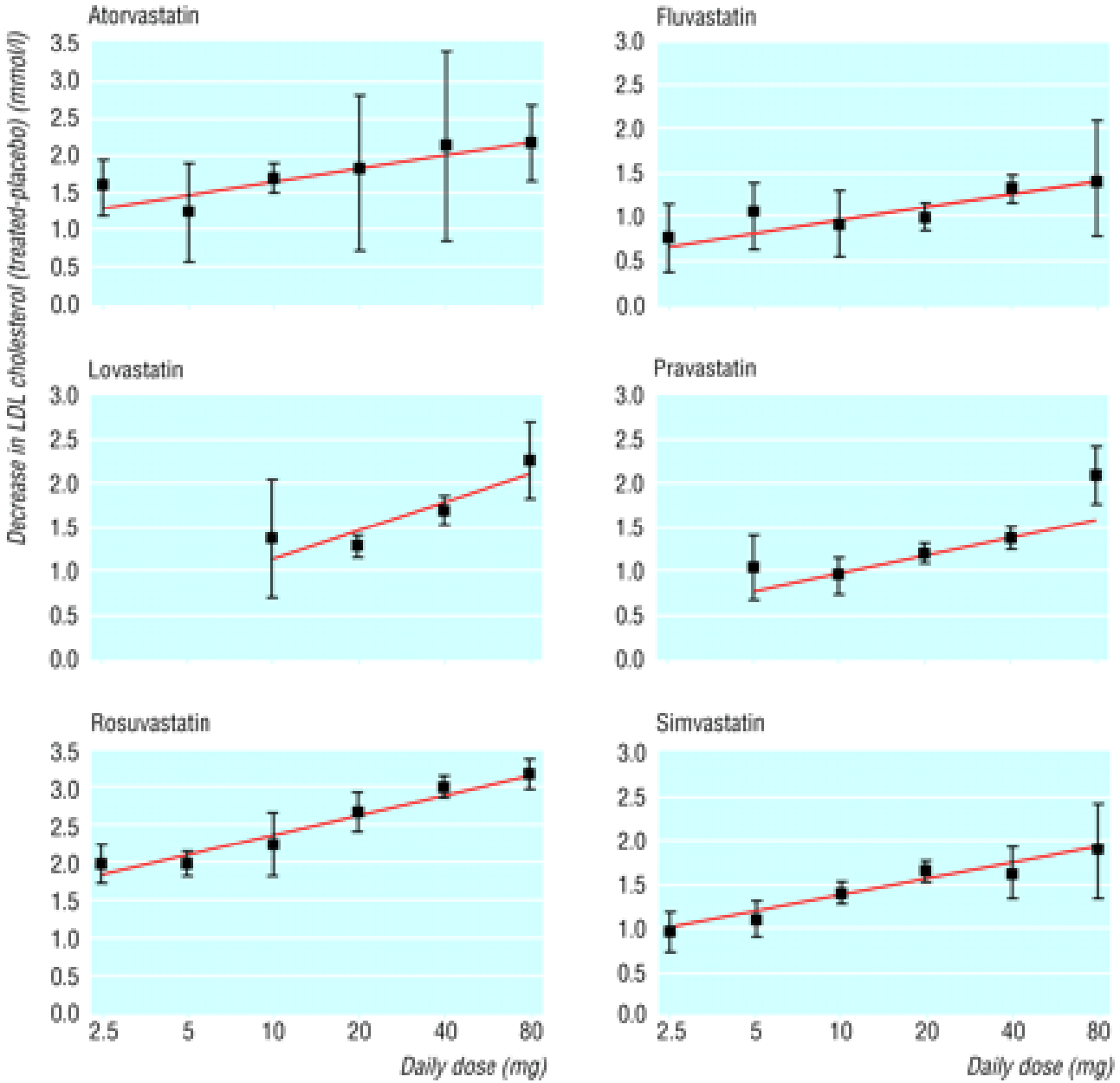
Randomisierungsrate

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 %


Evidence b(i)ased
BMJ 30.10.2004



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
- Im Einzelfall diskutieren
- Cave Multipharmakotherapie
- Evidenz einzelne Substanz vs. Klasseneffekt unklar
- Evidenz für Kombinationstherapie im hohen Lebensalter unklar
- Evidenz bei Multimorbidität unklar
- Lifestyle-Intervention generell empfohlen