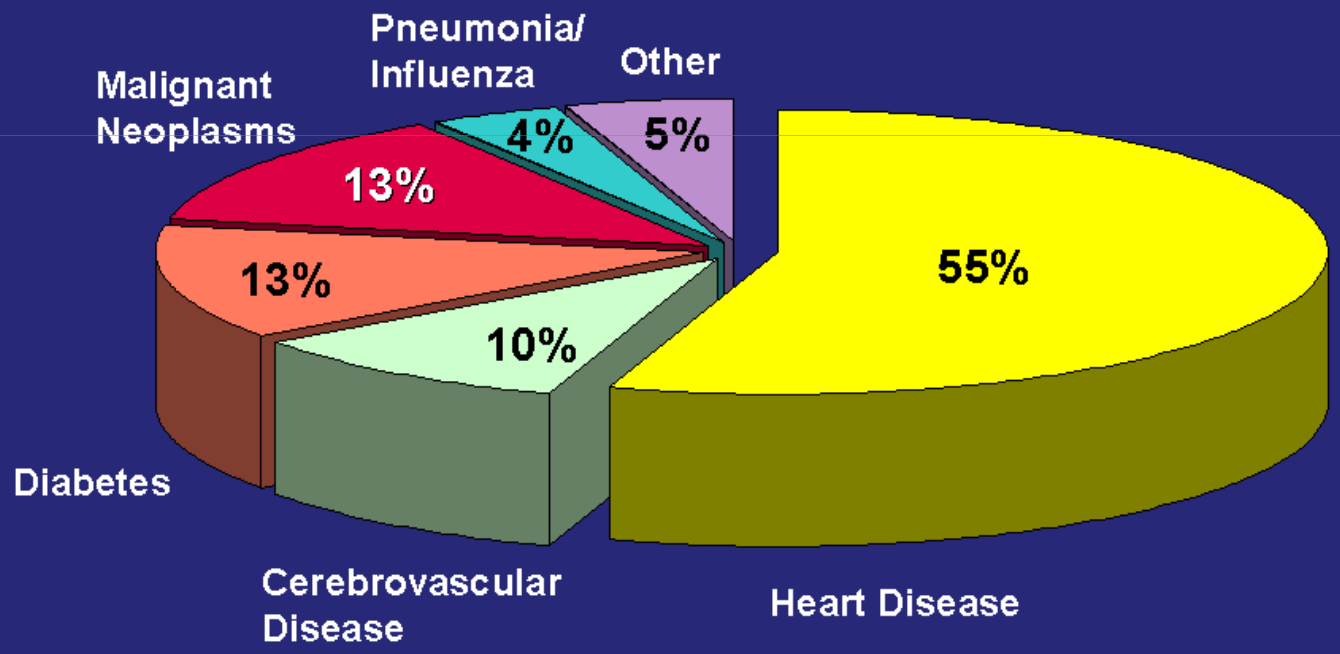
Dilemas em Cardio-Endocrinologia

O Diabetes por si já define a necessidade de uso de Estatina?

*Declaro não possuir conflito de Interesses com a minha apresentação

Causas de Morte em Pacientes com Diabetes Mellitus

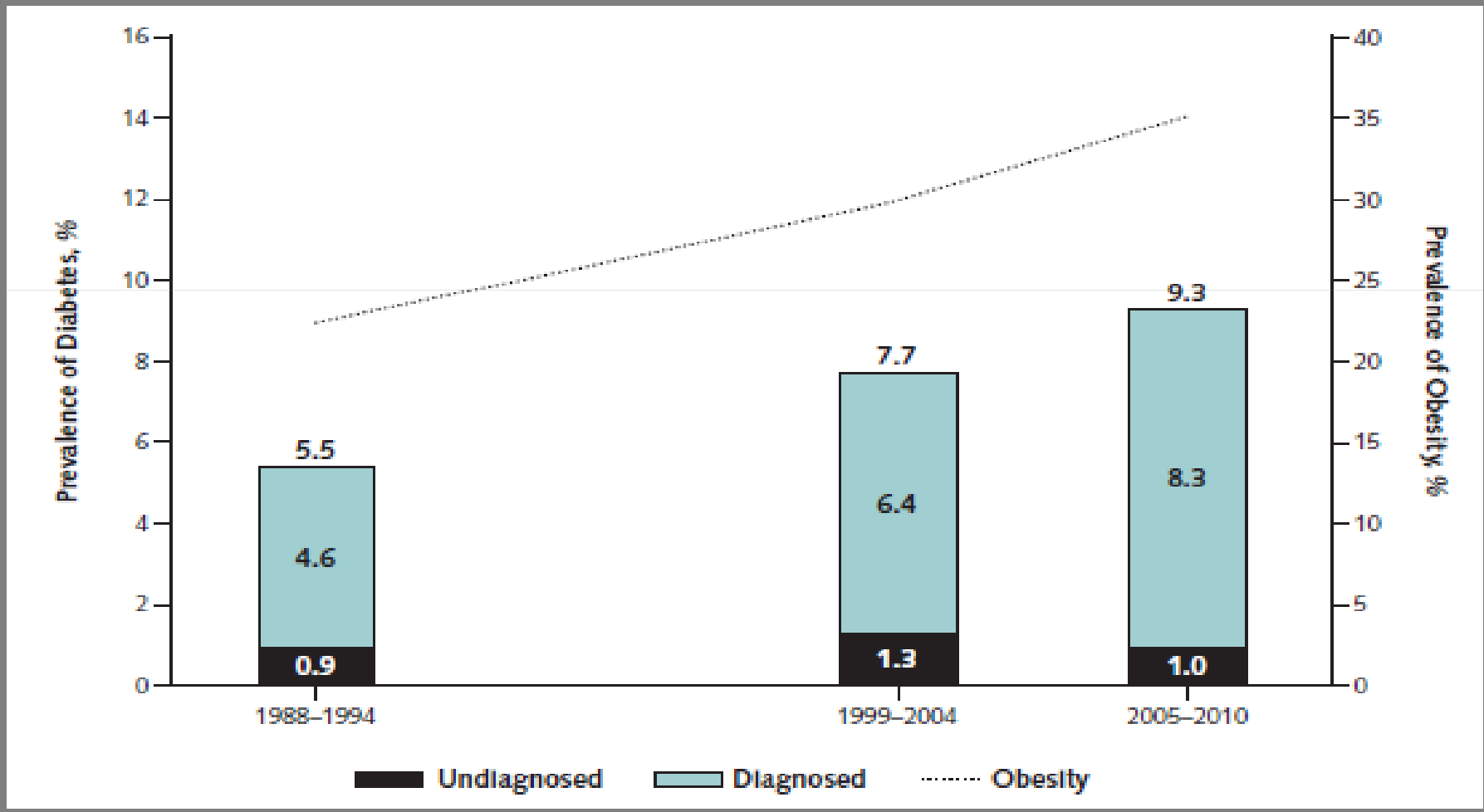
2/3 dos Diabéticos morrem de Causas Cardiovasculares



Geiss LS, et al. In: *Diabetes in America*. 2nd ed. NIH Publication No. 95-1468. 1995:233-257.

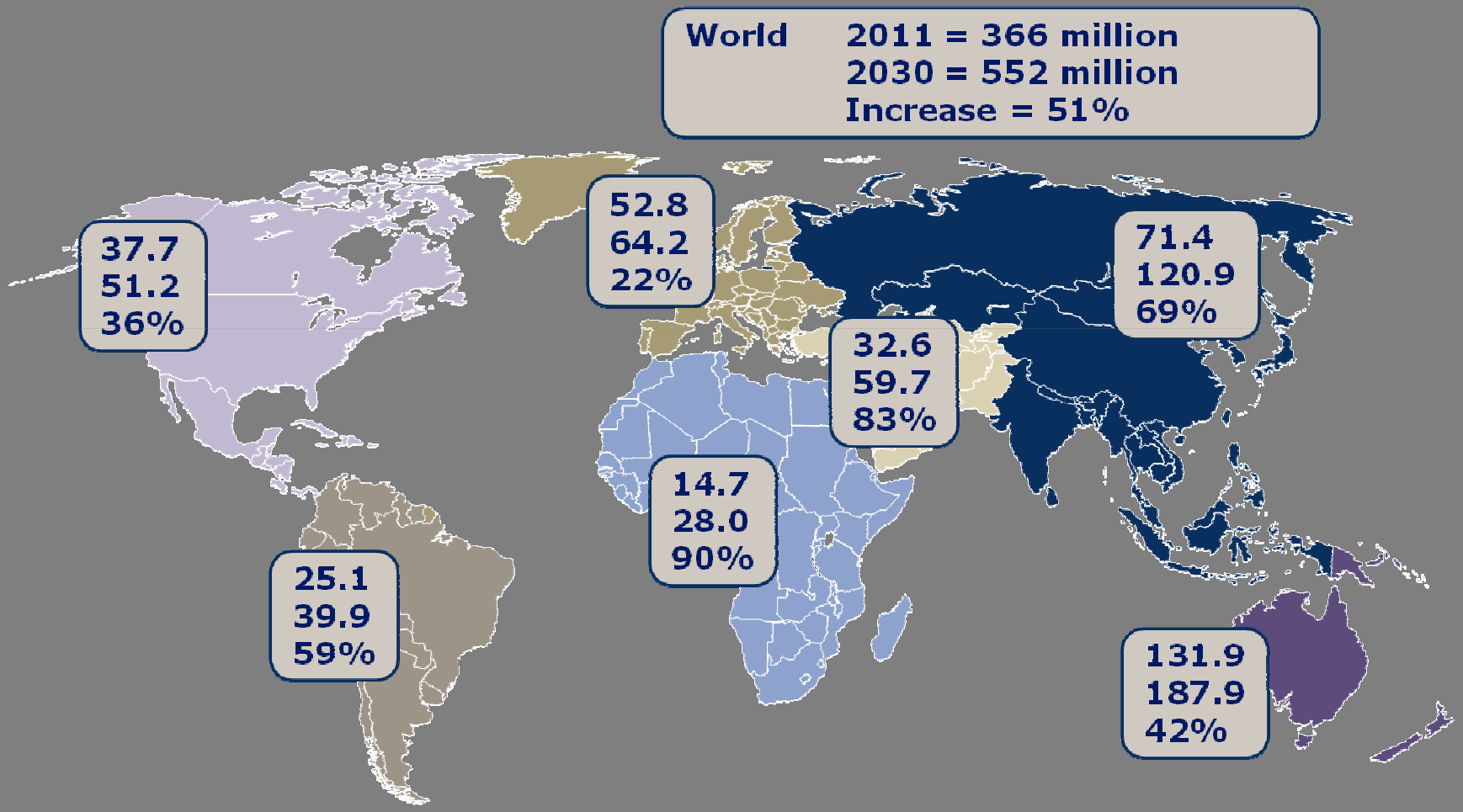
Crescimento da Prevalência de Diabetes Mellitus e Obesidade

- Dados dos NHANES (National Health and Nutrition Examination Survey)
- in 1988–1994 and 1999–2010, adultos ≥ 20 anos



Selvin et al. Ann Intern Med. 2014;160:517-525.

