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Saturday, June 10, 2017

9:45 - 10:00 Comorbidities as Hypertension and Lipids

CO-MORBIDITIES SUCH AS HYPERTENSION AND CHOLESTEROL

Patrick Kay, MD PhD
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How Significant is Hypertension as a Risk Factor?

In 1990, the leading risk factors for global disease burden were:

a. childhood underweight (7·9% [6·8–9·4]),
b. household air pollution from solid fuels (HAP; 6·8% [5·5–8·0]),
c. tobacco smoking including second-hand smoke (6·1% [5·4–6·8]).

In 2010, the leading risk factors for global disease burden were:

a. high blood pressure (7·0% [95% uncertainty interval 6·2–7·7] of global DALYs),
b. tobacco smoking including second-hand smoke (6·3% [5·5–7·0]),
c. household air pollution from solid fuels (4·3% [3·4–5·3]).


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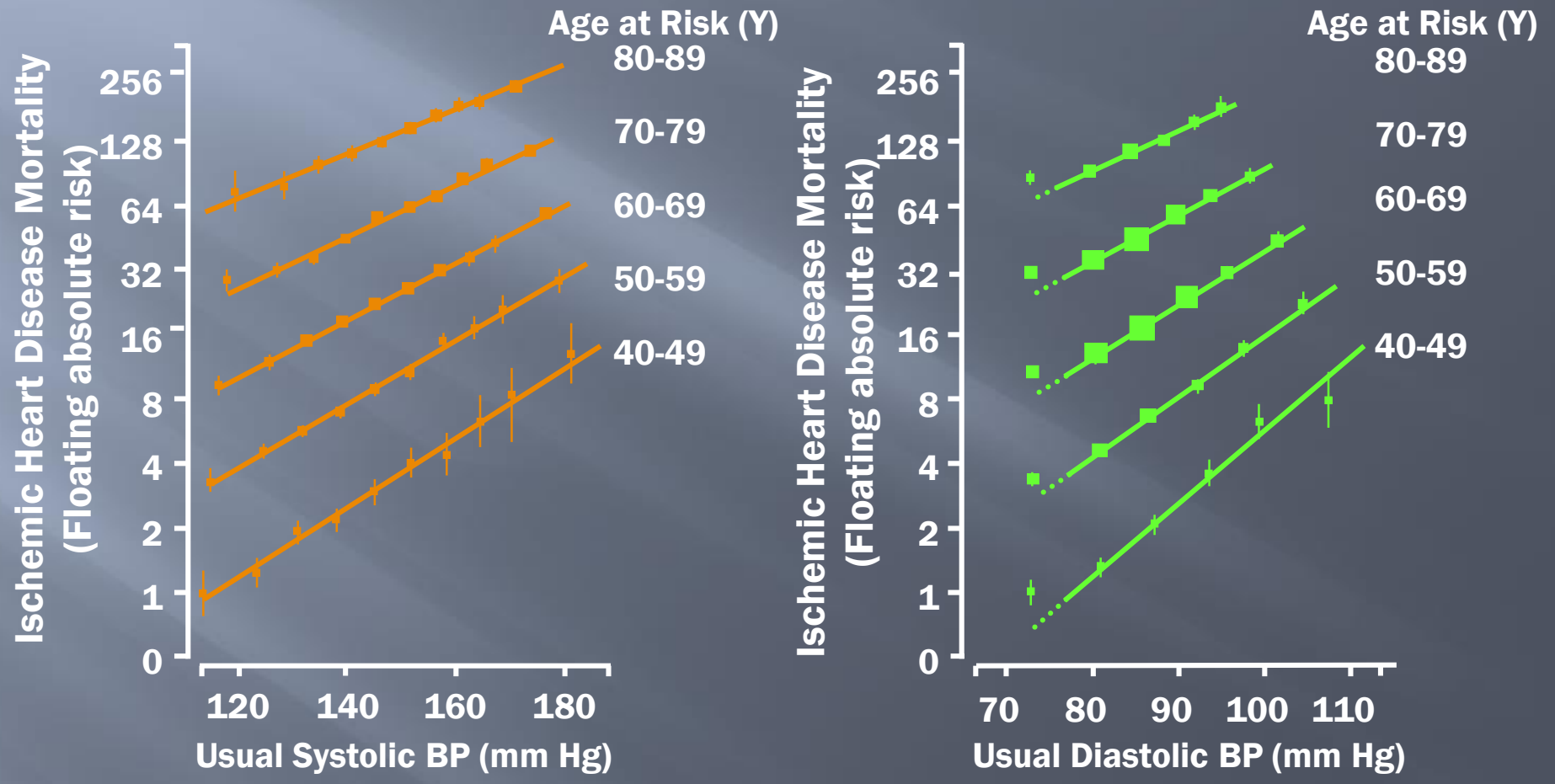
MINI
S GO 4001
S GO 4002

How much difference does intervention make?

High Blood Pressure Evidence: Increased Risk with Increased Levels

Ischemic heart disease mortality and blood pressure



BP=Blood pressure

Source: Prospective Studies Collaboration. *Lancet* 2002;360:1903-1913

When to Treat – The Guidelines…

ESC-Premise

- The initial evaluation of a patient with hypertension should
- 1. confirm the diagnosis of hypertension
- 2. detect causes of secondary hypertension
- 3. Assess CV risk and end-organ damage

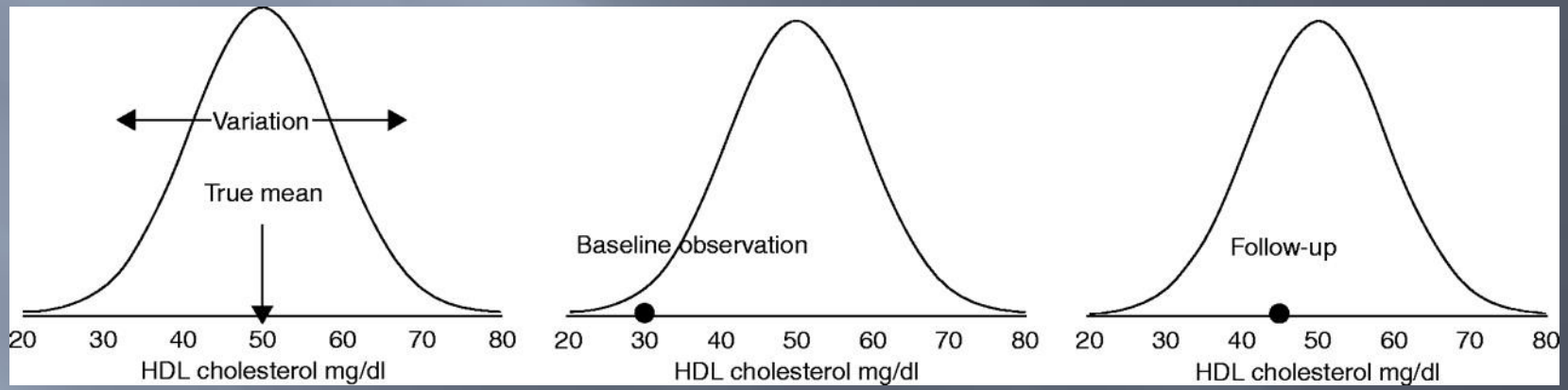
New Aspects of the Guidelines

New aspects

- Roles of ABPM and HBPM
- Update of the prognostic significance of night-time BP, white-coat hypertension and masked hypertension.
- Re-emphasis on integration of BP, cardiovascular (CV) risk factors, asymptomatic organ damage (OD) and clinical complications for total CV risk assessment.
- Update of the prognostic significance of asymptomatic OD, including heart, blood vessels, kidney, eye and brain. Increased attention to OD-guided therapy.
- Reconsideration of body mass index (BMI) in hypertension.
- Hypertension in young people.
- Initiation of antihypertensive treatment.
- Target BP for treatment. More evidence-based criteria and unified target systolic blood pressure (SBP) (<140 mmHg) in both higher and lower CV risk patients.
- Liberal approach to initial monotherapy, without any all-ranking purpose.
- Revised schema for priorital two-drug combinations.
- New therapeutic algorithms for achieving target BP.
- Revised recommendations on treatment of hypertension in the elderly.
- Special attention to resistant hypertension and new treatment approaches.
- New approaches to chronic management of hypertensive disease.

How Accurate is the Clinical Assessment of Blood Pressure?

