# Diabetes Mellitus: A Cardiovascular Disease

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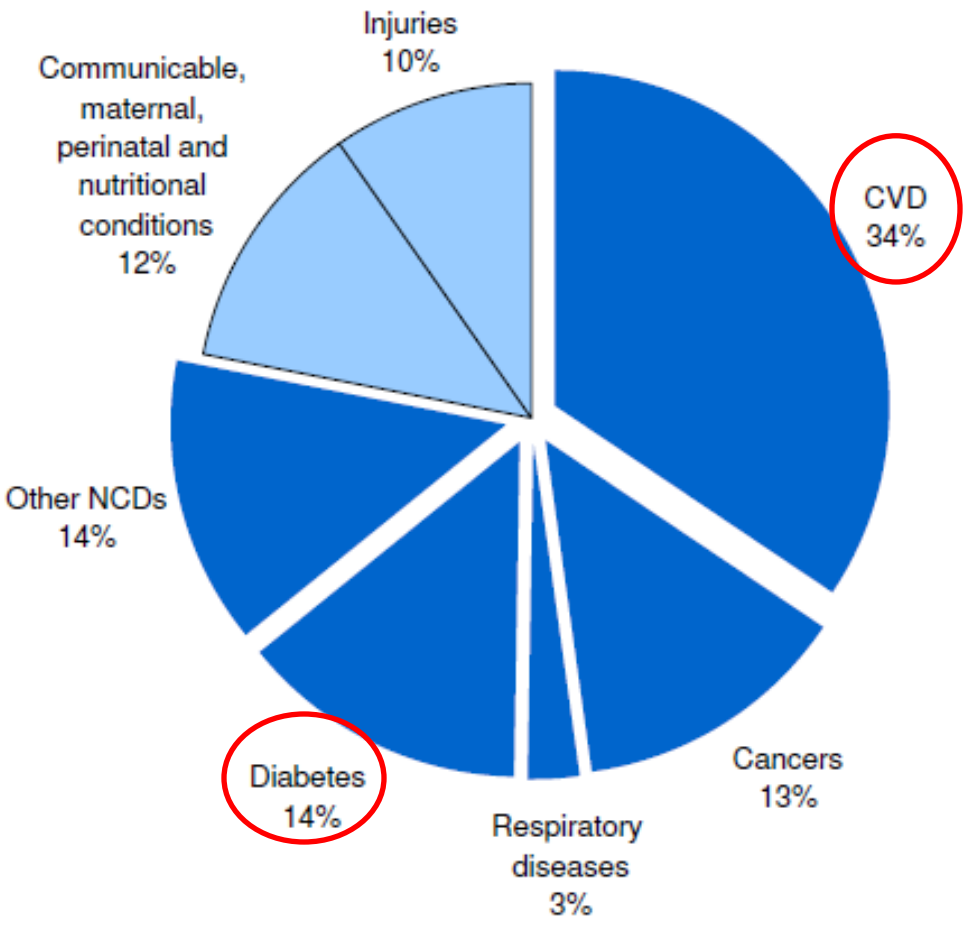
# The ABCs of cardiovascular risk reduction in diabetes

- **A for**
  - A1C
  - Anti-platelet therapy (aspirin)
- **B** for
  - Blood pressure
- **C** for
  - Cholesterol
  - Cigarettes (smoking cessation)
- **D** for
  - Diet
- **E** for
  - Exercise

# Trinidad and Tobago: 2010

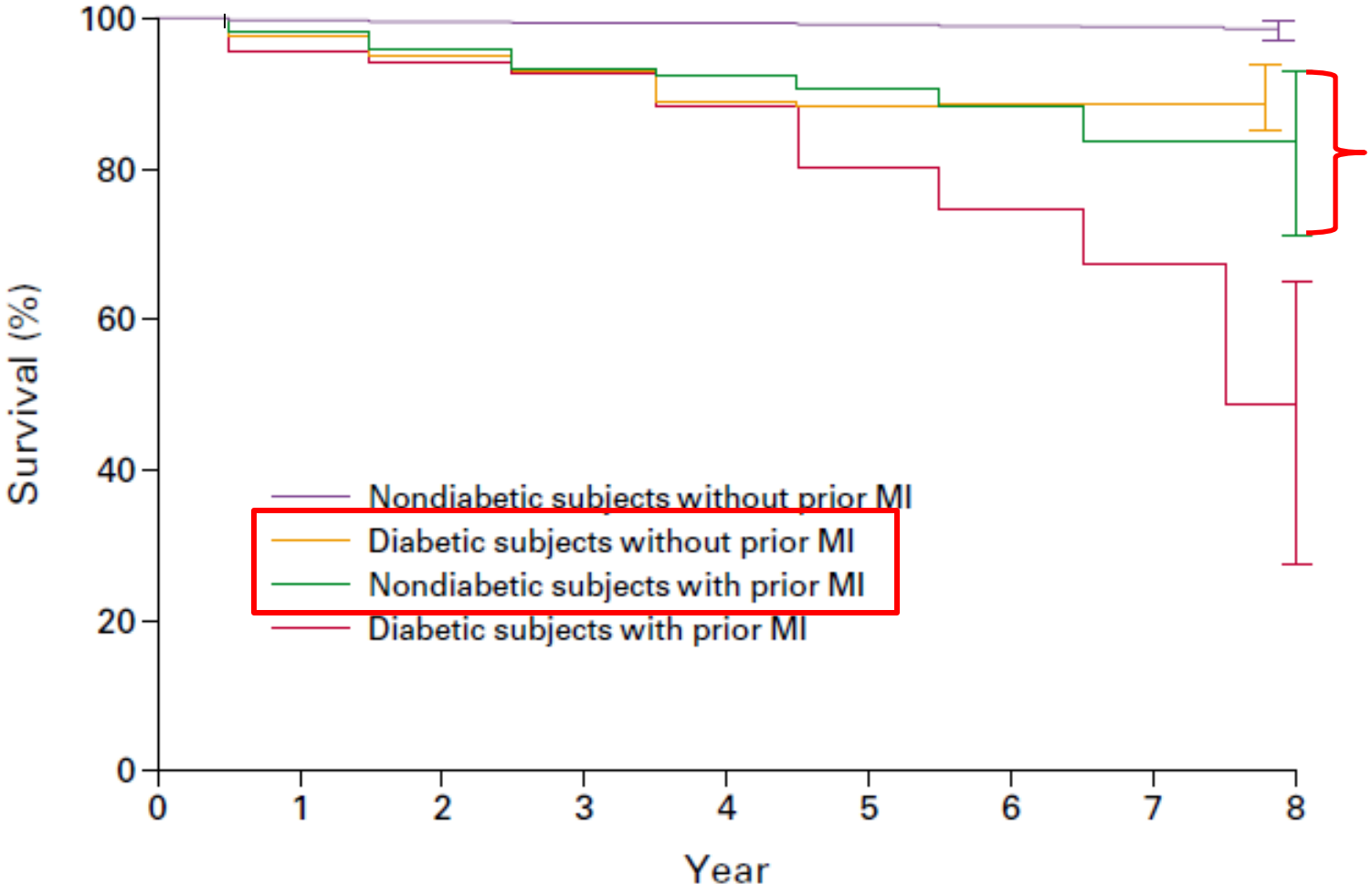
JOHNS HOPKINS MEDICINE

**Proportional mortality (% of total deaths, all ages)**




WHO- NCD Country Profiles, 2011

# Diabetes = CHD equivalent






Data from: Haffner SM, Lehto S, Ronnemaa T, et al. N Engl J Med 1998; 339:229.

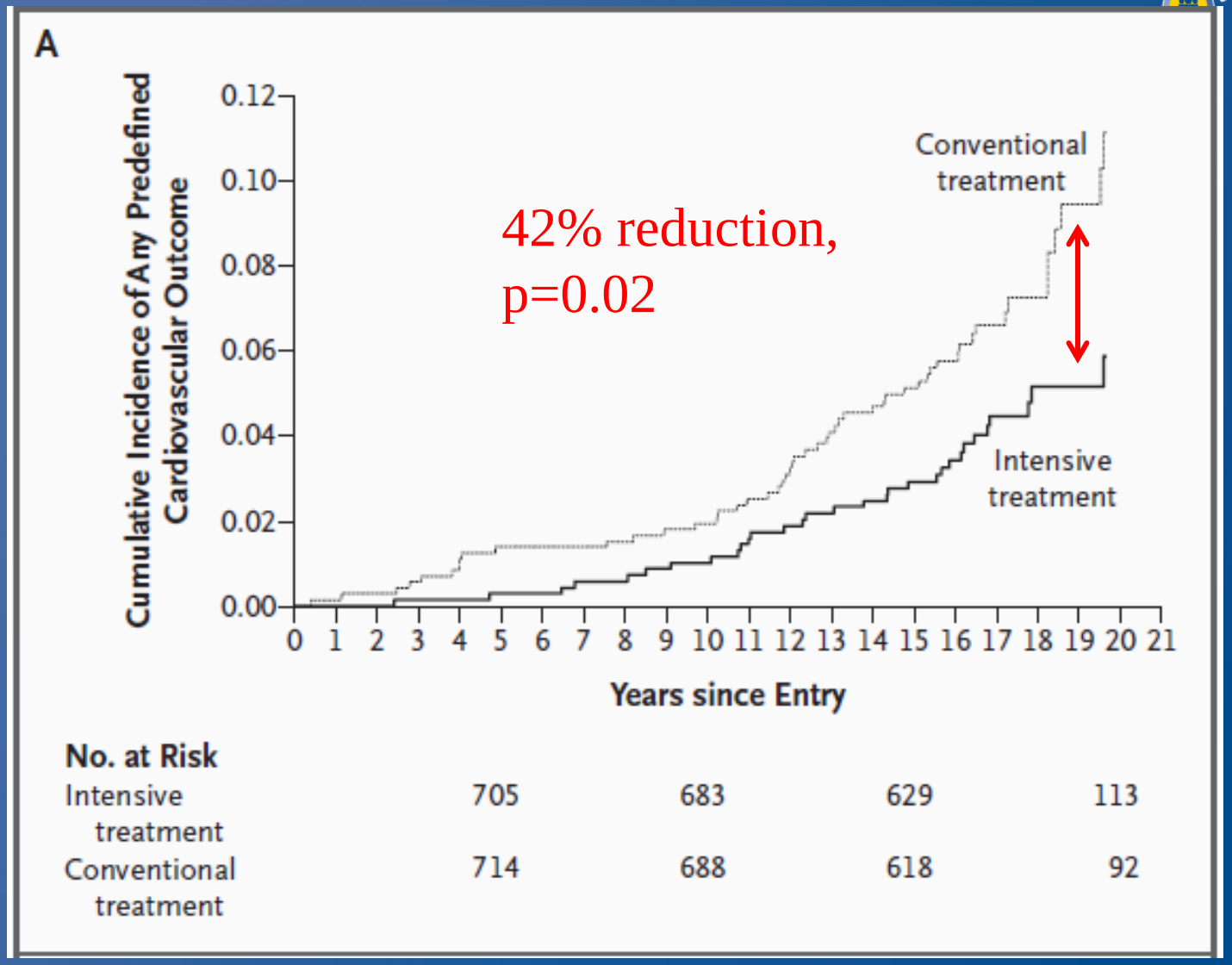
# Diabetes = CHD Equivalent

- Diabetes increases risk of CVD 2-4 fold
- Overall, CVD mortality and events appear to be declining in non-diabetics and diabetics
- Incident CVD risk is modified by:
  - Intensive glycemic control??
  - Blood pressure control
  - Statin therapy
  - Aspirin if high risk

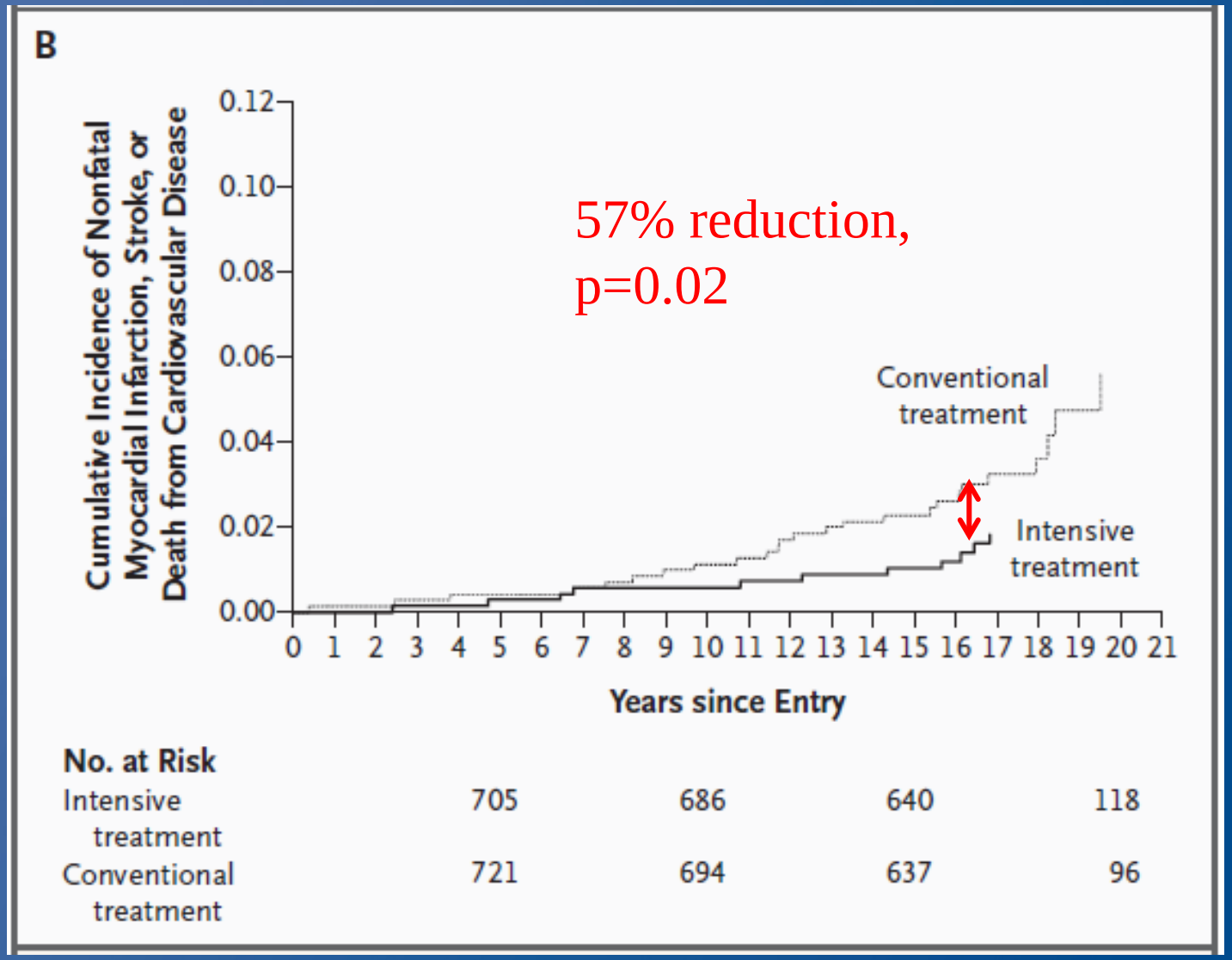
# A is for A1C

What is the impact of glycemic control on CVD risk reduction in diabetes?

