SEMI
LA VISIÓN GLOBAL DE LA PERSONA ENFERMA

Sademi
Sociedad Andaluza de Medicina Interna

XXXIV Congreso Nacional de la Sociedad Española de Medicina Interna (SEMI)

21-23
Noviembre 2013

Palacio de Ferias y Congresos de Málaga
Málaga

XXIX Congreso de la Sociedad Andaluza de Medicina Interna (SADEMI)

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PREVENCIÓN PRIMARIA CARDIOVASCULAR EN EL PACIENTE DIABÉTICO

Dr Joan Lima
Unidad de Lípidos y Riesgo Vascular
Hospital Vall d'Hebron
Barcelona

DIABETES Y RIESGO CARDIOVASCULAR

≈ 65% de la mortalidad es de causa CV

Riesgo de muerte por CI

↑ de 2-4 veces

Riesgo de ictus

↑ de 2-4 veces

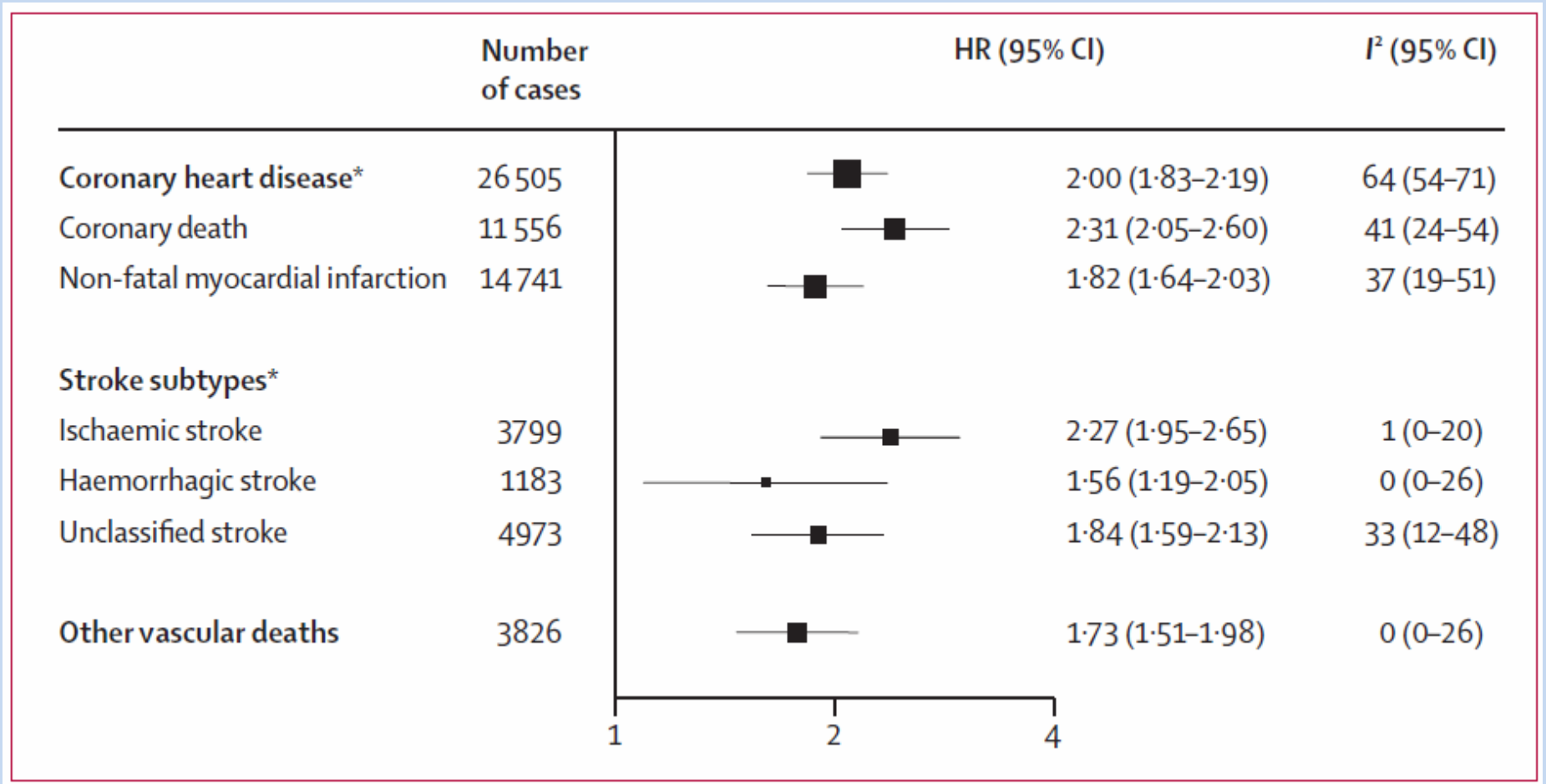
Insuficiencia cardiaca

↑ de 2-5 veces

Bell DSH. *Diabetes Care*. 2003;26:2433-41.
Centers for Disease Control (CDC). www.cdc.gov.