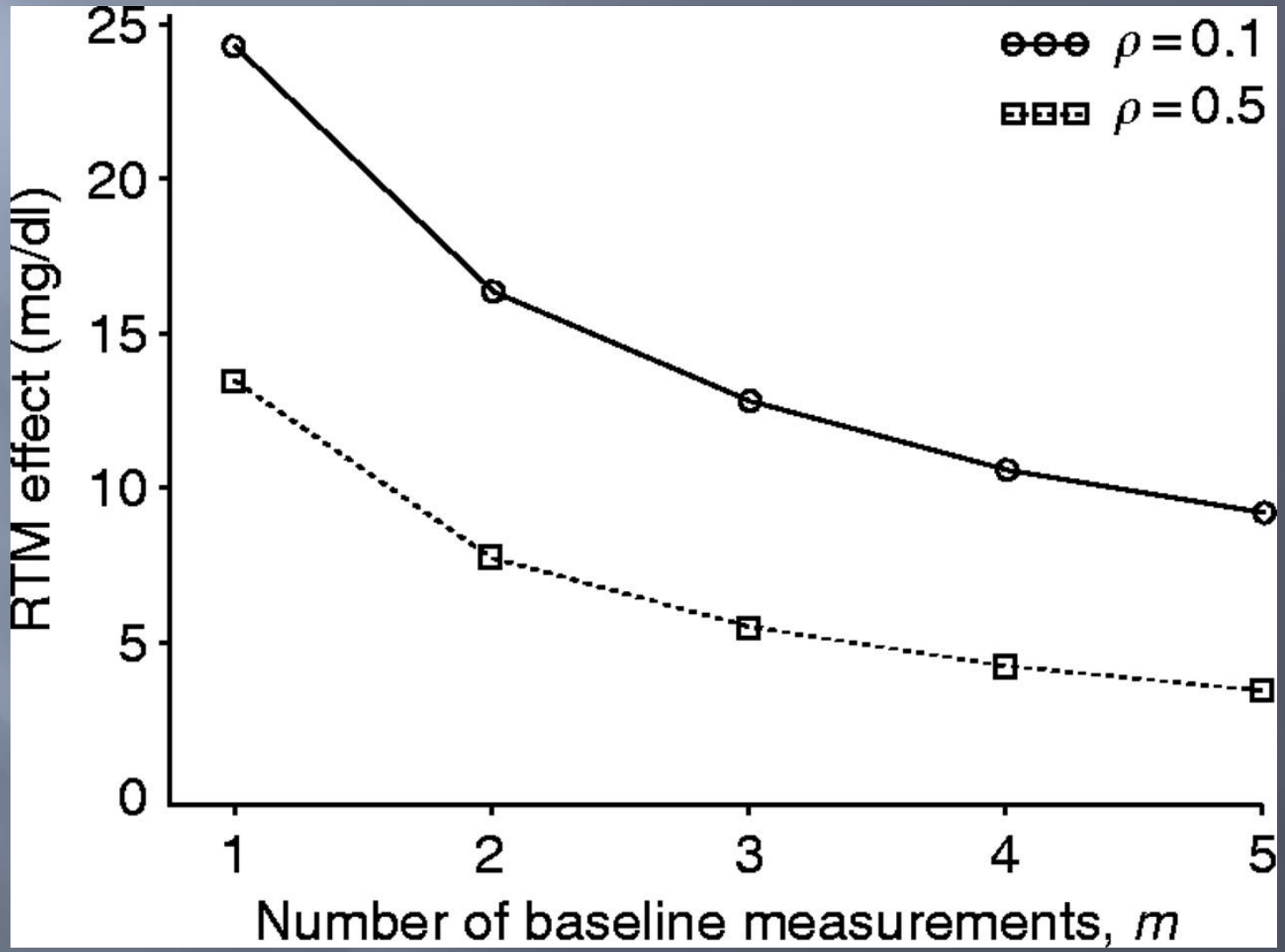
Graphical example of true mean and variation, and of regression to the mean using a Normal distribution.



Barnett A G et al. Int. J. Epidemiol. 2005;34:215-220

International Journal of Epidemiology

An example of the reduction in the regression to the mean (RTM) effect due to taking multiple baseline measurements and using each subject's mean as the selection variable.



Barnett A G et al. Int. J. Epidemiol. 2005;34:215-220

International Journal of Epidemiology

What Does this all mean?

- A single clinical BP is subject to random error
- To decrease random error we need more samples = clinic samples, Home BP measurements, Ambulatory BPM
- Minimize intra and inter observer variability by using electronic devices

In-Office-Most reproducible BP

- Electronic device
- Multiple recordings
- Quietened room
- Attended

Definitions of hypertension by office and out-of-office blood pressure levels

Category	Systolic BP (mmHg)		Diastolic BP (mmHg)
Office BP	≥140	and/or	≥90
Ambulatory BP			
Daytime (or awake)	≥135	and/or	≥85
Nighttime (or asleep)	≥120	and/or	≥70
24-h	≥130	and/or	≥80
Home BP	≥135	and/or	≥85

Premise

- The initial evaluation of a patient with hypertension should
- 1. confirm the diagnosis of hypertension
- 2. detect causes of secondary hypertension
- 3. Assess CV risk and end-organ damage

Secondary Hypertension: Important Rule -Outs

- OSA – do an Epworth Sleepiness Scale
- Dietary excesses – salt, liqorice etc
- Alcohol intake
- NSAIDs, Antidepressants, OCP, Venlafaxine, immune suppressants, steroids
- Endocrine – Cushings, Conns, Hypo/hyperthyroidism, Hyperparathyroidism
- CKD
- Phaeochromocytoma
- Renal Artery Stenosis, Coarctation
- Some dietary and herbal supplements (e.g., ginseng, ephedra, ma huang, bitter orange)

Premise

- The initial evaluation of a patient with hypertension should
- 1. confirm the diagnosis of hypertension
- 2. detect causes of secondary hypertension
- 3. Assess CV risk and end-organ damage

Therapy

- Right drugs:

1. ACE-I/ ARB
2. Amlodipine/Felodipine
3. Chlorthalidone
4. Spironolactone (watch Na+, K+ and renal fn)
5. Beta blocker
6. Despair

Summary

- Hypertension creates significant morbidity/mortality
- Accurate diagnosis – 24HR BP or Home recording
- Appropriate medications

Stratification of total CV risk in categories of low, moderate, high and very high risk according to SBP and DBP and prevalence of RFs, asymptomatic OD, diabetes, CKD stage or symptomatic CVD. Subjects with a high normal office but a raised out-of-office BP (masked hypertension) have a CV risk in the hypertension range.

Other risk factors, asymptomatic organ damage or disease	Blood Pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF		Low risk	Moderate risk	High risk
1–2 RF	Low risk	Moderate risk	Moderate to high risk	High risk
≥3 RF	Low to Moderate risk	Moderate to high risk	High Risk	High risk
OD, CKD stage 3 or diabetes	Moderate to high risk	High risk	High risk	High to very high risk
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	Very high risk	Very high risk	Very high risk	Very high risk

BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; HT = hypertension; OD = organ damage; RF = risk factor; SBP = systolic blood pressure.

Authors/Task Force Members et al. Eur Heart J 2013;eurheartj.eht151

European Heart Journal

STATIN THERAPY

AHA/ACC Guidelines:
There are 4 defined Statin Benefit groups

Secondary Prevention:

a. Patients with clinical ATHEROSCLEROSIS: ACS, CVA,PVD,PCI,CABG

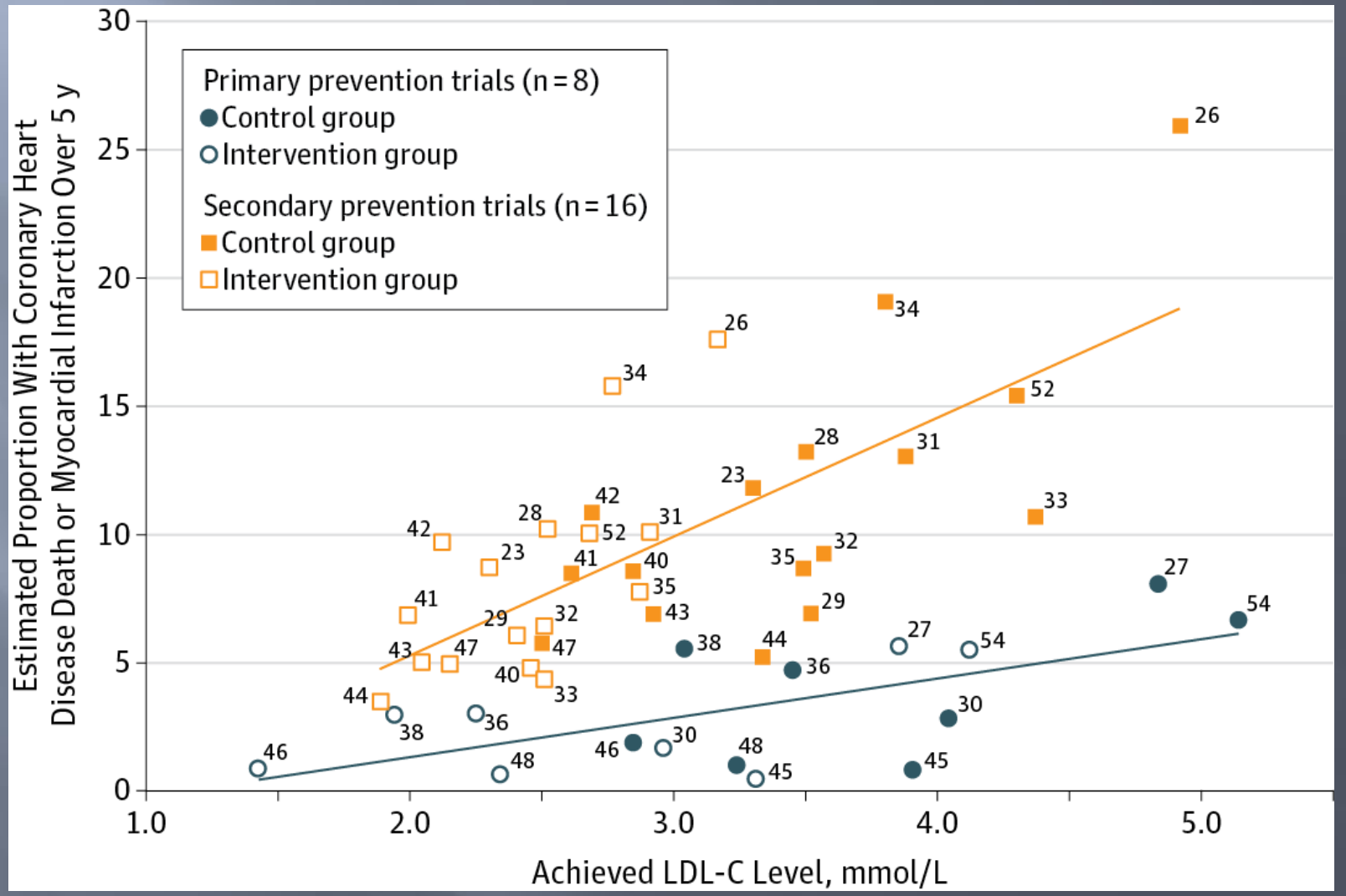
Primary Prevention:

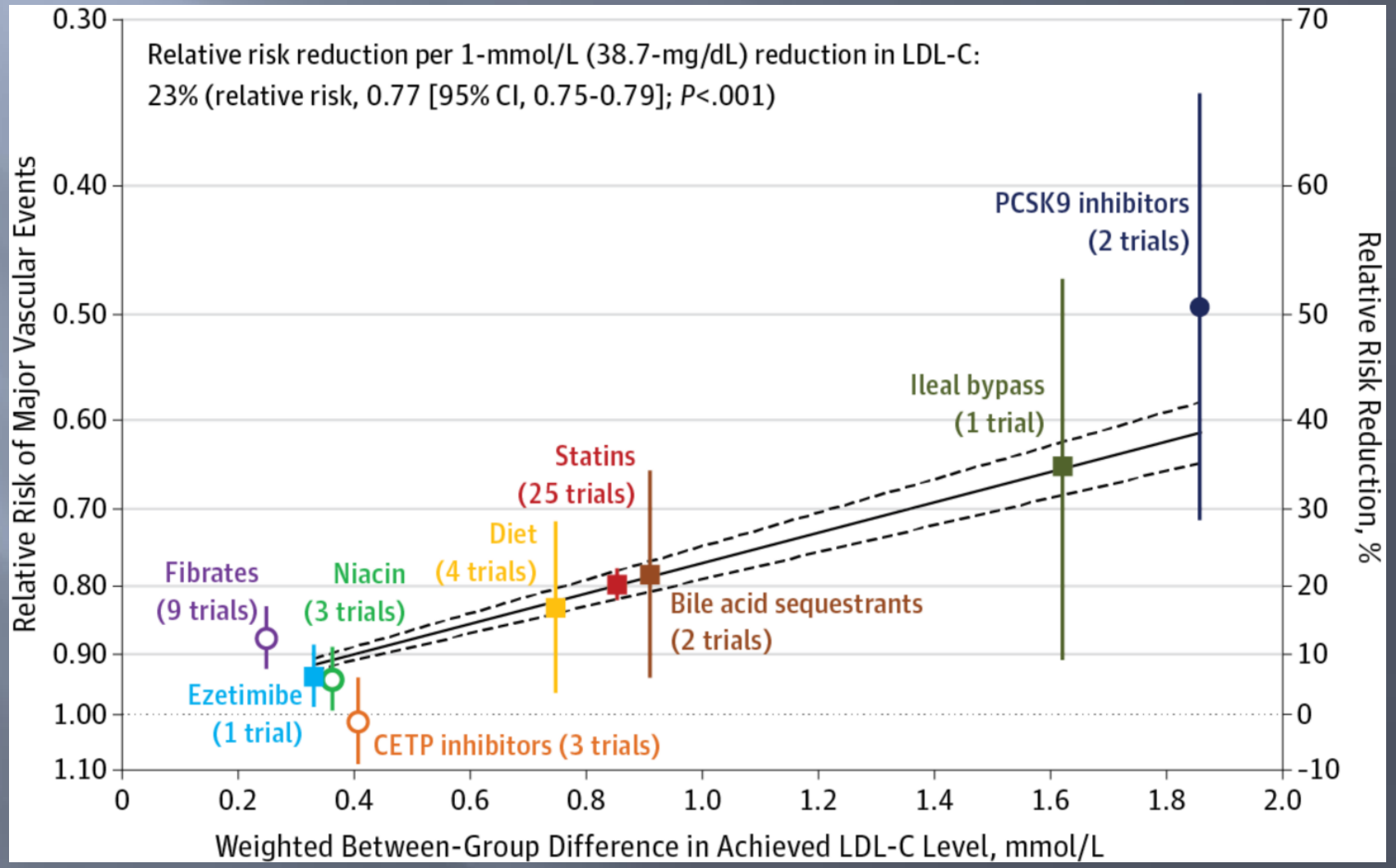
b. LDL greater than 4.9mmol/l

c. Patients with diabetes, age 40-75 years

d. Age 40-75 years that do not meet above criteria, but have a 10 year risk of >7.5 %

Primary vs Secondary Prevention - the effect of LDL lowering on outcome




Relative risk reduction per 1-mmol/L (38.7-mg/dL) reduction in LDL-C:
23% (relative risk, 0.77 [95% CI, 0.75-0.79]; P<.001)
Relative Risk of Major Vascular Events
Relative Risk Reduction, %
Weighted Between-Group Difference in Achieved LDL-C Level, mmol/L
0.30
0.40
0.50
0.60
0.70
0.80
0.90
1.00
1.10
70
60
50
40
30
20
10
0
-10
0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
PCSK9 inhibitors (2 trials)
Ileal bypass (1 trial)
Statins (25 trials)
Diet (4 trials)
Fibrates (9 trials)
Niacin (3 trials)
Bile acid sequestrants (2 trials)
Ezetimibe (1 trial)
CETP inhibitors (3 trials)

Secondary prevention

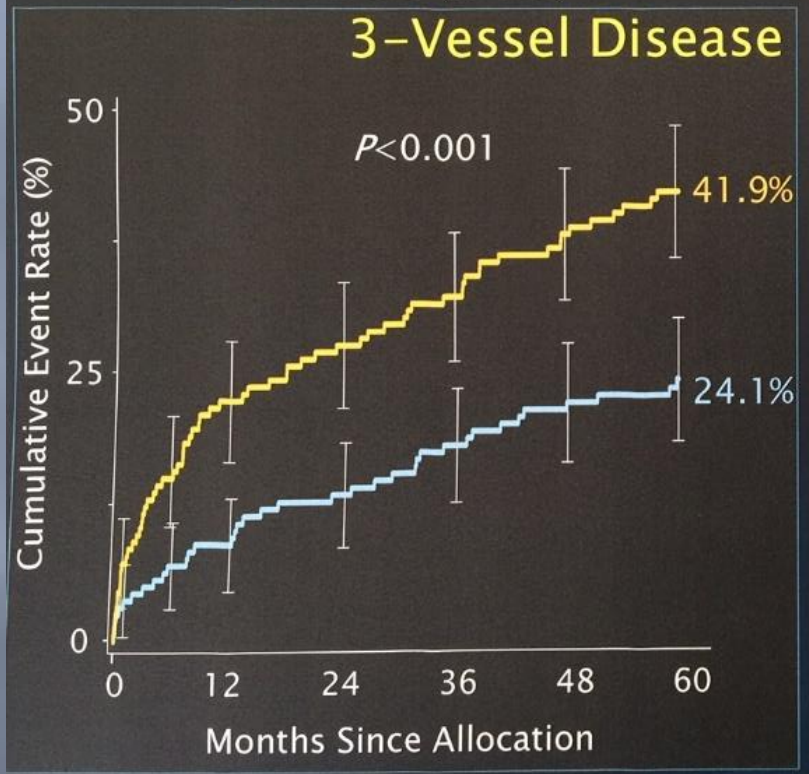
MACCE to 5 Years by SYNTAX Score Tercile