# DCCT/EDIC: Type 1 DM



# DCCT/EDIC: Type 1 DM



# UKPDS (1998): Type 2 DM

- Non-signficant improvement in CVD at 10 years in intensive vs. conventional groups
  - MI: RR 0.84 (0.71-1.00)
  - Stroke 1.11 (0.81-1.51)

# UKPDS (2008): Type 2 DM

| Cardiovascular Outcomes: Intensive vs. Conventional Therapy | | |
|---|---|---|
| | Risk Ratio (95% CI) | P-value |
| **SULFONYLUREA/INSULIN GROUP** | | |
| Myocardial Infarction | 0.85 (0.74-0.97) | 0.01 |
| Stroke | 0.91 (0.73-1.13) | 0.39 |
| Peripheral Vascular Disease | 0.82 (0.56-1.19) | 0.29 |
| **METFORMIN GROUP** | | |
| Myocardial Infarction | 0.67 (0.51-0.89) | 0.005 |
| Stroke | 0.80 (0.50-1.27) | 0.35 |
| Peripheral Vascular Disease | 0.63 (0.32-1.27) | 0.19 |

# Summary: Glycemic control & MI

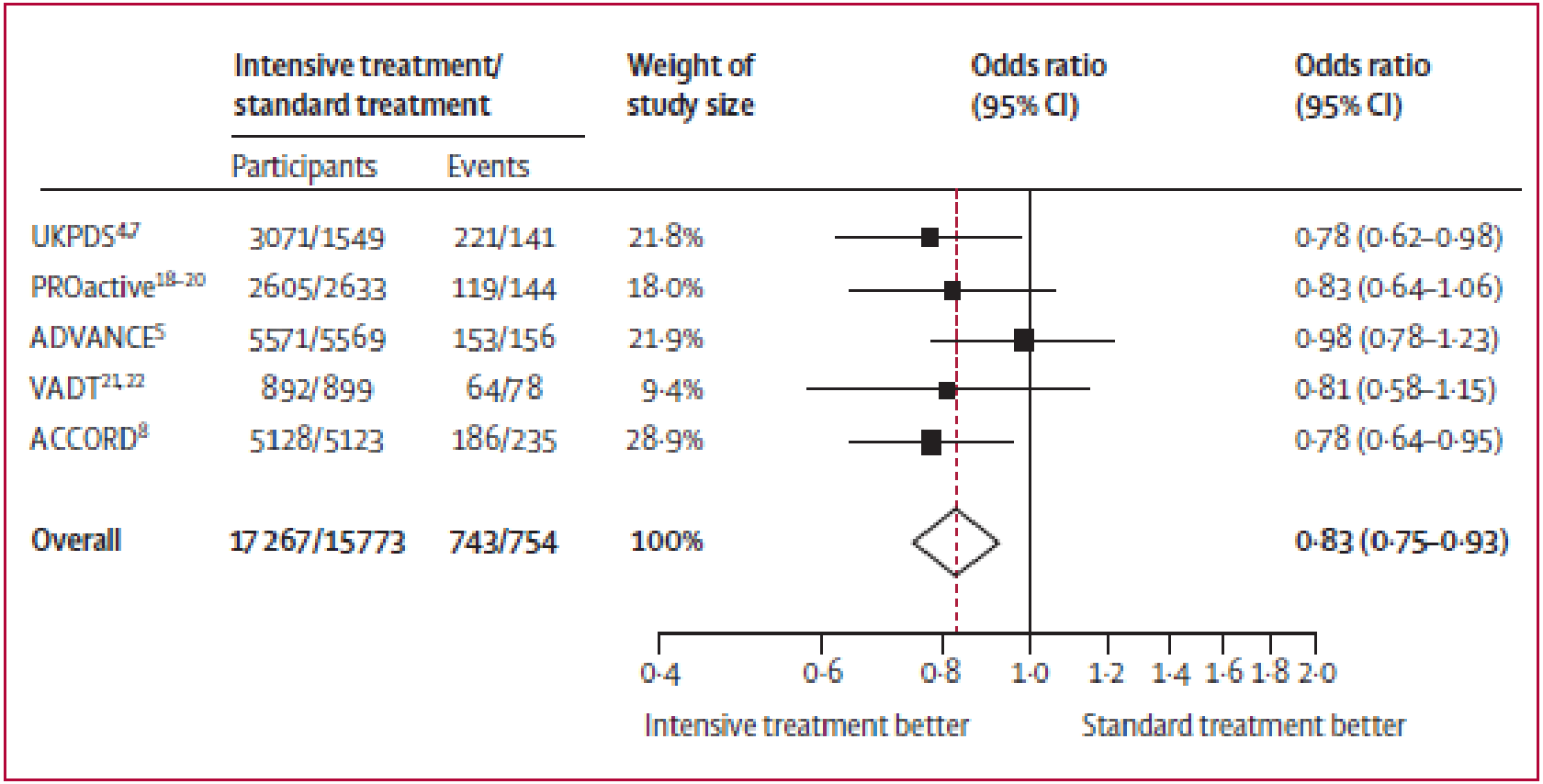



*Figure 1*: Probability of events of non-fatal myocardial infarction with intensive glucose-lowering versus standard treatment

# Summary: Glycemic control & CHD

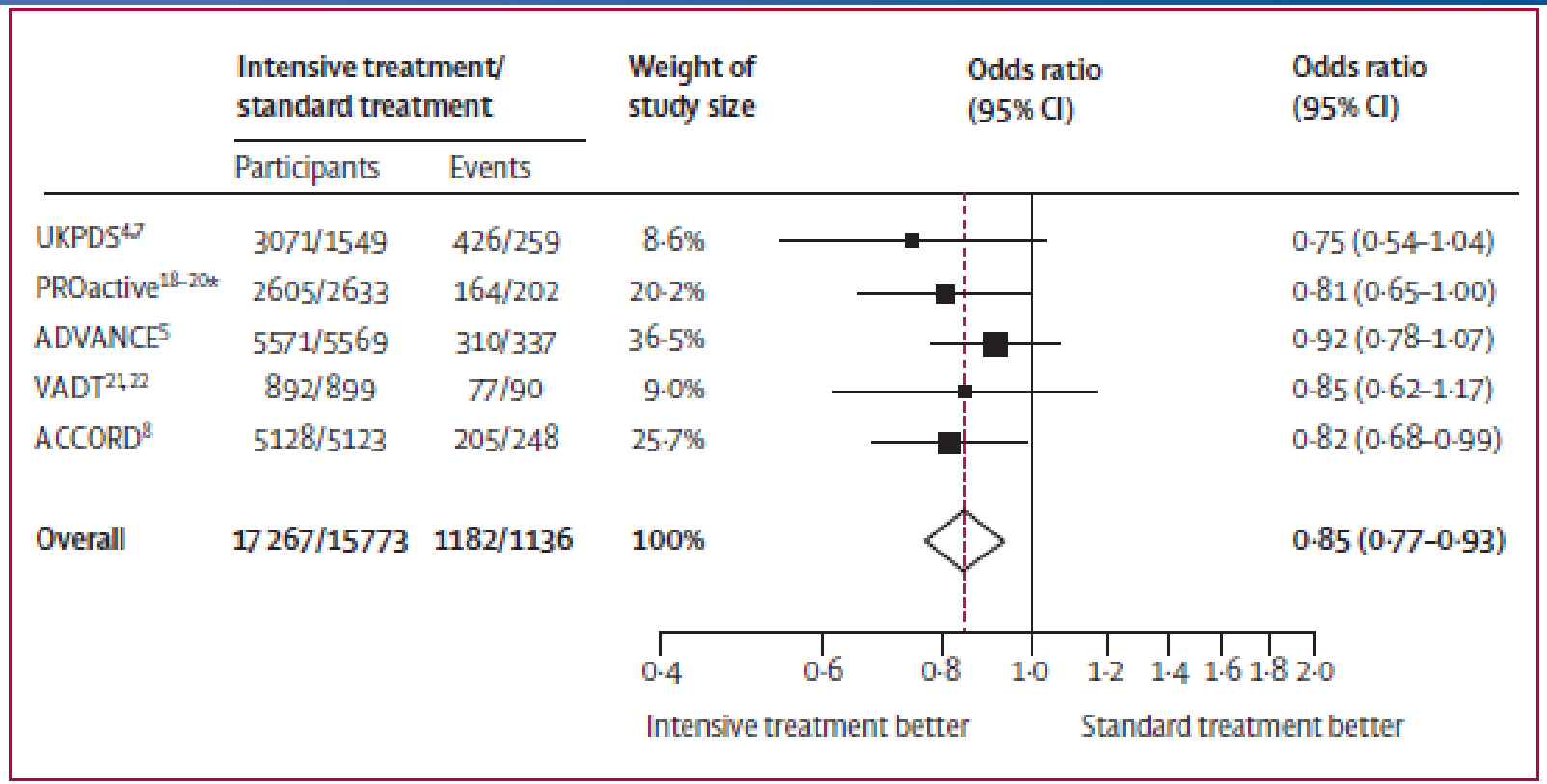



***Figure 2*: Probability of events of coronary heart disease with intensive glucose-lowering versus standard treatment**

*Included non-fatal myocardial infarction and death from all-cardiac mortality.

# Summary:
# Glycemic control & mortality

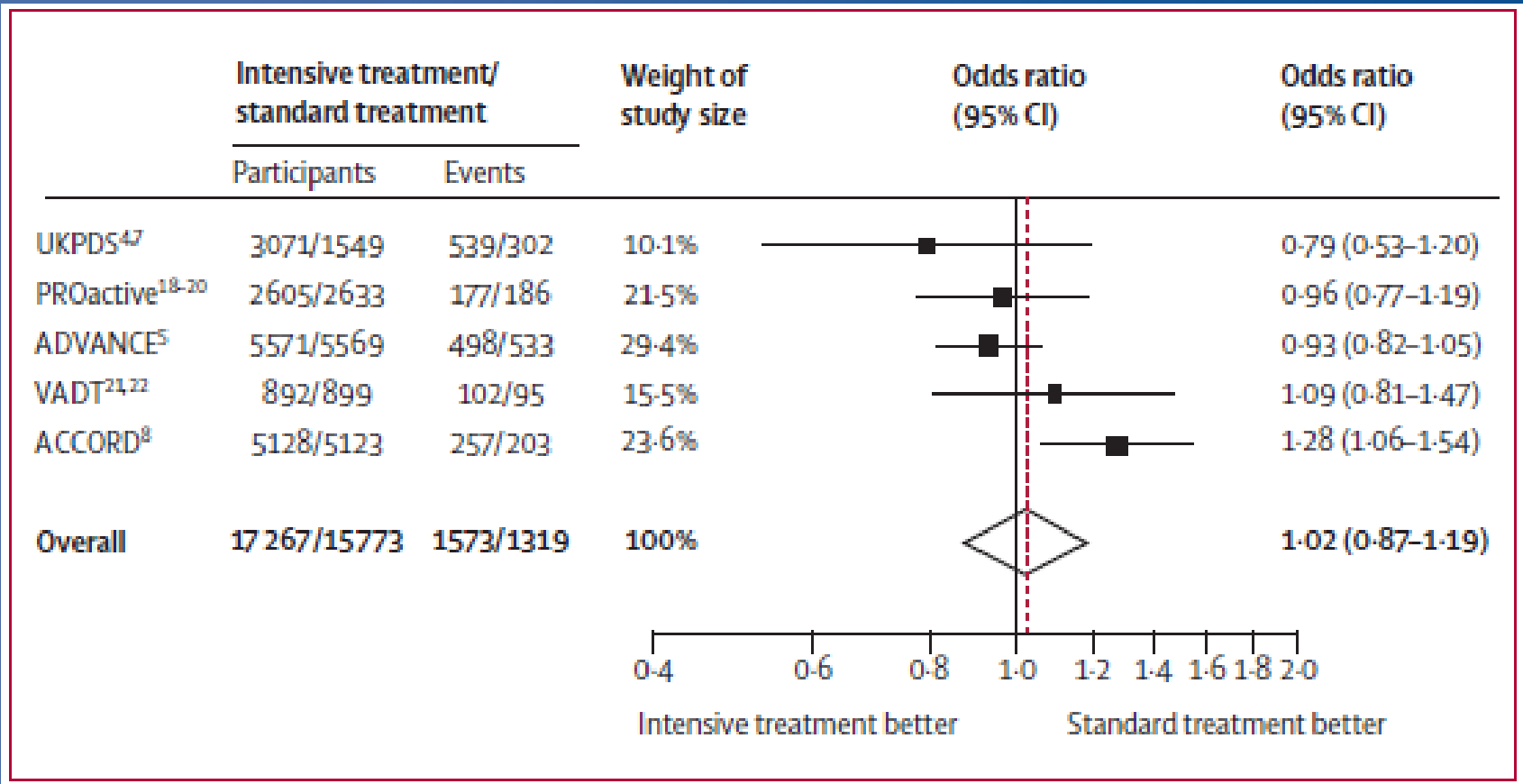
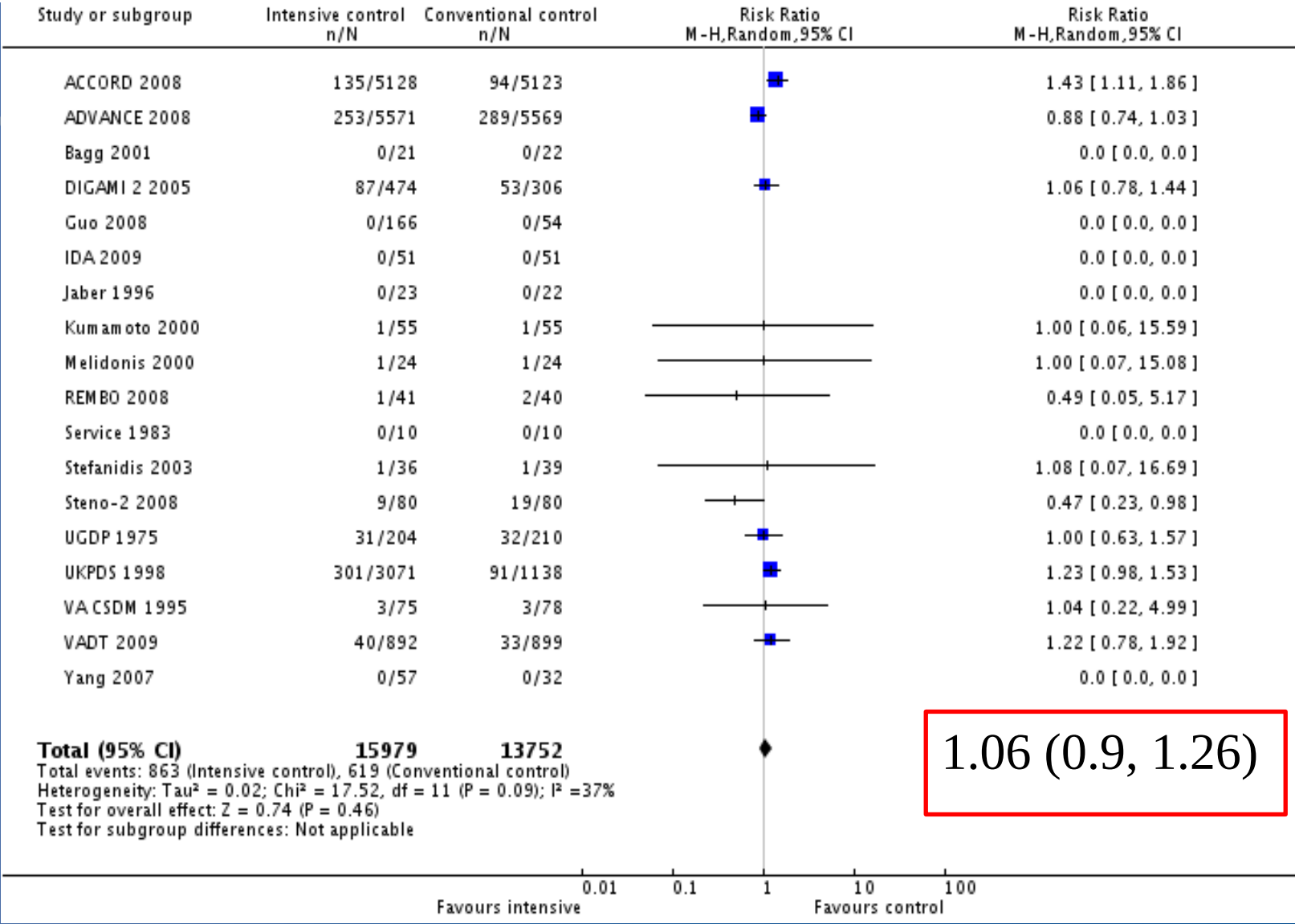