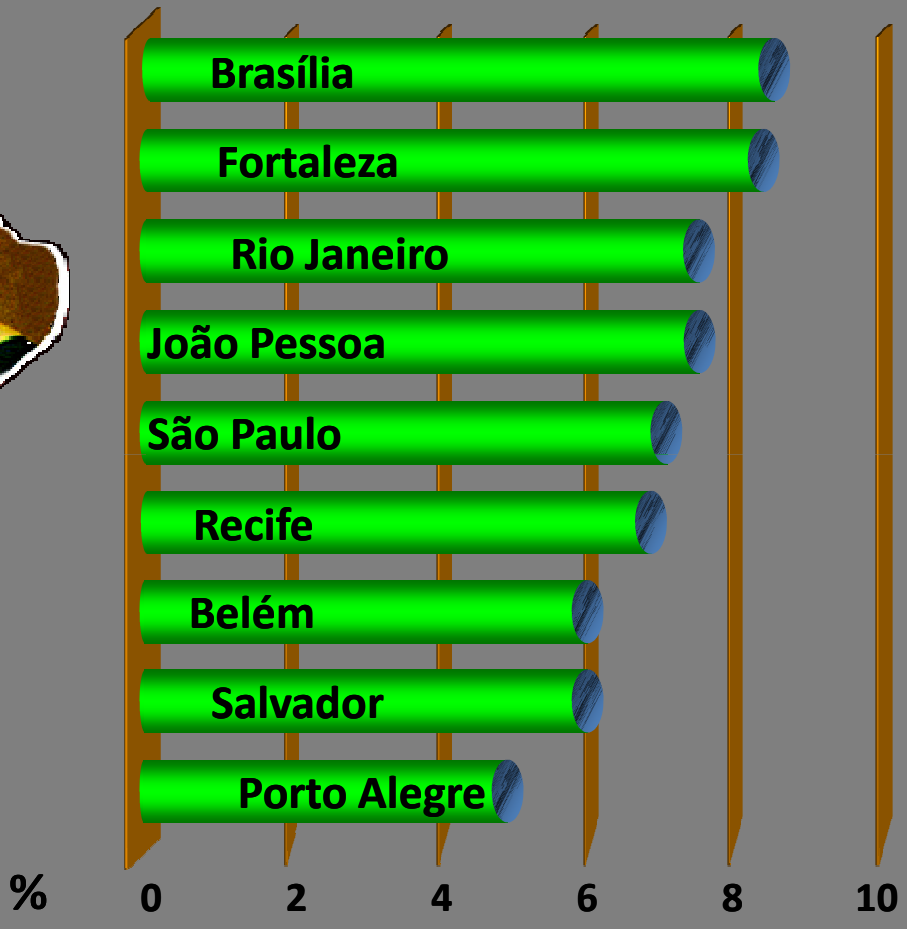
Epidemia de Diabetes Mellitus
Projeção Global 2010-2030



IDF. Diabetes Atlas 5th Ed. 2011

Prevalência de Diabetes Mellitus no Brasil

7,6%



População urbana, 30 - 69 anos
Ministério da Saúde, Brasil 1986-88

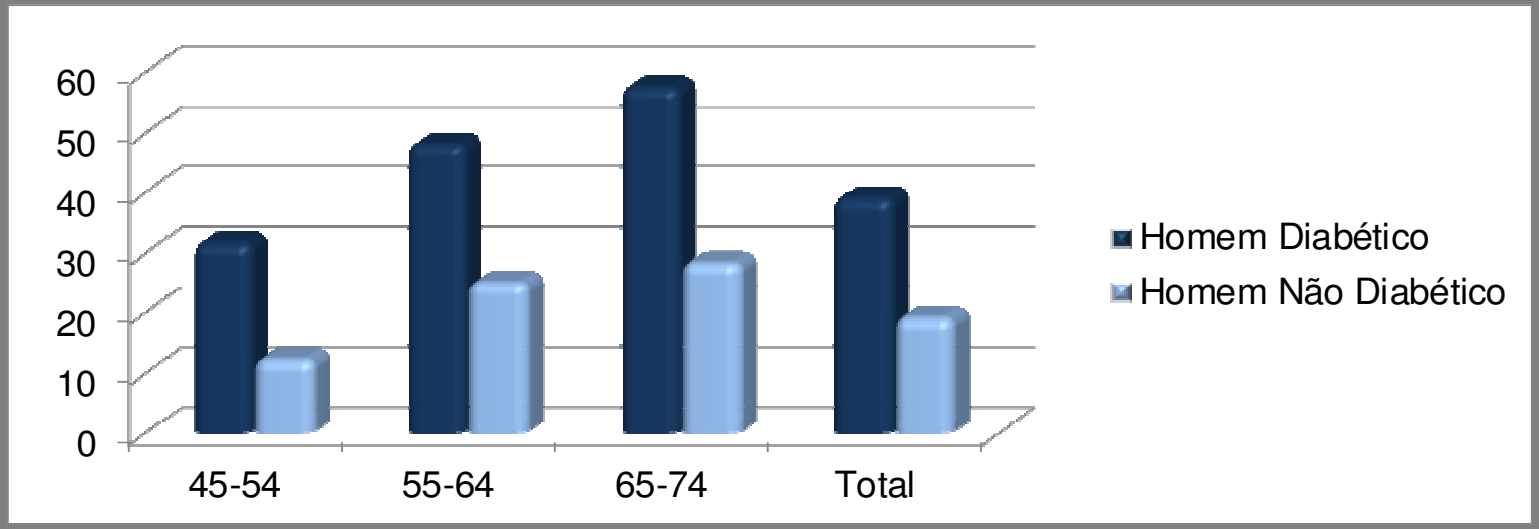
Ministério da Saúde, Brasil 1986-1988

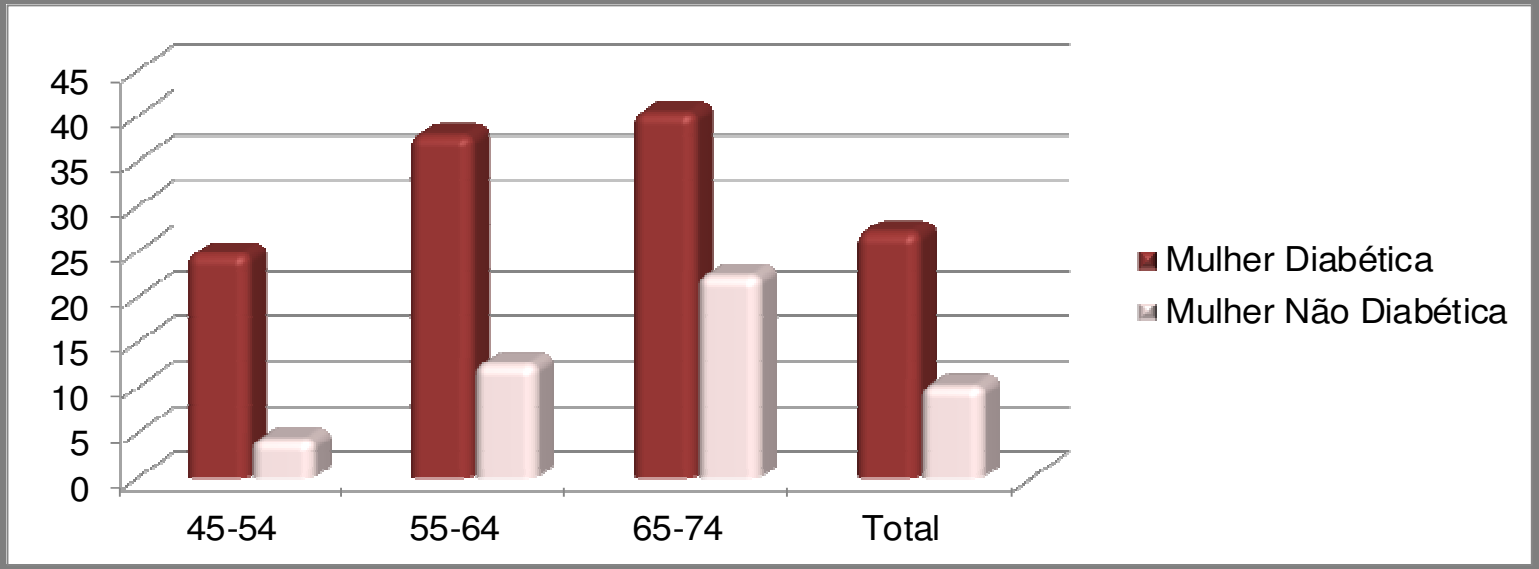
Prevalência Global de DM: Estimativa para o ano 2000 e Projeção para 2030

	2000		2030	
Ranking	Country	People with diabetes (millions)	Country	People with diabetes (millions)
1	India	31.7	India	79.4
2	China	20.8	China	42.3
3	U.S.	17.7	U.S.	30.3
4	Indonesia	8.4	Indonesia	21.3
5	Japan	6.8	Pakistan	13.9
6	Pakistan	5.2	Brazil	11.3
7	Russian Federation	4.6	Bangladesh	11.1
8	Brazil	4.6	Japan	8.9
9	Italy	4.3	Philippines	7.8
10	Bangladesh	3.2	Egypt	6.7

Diabetes Care. 27(5):1047-1053, May 2004.

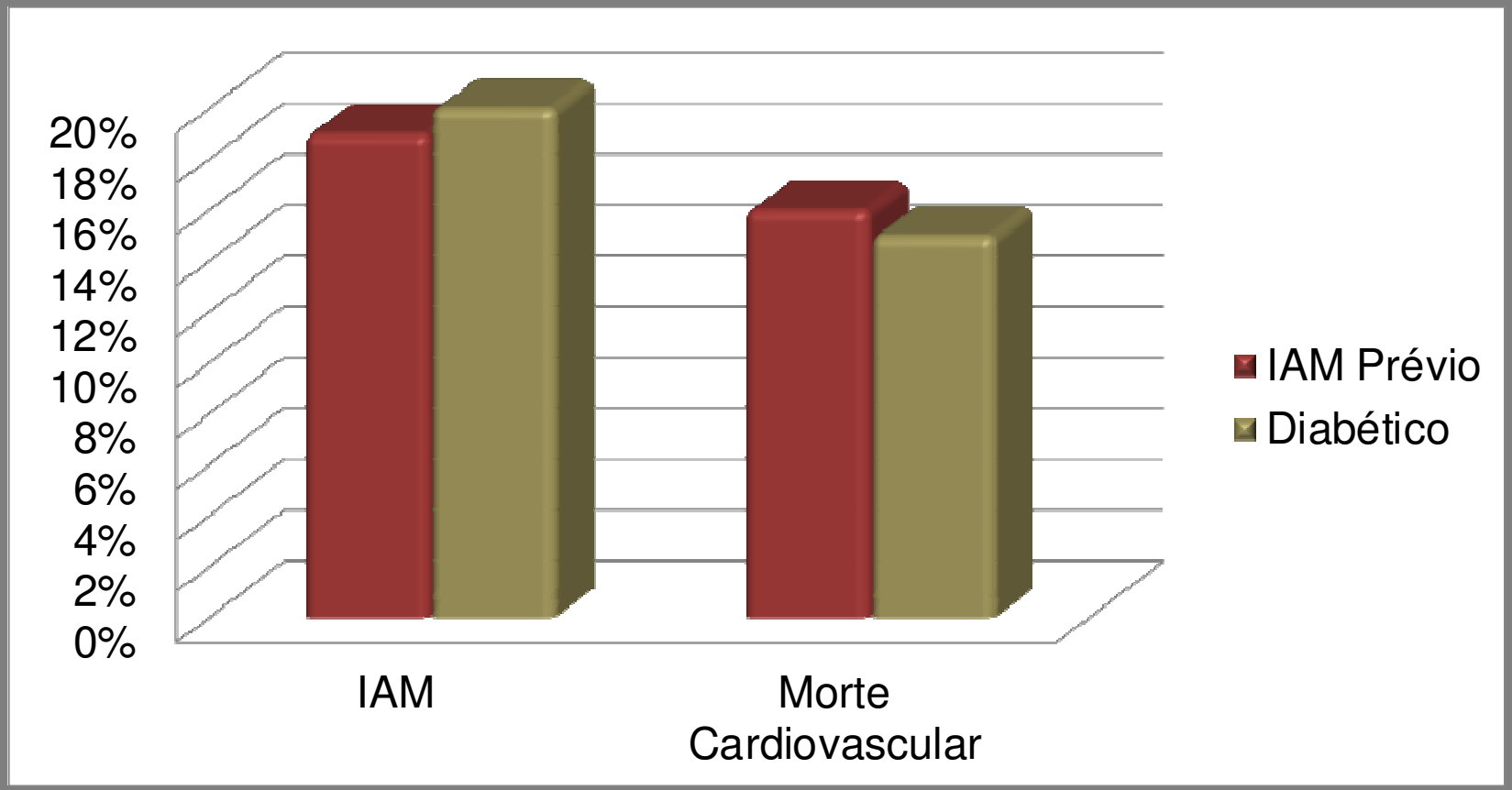
Framingham Heart Study – Incidência Anual de Doença Cardiovascular