3VD Subset High Scores ≥33

SYNTAX

CABG (N=166)

TAXUS (N=155)



	CABG	PCI	*P* value
Death	8.8%	17.8%	0.02
CVA	2.6%	5.1%	0.31
MI	1.9%	8.7%	0.008
Death, CVA or MI	12.5%	26.2%	0.002
Revasc.	12.6%	28.2%	<0.001

Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value Site-reported Data; ITT population

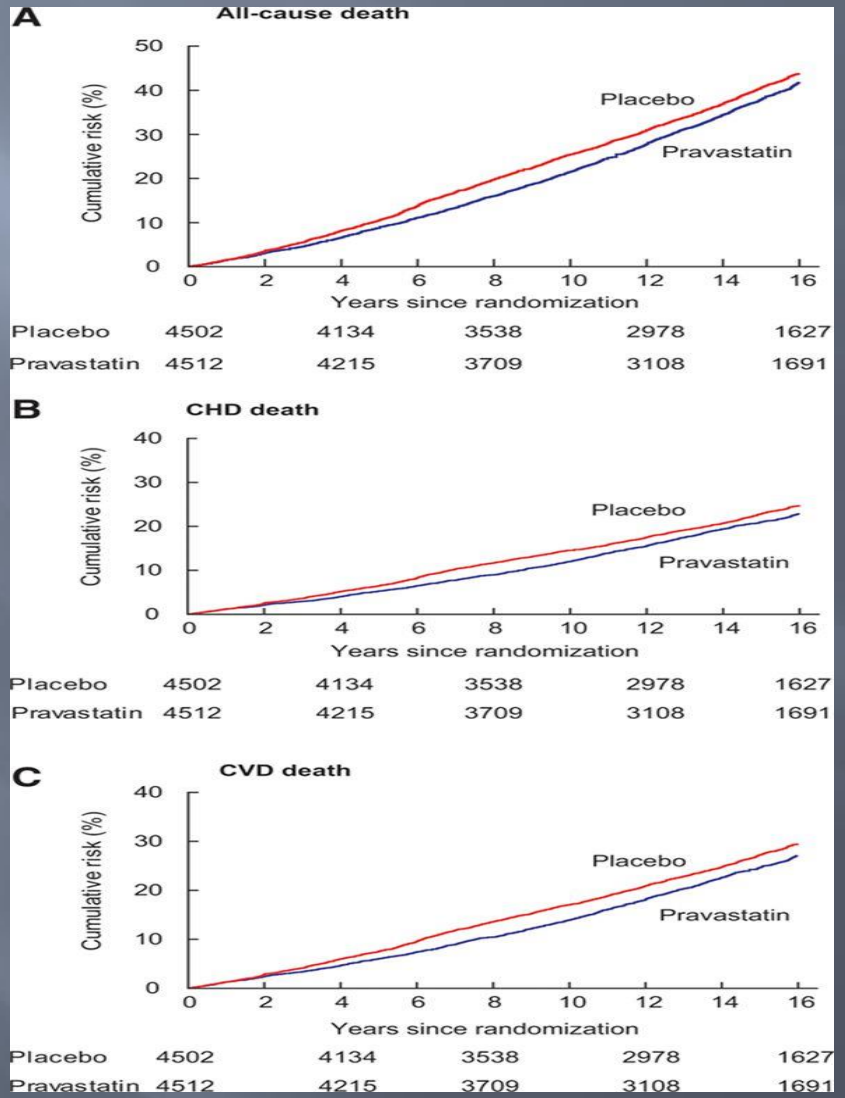
Lancet 2013; 381: 629-38

Long-Term Efficacy and Statins

Long-Term Effectiveness and Safety of Pravastatin in Patients With Coronary Heart Disease: Sixteen Years of Follow-Up of the LIPID Study

- The LIPID (Long-term Intervention with Pravastatin in Ischemic Disease) trial, showed that 6 years of pravastatin treatment resulted in better survival, in line with other statin trials.

Cumulative risk of cause-specific death over 16 years of follow-up among patients randomly assigned to initial pravastatin or placebo for an average of 6 years followed by optional statin therapy, with numbers of patients alive and followed up.



Wendy E. Hague et al. Circulation. 2016;133:1851-1860

Conclusions

- In 7721 patients with a history of CHD who participated in the extended follow-up of the LIPID study, the absolute survival benefit from 6 years of pravastatin treatment appeared to be maintained over another 10 years.
- The survival benefit was primarily related to CV-deaths and treatment with statins did not influence cancer incidence/death nor death from other non-CV causes during long-term follow-up.

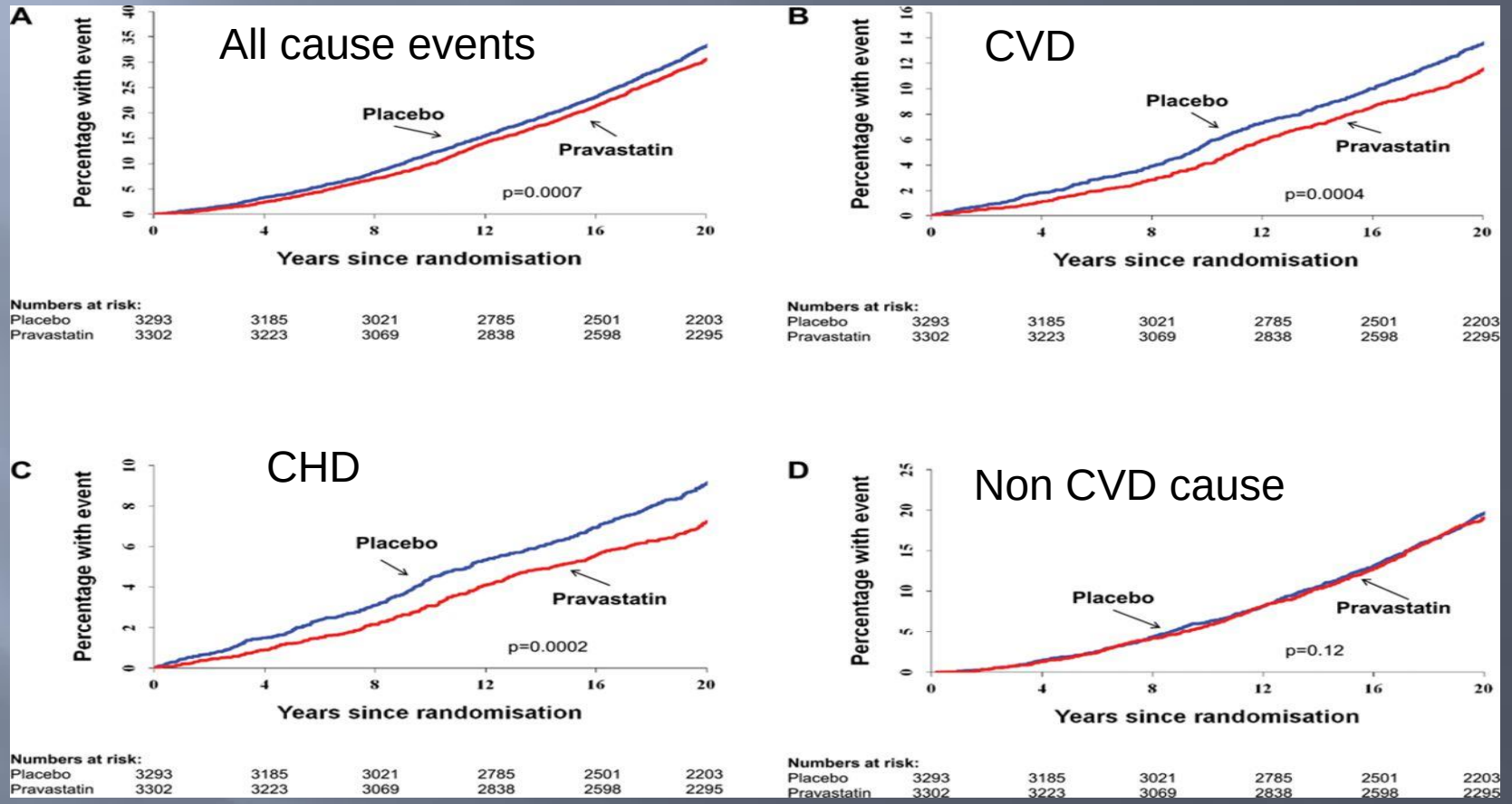
Primary prevention
Long-term outcomes

WOSCOPS

Long-Term Safety and Efficacy of Lowering Low-Density Lipoprotein Cholesterol With Statin Therapy