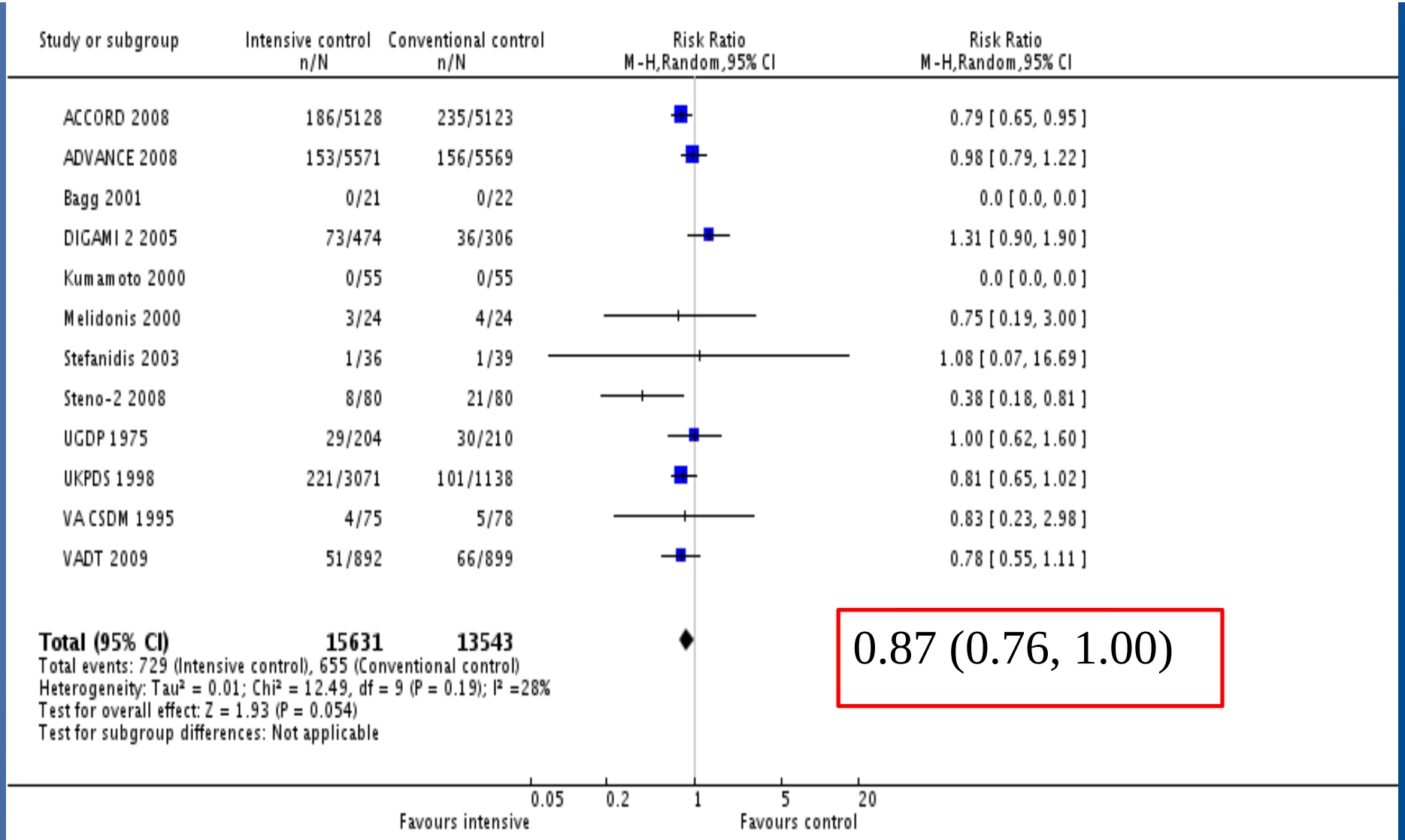

*Figure 4:* **Probability of events of all-cause mortality with intensive glucose-lowering versus standard treatment**

# CVD Mortality




1.06 (0.9, 1.26)

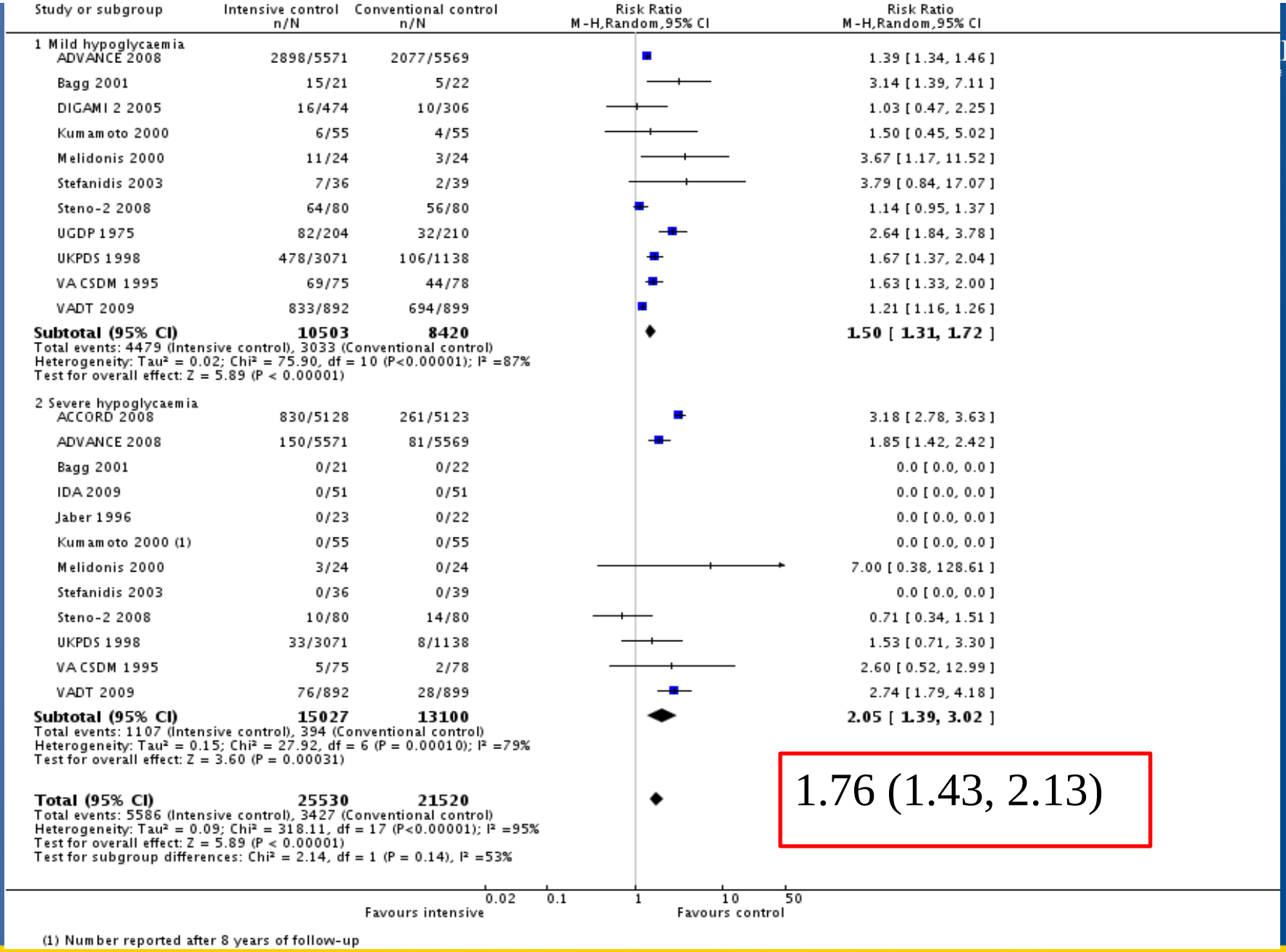
# Non-fatal MI




0.87 (0.76, 1.00)

Cochrane Library, June 2011

# Hypoglycemia



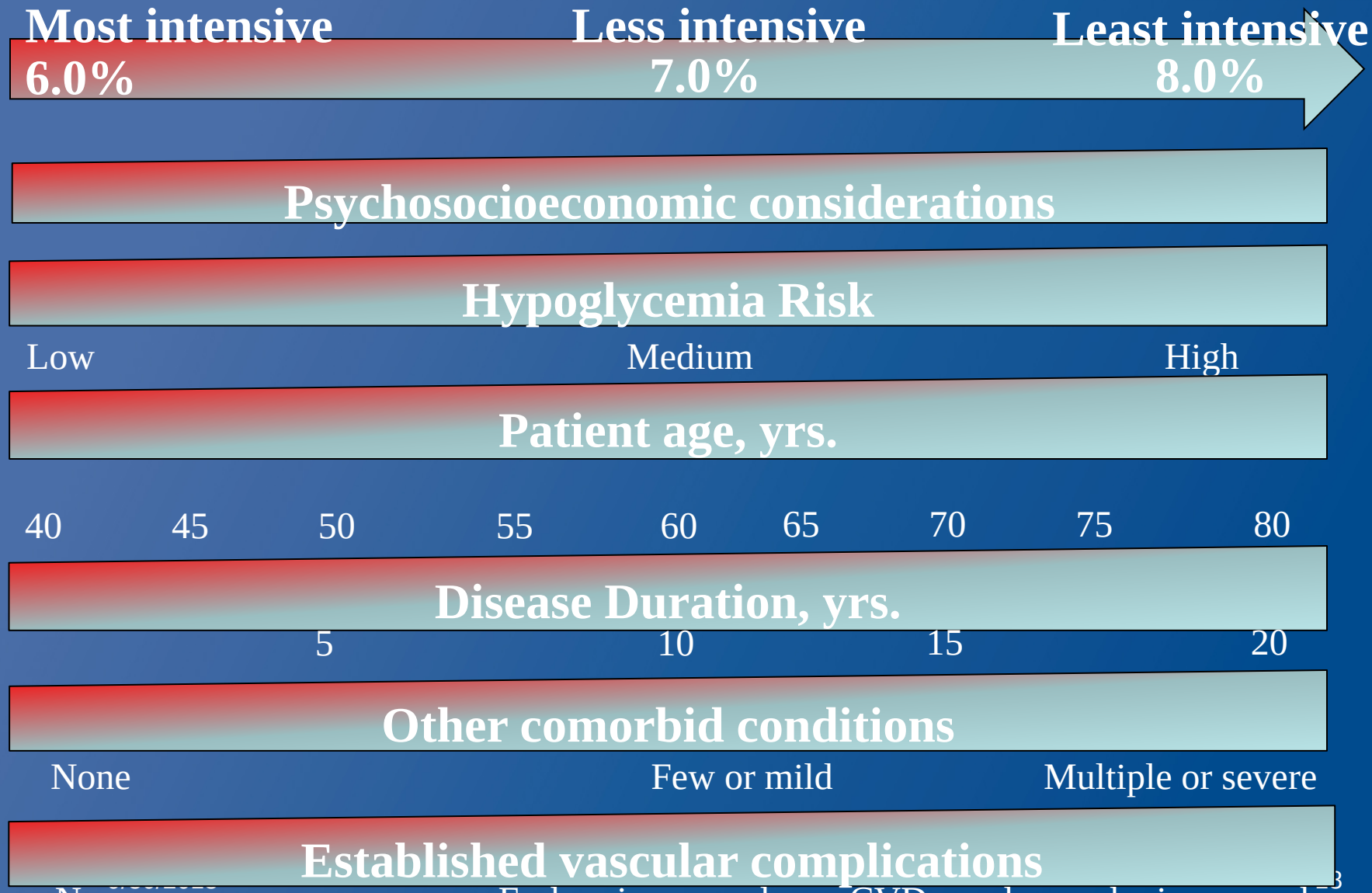

1.76 (1.43, 2.13)

(1) Number reported after 8 years of follow-up

# Summary: A is for A1C

- Conflicting evidence for intensive glycemic control on CVD outcomes
  - Varies with specific CVD outcomes, study design, and interventions
- Well established hypoglycemia risk with intensive glycemic control