Circulation 1979;59:8

Risco de Eventos Cardiovasculares em Indivíduos Diabéticos x Indivíduos não Diabéticos com IAM Prévio



Haffner N Engl J Med 1998; 339:229

Diabetes Mellitus Realmente Equivalente a DAC?
Revisão Sistemática/Meta-análise

***13 Estudos, 45.108 pacts. Seguimento de 5–25 aa (média de 13.4 aa) e Idade de 25–84aa.**

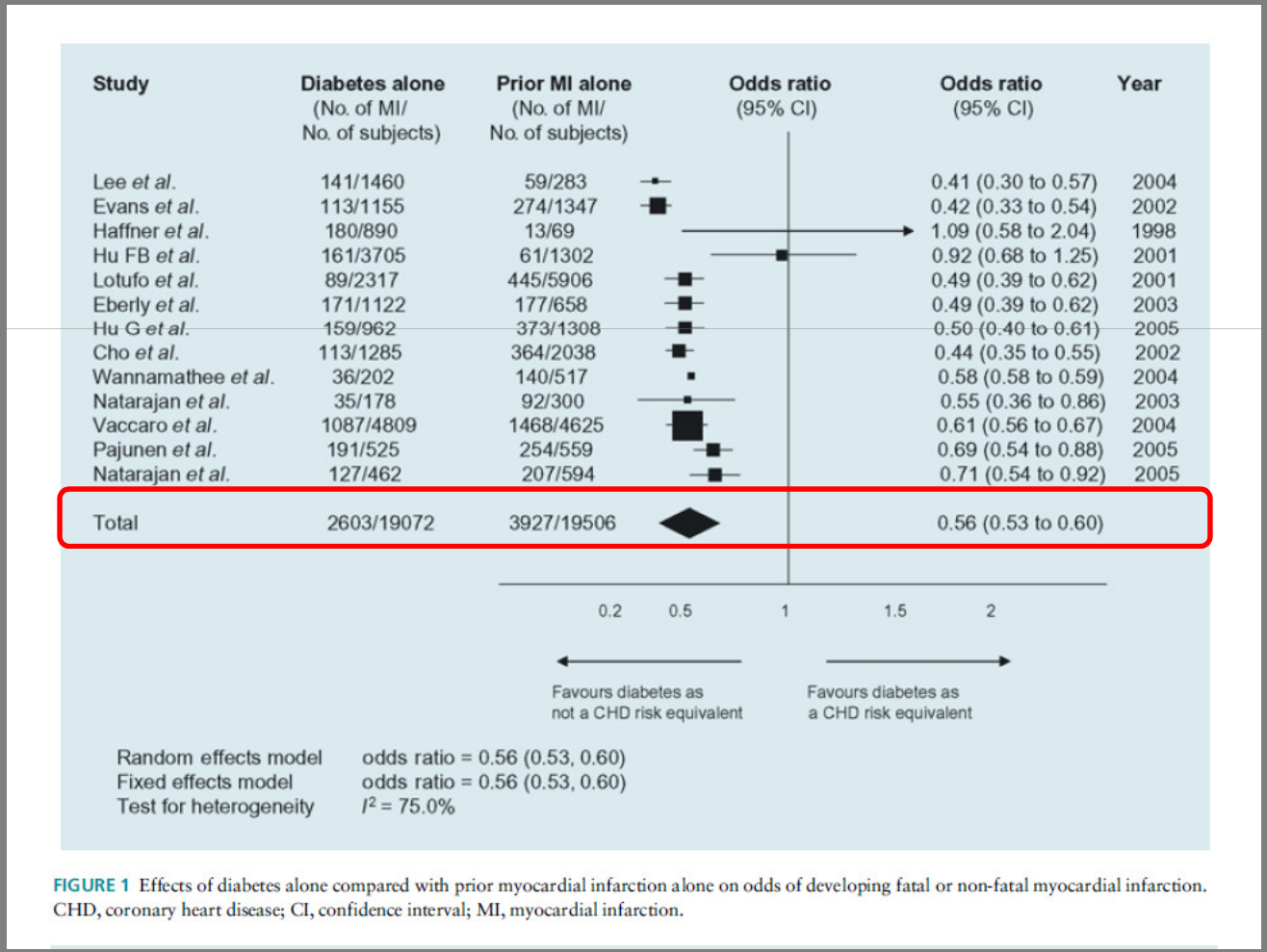
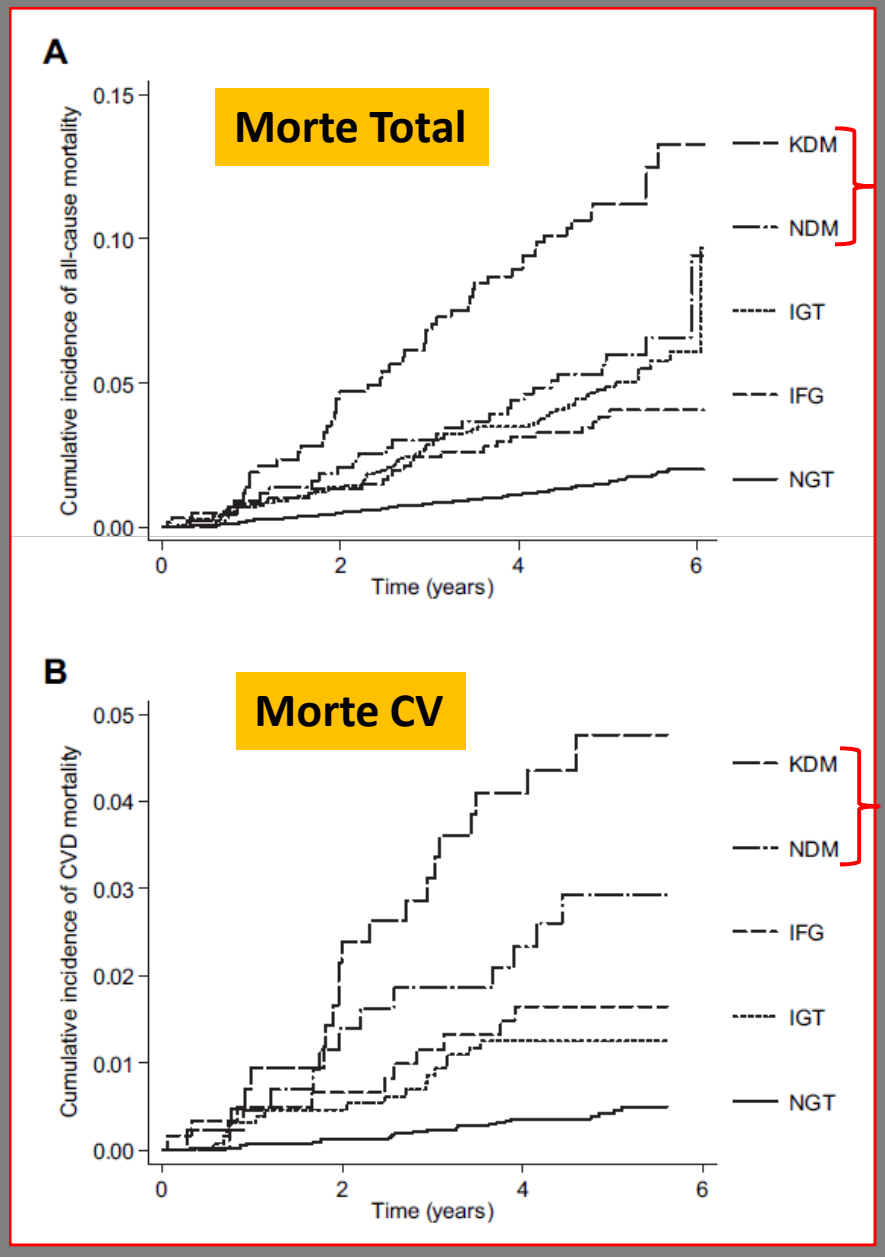


FIGURE 1 Effects of diabetes alone compared with prior myocardial infarction alone on odds of developing fatal or non-fatal myocardial infarction. CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction.

Diabet. Med. 26, 142–148 (2009)