20-Year Follow-Up of West of Scotland Coronary Prevention Study

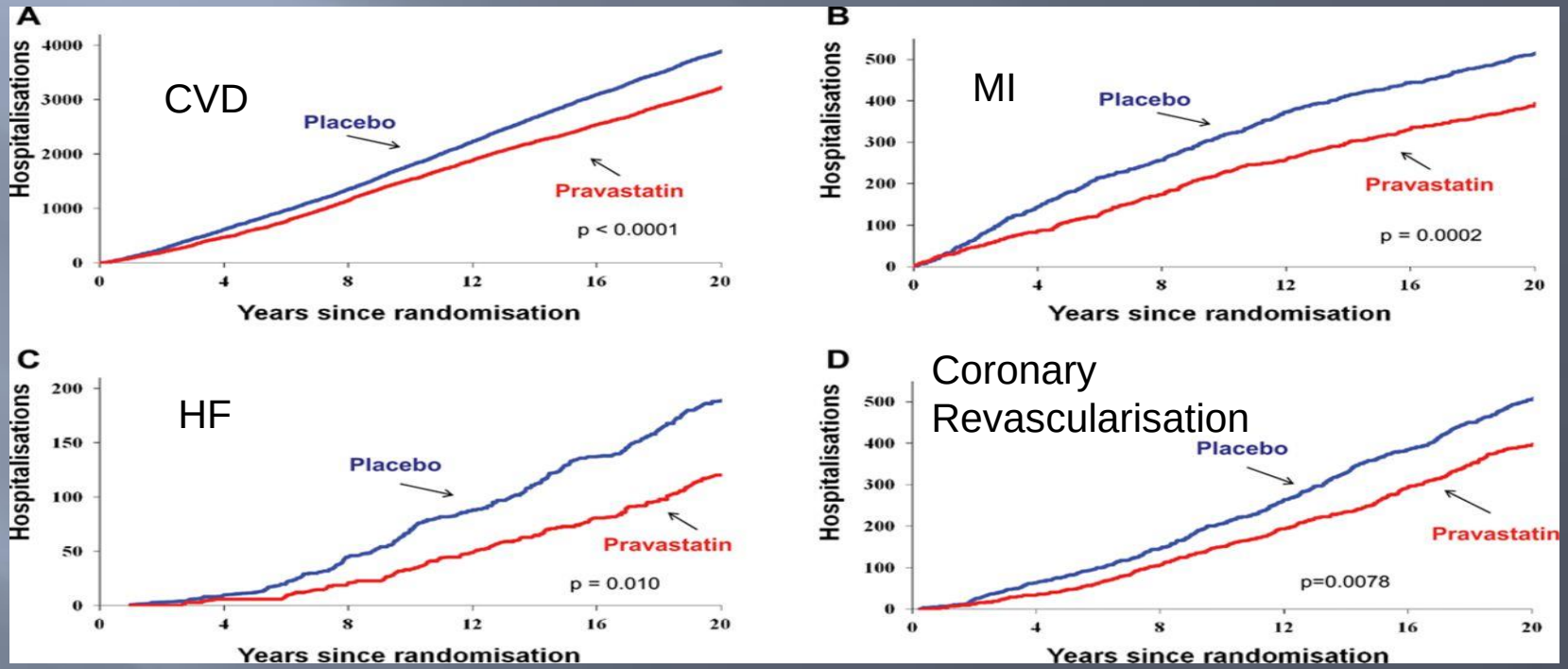
Cumulative events over the 20-year follow-up period (Legacy Benefit).



Cumulative events over the 20-year follow-up period.
Cumulative incidence functions are provided for the outcomes of death resulting from (**A**) all causes, (**B**) cardiovascular disease, (**C**) coronary heart disease, and (**D**) non-cardiovascular disease.

Ian Ford et al. Circulation. 2016;133:1073-1080

Cumulative numbers of hospital admissions for the outcomes of (A) cardiovascular disease, (B) myocardial infarction, (C) heart failure, and (D) coronary revascularization.



Ian Ford et al. Circulation. 2016;133:1073-1080

Cumulative numbers of hospital admissions for the outcomes of
(**A**) cardiovascular disease, (**B**) myocardial infarction, (**C**) heart failure, and (**D**) coronary revascularization.

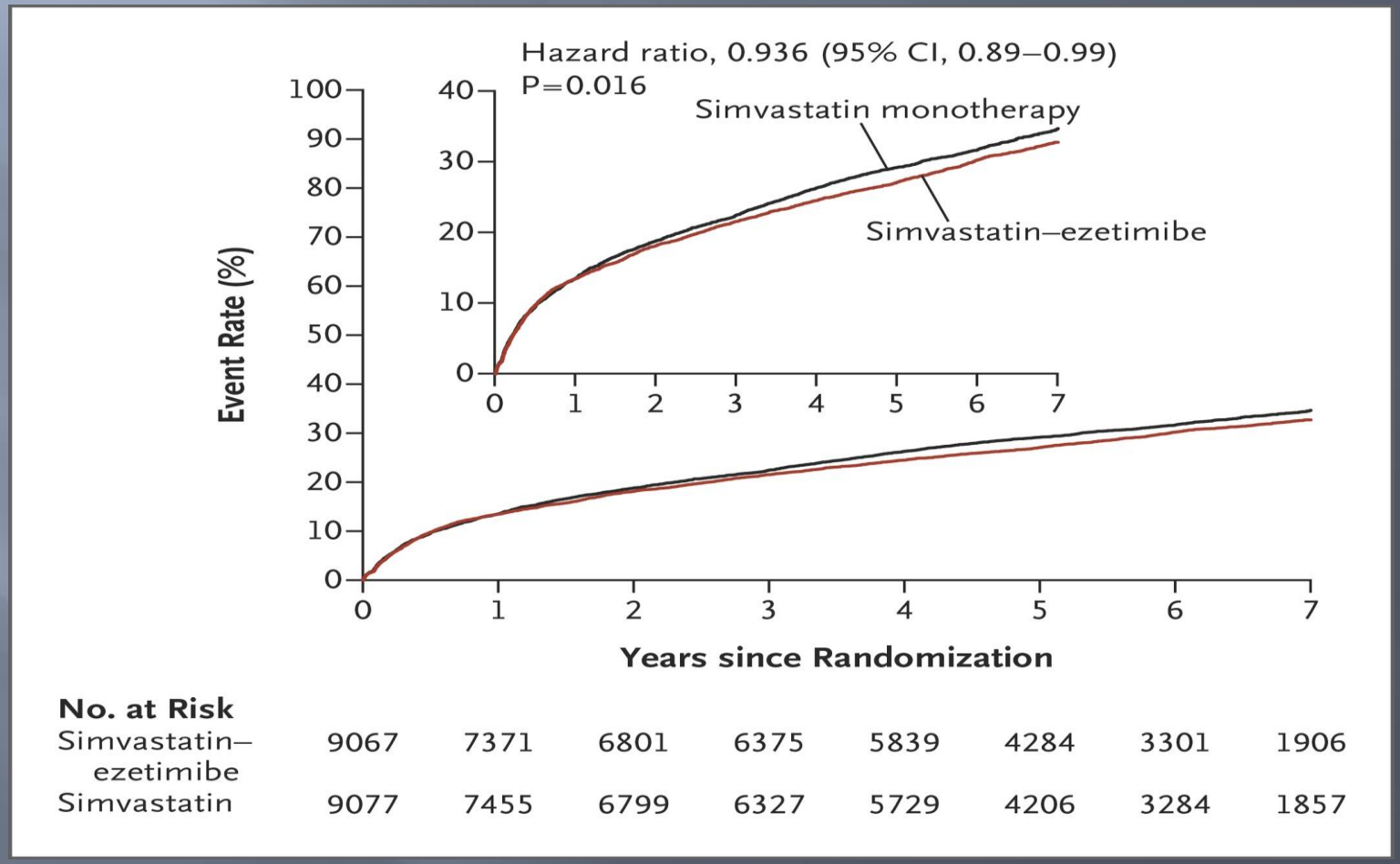
Results

- For every 1000 patients assigned to pravastatin, compared with placebo, over 16 years there were:
- 25 fewer CVD deaths (23 over 6 years)
- 18 fewer CHD deaths (19 over 6 years)

Ezetimibe

Improve-It Study

Kaplan–Meier Curves for the Primary Efficacy End Point.