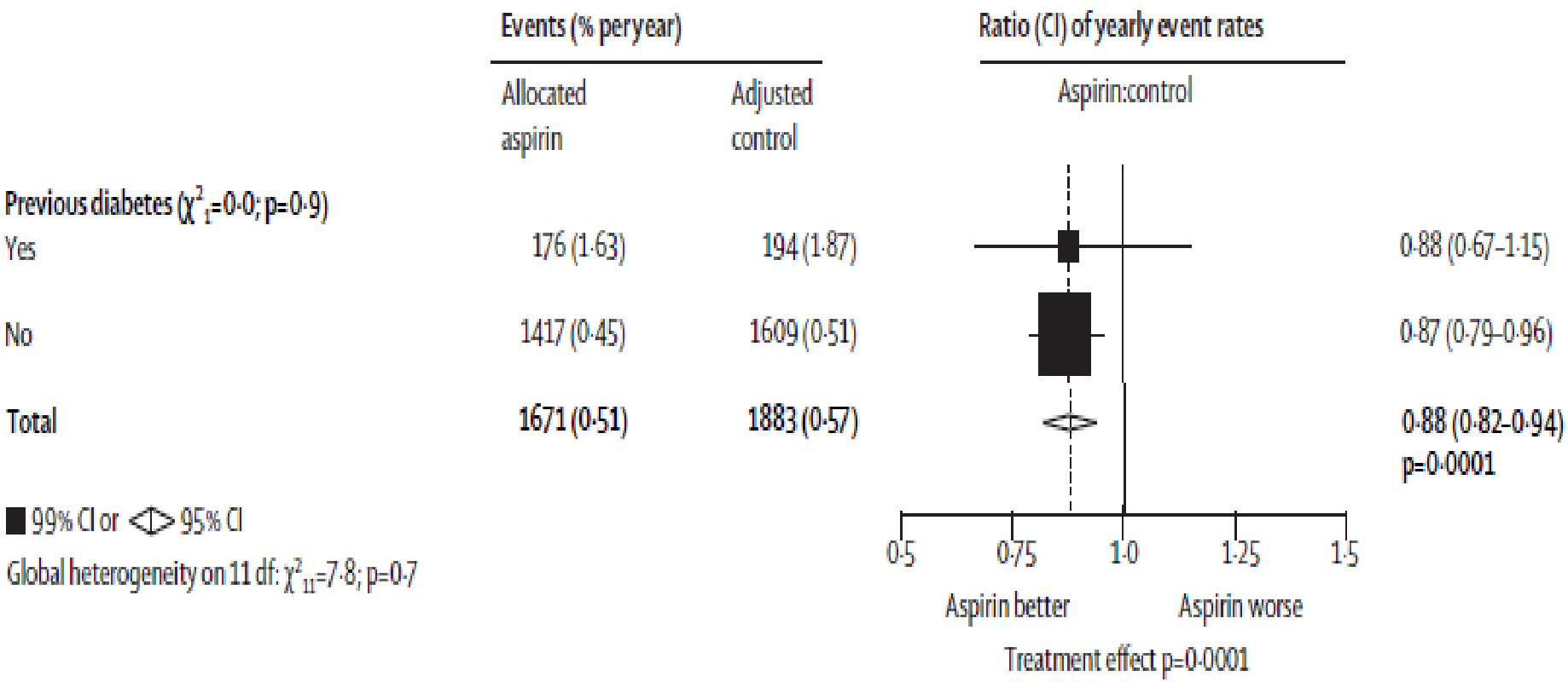
# Individualized glycemic targets



# A is for Aspirin

- What is the impact of antiplatelet therapy on CVD risk reduction in diabetes?

# Aspirin and Primary Prevention of CVD in Diabetes




Lancet 2009; 373: 1849–60

# Aspirin and Primary Prevention of CVD in Diabetes

JOHNS HOPKINS MEDICINE

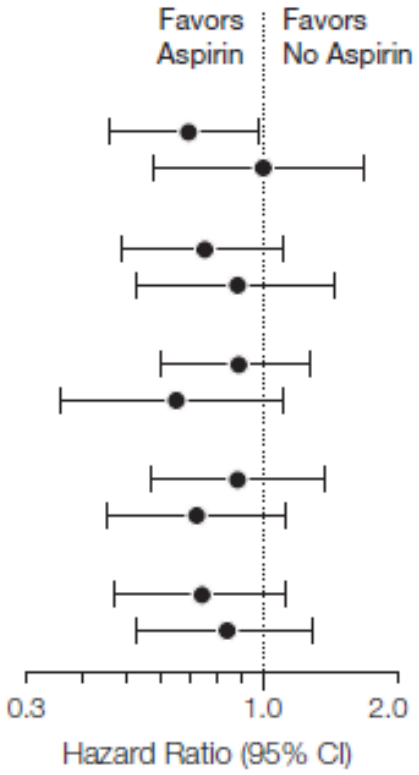
**Table 2.** Atherosclerotic Events

| | Aspirin Group | | Nonaspirin Group | | | |
|---|---|---|---|---|---|---|
| | No. (%) | No. per 1000 Person-Years | No. (%) | No. per 1000 Person-Years | Hazard Ratio (95% CI) | *P* Value |
| Primary end point: all atherosclerotic events | 68 (5.4) | 13.6 | 86 (6.7) | 17.0 | 0.80 (0.58-1.10) | .16 |
| Coronary and cerebrovascular mortality | 1 (0.08) | 0.2 | 10 (0.8) | 2.0 | 0.10 (0.01-0.79) | .0037 |
| CHD events (fatal + nonfatal) | 28 (2.2) | 5.6 | 35 (2.7) | 6.9 | 0.81 (0.49-1.33) | .40 |
| Fatal MI | 0 | 0 | 5 (0.4) | 1.0 | | |
| Nonfatal MI | 12 (1.0) | 2.4 | 9 (0.7) | 1.8 | 1.34 (0.57-3.19) | .50 |
| Unstable angina | 4 (0.3) | 0.8 | 10 (0.8) | 2.0 | 0.40 (0.13-1.29) | .13 |
| Stable angina | 12 (1.0) | 2.4 | 11 (0.9) | 2.2 | 1.10 (0.49-2.50) | .82 |
| Cerebrovascular disease (fatal + nonfatal) | 28 (2.2) | 5.6 | 32 (2.5) | 6.3 | 0.84 (0.53-1.32) | .44 |
| Fatal stroke | 1 (0.08) | 0.2 | 5 (0.4) | 1.0 | 0.20 (0.024-1.74) | .15 |
| Nonfatal stroke | | | | | | |
| Ischemic | 22 (1.7) | 4.4 | 24 (1.9) | 4.6 | 0.93 (0.52-1.66) | .80 |
| Hemorrhagic | 5 (0.4) | 1.0 | 3 (0.2) | 0.6 | 1.68 (0.40-7.04) | .48 |
| Transient ischemic attack | 5 (0.4) | 1.0 | 8 (0.6) | 1.6 | 0.63 (0.21-1.93) | .42 |
| Peripheral artery disease[a] | 7 (0.6) | 1.4 | 11 (0.9) | 2.2 | 0.64 (0.25-1.65) | .35 |

# Aspirin and Primary Prevention of CVD in Diabetes

**Figure 3.** Subgroup Analysis of Incidence of Atherosclerotic Events

| | Events, No./Total No. | | |
|---|---|---|---|
| | Aspirin Group | Nonaspirin Group | Hazard Ratio (95% CI) |
| Age, y | | | |
| ≥65 | 45/719 | 59/644 | 0.68 (0.46-0.99) |
| <65 | 23/543 | 27/633 | 1.0 (0.57-1.70) |
| Sex | | | |
| Male | 40/706 | 51/681 | 0.74 (0.49-1.12) |
| Female | 28/556 | 35/596 | 0.88 (0.53-1.44) |
| Hypertensive status | | | |
| Hypertensive | 49/742 | 55/731 | 0.88 (0.60-1.30) |
| Normotensive | 19/520 | 31/546 | 0.64 (0.36-1.13) |
| Lipid status | | | |
| Dyslipidemia | 38/680 | 43/665 | 0.88 (0.57-1.37) |
| Normolipidemia | 30/582 | 43/612 | 0.71 (0.45-1.14) |
| Smoking | | | |
| Current or past | 36/565 | 42/494 | 0.73 (0.47-1.14) |
| Nonsmoker | 32/697 | 44/783 | 0.83 (0.53-1.31) |





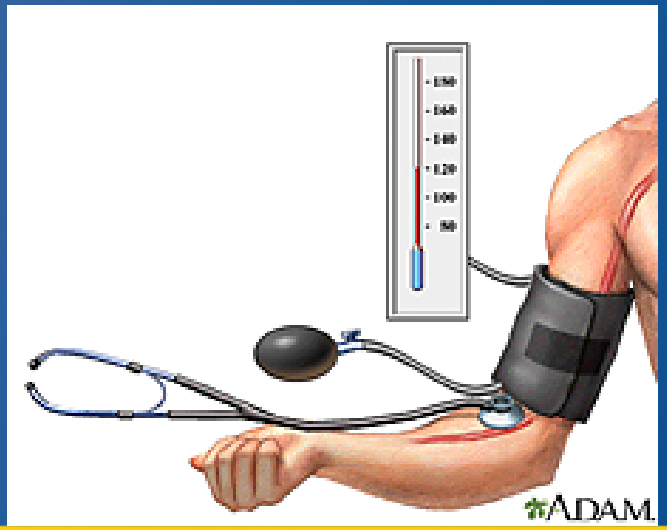

*JAMA.* 2008;300(18):2134-2141

# Aspirin Recommendations

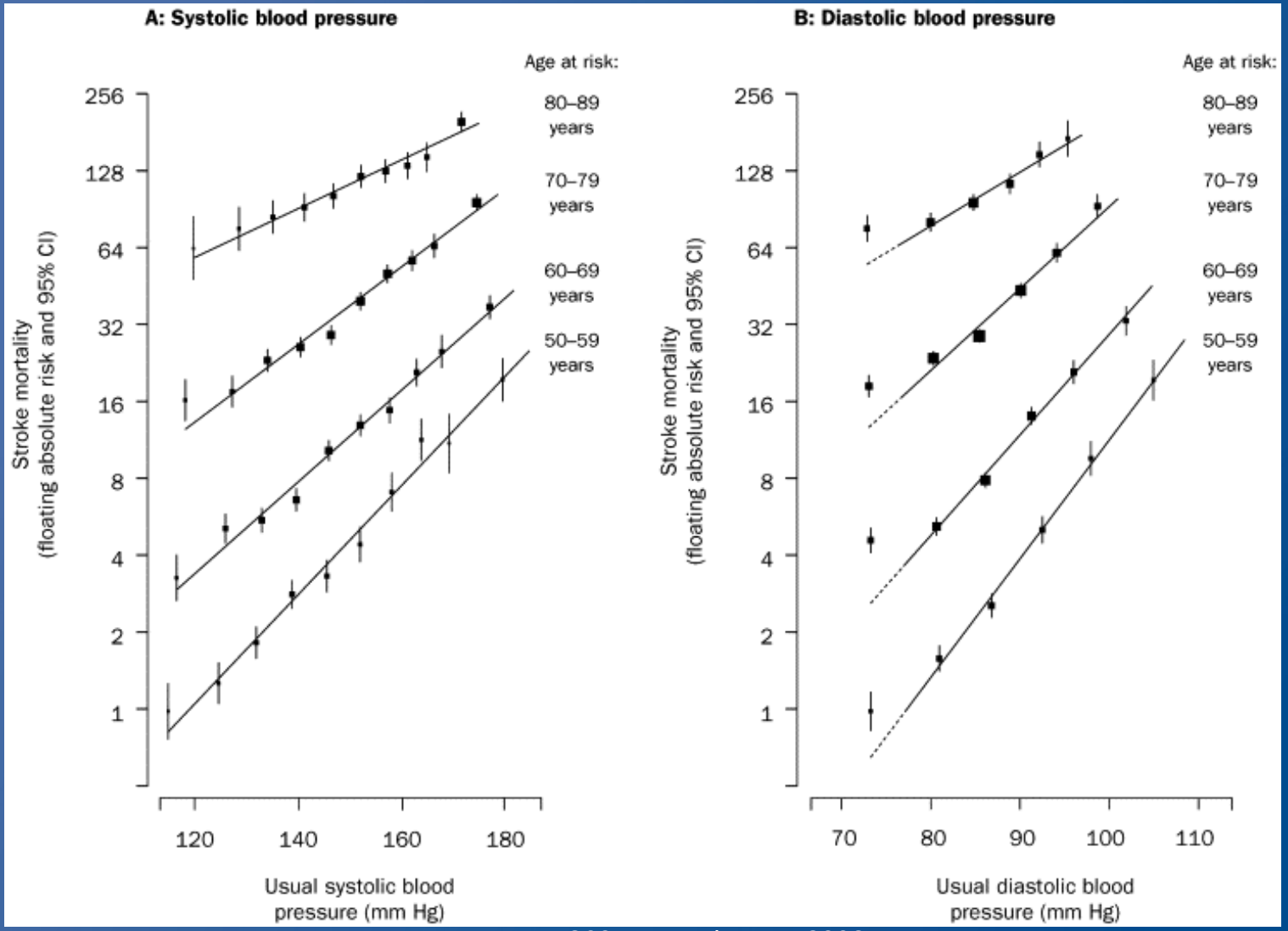
- Men >50 or women >60 with at least one additional major risk factor:
  - Hypertension
  - Smoking
  - Family history of CVD
  - Dyslipidemia
  - Albuminuria

# B is for Blood Pressure

- What is the impact of blood pressure control on CVD risk reduction in diabetes?