Risco de Morte e Morte CV de acordo com Metabolismo Glicêmico- Estudo AusDiab



Circulation. 2007;116:151-157

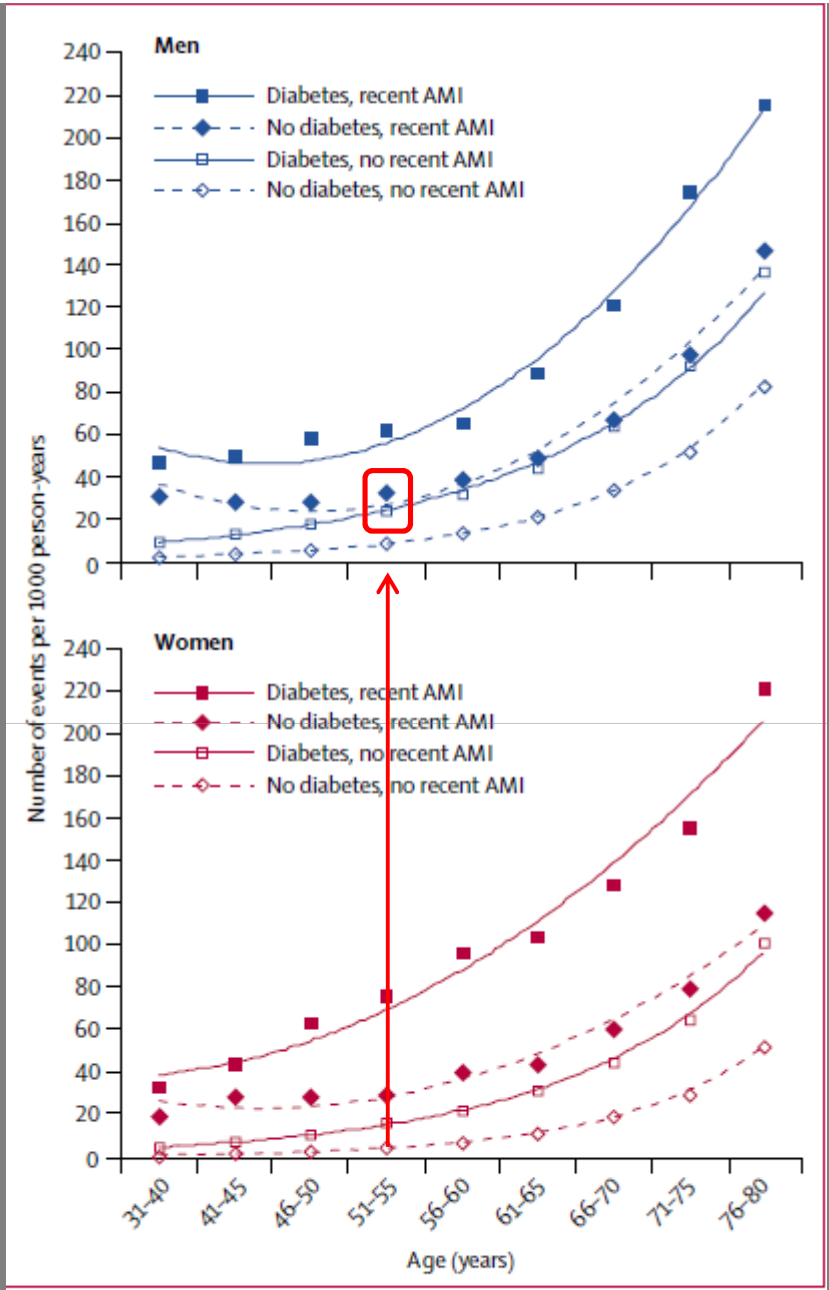
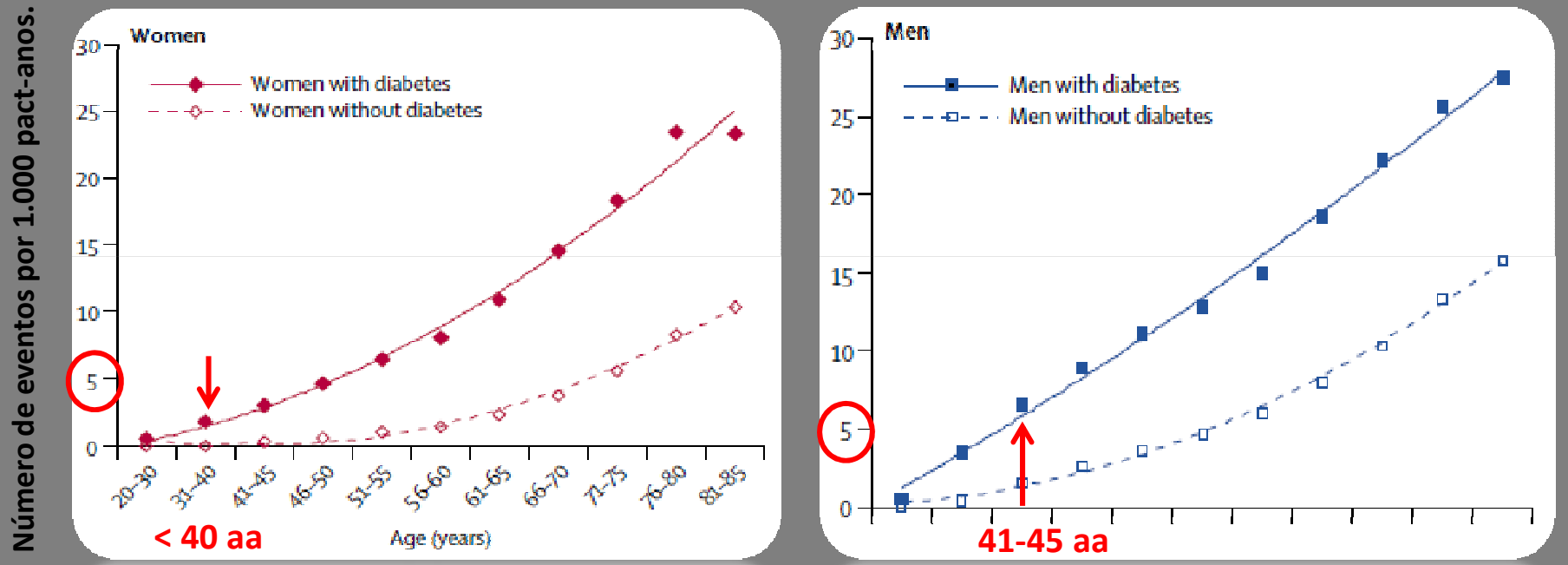


Figure 2: **Relation between age and rates of AMI or death from any cause in men and women according to presence of diabetes and previous AMI**
Recent AMI: polynomial distribution. No recent AMI: exponential distribution. R^2>0·97 for each fitted line. Recent AMI=within 3 years of baseline.

Lancet 2006;368:29

Relação entre Idade e Taxa de IAM de Acordo com o Status de Diabetes Mellitus



Lancet 2006;368:29

Idade Melhor Relação Custo-Efetividade para Iniciar Estatina Prevenção Primária

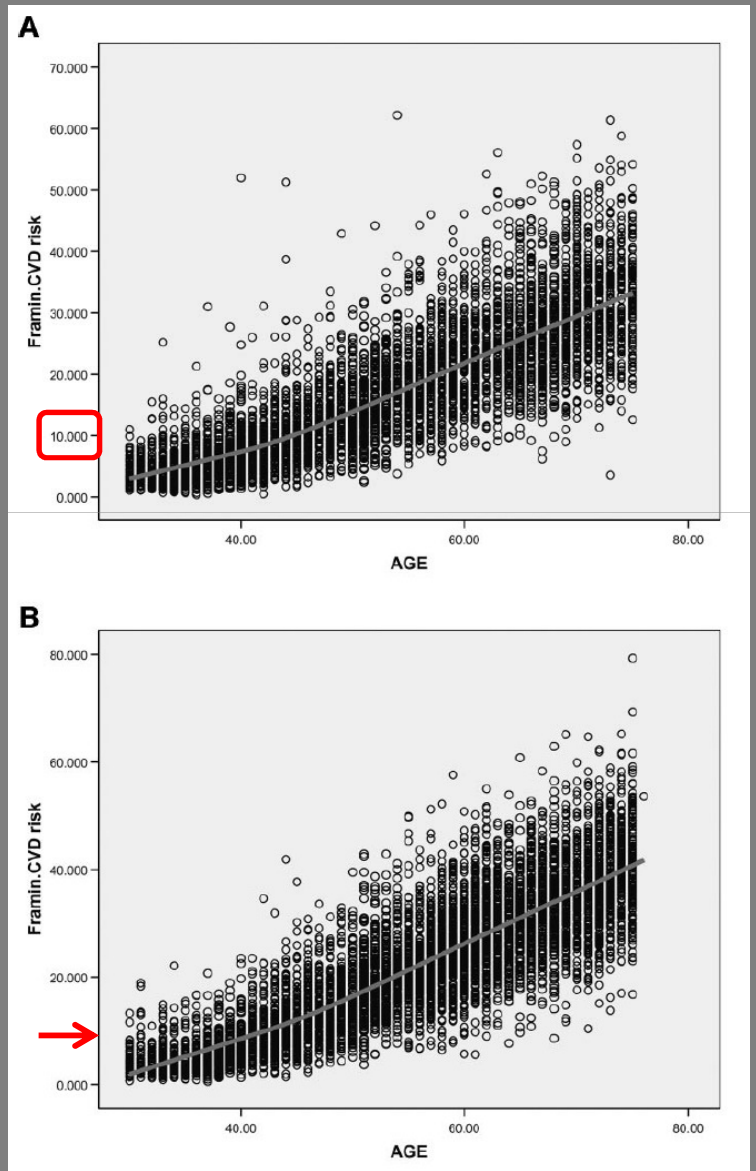


Figure 1—*Relation between age and baseline 10-year CVD risk estimates in women (A) and men (B). The line of best fit is fitted according to polynomial equation.*

Table 2—*Age (years) of transition from between risk levels, moderate-risk cutoff (10% 10-year CVD risk), and high-risk cutoff (20% 10-year CVD risk)*

	Men	Women
Low-to-moderate risk	40.6	44.2
Moderate-to-high risk	52.4	59.3
Moderate risk cutoff		
Sensitivity (%)	92.2	90.3
Specificity (%)	84.4	81.3
High-risk cutoff		
Sensitivity (%)	92.4	90.2
Specificity (%)	77.7	79.8

baseline CVD risk. Baseline CVD risk in people with diabetes reached a threshold for moderate/high risk at ~40 years for men and 45 years for women. This age cutoff confers high sensitivity and specificity for individuals with diabetes to have a moderate baseline risk of developing CVD. Because the number of patients

Diabetes Care 30:2025–2029, 2007

MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial

*Heart Protection Study Collaborative Group**

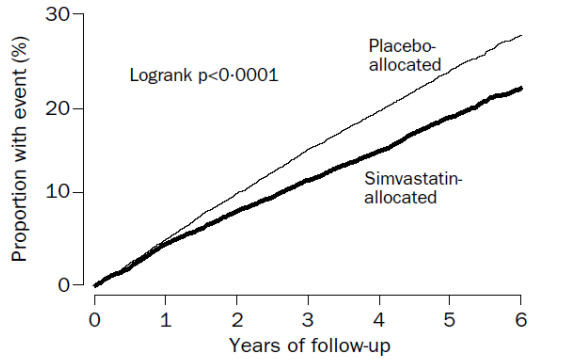
Summary

Background Throughout the usual LDL cholesterol range in Western populations, lower blood concentrations are associated with lower cardiovascular disease risk. In such populations, therefore, reducing LDL cholesterol may reduce the development of vascular disease, largely irrespective of initial cholesterol concentrations.

Methods 20 536 UK adults (aged 40–80 years) with coronary disease, other occlusive arterial disease, or diabetes were randomly allocated to receive 40 mg simvastatin daily (average compliance: 85%) or matching placebo (average non-study statin use: 17%). Analyses are

participant studied, including: those without diagnosed coronary disease who had cerebrovascular disease, or had peripheral artery disease, or had diabetes; men and, separately, women; those aged either under or over 70 years at entry; and—most notably—even those who presented with LDL cholesterol below 3·0 mmol/L (116 mg/dL), or total cholesterol below 5·0 mmol/L (193 mg/dL). The benefits of simvastatin were additional to those of other cardioprotective treatments. The annual excess risk of myopathy with this regimen was about 0·01%. There were no significant adverse effects on cancer incidence or on hospitalisation for any other non-vascular cause.