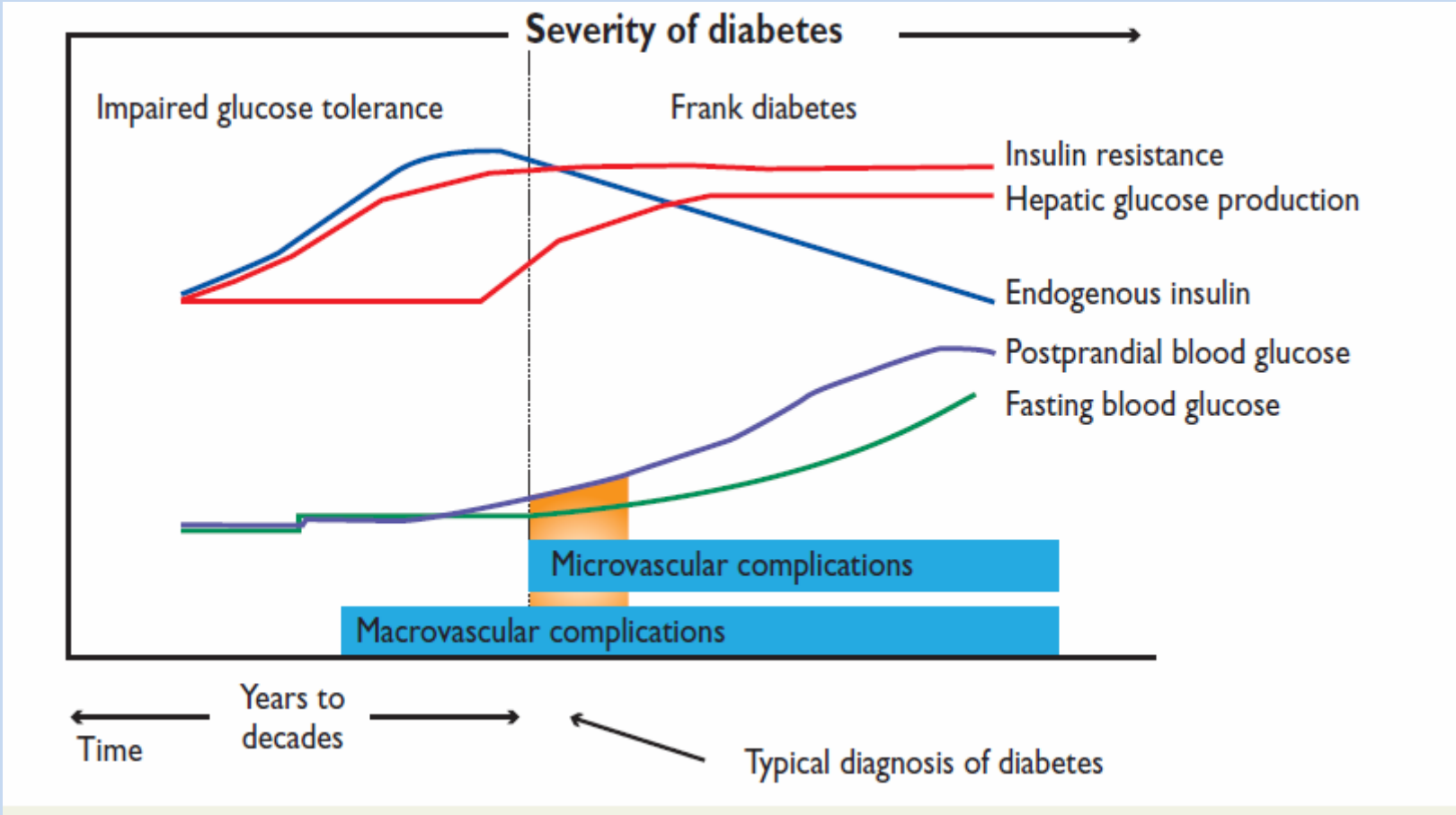
Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies

*The Emerging Risk Factors Collaboration**



Lancet 2010; 375: 2215–22

Glycaemic continuum and cardiovascular disease

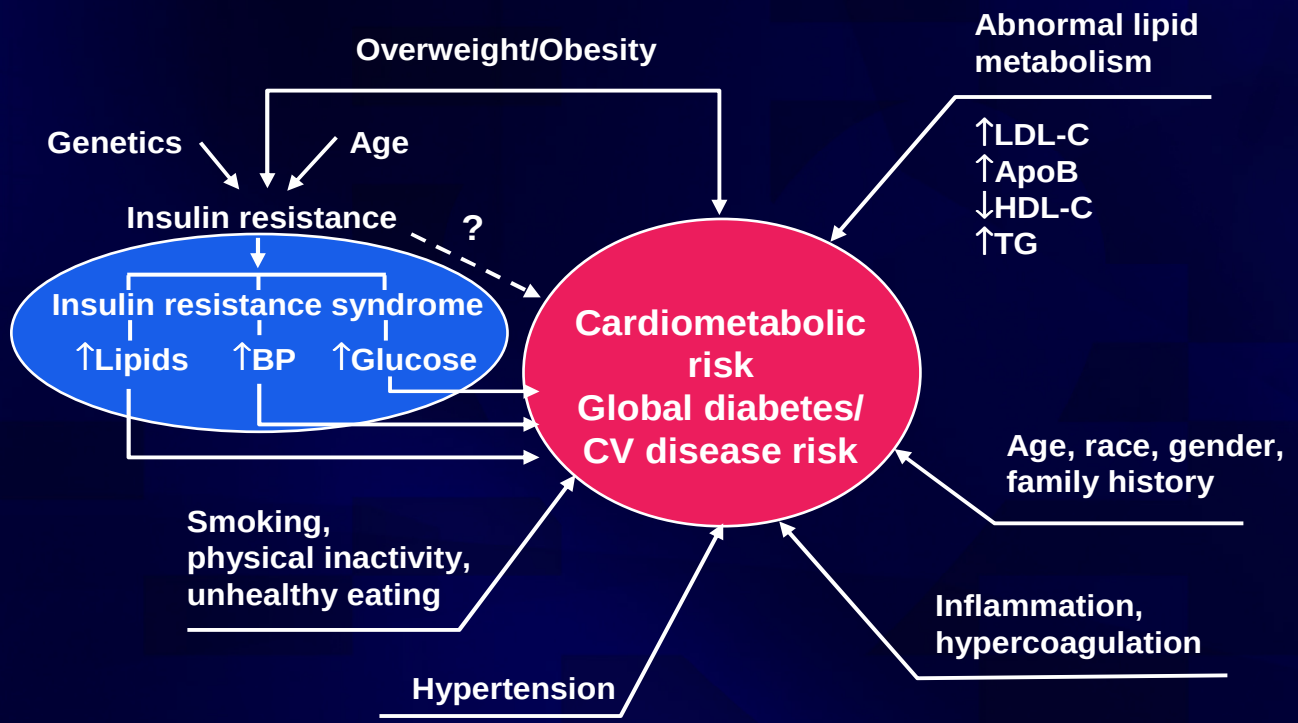


European Heart Journal
doi:10.1093/eurheartj/eht108

DIABETES Y RIESGO CARDIOVASCULAR.