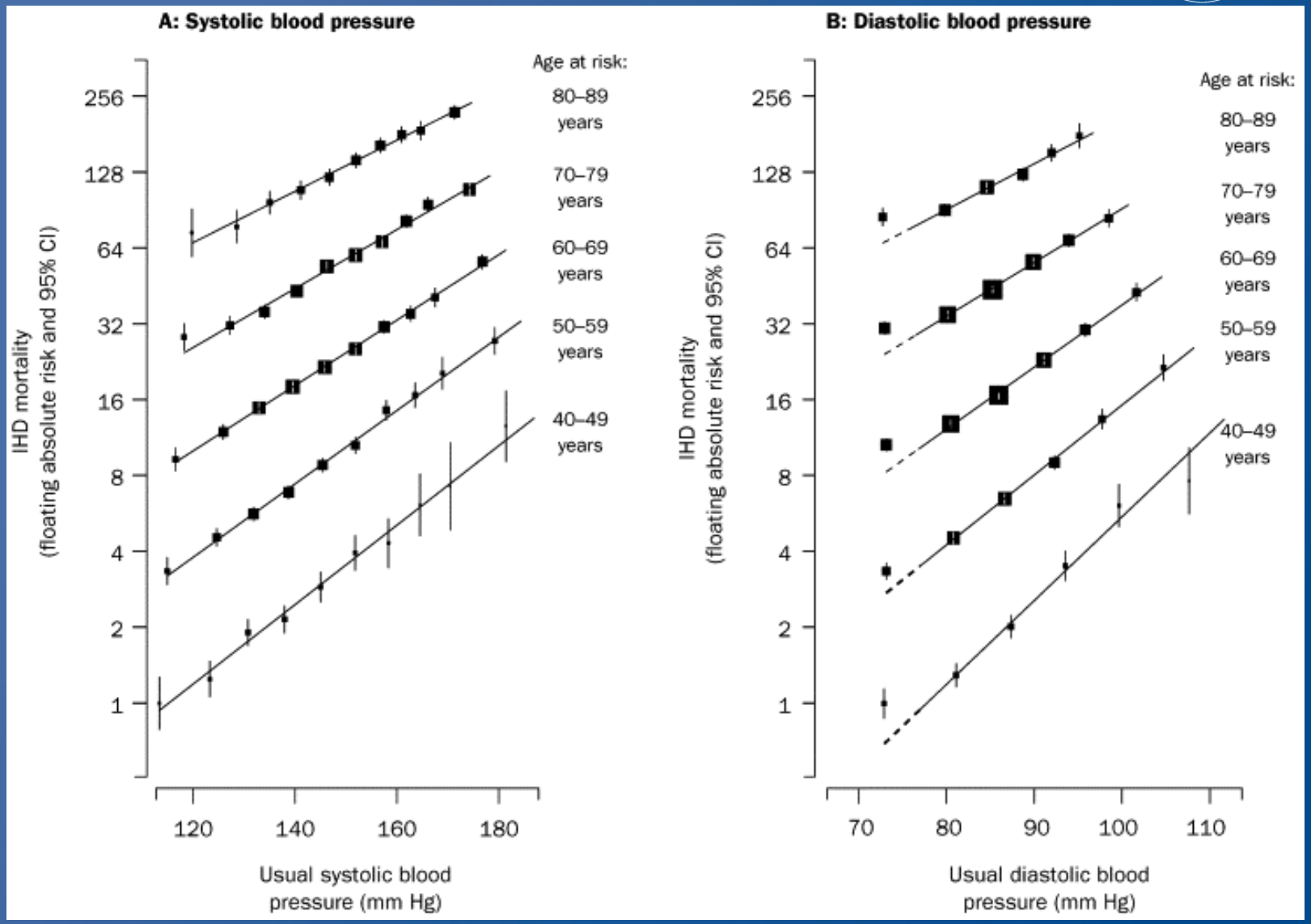


# Blood pressure and Stroke Risk



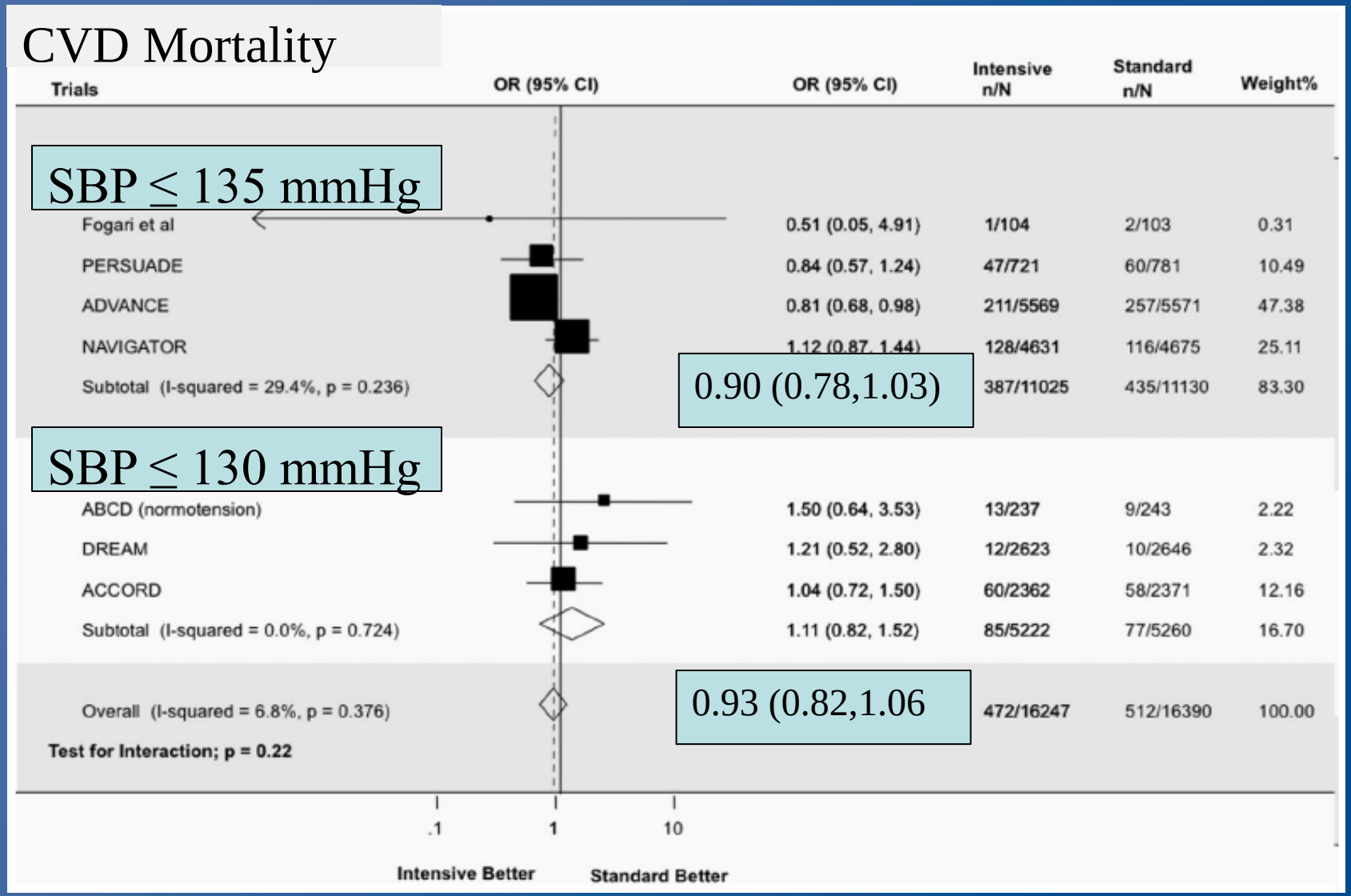

Lancet. 360. December 14, 2002

# Blood pressure and CHD Risk



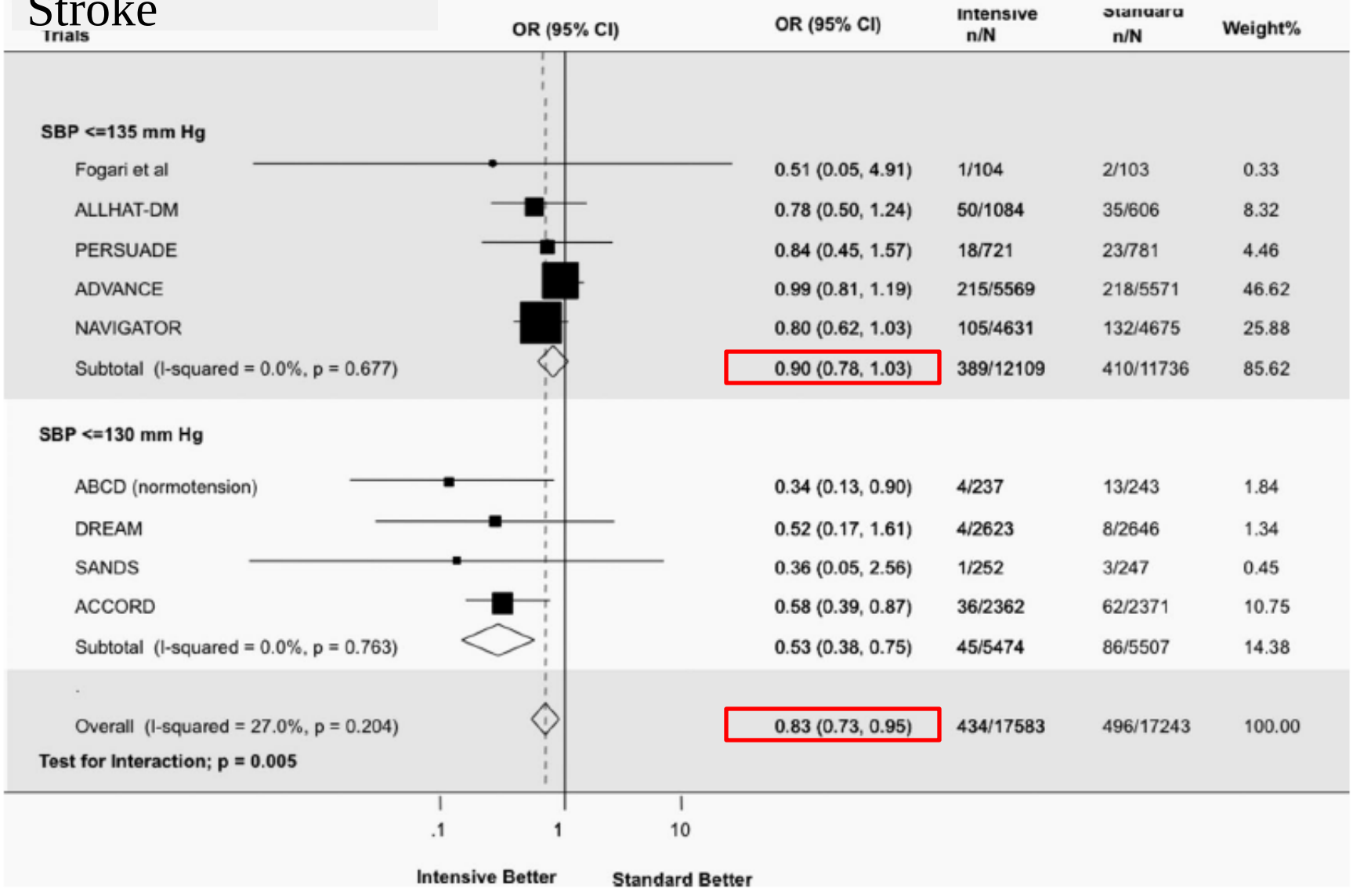

Lancet. 360. December 14, 2002

# Systolic BP Targets in Diabetes




Circulation.**2011; 123: 2799-2810**

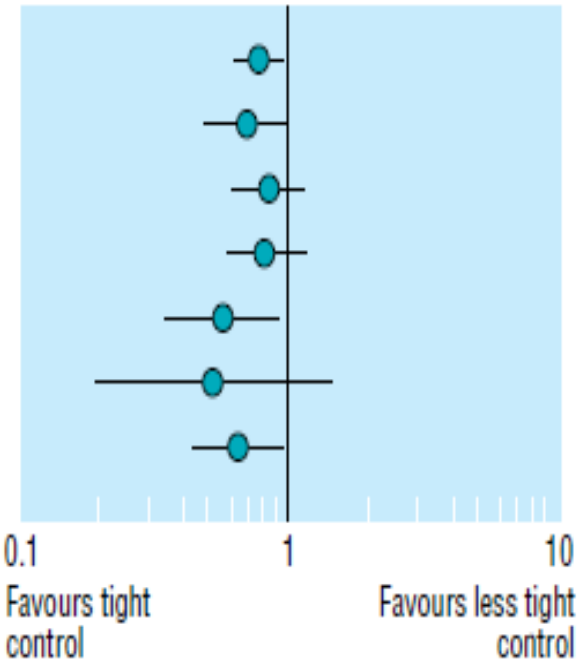
# Stroke




Circulation.**2011; 123: 2799-2810**

# UKPDS 38: BP target <150/85

| Clinical end point | Patients with aggregate end points: Tight control (n=758) | Patients with aggregate end points: Less tight control (n=390) | Absolute risk (events per 1000 patient years): Tight control | Absolute risk (events per 1000 patient years): Less tight control | P value | Relative risk for tight control (95% CI) |
|---|---|---|---|---|---|---|
| Any diabetes related end point | 259 | 170 | 50.9 | 67.4 | 0.0046 | 0.76 (0.62 to 0.92) |
| Deaths related to diabetes | 82 | 62 | 13.7 | 20.3 | 0.019 | 0.68 (0.49 to 0.94) |
| All cause mortality | 134 | 83 | 22.4 | 27.2 | 0.17 | 0.82 (0.63 to 1.08) |
| Myocardial infarction | 107 | 69 | 18.6 | 23.5 | 0.13 | 0.79 (0.59 to 1.07) |
| Stroke | 38 | 34 | 6.5 | 11.6 | 0.013 | 0.56 (0.35 to 0.89) |
| Peripheral vascular disease | 8 | 8 | 1.4 | 2.7 | 0.17 | 0.51 (0.19 to 1.37) |
| Microvascular disease | 68 | 54 | 12.0 | 19.2 | 0.0092 | 0.63 (0.44 to 0.89) |



# Summary

- More intensive blood pressure target, SBP<130 mmHg, does not have proven CVD mortality benefits
  - Evidence to support stroke reduction with lower targets
- Greater risk of adverse events with lower BP targets

# 2012 ADA Blood Pressure Recommendations

- SBP <140 mmHg
  - Patients with hypertension and diabetes mellitus
- SBP <130 mmHg
  - Younger patients if attainable without undue treatment burden
- DBP <80 mmHg

Diabetes Care 36 (S1) January 2013

# C is for Cholesterol

- What is the impact of statin therapy on CVD risk reduction in diabetes?