Interpretation Adding simvastatin to existing treatments

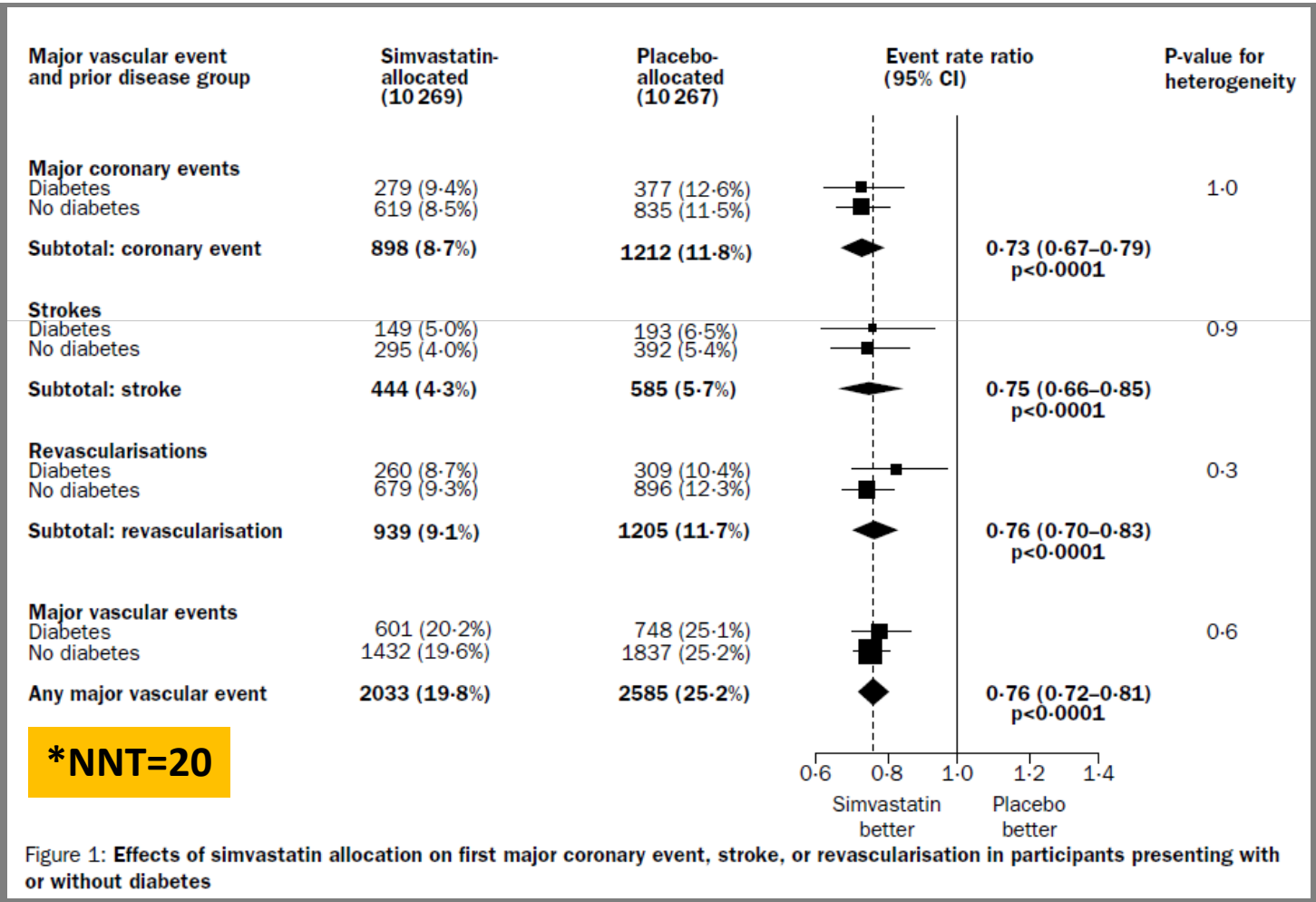


Benefit (SE)/1000 allocated simvastatin	5 (3)	20 (4)	35 (5)	46 (5)	54 (7)	60 (18)

Lancet 2002; 360: 7–22

MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial

*Heart Protection Study Collaborative Group**



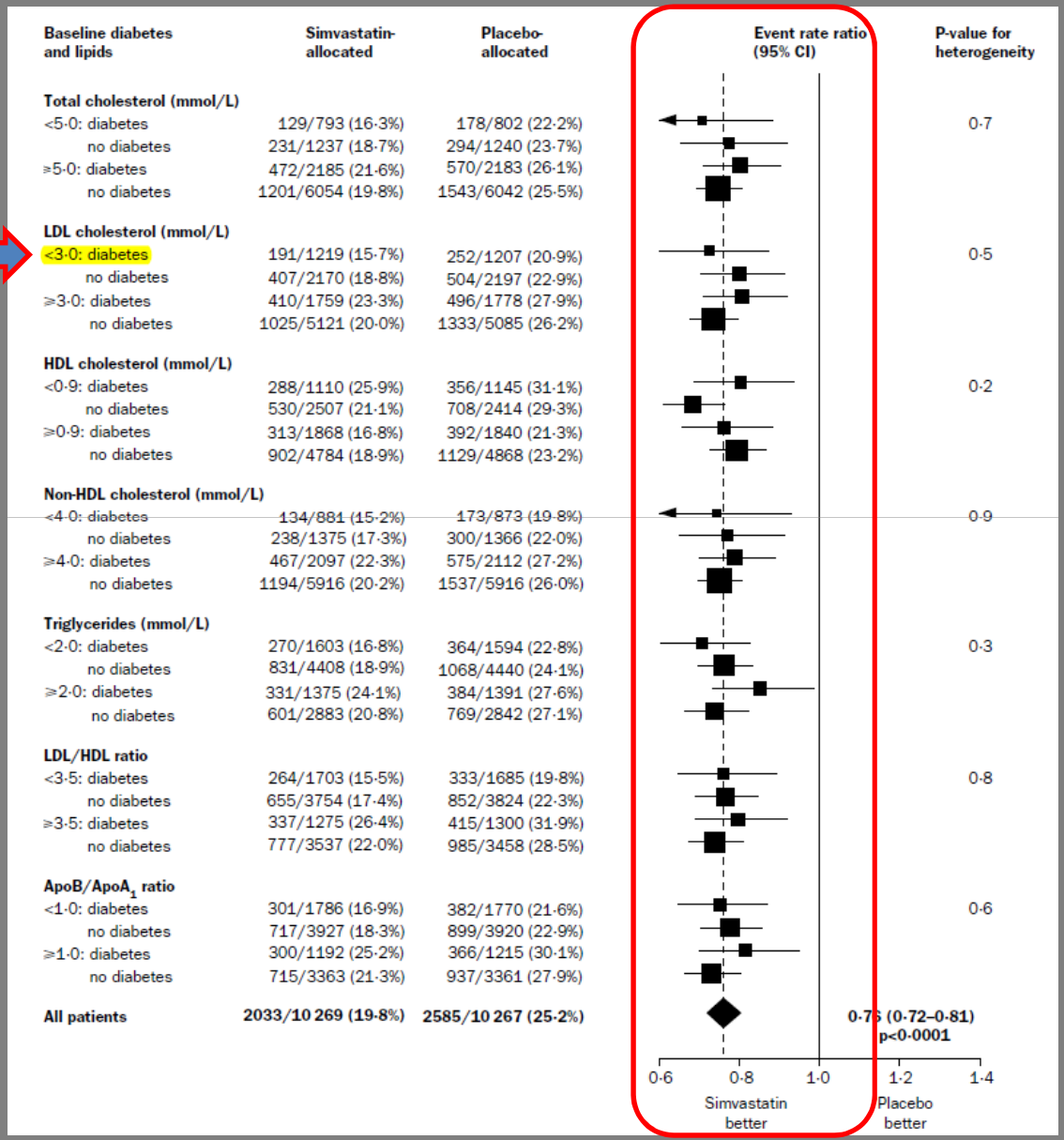
***NNT=20**

Figure 1: **Effects of simvastatin allocation on first major coronary event, stroke, or revascularisation in participants presenting with or without diabetes**

Lancet 2003; 361: 2005–16

HPS - População de Pacientes com Diabetes Mellitus
Benefício da Estatina Independente do Perfil Lipídico

Pacientes com LDL-normal



Baseline diabetes and lipids	Simvastatin-allocated	Placebo-allocated	P-value for heterogeneity
Total cholesterol (mmol/L)			
<5·0: diabetes	129/793 (16·3%)	178/802 (22·2%)	0·7
no diabetes	231/1237 (18·7%)	294/1240 (23·7%)	
≥5·0: diabetes	472/2185 (21·6%)	570/2183 (26·1%)	
no diabetes	1201/6054 (19·8%)	1543/6042 (25·5%)	
LDL cholesterol (mmol/L)			
<3·0: diabetes	191/1219 (15·7%)	252/1207 (20·9%)	0·5
no diabetes	407/2170 (18·8%)	504/2197 (22·9%)	
≥3·0: diabetes	410/1759 (23·3%)	496/1778 (27·9%)	
no diabetes	1025/5121 (20·0%)	1333/5085 (26·2%)	
HDL cholesterol (mmol/L)			
<0·9: diabetes	288/1110 (25·9%)	356/1145 (31·1%)	0·2
no diabetes	530/2507 (21·1%)	708/2414 (29·3%)	
≥0·9: diabetes	313/1868 (16·8%)	392/1840 (21·3%)	
no diabetes	902/4784 (18·9%)	1129/4868 (23·2%)	
Non-HDL cholesterol (mmol/L)			
<4·0: diabetes	134/881 (15·2%)	173/873 (19·8%)	0·9
no diabetes	238/1375 (17·3%)	300/1366 (22·0%)	
≥4·0: diabetes	467/2097 (22·3%)	575/2112 (27·2%)	
no diabetes	1194/5916 (20·2%)	1537/5916 (26·0%)	
Triglycerides (mmol/L)			
<2·0: diabetes	270/1603 (16·8%)	364/1594 (22·8%)	0·3
no diabetes	831/4408 (18·9%)	1068/4440 (24·1%)	
≥2·0: diabetes	331/1375 (24·1%)	384/1391 (27·6%)	
no diabetes	601/2883 (20·8%)	769/2842 (27·1%)	
LDL/HDL ratio			
<3·5: diabetes	264/1703 (15·5%)	333/1685 (19·8%)	0·8
no diabetes	655/3754 (17·4%)	852/3824 (22·3%)	
≥3·5: diabetes	337/1275 (26·4%)	415/1300 (31·9%)	
no diabetes	777/3537 (22·0%)	985/3458 (28·5%)	
ApoB/ApoA$_1$ ratio			
<1·0: diabetes	301/1786 (16·9%)	382/1770 (21·6%)	0·6
no diabetes	717/3927 (18·3%)	899/3920 (22·9%)	
≥1·0: diabetes	300/1192 (25·2%)	366/1215 (30·1%)	
no diabetes	715/3363 (21·3%)	937/3361 (27·9%)	
All patients	**2033/10 269 (19·8%)**	**2585/10 267 (25·2%)**	

Event rate ratio (95% CI)

0·76 (0·72–0·81)
p<0·0001

0·6 0·8 1·0 1·2 1·4

Simvastatin better | Placebo better

Lancet 2003; 361: 2005–16

Reduction in Cardiovascular Events With Atorvastatin in 2,532 Patients With Type 2 Diabetes

Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA)

PETER S. SEVER, FRCP[1]
NEIL R. POULTER, FRCP[1]
BJÖRN DAHLÖF, MD[2]
HANS WEDEL, PHD[3]
RORY COLLINS, FRCP[4]
GARETH BEEVERS, FRCP[5]
MARK CAULFIELD, FRCP[6]
SVERRE E. KJELDSEN, MD[7,8]
ARNI KRISTINSSON, MD[9]
GORDON T. MCINNES, FRCP[10]
JESPER MEHLSEN, MD[11]
MARKKU NIEMINEN, FESC[12]
EOIN O'BRIEN, FRCP[13]
JAN OSTERGREN, MD[14]
FOR THE ASCOT INVESTIGATORS

allocated atorvastatin compared with placebo. There were 116 (9.2%) major cardiovascular events or procedures in the atorvastatin group and 151 (11.9%) events in the placebo group (hazard ratio 0.77, 95% CI 0.61–0.98; P = 0.036). For the individual components of this composite end point, the number of events occurring in the diabetes subgroup was small. Therefore, although fewer coronary events

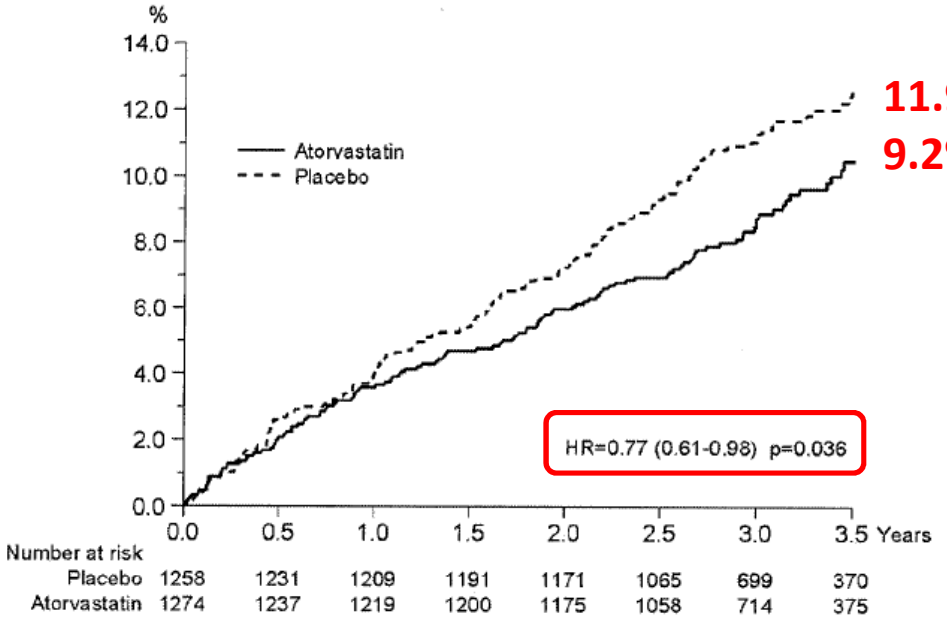


Figure 1—*Cumulative incidence for total cardiovascular events and procedures among diabetic participants in ASCOT-LLA.*

11.9%
9.2%

n = 10.305 pacts
Idade: 40-79 aa
Colesterol médio 212 mg/dl
LDL-C médio 131 mg/dl
Seguimento 3.3 anos
Desfecho Primário:
IAM não fatal e DAC fatal.