Cannon CP et al. N Engl J Med 2015;372:2387-2397

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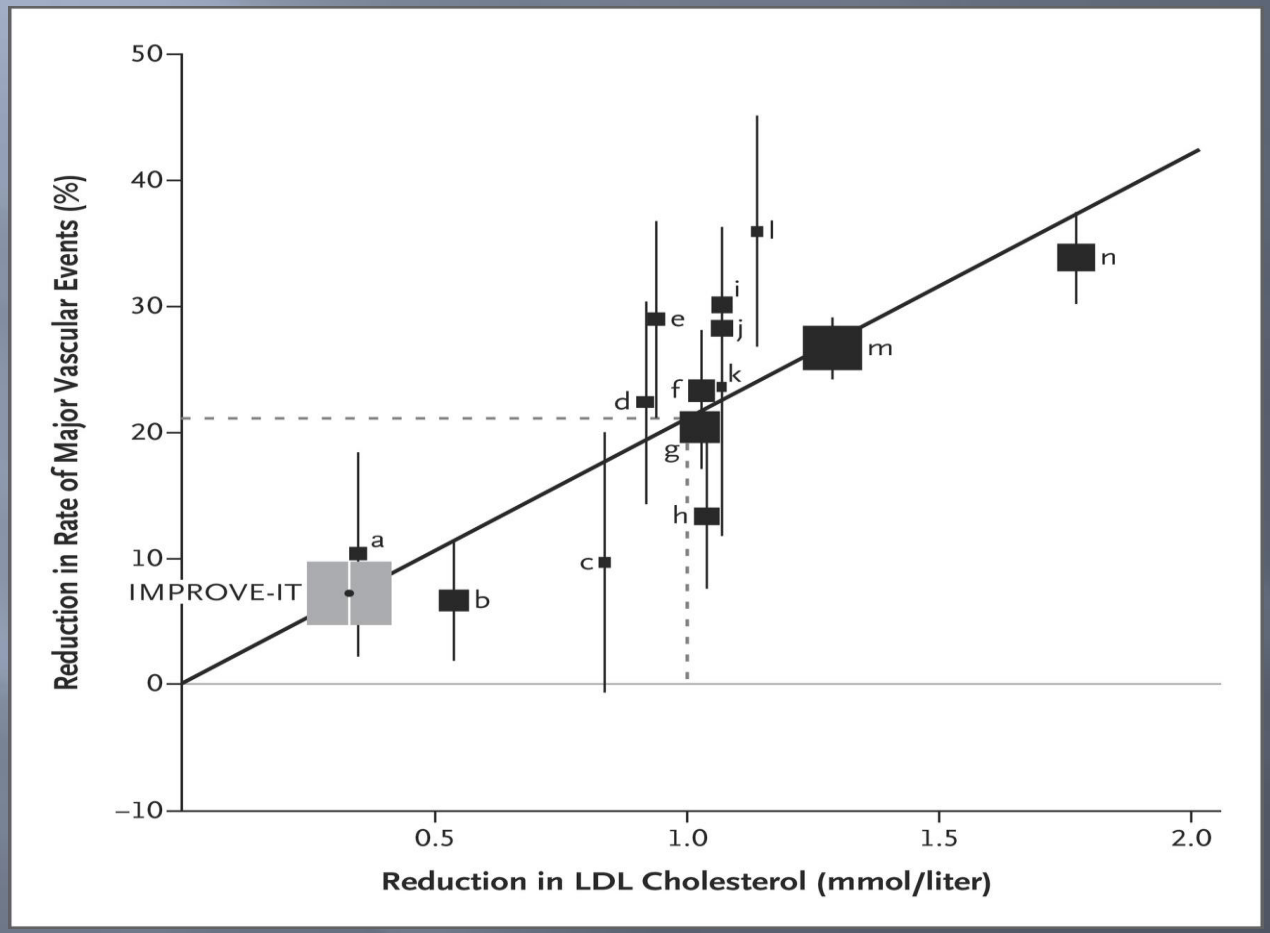
Plot of the IMPROVE-IT Trial Data and Statin Trials for Change in Low-Density Lipoprotein (LDL) Cholesterol versus Clinical Benefit.



a IMPROVE-IT
b ALLHAT LLT
c ALERT
d LIPS
e AFCAPS/TEXCAPS
f CARE
g LIPID
h PROSPER
i ASCOT-LLA
j WOSCOPS
n 4S

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Cognitive issues
Forgetfulness vs Alzheimers Prevention

HOPE-3 substudy AHA New Orleans Nov 2016

- N=1,600 people at moderate risk for cardiovascular disease.
- Age > 70 years
- All had risk factors such as abdominal obesity, smoking, diabetes or high BP that was under control.
- Received either the blood pressure drug candesartan/hydrochlorothiazide, the statin rosuvastatin, a combination of the two drugs, or a placebo.
- Five and a half years later, every group — including those on the statin drug — had roughly the same declines in processing speed, reaction time and executive functions such as attention and decision-making.

CONCLUSION

There was no deterioration in cognitive function on statins, nor was there a protective aspect to being on statins (eg decrease in dementia) in an elderly population.

The primary outcome

Processing speed (measured by Digit Symbol Substitution Test [DSST] at study end)

- for rosuvastatin vs. placebo: 29.1 vs. 29.4 (p = 0.38);
- for BP lowering vs. placebo: 29.1 vs. 29.4 (p = 0.86);
- for combination vs. placebo: 29.3 vs. 29.9 (p = 0.63).
- any functional impairment for rosuvastatin vs. placebo: 57% vs. 59%, p = 0.89;
- for BP lowering vs. placebo: 59% vs. 56%, p = 0.19.

“Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning”

Winston Churchill, 1942

PCSK9 Inhibitors

PCSK9

Proprotein convertase subtilisin/kexin type 9

- PCSK9 binds to the receptor for low-density lipoprotein (LDL) cholesterol.
- In the liver, the LDL receptor removes LDL cholesterol from the blood.
- When PCSK9 binds to the LDL receptor, the receptor is broken down and can no longer remove LDL cholesterol from the blood.
- If PCSK9 is blocked, more LDL receptors will be present on the surface of the liver and will remove more LDL cholesterol from the blood. Therefore, blocking PCSK9 can lower blood cholesterol levels.

PCSK9 Inhibitor Studies

- PCSK9 inhibitors are injected monoclonal antibodies
- Dosing weekly to twice monthly
- 2 competing products (legal wrangles)
- Designed to add PCSK9 inhibitors to existing statin therapy
- Homozygous and Heterozygous FH studied
- Recent ‘hard endpoint’ study published

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators

N Engl J Med
Volume 376(18):1713-1722
May 4, 2017

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Study Overview

- In this trial, 27,564 patients with cardiovascular disease and LDL cholesterol levels of 70 mg per deciliter or higher on statin therapy were assigned to either evolocumab or placebo.
- At 2.2 years, the evolocumab group had a significantly lower rate of major adverse cardiovascular events.

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Characteristics of the Patients at Baseline.

Table 1. Characteristics of the Patients at Baseline.*

Characteristics	Evolocumab (N = 13,784)	Placebo (N = 13,780)
Age — yr	62.5±9.1	62.5±8.9
Male sex — no. (%)	10,397 (75.4)	10,398 (75.5)
White race — no. (%)†	11,748 (85.2)	11,710 (85.0)
Weight — kg	85.0±17.3	85.5±17.4
Region		
North America	2,287 (16.6)	2,284 (16.6)
Europe	8,666 (62.9)	8,669 (62.9)
Latin America	913 (6.6)	910 (6.6)
Asia Pacific and South Africa	1,918 (13.9)	1,917 (13.9)
Type of atherosclerosis‡		
Myocardial infarction — no. (%)	11,145 (80.9)	11,206 (81.3)
Median time from most recent previous myocardial infarction (IQR) — yr	3.4 (1.0–7.4)	3.3 (0.9–7.7)
Nonhemorrhagic stroke	2686 (19.5)	2651 (19.2)
Median time from most recent previous stroke (IQR) — yr	3.2 (1.1–7.1)	3.3 (1.1–7.3)
Peripheral artery disease — no. (%)	1,858 (13.5)	1,784 (12.9)
Cardiovascular risk factors		
Hypertension — no./total no. (%)	11,045/13,784 (80.1)	11,039/13,779 (80.1)
Diabetes mellitus — no. (%)	5,054 (36.7)	5,027 (36.5)
Current cigarette use — no./total no. (%)	3854/13,783 (28.0)	3923/13,779 (28.5)
Statin use — no. (%)§		
High intensity	9,585 (69.5)	9,518 (69.1)
Moderate intensity	4,161 (30.2)	4,231 (30.7)
Low intensity, unknown intensity, or no data	38 (0.3)	31 (0.2)
Ezetimibe — no. (%)	726 (5.3)	714 (5.2)
Other cardiovascular medications — no./total no. (%)		
Aspirin, $P2Y_{12}$ inhibitor, or both	12,766/13,772 (92.7)	12,666/13,767 (92.0)
Beta-blocker	10,441/13,772 (75.8)	10,374/13,767 (75.4)
ACE inhibitor or ARB, aldosterone antagonist, or both	10,803/13,772 (78.4)	10,730/13,767 (77.9)
Median lipid measures (IQR)		
LDL cholesterol — mg/dl	92 (80–109)	92 (80–109)
Total cholesterol — mg/dl	168 (151–188)	168 (151–189)
HDL cholesterol — mg/dl	44 (37–53)	44 (37–53)
Triglycerides — mg/dl	134 (101–183)	133 (99–181)
Lipoprotein(a) — nmol/liter	37 (13–166)	37 (13–164)