FACTORES QUE CONTRIBUYEN AL RIESGO CARDIOVASCULAR

ADA/ACC Consensus Statement



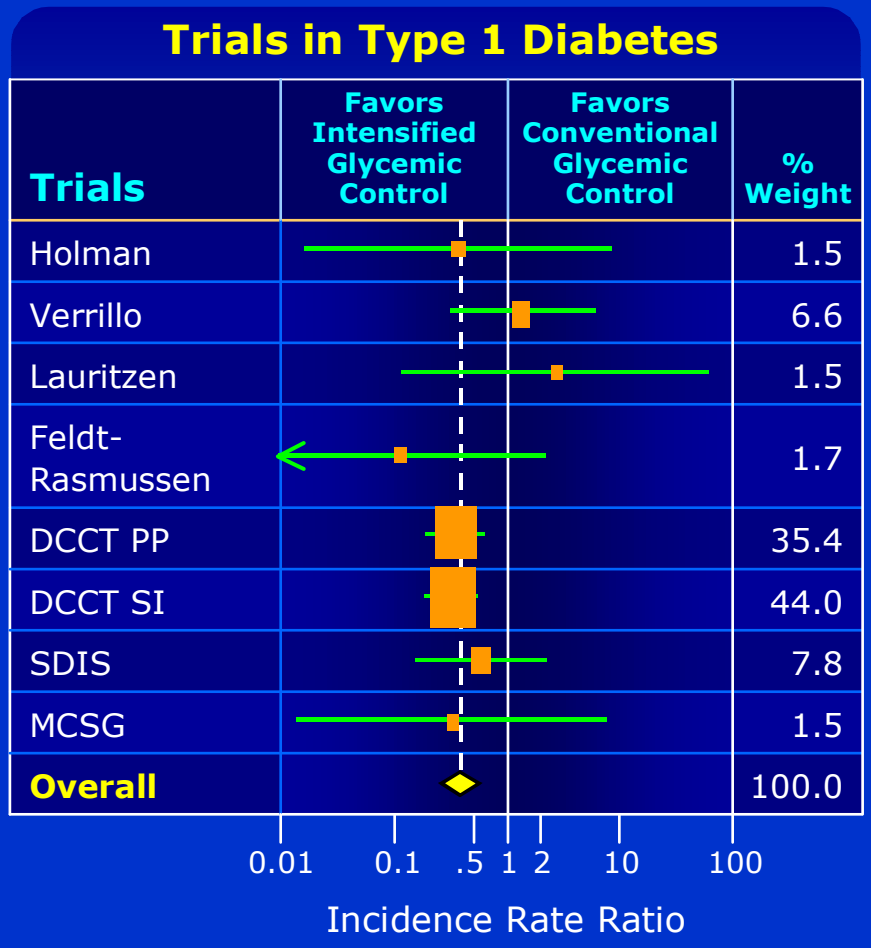
Brunzell JD et al. *Diabetes Care.* 2008;31:811-22.

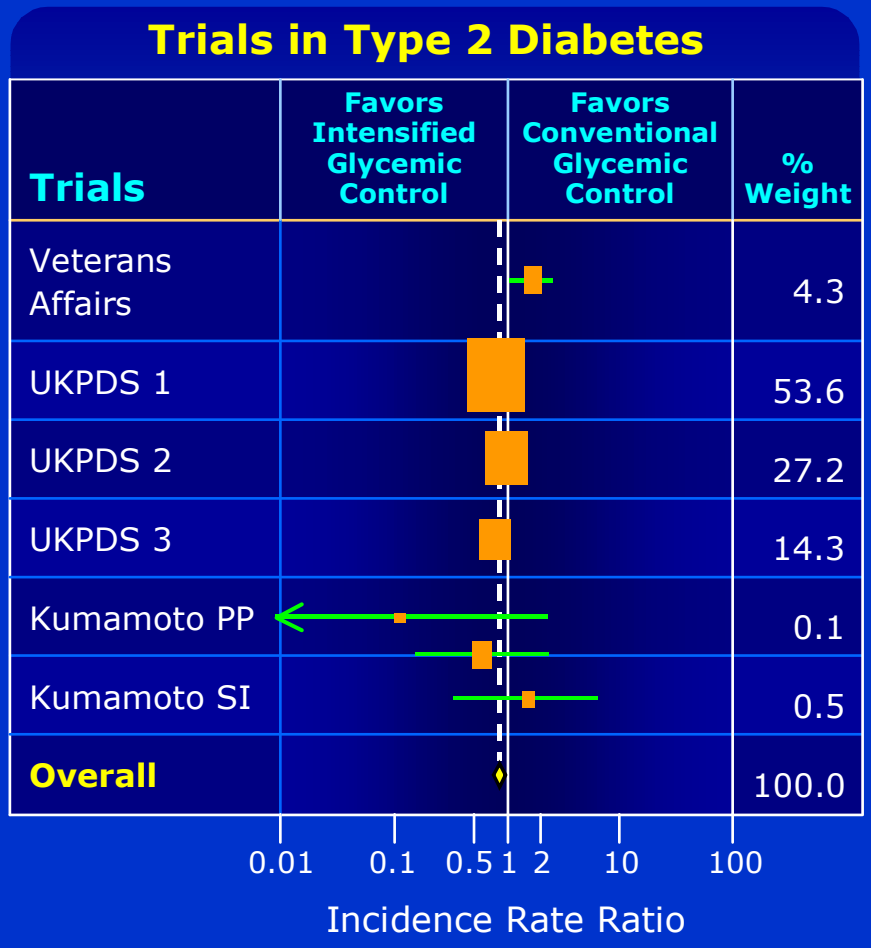
Cardiovascular risk factors in type 1 and type 2 diabetes: contrasts and commonalities

	Type 1 diabetes	Type 2 diabetes
Dyslipidemia	• More favorable lipids than nondiabetic individuals • Modest CVD risk factor	• Low HDL-cholesterol and high triglycerides common • Low HDL-cholesterol and elevated triglycerides and LDL-cholesterol associated with CVD
Hypertension	• High prevalence of hypertension • Poorly treated and controlled • Higher systolic blood pressure and pulse pressure associated with CVD	• Hypertension is common • Component of the metabolic syndrome that contributes to type 2 diabetes risk • Increases the risk of CVD
Renal disease	• Potent CVD risk factor • May explain all excess CVD risk in type 1 diabetes	• Renal disease often present at time of diagnosis • Lower GFR or proteinuria increase CVD risk
Obesity	• Typically not more obese than the general population • Obesity increases risk for CVD	• Obesity is a risk factor for type 2 diabetes • Visceral adiposity is associated with CVD, independent of diabetes status
Hyperglycemia	• Intensive treatment and improved blood sugar levels decrease CVD events	• Intensive treatment to normalize blood sugar did not decrease CVD in several trials among type 2 diabetic patients