Diabetes Care 28:1151–1157, 2005

Prevenção Primária em Diabetes Mellitus
Estudo CARDS

DM + 01 FR (HAS, Tabagismo, Albuminúria ou Retinopatia)

Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial

*Helen M Colhoun, D John Betteridge, Paul N Durrington, Graham A Hitman, H Andrew W Neil, Shona J Livingstone, Margaret J Thomason, Michael I Mackness, Valentine Charlton-Menys, John H Fuller, on behalf of the CARDS investigators**

Lancet 2004; 364: 685–96

See Comment page 641

EURODIAB, Department of Epidemiology and Public Health, Royal Free and University College Medical School, London, UK (Prof H M Colhoun MD, S J Livingstone MSc, M J Thomason PhD, Prof J H Fuller MRCP); University College London, Middlesex Hospital, London, UK (Prof D J Betteridge PhD); University of Manchester, Department of Medicine, Manchester Royal Infirmary, Manchester, UK (Prof P N Durrington MD, M I Mackness PhD, V Charlton-Menys PhD); Centre for Diabetes and Metabolic Medicine, Barts and the London, Queen Mary's School of Medicine and Dentistry, London, UK (Prof G A Hitman MD); and University of Oxford, Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford, UK (A W Neil DSc)

*Members listed at end of report.

Correspondence to:
Prof Helen M Colhoun, The Conway Institute, University

Summary

Background Type 2 diabetes is associated with a substantially increased risk of cardiovascular disease, but the role of lipid-lowering therapy with statins for the primary prevention of cardiovascular disease in diabetes is inadequately defined. We aimed to assess the effectiveness of atorvastatin 10 mg daily for primary prevention of major cardiovascular events in patients with type 2 diabetes without high concentrations of LDL-cholesterol.

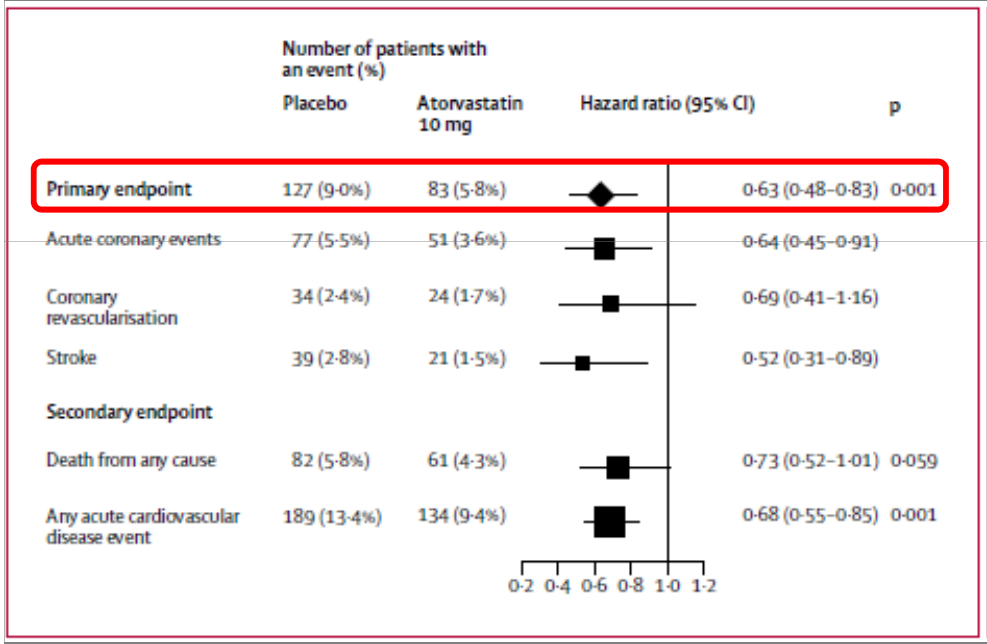
Methods 2838 patients aged 40–75 years in 132 centres in the UK and Ireland were randomised to placebo (n=1410) or atorvastatin 10 mg daily (n=1428). Study entrants had no documented previous history of cardiovascular disease, an LDL-cholesterol concentration of 4·14 mmol/L or lower, a fasting triglyceride amount of 6·78 mmol/L or less, and at least one of the following: retinopathy, albuminuria, current smoking, or hypertension. The primary endpoint was time to first occurrence of the following: acute coronary heart disease events, coronary revascularisation, or stroke. Analysis was by intention to treat.

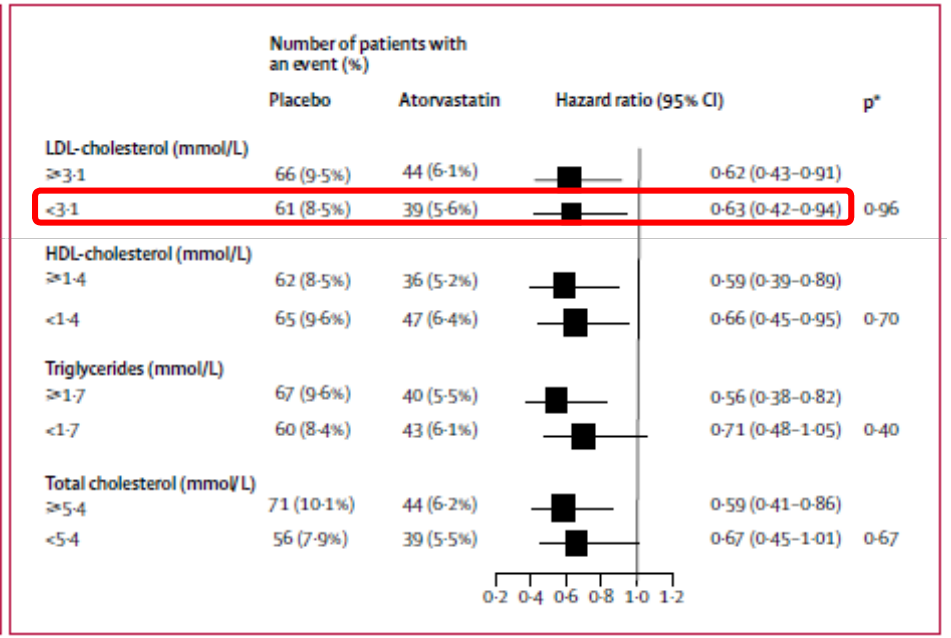
Findings The trial was terminated 2 years earlier than expected because the prespecified early stopping rule for efficacy had been met. Median duration of follow-up was 3·9 years (IQR 3·0–4·7). 127 patients allocated placebo (2·46 per 100 person-years at risk) and 83 allocated atorvastatin (1·54 per 100 person-years at risk) had at least one major cardiovascular event (rate reduction 37% [95% CI −52 to −17], p=0·001). Treatment would be expected to prevent at least 37 major vascular events per 1000 such people treated for 4 years. Assessed separately, acute coronary heart disease events were reduced by 36% (−55 to −9), coronary revascularisations by 31% (−59 to 16), and rate of stroke by 48% (−69 to −11). Atorvastatin reduced the death rate by 27% (−48 to 1, p=0·059). No excess of adverse events was noted in the atorvastatin group.

Interpretation Atorvastatin 10 mg daily is safe and efficacious in reducing the risk of first cardiovascular disease events, including stroke, in patients with type 2 diabetes without high LDL-cholesterol. No justification is available for having a particular threshold level of LDL-cholesterol as the sole arbiter of which patients with type 2 diabetes should receive statins. The debate about whether all people with this disorder warrant statin treatment should now focus on whether any patients are at sufficiently low risk for this treatment to be withheld.

Prevenção Primária em Diabetes Mellitus
Estudo CARDS

Desfecho Primário: Evento Coronário Agudo, Revascularização Coronária e AVC





RRA: 3,2% → NNT = 26

Lancet 2004; 364: 685–96

Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis

*Cholesterol Treatment Trialists' (CTT) Collaborators**

Summary

Background Although statin therapy reduces the risk of occlusive vascular events in people with diabetes mellitus, there is uncertainty about the effects on particular outcomes and whether such effects depend on the type of diabetes, lipid profile, or other factors. We undertook a prospective meta-analysis to help resolve these uncertainties.

Methods We analysed data from 18 686 individuals with diabetes (1466 with type 1 and 17 220 with type 2) in the context of a further 71 370 without diabetes in 14 randomised trials of statin therapy. Weighted estimates were obtained of effects on clinical outcomes per 1·0 mmol/L reduction in LDL cholesterol.

Findings During a mean follow-up of 4·3 years, there were 3247 major vascular events in people with diabetes. There was a 9% proportional reduction in all-cause mortality per mmol/L reduction in LDL cholesterol in participants with diabetes (rate ratio [RR] 0·91, 99% CI 0·82–1·01; p=0·02), which was similar to the 13% reduction in those without diabetes (0·87, 0·82–0·92; p<0·0001). This finding reflected a significant reduction in vascular mortality (0·87, 0·76–1·00; p=0·008) and no effect on non-vascular mortality (0·97, 0·82–1·16; p=0·7) in participants with diabetes. There was a significant 21% proportional reduction in major vascular events per mmol/L reduction in LDL cholesterol in people with diabetes (0·79, 0·72–0·86; p<0·0001), which was similar to the effect observed in those without diabetes (0·79, 0·76–0·82; p<0·0001). In diabetic participants there were reductions in myocardial infarction or coronary death (0·78, 0·69–0·87; p<0·0001), coronary revascularisation (0·75, 0·64–0·88; p<0·0001), and stroke (0·79, 0·67–0·93; p=0·0002). Among people with diabetes the proportional effects of statin therapy were similar irrespective of whether there was a prior history of vascular disease and irrespective of other baseline characteristics. After 5 years, 42 (95% CI 30–55) fewer people with diabetes had major vascular events per 1000 allocated statin therapy.

Interpretation Statin therapy should be considered for all diabetic individuals who are at sufficiently high risk of vascular events.