* There were no nominally significant differences between the two groups in baseline characteristics with the exception of weight (P=0.01) and the use of aspirin, a $P2Y_{12}$ inhibitor, or both (P=0.03). To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, HDL high-density lipoprotein, IQR interquartile range, and LDL low-density lipoprotein.
† Race was reported by the patients.
‡ Patients could have more than one type of atherosclerosis.
§ Statin intensity was categorized in accordance with the guidelines of the American College of Cardiology and American Heart Association.[12]

Sabatine MS et al. N Engl J Med 2017;376:1713-1722

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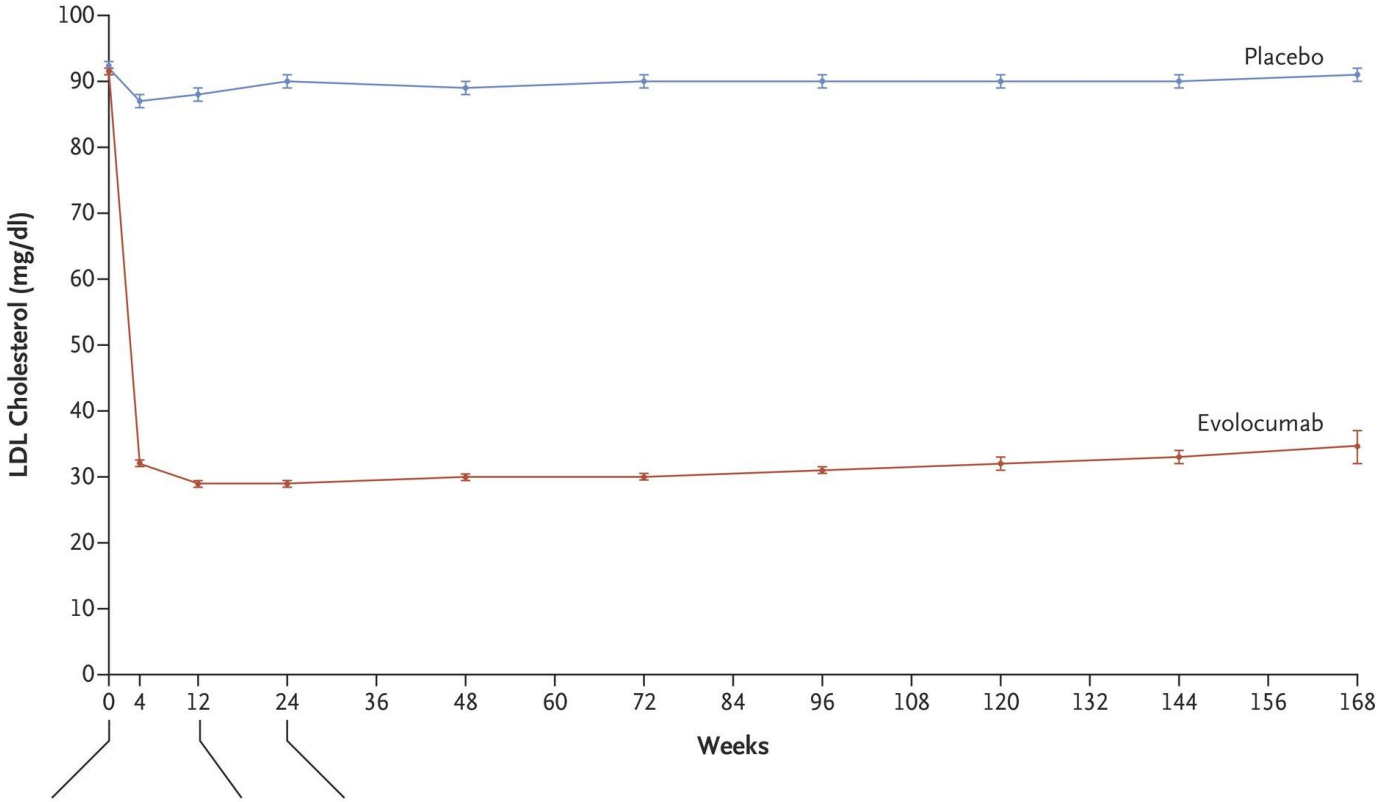
Low-Density Lipoprotein (LDL) Cholesterol Levels over Time.



No. at Risk									
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6926	3352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6958	3323	768
Absolute difference (mg/dl)		54	58	57	56	55	54	52	53	50
Percentage difference		57	61	61	59	58	57	55	56	54
P value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Sabatine MS et al. N Engl J Med 2017;376:1713-1722

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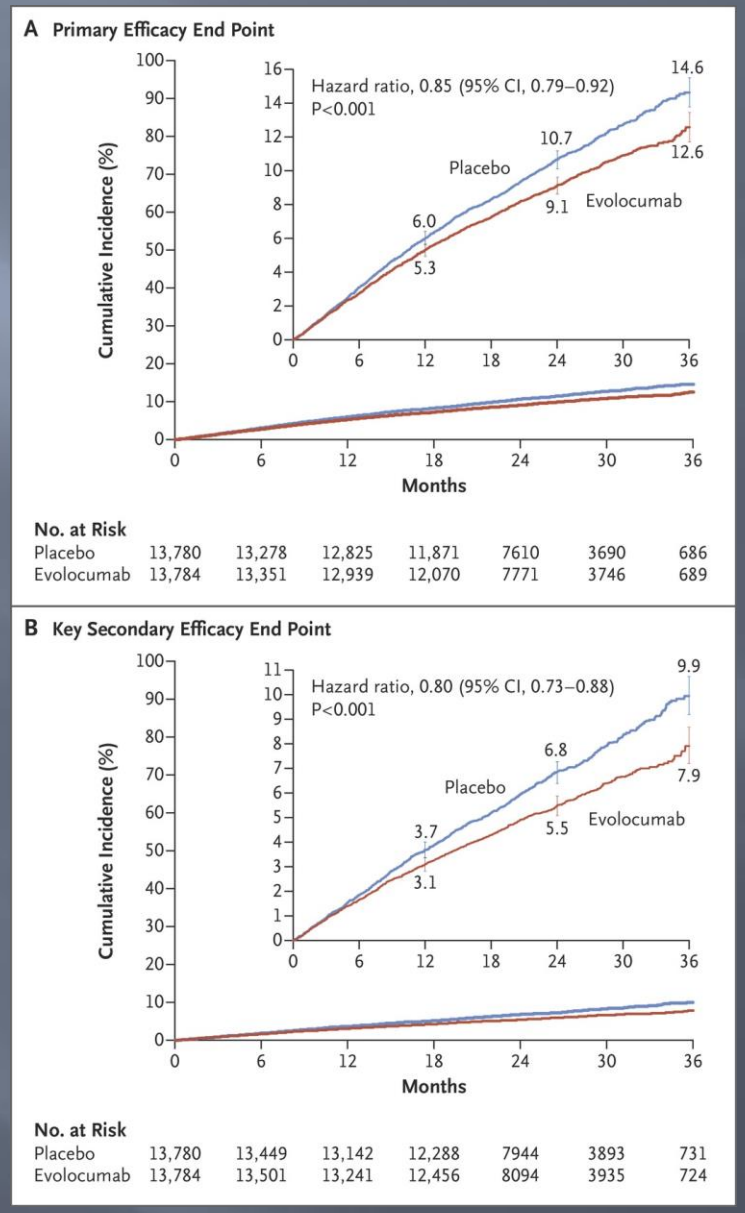
Cumulative Incidence of Cardiovascular Events.