Curr Diab Rep (2013) 13:350–361

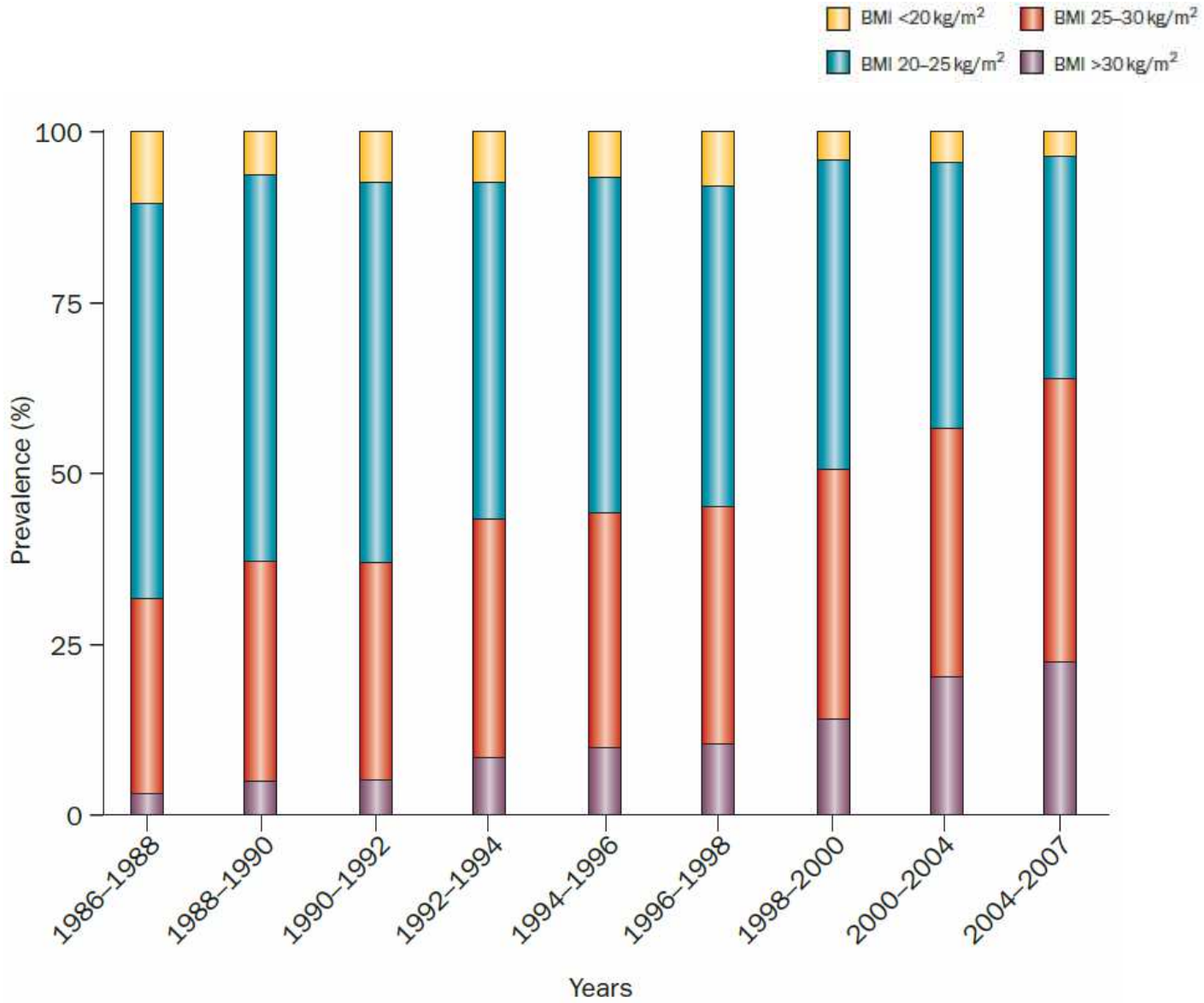
Glycemic Control and Macrovascular Disease in Patients With Type 1 or Type 2 Diabetes: Meta-analysis of Clinical Trials





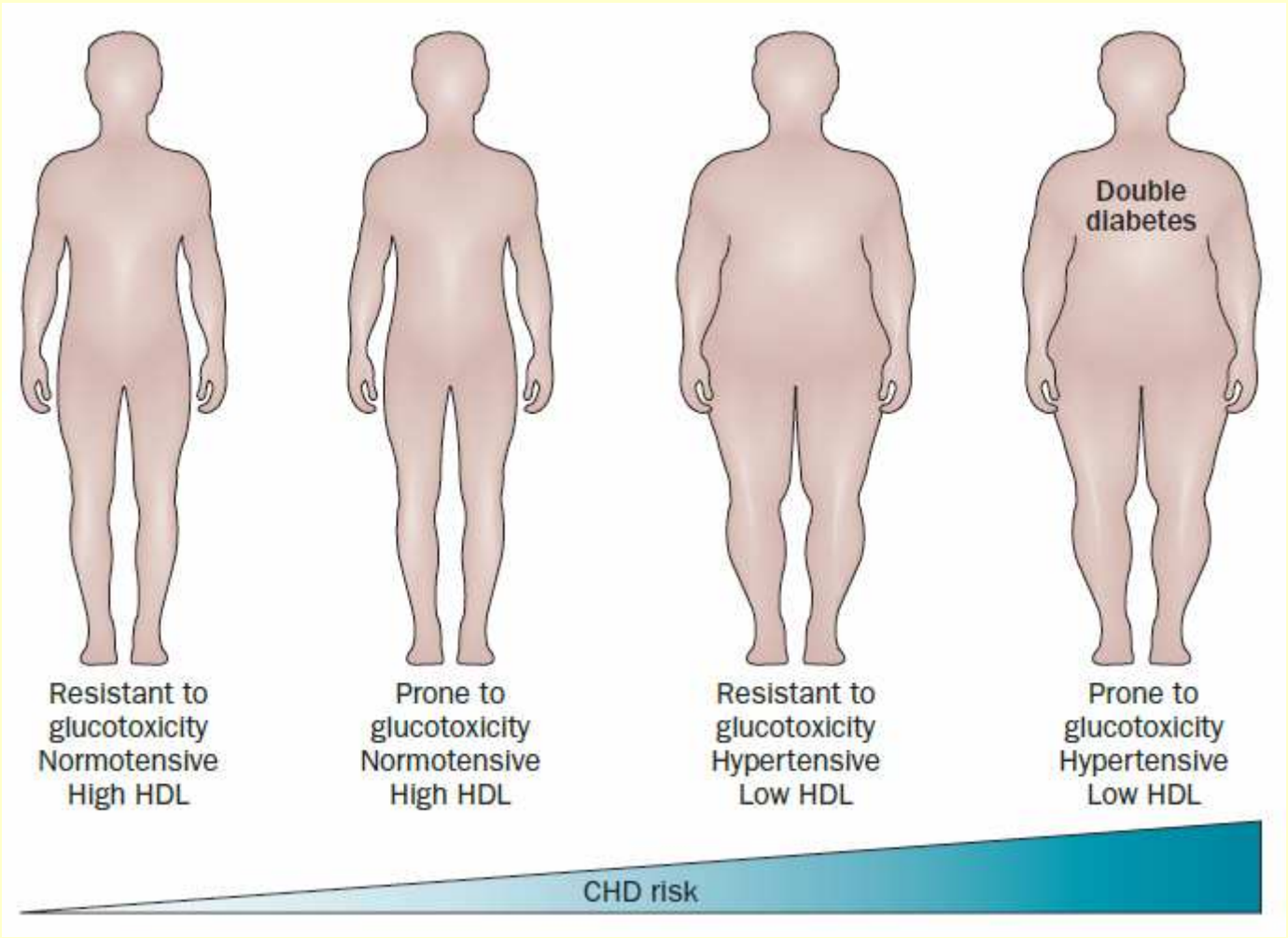
Reprinted from Stettler C, et al. *Am Heart J.* 2006; 152:27–38, with permission from Elsevier.