# Statin Therapy in Diabetes

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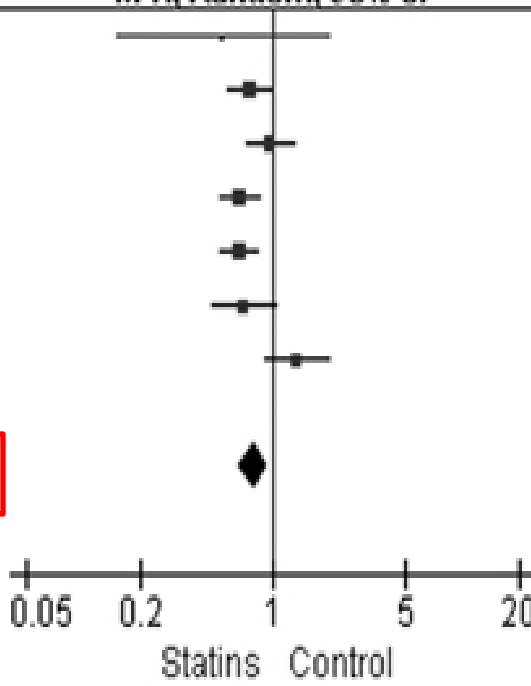
| Study or Subgroup | Statins group Events | Total | Control group Events | Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| AFCAPS/TexCAPS 1998 | 4 | 84 | 6 | 71 | 1.8% | 0.54 [0.15, 2.00] |
| ASCOT-LLA 2003 | 116 | 1258 | 151 | 1274 | 18.2% | 0.76 [0.59, 0.98] |
| ASPEN 2006 | 100 | 959 | 102 | 946 | 16.4% | 0.96 [0.72, 1.29] |
| CARDS 2004 | 134 | 1428 | 189 | 1410 | 19.2% | 0.67 [0.53, 0.85] |
| HPS 2003 | 135 | 1455 | 196 | 1457 | 19.4% | 0.66 [0.52, 0.83] |
| MEGA 2006 | 46 | 853 | 68 | 893 | 12.5% | 0.69 [0.47, 1.02] |
| PROSPER 2002 | 70 | 303 | 59 | 320 | 12.4% | 1.33 [0.90, 1.96] |
| **Total (95% CI)** | | **6340** | | **6371** | **100.0%** | **0.79 [0.66, 0.95]** |
| Total events | 605 | | 771 | | | |

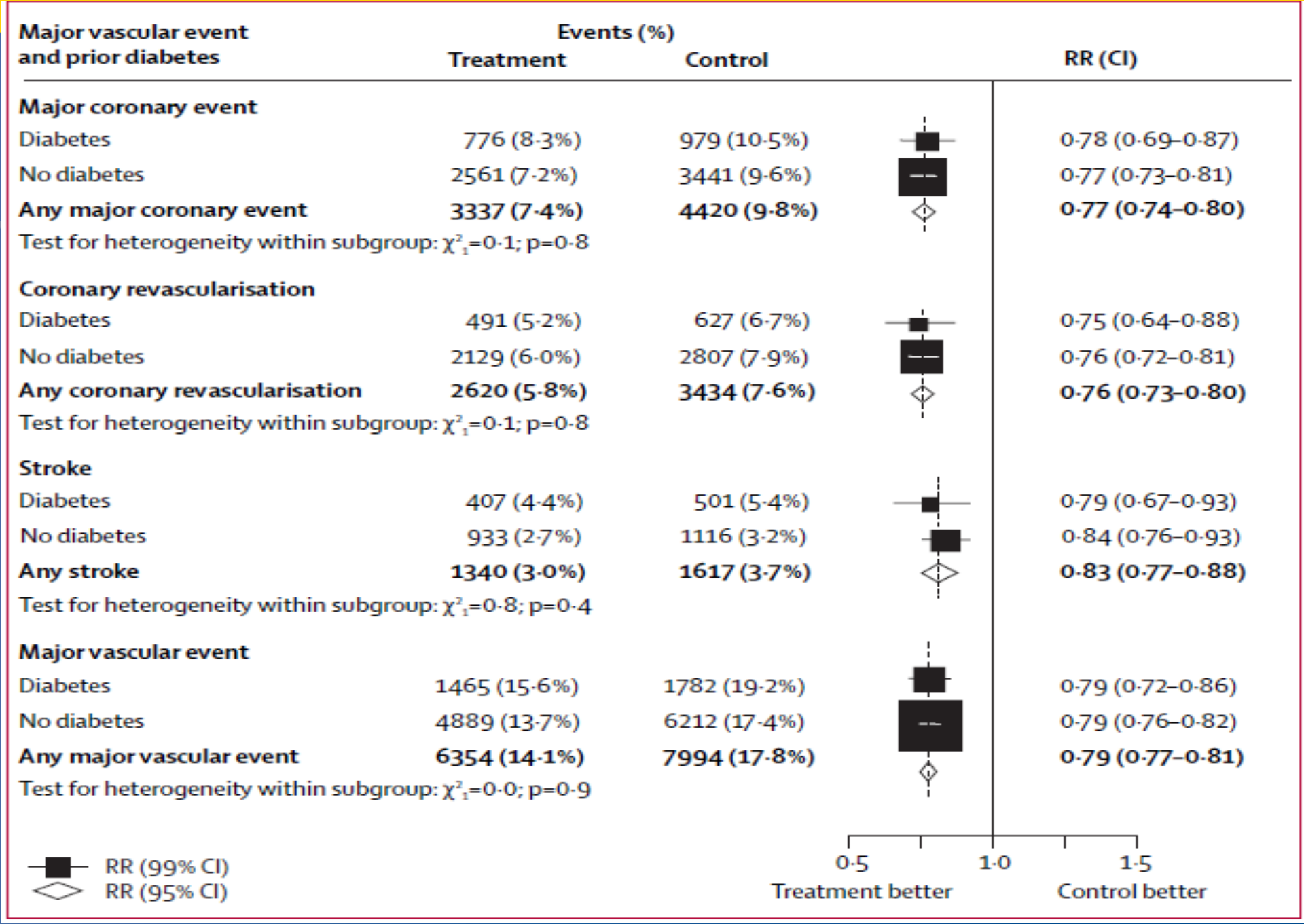
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 13.56$, $df = 6$ ($P = 0.04$); $I^2 = 56\%$

Test for overall effect: $Z = 2.54$ ($P = 0.01$)




Odds ratios of major adverse cardiovascular and cerebrovascular events associated with statin vs. control therapy in patients with diabetes

Exp Clin Endocrinol Diabetes 2012; 120(02): 116-120




Lancet 2008; 371: 117–25

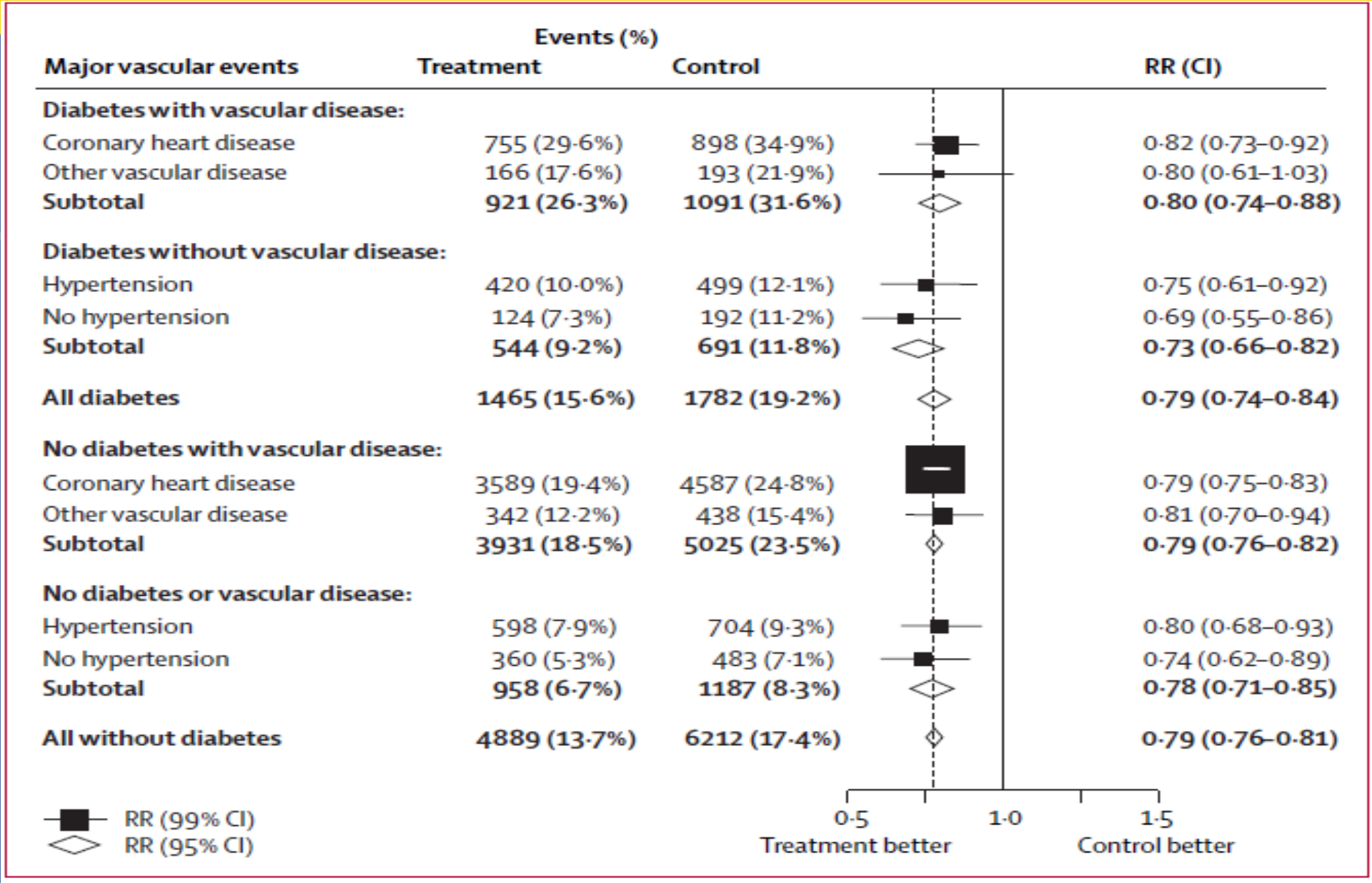
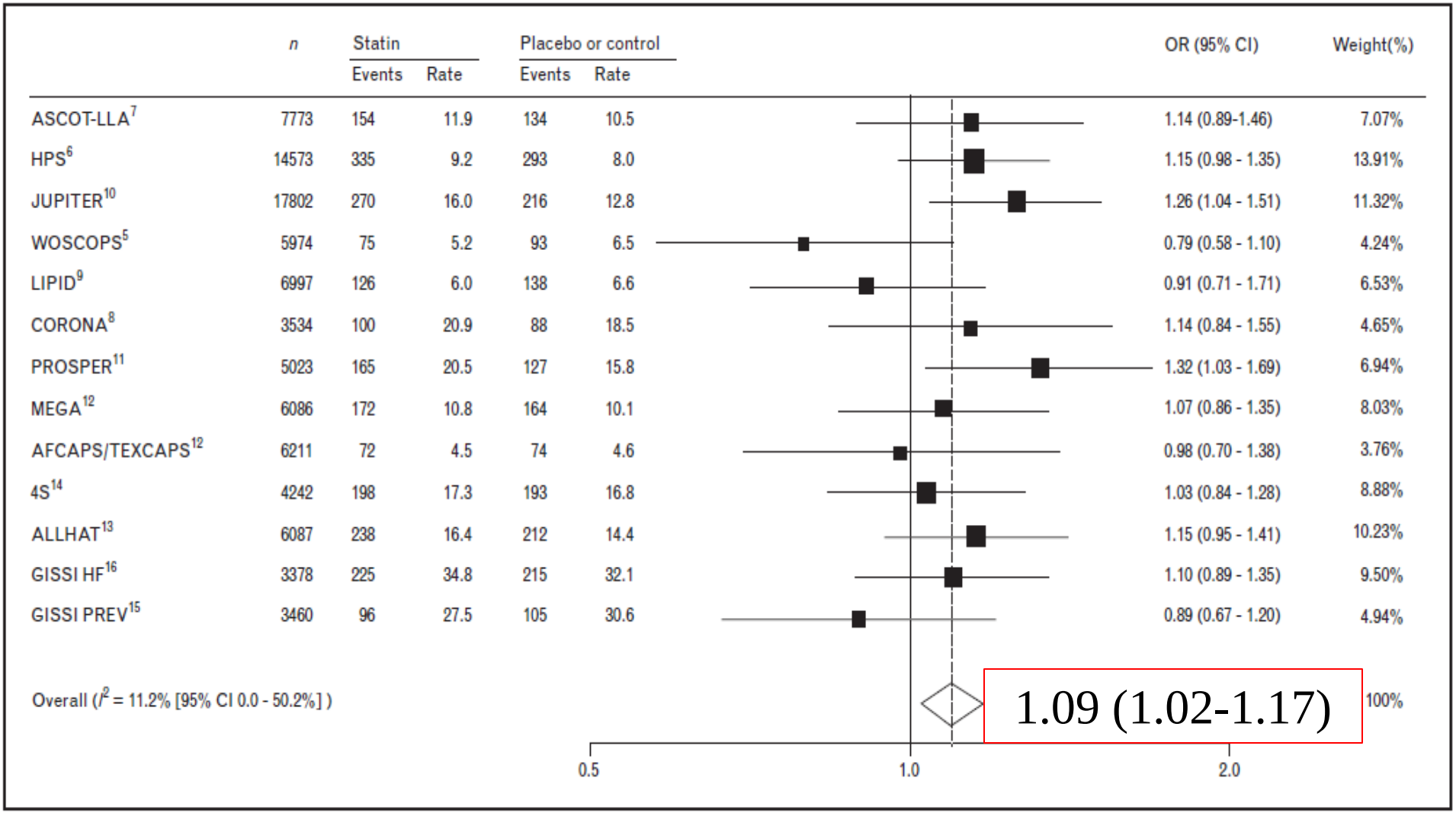



*Figure 3:* Proportional effects on major vascular events per mmol/L reduction in LDL cholesterol in participants with and without diabetes by history of vascular disease

Lancet 2008; 371: 117–25

# Incident Diabetes and Statins




Current Opinion in Lipidology 2011, 22:460–466

# Intensive vs. Moderate Dose Statins

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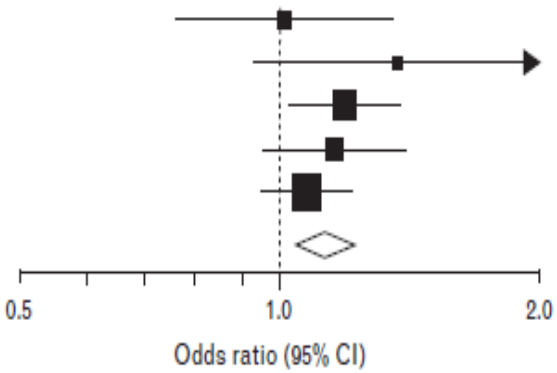
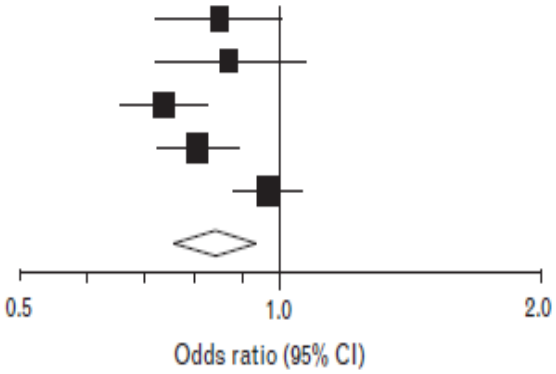
| | Cases/Total, No.(%) | | |
|---|---|---|---|
| | Intensive Dose | Moderate Dose | OR (95% CI) |
| Incident diabetes | | | |
| PROVE IT-TIMI 22,[25] 2004 | 101/1707(5.9) | 99/1688(5.9) | 1.01 (0.76-1.34) |
| A to Z,[26] 2004 | 65/1768 (3.7) | 47/1736 (2.7) | 1.37 (0.94-2.01) |
| TNT,[23] 2005 | 418/3798 (11.0) | 358/3797 (9.4) | 1.19 (1.02-1.38) |
| IDEAL,[24] 2005 | 240/3737 (6.4) | 209/3724 (5.6) | 1.15 (0.95-1.40) |
| SEARCH,[27] 2010 | 625 | | |
| Pooled odds ratio | 1449 | | |
| Heterogeneity: $I^2 = 0\%$; $P = 0.60$ | | | |

Incident DM OR 1.12 (1.04-1.22)