Sabatine MS et al. N Engl J Med 2017;376:1713-1722

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Conclusions

- In our trial, inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg per deciliter (0.78 mmol per liter) and reduced the risk of cardiovascular events.
- These findings show that patients with atherosclerotic cardiovascular disease benefit from lowering of LDL cholesterol levels below current targets.

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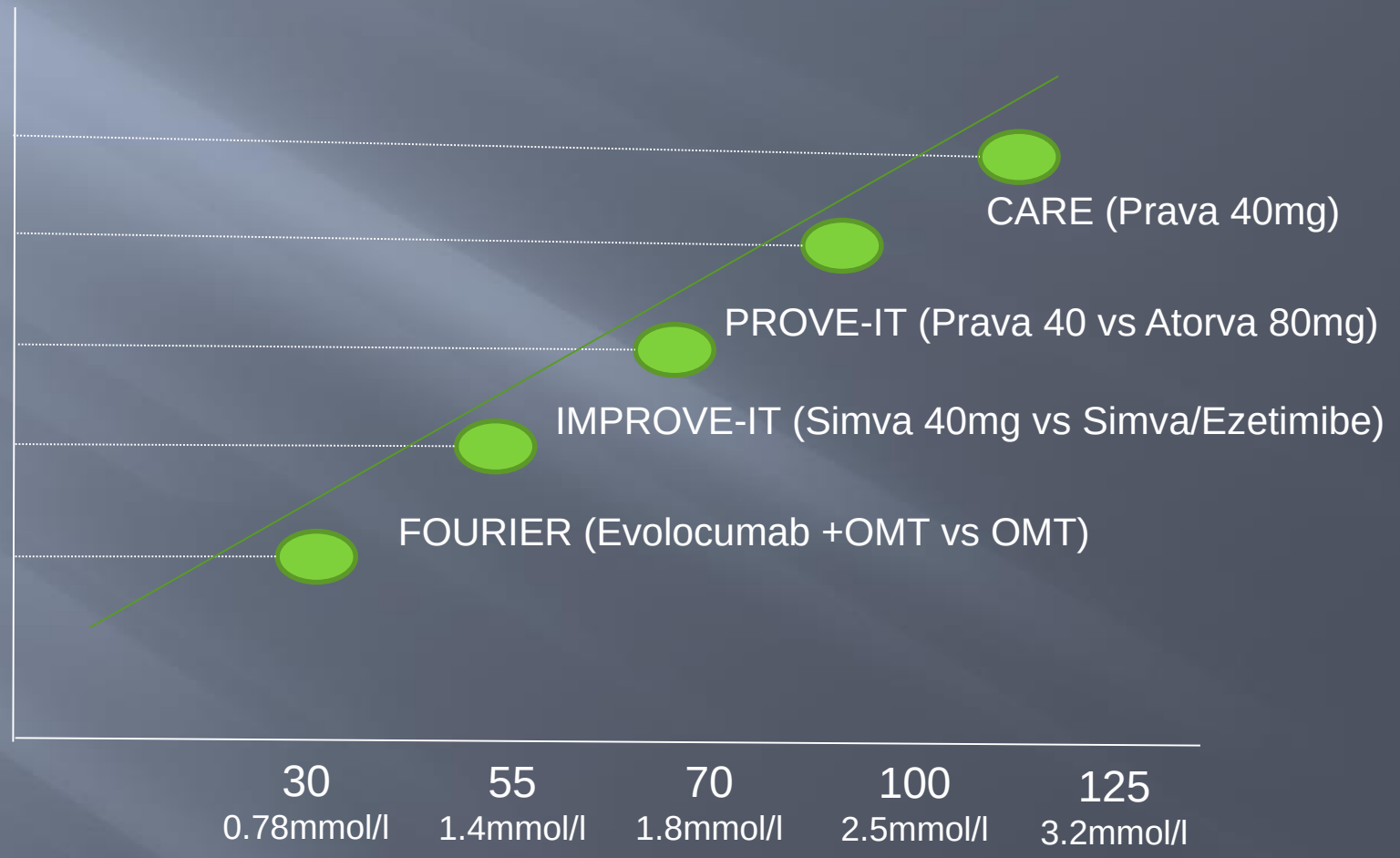
Perspective Secondary Prevention



Recommendations for PCSK9 are in Evolution

Likely medium term recipients will be:

- FH homozygous and heterozygous groups (primary prevention)
- Intolerant to statin therapy (primary and secondary high risk)
- Not achieving goal in a high risk environment

Inherent problems with statin therapy

- In secondary prevention:

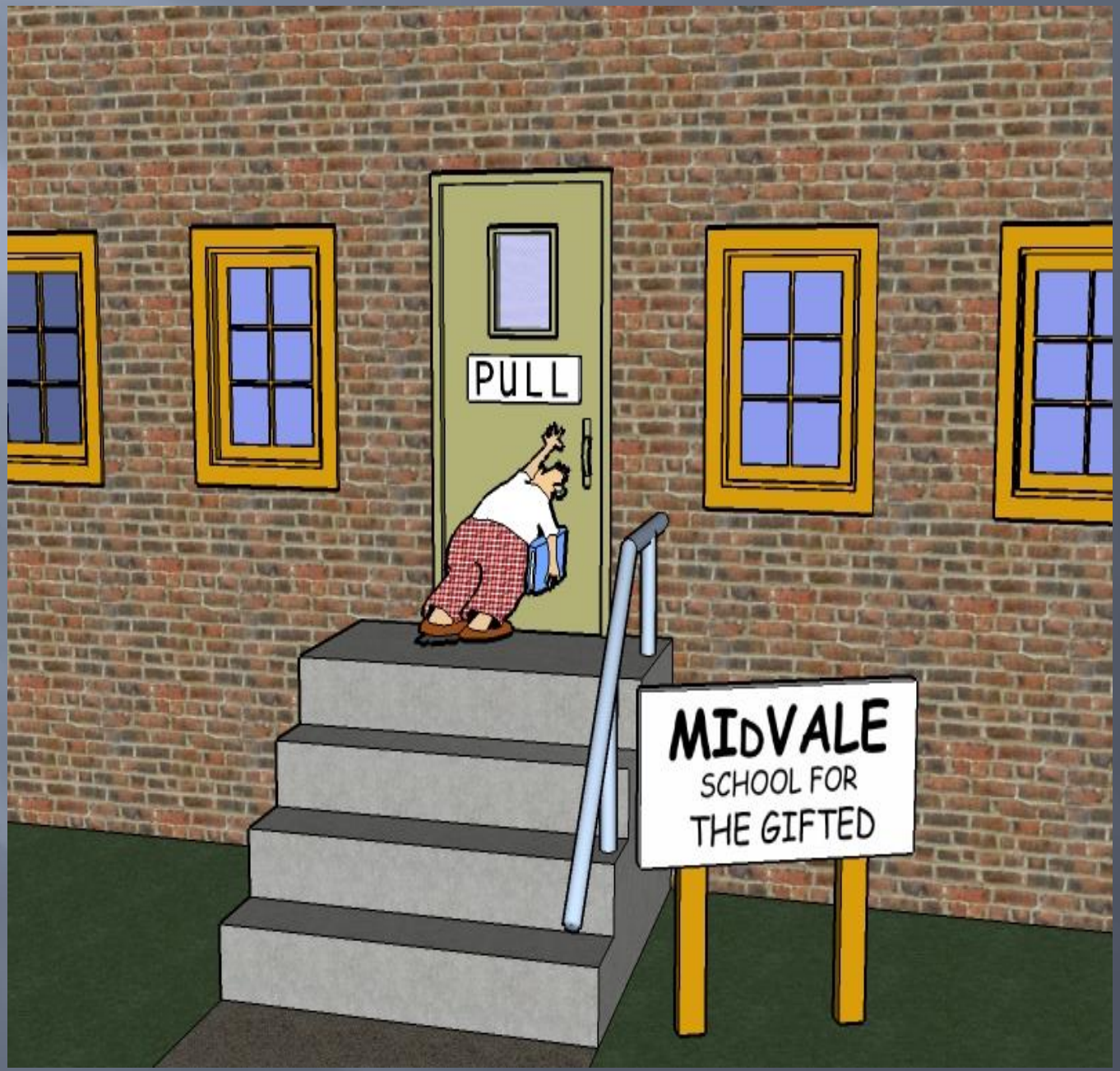
Adherence: 90% tolerance, 50% adherence at 1yr

Goals not attained – at patient level and at level of physician

- In Primary prevention:

Credibility gap – public perception

Efficacy gap


PULL
MIDVALE
SCHOOL FOR
THE GIFTED