Changing BMI profiles in patients with T1DM in the Pittsburgh EDC Prospective Cohort Trial



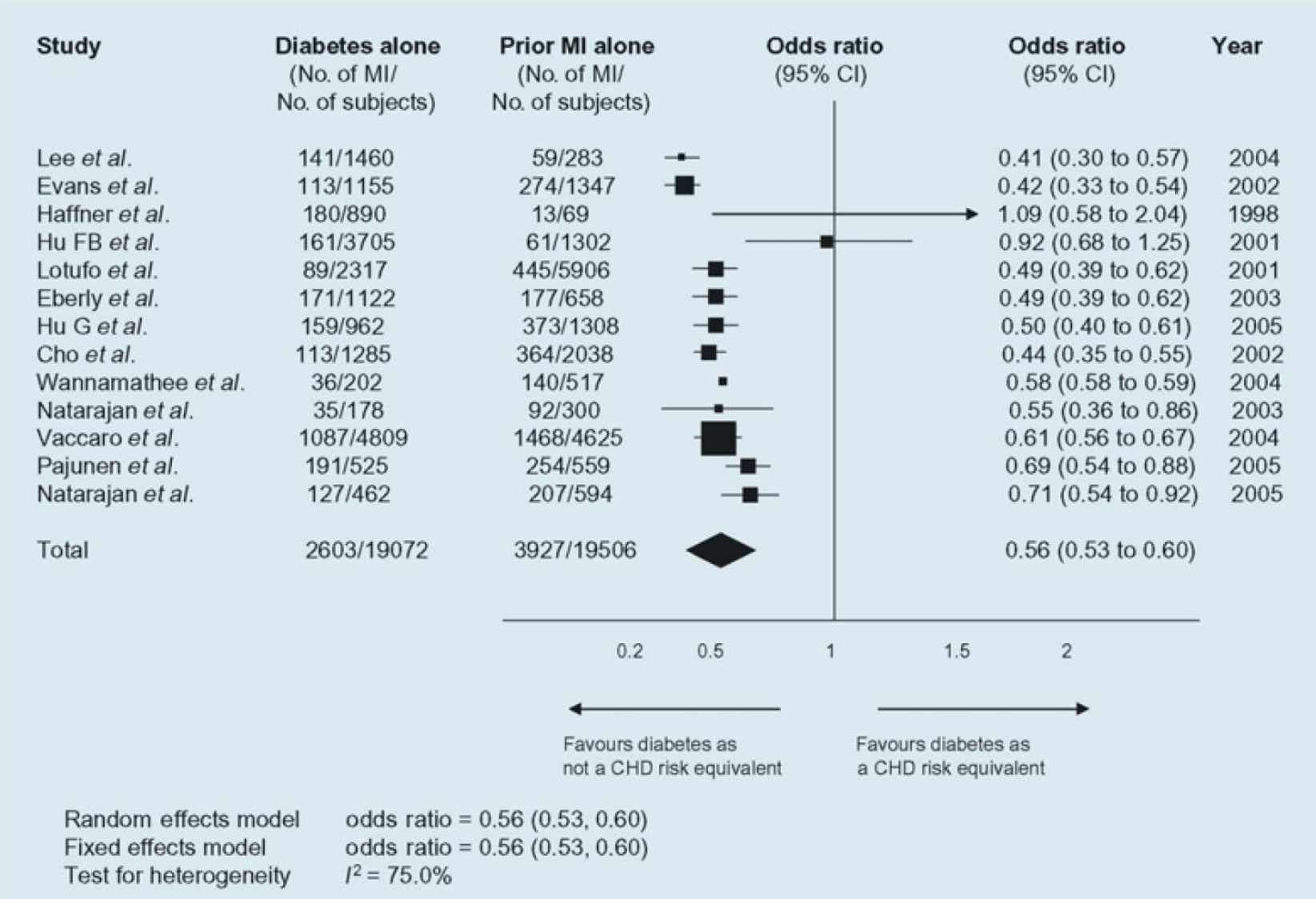
Cleland, S. J. *Nat. Rev. Endocrinol.* **8**, 476–485 (2012)

Proposed model of increasing coronary risk for patients with type 1 diabetes mellitus



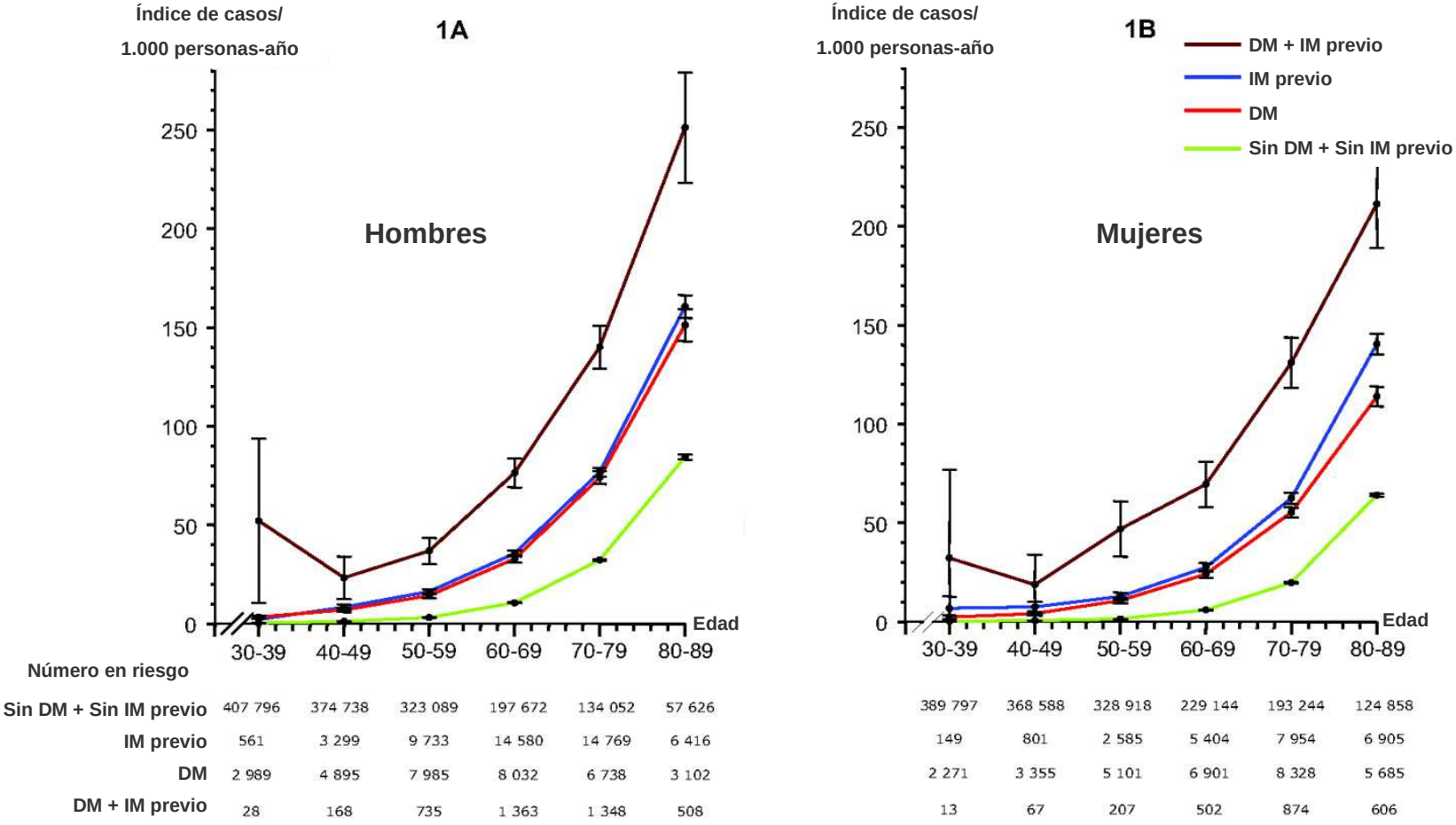
Cleland, S. J. *Nat. Rev. Endocrinol.* **8**, 476–485 (2012)