Lancet 2008; 371: 117–25

See Comment page 94

*Collaborators listed at end of paper

Correspondence to:
CTT Secretariat, Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, UK
ctt@ctsu.ox.ac.uk

or

National Health and Medical Research Council (NHMRC) Clinical Trial Centre, Mallett Street Campus M02, University of Sydney, NSW 2006, Australia
ctt@ctc.usyd.edu.au

Metanálise Trialistas: Redução de Eventos CV Proporcional à Redução do Colesterol

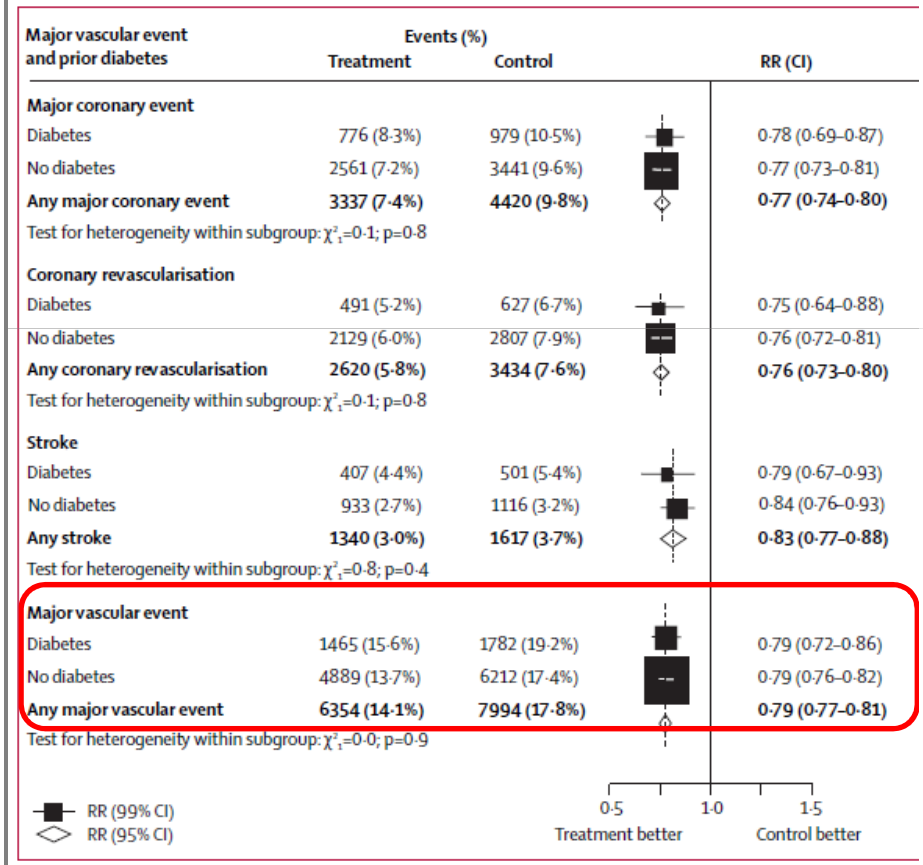


Figure 2: **Proportional effects on major vascular events per mmol/L reduction in LDL cholesterol in participants presenting with or without diabetes**
Symbols and conventions as in figure 1.

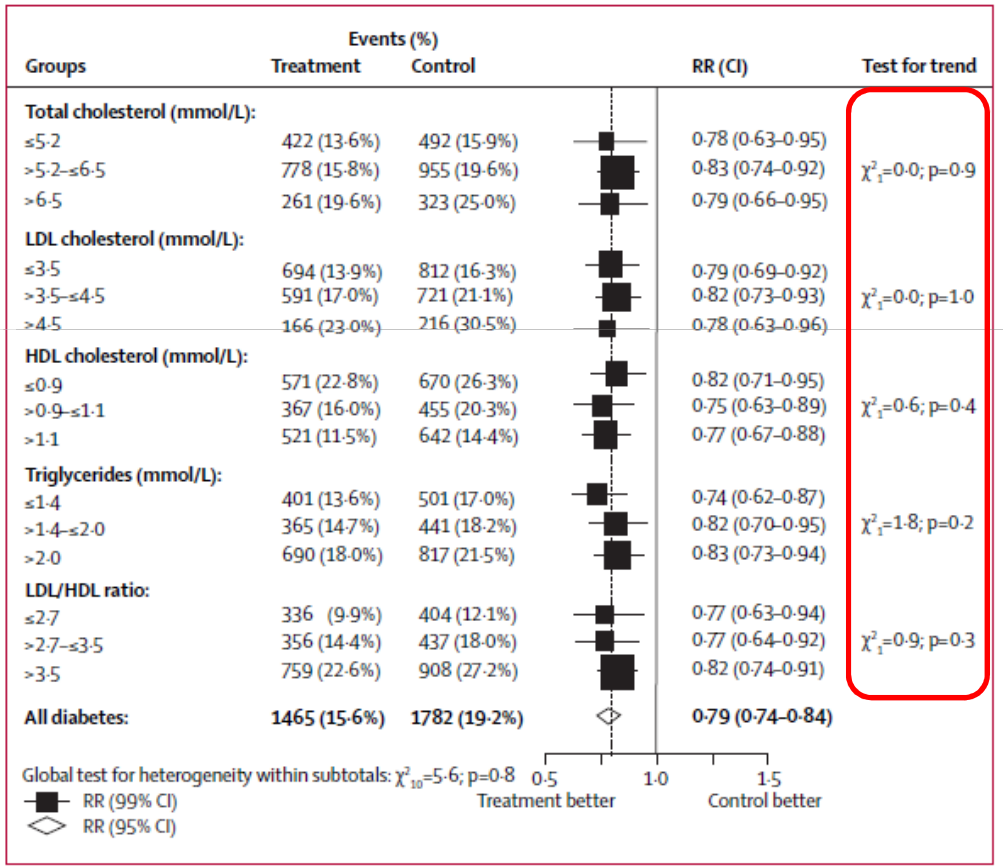


Figure 5: **Proportional effects on major vascular events per mmol/L reduction in LDL cholesterol by baseline lipid profile in participants with diabetes**
Symbols and conventions as in figure 4.

Lancet 2008; 371: 117–25

O Diabetes por si já define a necessidade de uso de Estatina?

O que dizem as Diretrizes?

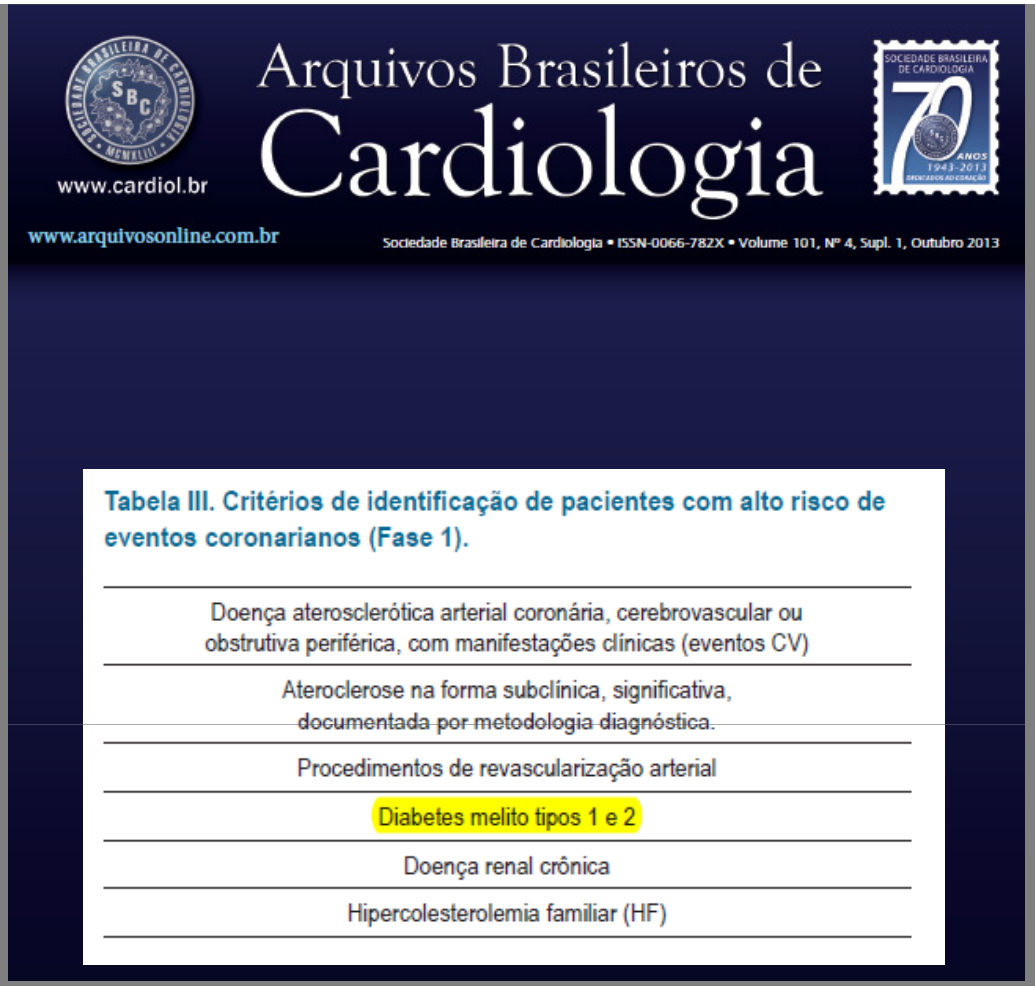


Tabela III. Critérios de identificação de pacientes com alto risco de eventos coronarianos (Fase 1).

Doença aterosclerótica arterial coronária, cerebrovascular ou obstrutiva periférica, com manifestações clínicas (eventos CV)
Aterosclerose na forma subclínica, significativa, documentada por metodologia diagnóstica.
Procedimentos de revascularização arterial
Diabetes melito tipos 1 e 2
Doença renal crônica
Hipercolesterolemia familiar (HF)