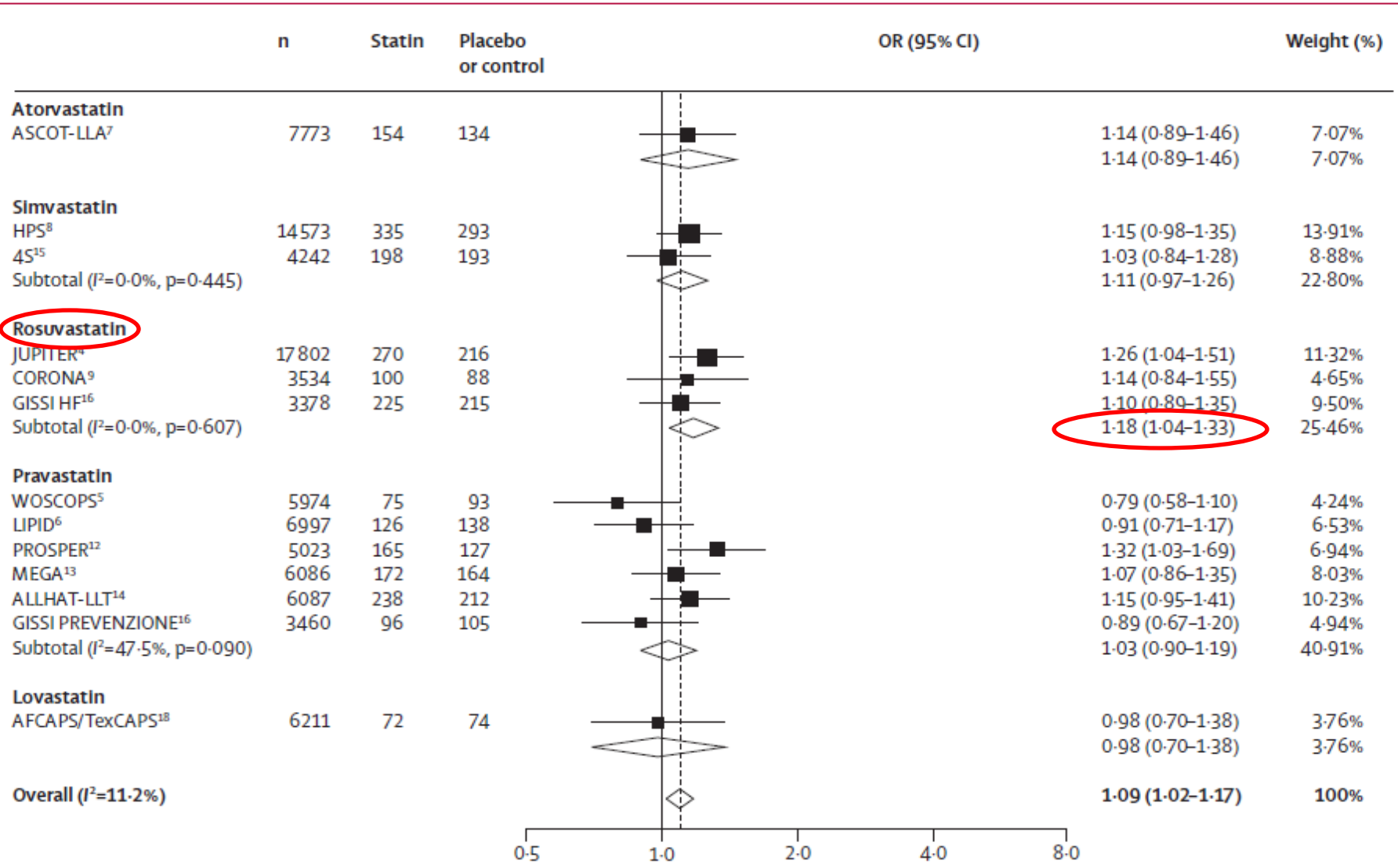

| | | | |
|---|---|---|---|
| Incident CVD | | | |
| PROVE IT–TIMI 22,[25] 2004 | 315/1707(18.4) | 355/1688 (21.0) | 0.85 (0.72-1.01) |
| A to Z,[26] 2004 | 212/1768 (12.0) | 234/1736 (13.5) | 0.87 (0.72-1.07) |
| TNT,[23] 2005 | 647/3798 (17.0) | 830/3797 (21.9) | 0.73 (0.65-0.82) |
| IDEAL,[24] 2005 | 776/3737 (20.8) | 917/3724 (24.6) | 0.80 (0.72-0.89) |
| SEARCH,[27] 2010 | 11 | | |
| Pooled odds ratio | 3134/16408 (19.1) | 3550/16344 (21.7) | 0.84 (0.75-0.94) |
| Heterogeneity: $I^2 = 74\%$; $P = 0.004$ | | | |

Incident CVD OR 0.84 (0.75-0.94)




Current Opinion in Lipidology 2011, 22:460–466

# Statin Classes and Incident Diabetes




Lancet 2010; 375: 735–42

# Summary

- Statins reduced the risk of incident and recurrent CVD events in nondiabetics and diabetics
- Evidence shows an association between statins and incident diabetes
  - Uncertainty of causal relationship
- Cardiovascular benefits outweigh potential risks of diabetes mellitus

# Lipid Goals in Diabetes: ADA Recommendations

- LDL cholesterol < 100 mg/dL (2.6 mmol/L)
  - Diabetes without overt CVD
- LDL cholesterol < 70 mg/dL (1.8 mmol/L)
  - Diabetes with overt CVD
- LDL cholesterol reduction of 30–40% from baseline is an alternative therapeutic goal if unable to achieve targets on maximal tolerated statin therapy

Diabetes Care 36 (S1) January 2013

# Lipid Goals in Diabetes: ADA Recommendations

- Triglycerides levels <150 mg/dL (1.7mmol/L)
- HDL cholesterol > 40 mg/dL (1.0 mmol/L) in men and 50 mg/dL (1.3 mmol/L) in women
- LDL cholesterol–targeted statin therapy remains the preferred strategy

Diabetes Care 36 (S1) January 2013

# Lipid-Lowering Strategies

- Nutrition:
  - Reduce saturated fat, cholesterol, and trans unsaturated fat intake
  - Increase n-3 fatty acids, viscous fiber, and plant stanols/sterols
- Glycemic control:
  - High triglycerides and poor glycemic control

# Treatment

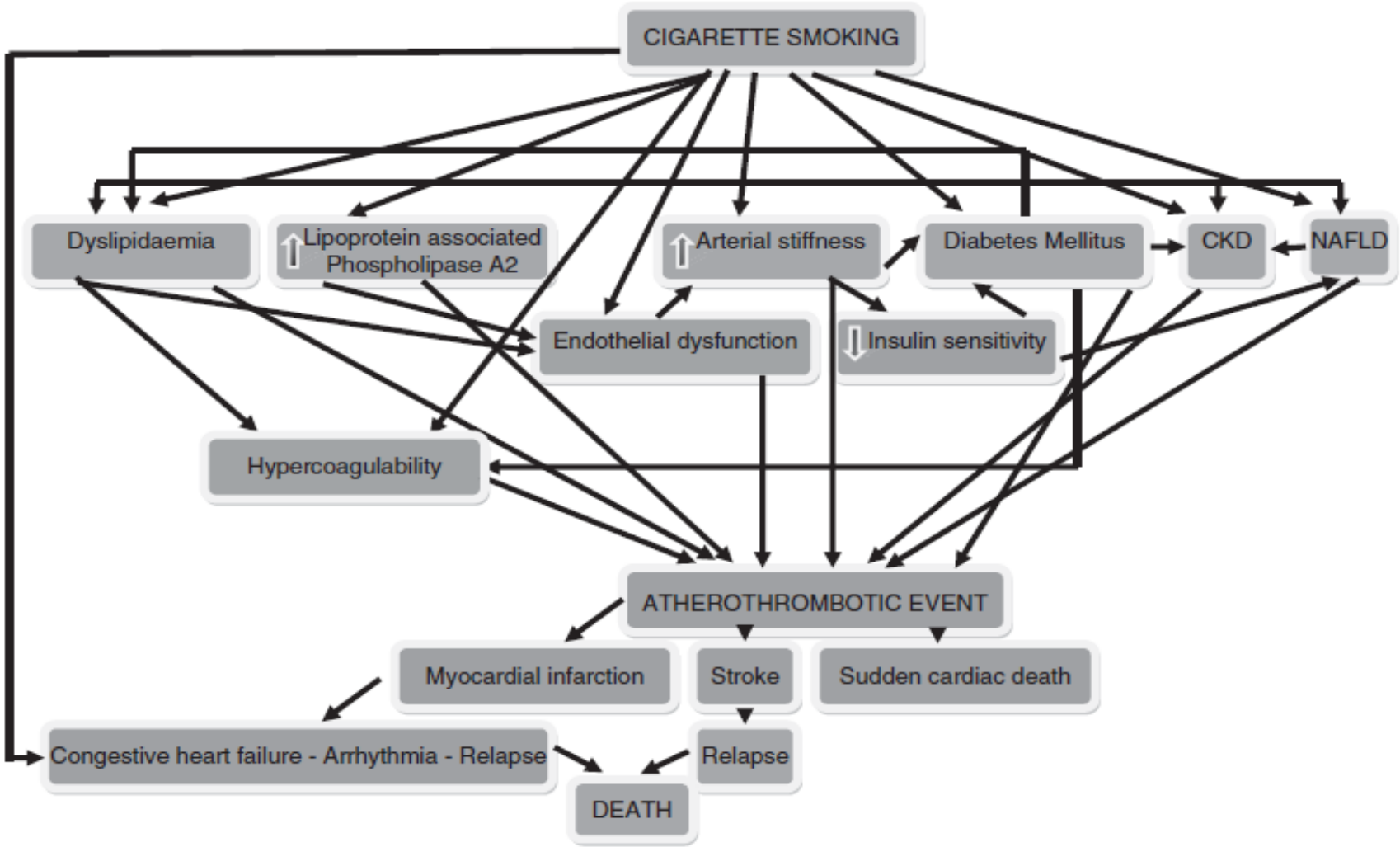
- Statin:
  - Clinical CVD **
  - > 40 years with other CVD risk factors **
  - Inadequate LDL cholesterol response to lifestyle modifications and improved glucose control
  - Increased cardiovascular risk

**should be started regardless of LDL level

# C is for Cigarettes

- What is the impact of smoking cessation on CVD risk reduction in diabetes?

# Smoking and CVD Risk





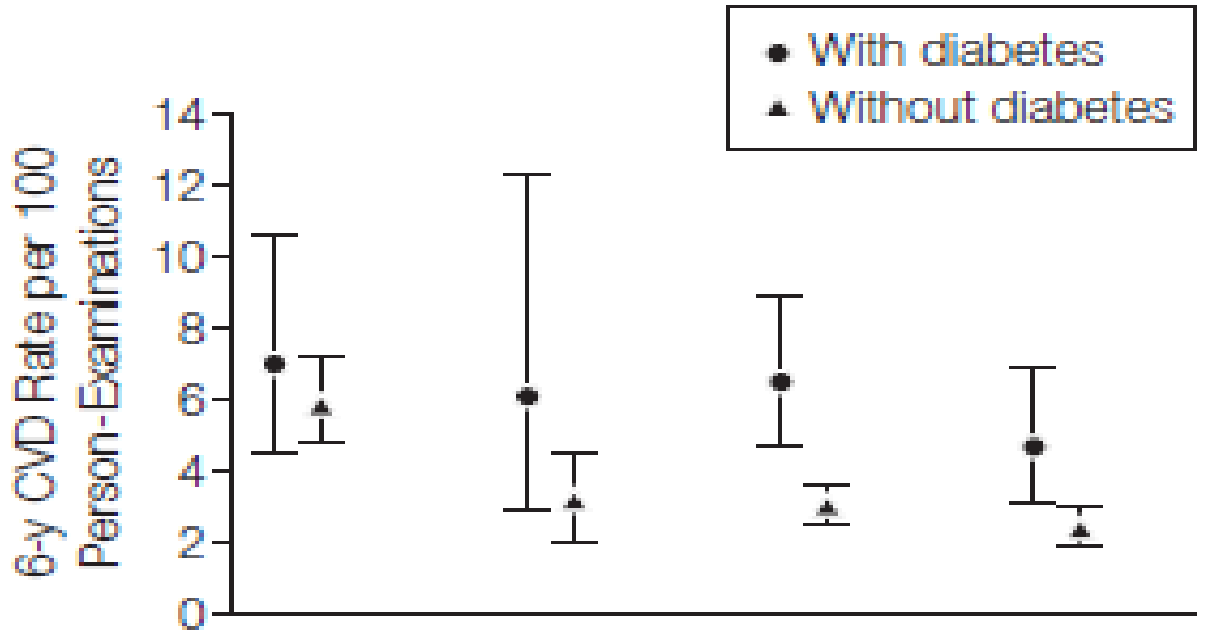

Athyros V et al, Current Medical Research & Opinion, 2013, 1-12

# Smoking cessation and CVD

- Smoking cessation improves CVD Risk factors
  - Lipid profile
  - Endothelial function
  - Microalbuminuria
  - Chronic Kidney Disease
- Meta-analysis of 61 large international studies showed 36% reduction in RR of mortality


Vouglari C, Metabolism, 2011;60:1456-1464.