Is diabetes a coronary risk equivalent? Systematic review and meta-analysis



Diabet. Med. 26, 142–148 (2009)

DIABETES Y RIESGO CARDIOVASCULAR: ¿Es un equivalente de riesgo coronario?



Estudio en Dinamarca con más de 3 millones de personas; 71801pacientes diabéticos de más de 30 años y 79575 con IAM. Seguimiento 5 años.

Schramm et al, *Circulation* 2008; 117: 1945

European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)

1. Very high risk
Subjects with any of the following:

- Documented CVD by invasive or non-invasive testing (such as coronary angiography, nuclear imaging, stress echocardiography, carotid plaque on ultrasound), previous myocardial infarction, ACS, coronary revascularization (PCI, CABG), and other arterial revascularization procedures, ischaemic stroke, peripheral artery disease (PAD).
- Diabetes mellitus (type 1 or type 2) with one or more CV risk factors and/or target organ damage (such as microalbuminuria: 30–300 mg/24 h).
- Severe chronic kidney disease (CKD) (GFR <30 mL/min/1.73 m^2).
- A calculated SCORE $\geq 10\%$.

European Heart Journal
doi:10.1093/eurheartj/ehs092

European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)

2. High risk
Subjects with any of the following:

- Markedly elevated single risk factors such as familial dyslipidaemias and severe hypertension.
- Diabetes mellitus (type 1 or type 2) but without CV risk factors or target organ damage.
- Moderate chronic kidney disease (GFR 30–59 mL/min/1.73 m^2).
- A calculated SCORE of $\geq$5% and $<$10% for 10-year risk of fatal CVD.

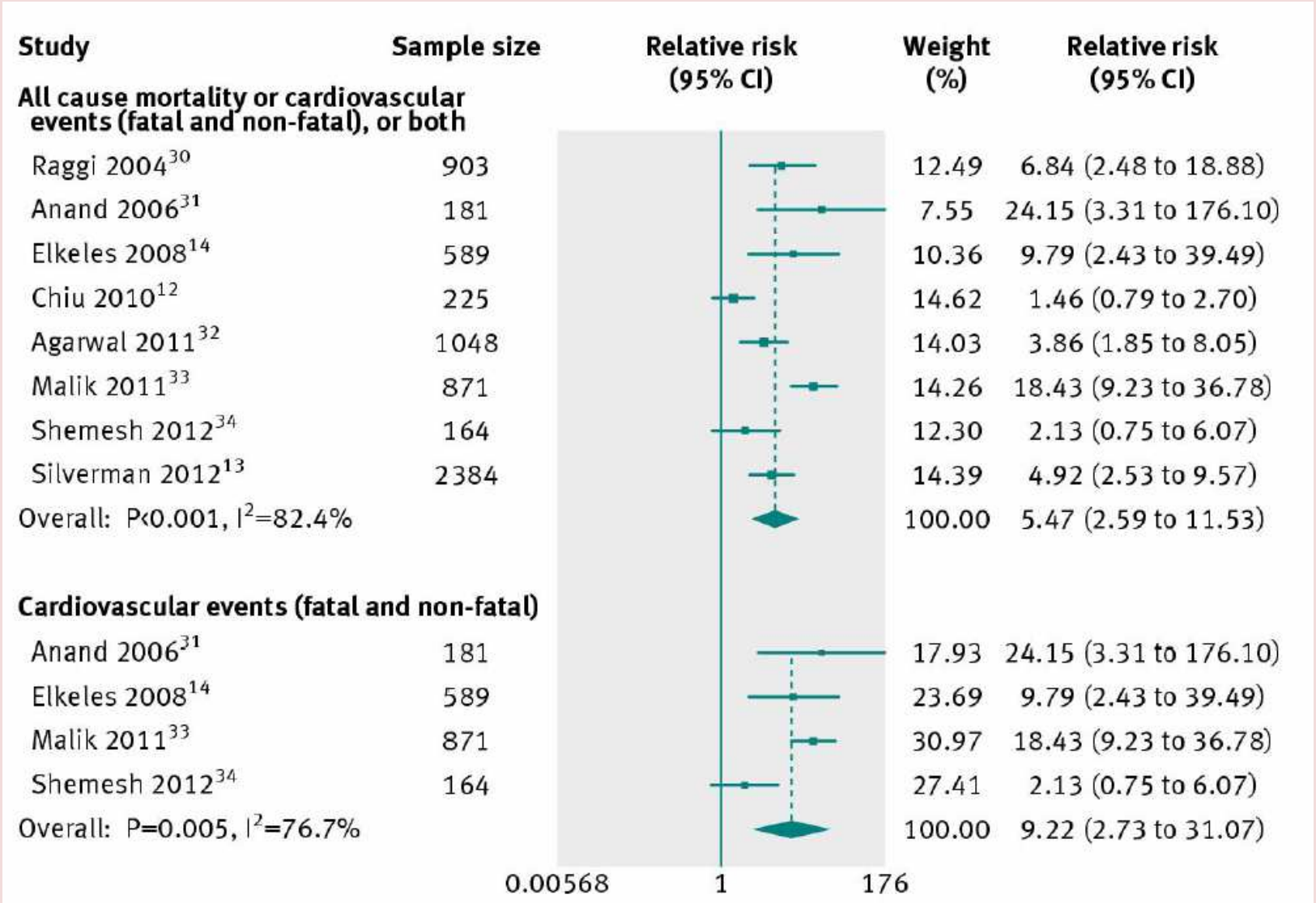
European Heart Journal
doi:10.1093/eurheartj/ehs092

ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

Cardiovascular risk assessment in diabetes			
Recommendations	**Class** [a]	**Level** [b]	**Ref.** [c]
It should be considered to classify patients with DM as at very high or high risk for CVD depending on the presence of concomitant risk factor and target organ damage.	IIa	C	-
It is not recommended to assess the risk for CVD in patients with DM based on risk scores developed for the general population.	III	C	-
It is indicated to estimate the urinary albumin excretion rate when performing risk stratification in patients with DM.	I	B	43
Screening for silent myocardial ischaemia may be considered in selected high risk patients with DM.	IIb	C	-

European Heart Journal
doi:10.1093/eurheartj/eht108

Meta-analysis of association between coronary artery calcium score and outcome in type 2 diabetes

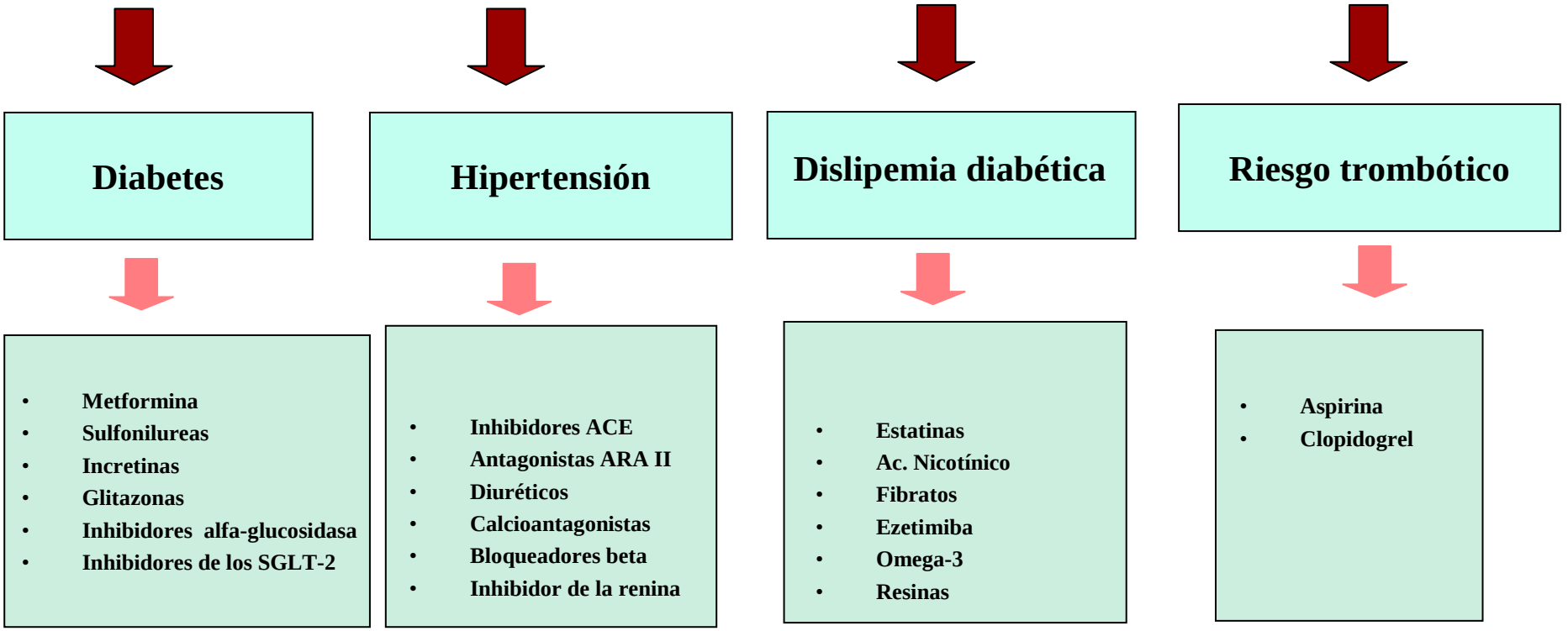


BMJ 2013;346:f1654 doi: 10.1136/bmj.f1654

MODIFICACIÓN DEL RIESGO DE ATEROSCLEROSIS EN LA DIABETES: TRATAMIENTO DE LOS FACTORES DE RIESGO CARDIOVASCULAR

Modificación del estilo de vida

Tratamiento farmacológico

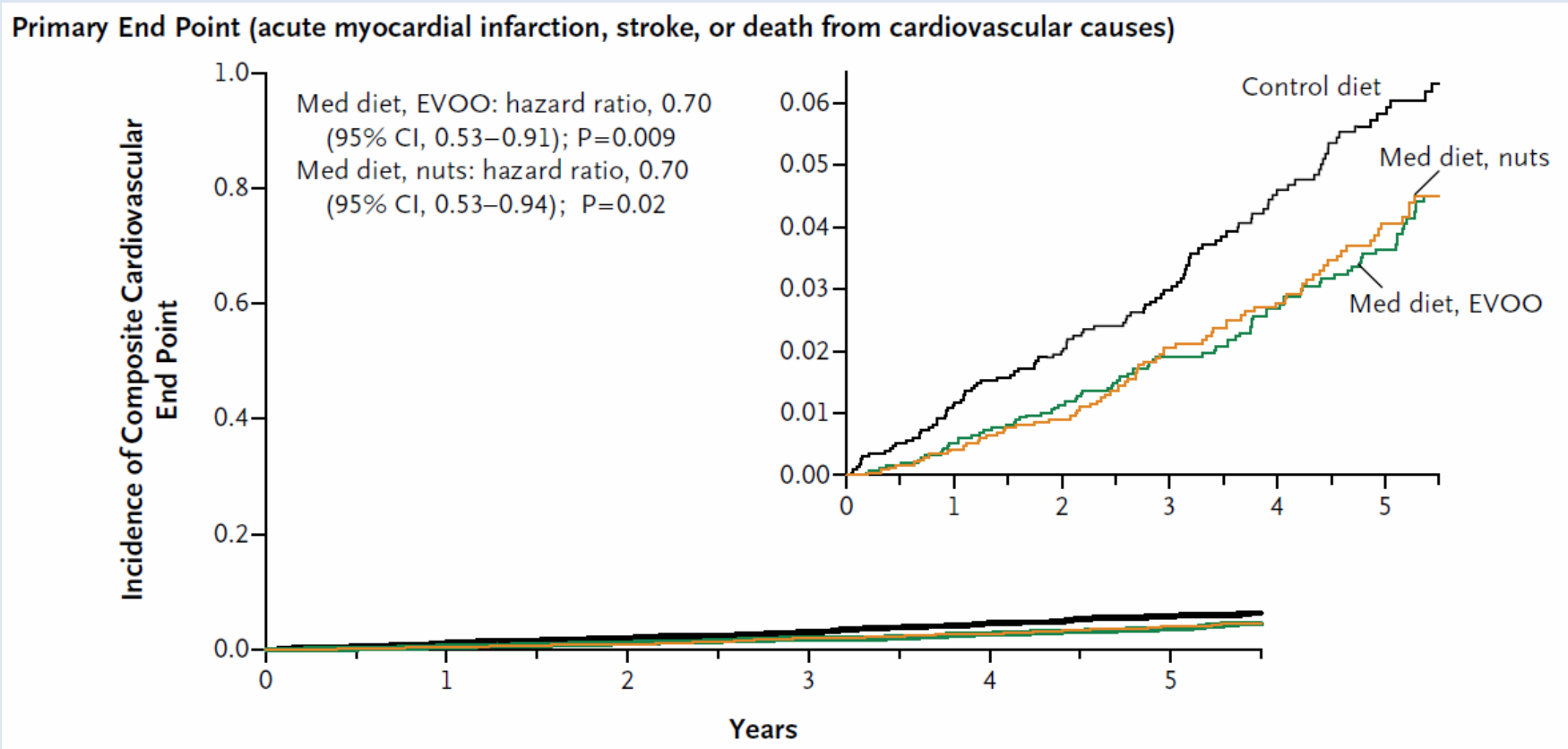


ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

Life style modifications in diabetes		