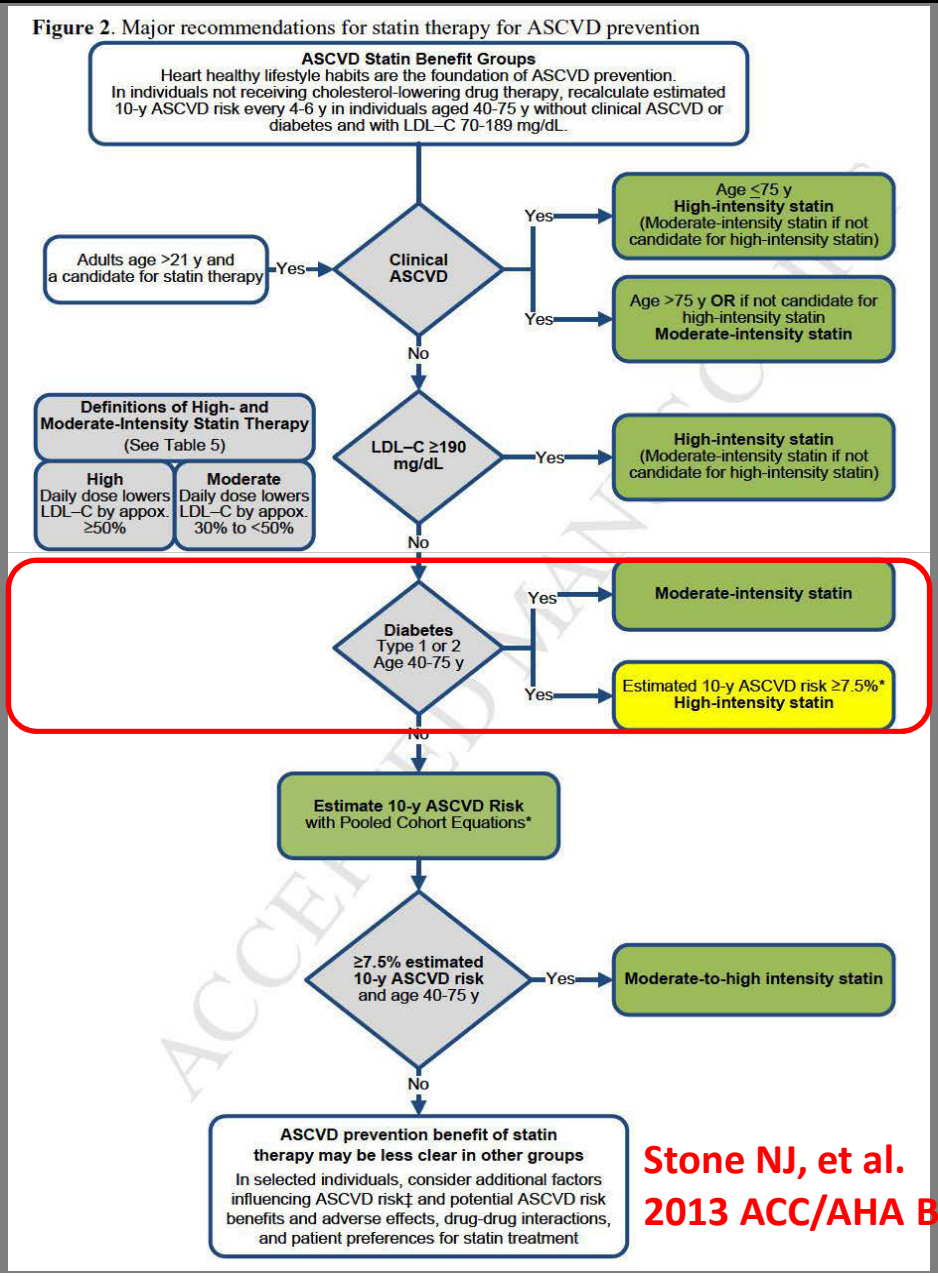
Tabela XIV. Metas lipídicas de acordo com o risco cardiovascular

Nível de risco	Meta primária: LDL-C (mg/dl)	Meta secundária (mg/dl)
ALTO	LDL-C < 70	Colesterol não-HDL < 100
INTERMEDIÁRIO	LDL-C < 100	Colesterol não-HDL< 130
BAIXO*	Meta individualizada	Meta individualizada

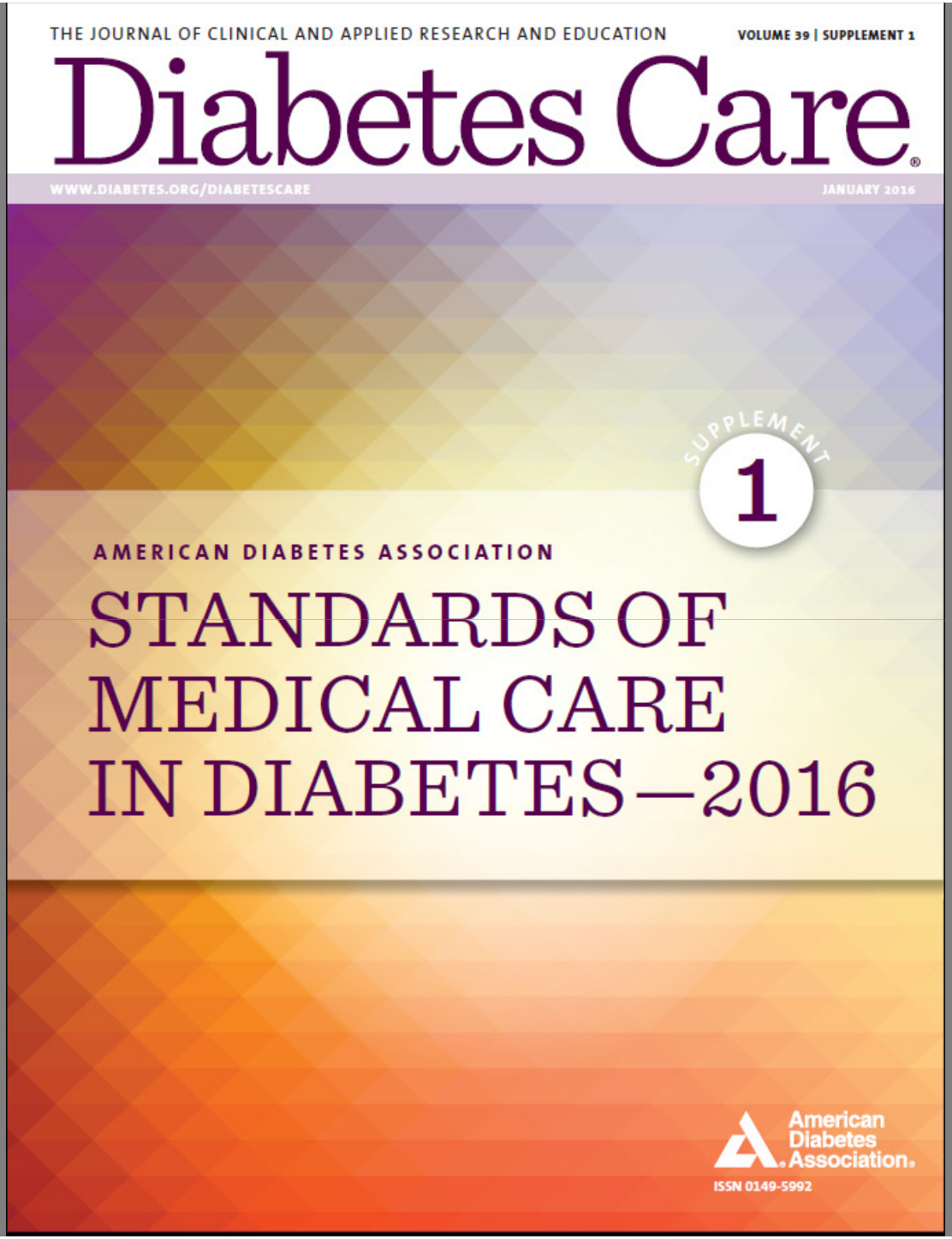
**Pacientes de baixo risco CV deverão receber orientação individualizada, com as metas estabelecidas pelos valores referenciais do perfil lipídico (apresentados na Tabela II) e foco no controle e na prevenção dos demais fatores de risco CV.*

Arq Bras Cardiol. 2013; 101(4Supl.1): 1-22

Tratamento do Colesterol e Redução da Aterosclerose
Diretriz Americana (ACC/AHA) - 2013



Stone NJ, et al.
2013 ACC/AHA Blood Cholesterol Guideline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Recomendações para uso de Estatinas em DM
ADA - 2016

Idade	Fatores de Risco	Recomendação Estatina	Intensidade da Estatina
< 40 anos	Nenhum	Não	
	Fator de Risco +	Sim	Moderada a alta
	Doença CV	Sim	Alta
40-75 anos	Nenhum	Sim	Moderada
	Fator de Risco +	Sim	Alta
	Doença CV	Sim	Alta
> 75 anos	Nenhum	Sim	Moderada
	Fatores de Risco +	Sim	Moderada a Alta

*Fatores de Risco: LDL≥ 100 mg/dl, tabagismo, HAS, sobrepeso obesidade, hx familiar de DAC prematura.

O Diabetes por si já define a necessidade de uso de Estatina?

Conclusão:

1. Não de forma sistemática, mas...
2. A não utilização de Estatinas deve ser exceção e não regra.
3. Com base nos estudos de intervenção e no risco cardiovascular ao menos moderado, usar naqueles $> 40\ aa$.
4. Usar nos diabéticos com outros FR e/ou evidência de lesão de órgão-alvo.

Prevalência de Alcance de Metas em Diabéticos NHANES 1988-2010

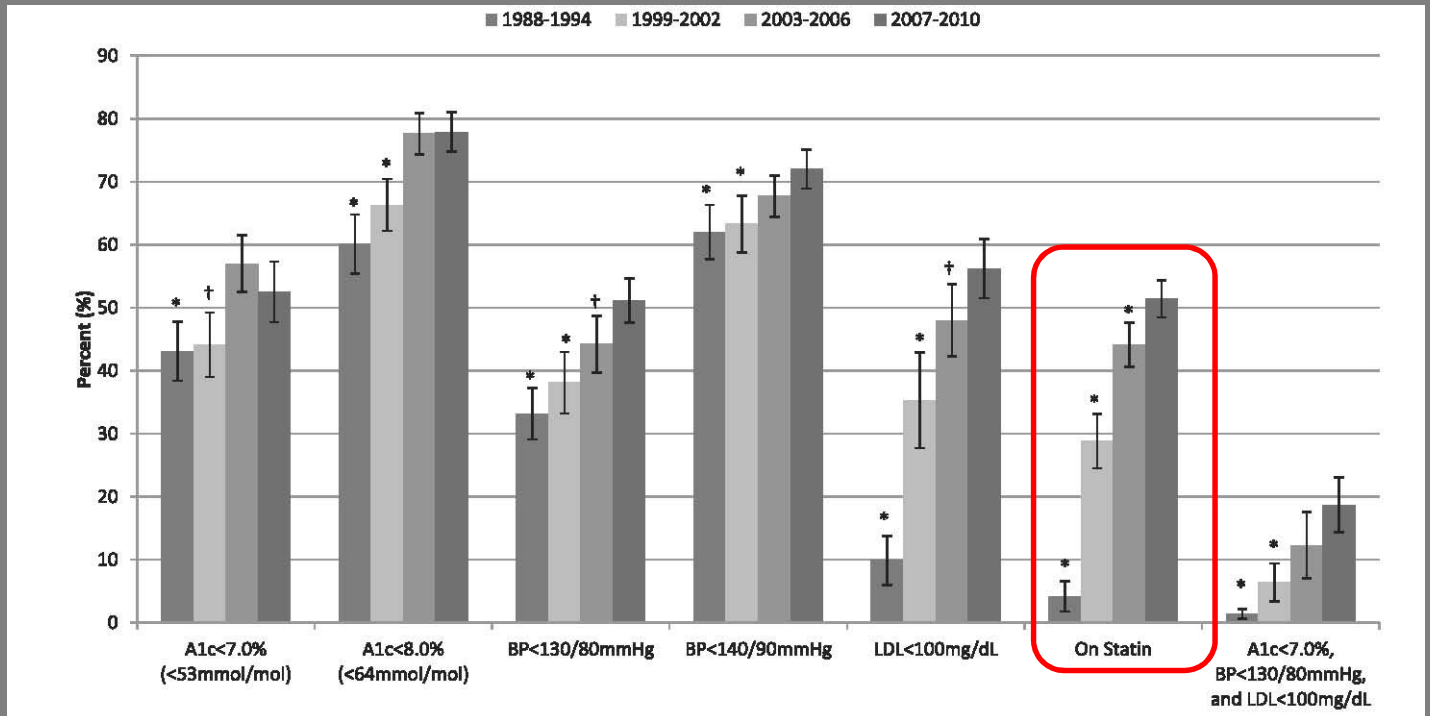

Figure 1—*Prevalence of meeting ABC goals among adults aged ≥20 years with diagnosed diabetes, NHANES 1988–2010. Estimates are age and sex standardized to the 2007–2010 diabetic NHANES population. *P < 0.01, estimates are compared with those of 2007–2010. †P < 0.05, estimates are compared with those of 2007–2010.*

Casagrande S. S. et al. Diabetes Care 2013;36:2271-2279