# Smoking cessation and CVD Risk

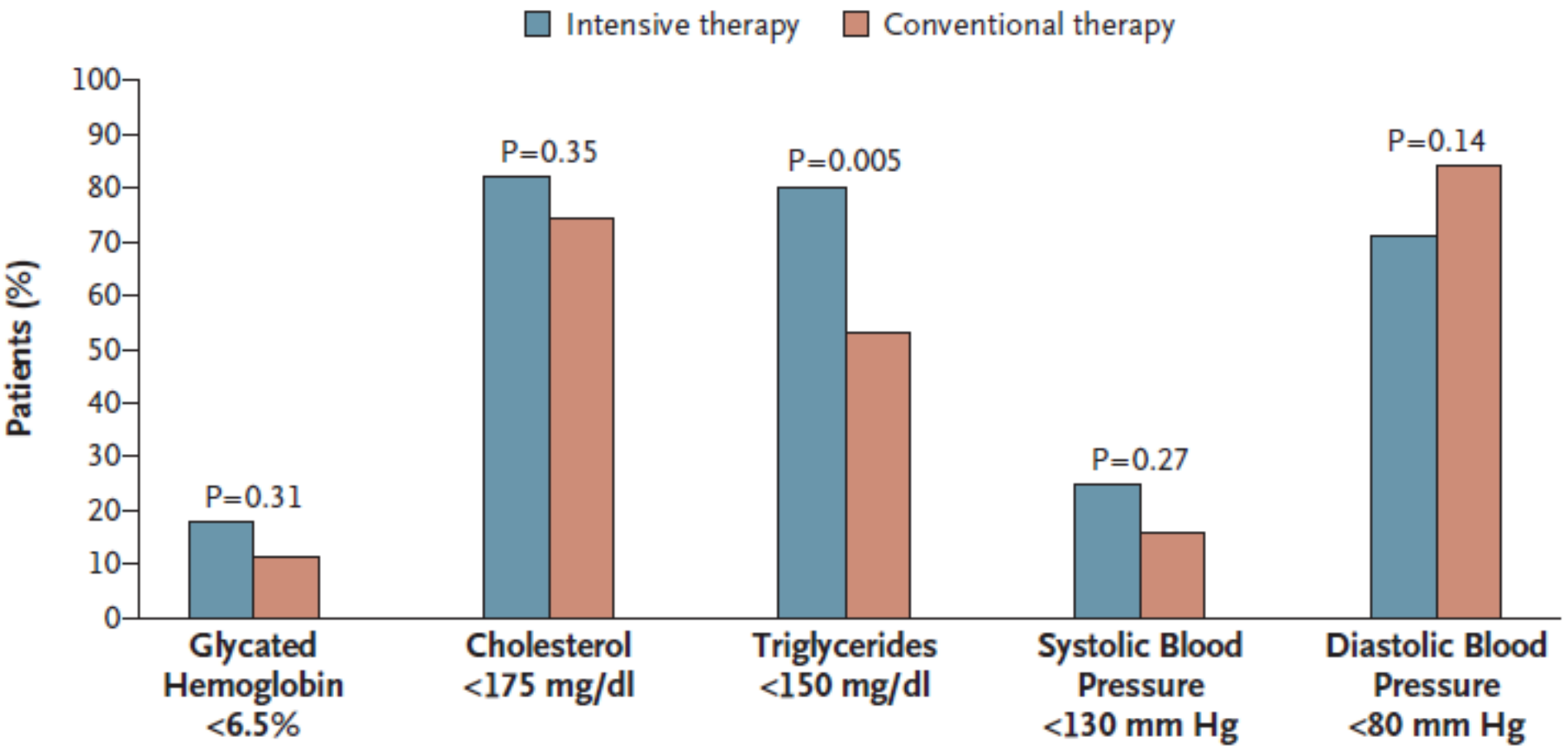



| No. | Smokers | Quit for ≤4 y | Quit for >4 y | Nonsmokers |
|---|---|---|---|---|
| CVD events | | | | |
| With diabetes | 23 | 8 | 59 | 35 |
| Without diabetes | 143 | 29 | 218 | 116 |
| Person-examinations | | | | |
| With diabetes | 279 | 92 | 603 | 506 |
| Without diabetes | 1924 | 591 | 3761 | 3392 |

# Summary

- Smoking is clearly associated with increased risk of CVD
- Smoking cessation improves CVD risk factors and in large studies including diabetic and non-diabetics, lowers risk of CVD and mortality
- Unclear how many years of smoking cessation are required to lower CVD risk in diabetics

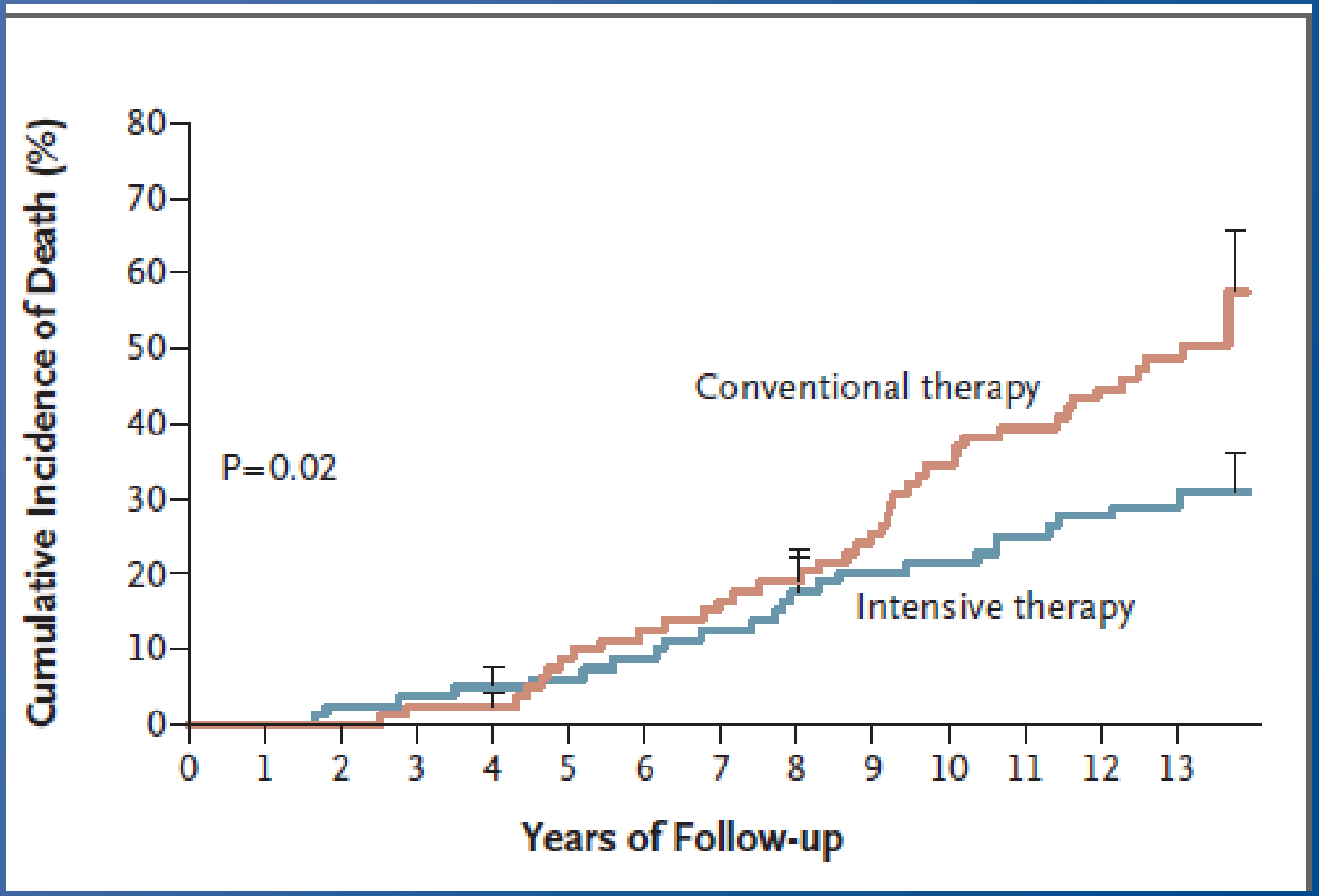
# Putting it all together… the STENO-2 trial






Gaede et al, NEJM, 2008; 358;580-591.

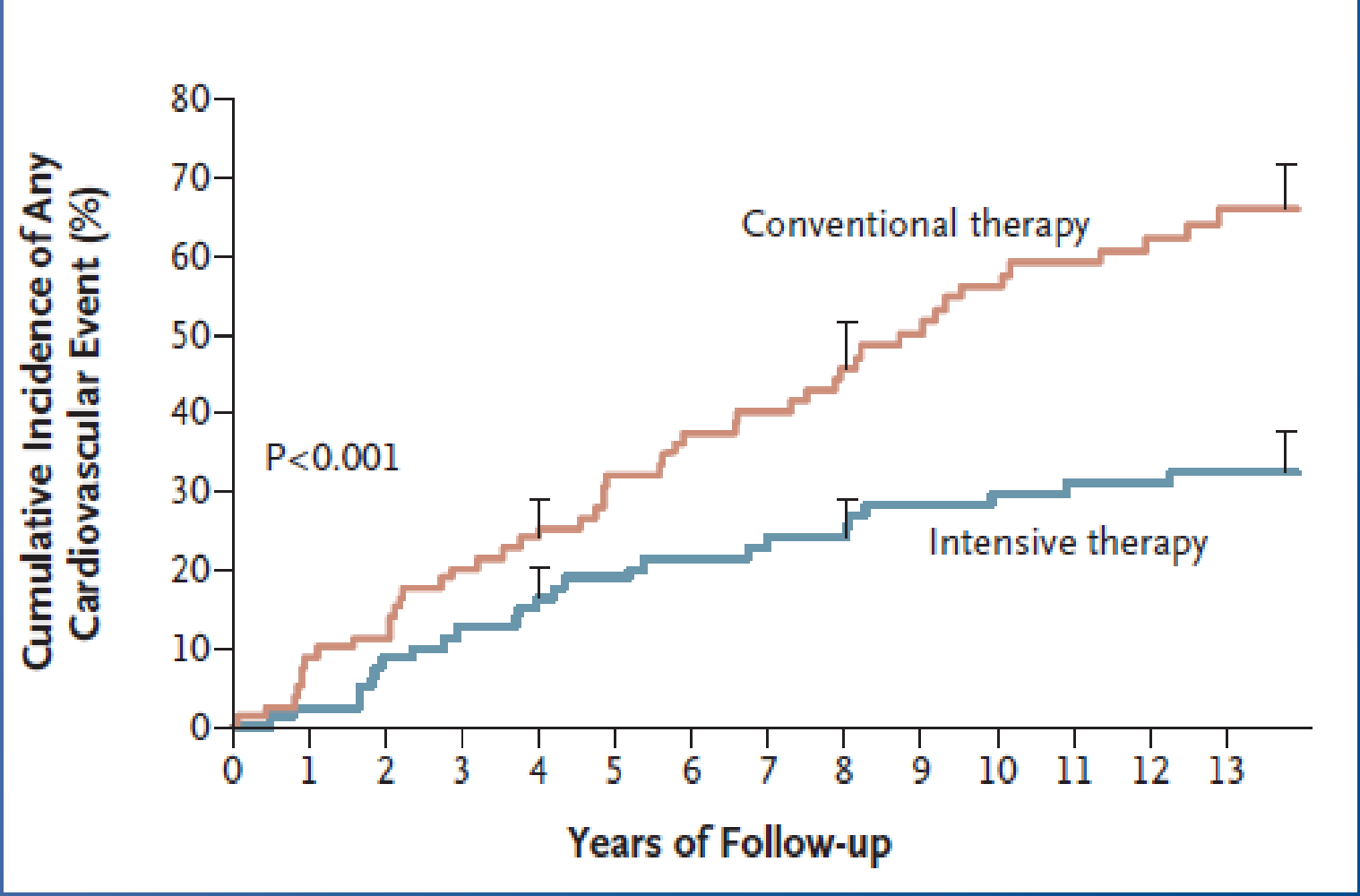
# Multifactorial Intervention Reduces Death






Gaede et al, NEJM, 2008; 358;580-591.

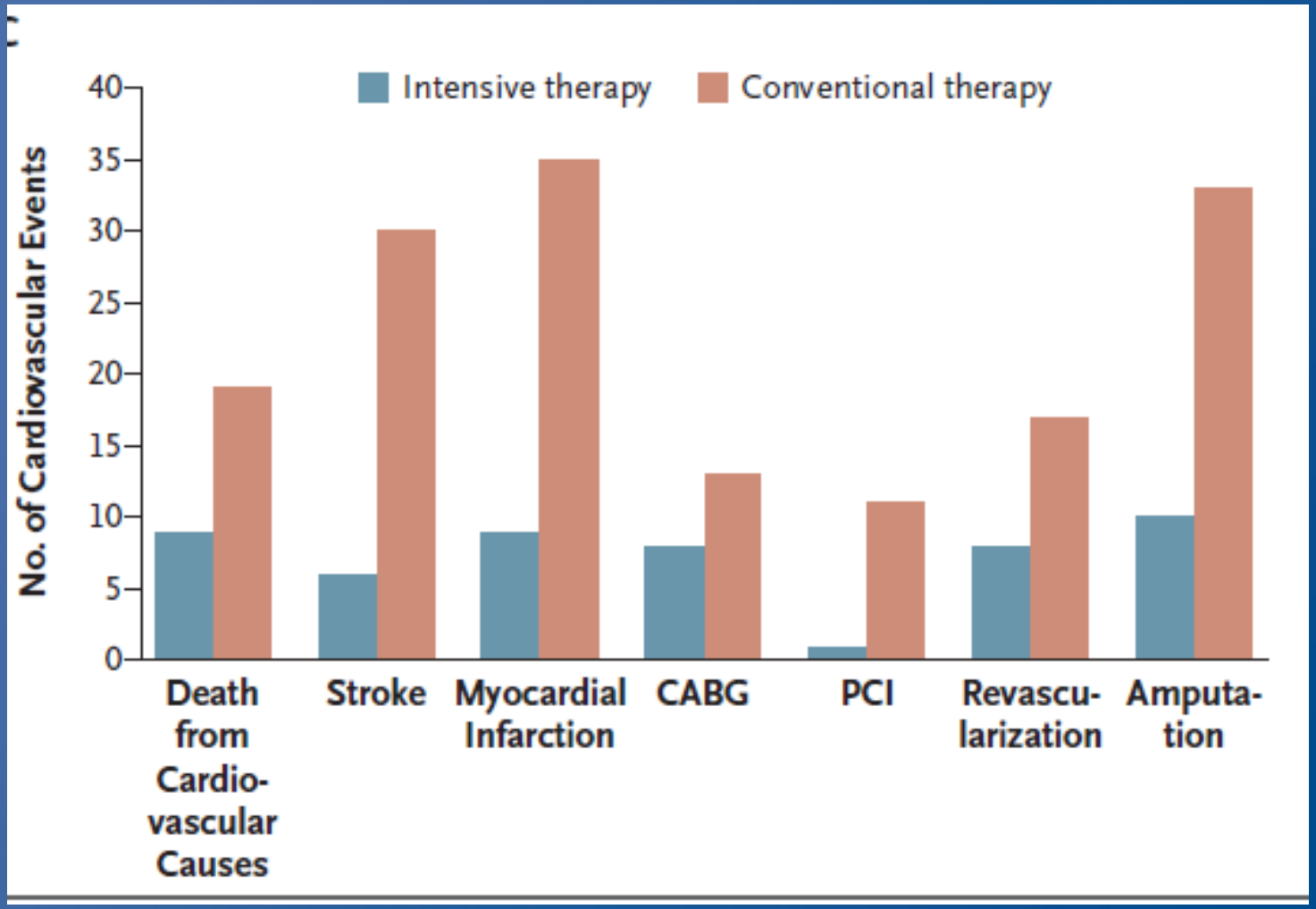
# Multifactorial Intervention Reduces CV Events






Gaede et al, NEJM, 2008; 358;580-591.

# Multifactorial Intervention Reduces CVD






Gaede et al, NEJM, 2008; 358;580-591.

# Who should be screened for CHD?

- ADA does **not** recommend routine screening for CHD in patients with diabetes
- ADA guidelines recommend annual assessment of risk criteria to identify patients who might benefit from interventions such as aspirin, ACE inhibitors, or statins, but no longer recommend that these criteria be used to identify patients for stress testing

# Conclusion

- **A for**
  - A1C
  - Anti-platelet therapy (aspirin)
- **B** for
  - Blood pressure
- **C** for
  - Cholesterol
  - Cigarettes (smoking cessation)
- **D** for
  - Diet
- **E** for
  - Exercise