Recommendations	**Class** [a]	**Level** [b]
Smoking cessation guided by structured advice is recommended in all subjects with DM and IGT.	I	A
It is recommended that in the prevention of T2DM and control of DM total fat intake should be <35%, saturated fat <10%, and monounsaturated fatty acids >10% of total energy.	I	A
It is recommended that dietary fibre intake should be >40 g/day (or 20 g/1000 Kcal/day) in the prevention of T2DM and control of DM.	I	A
Any diet with reduced energy intake can be recommended in lowering excessive body weight in DM.	I	B
Vitamin or micronutrient supplementation to reduce the risk of T2DM or CVD in DM is not recommended.	III	B
Moderate to vigorous physical activity of ≥150 min/week is recommended for the prevention and control of T2DM, and prevention of CVD in DM.	I	A
Aerobic exercise and resistance training are recommended in the prevention of T2DM and control of DM, but best when combined.	I	A

European Heart Journal
doi:10.1093/eurheartj/eht108

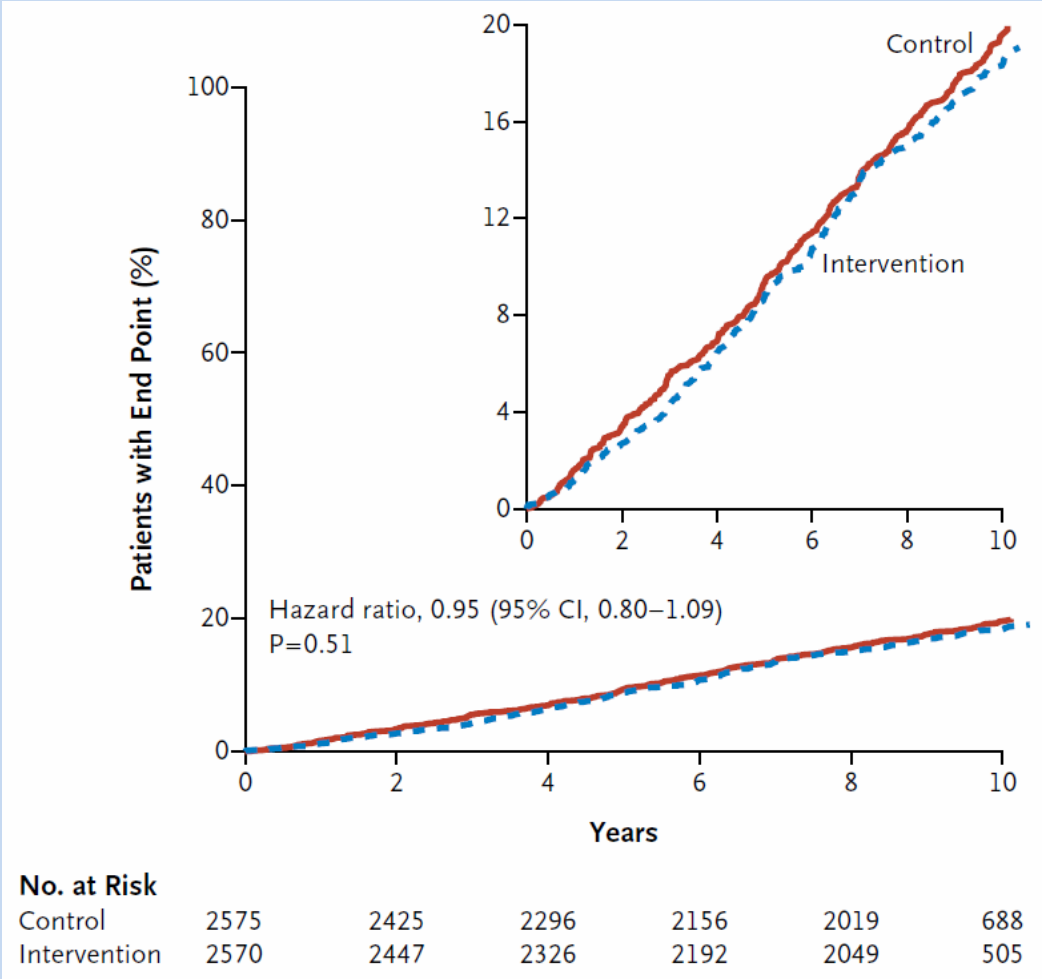
Primary Prevention of Cardiovascular Disease with a Mediterranean Diet



N Engl J Med 2013;368:1279-90.
DOI: 10.1056/NEJMoa1200303

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*



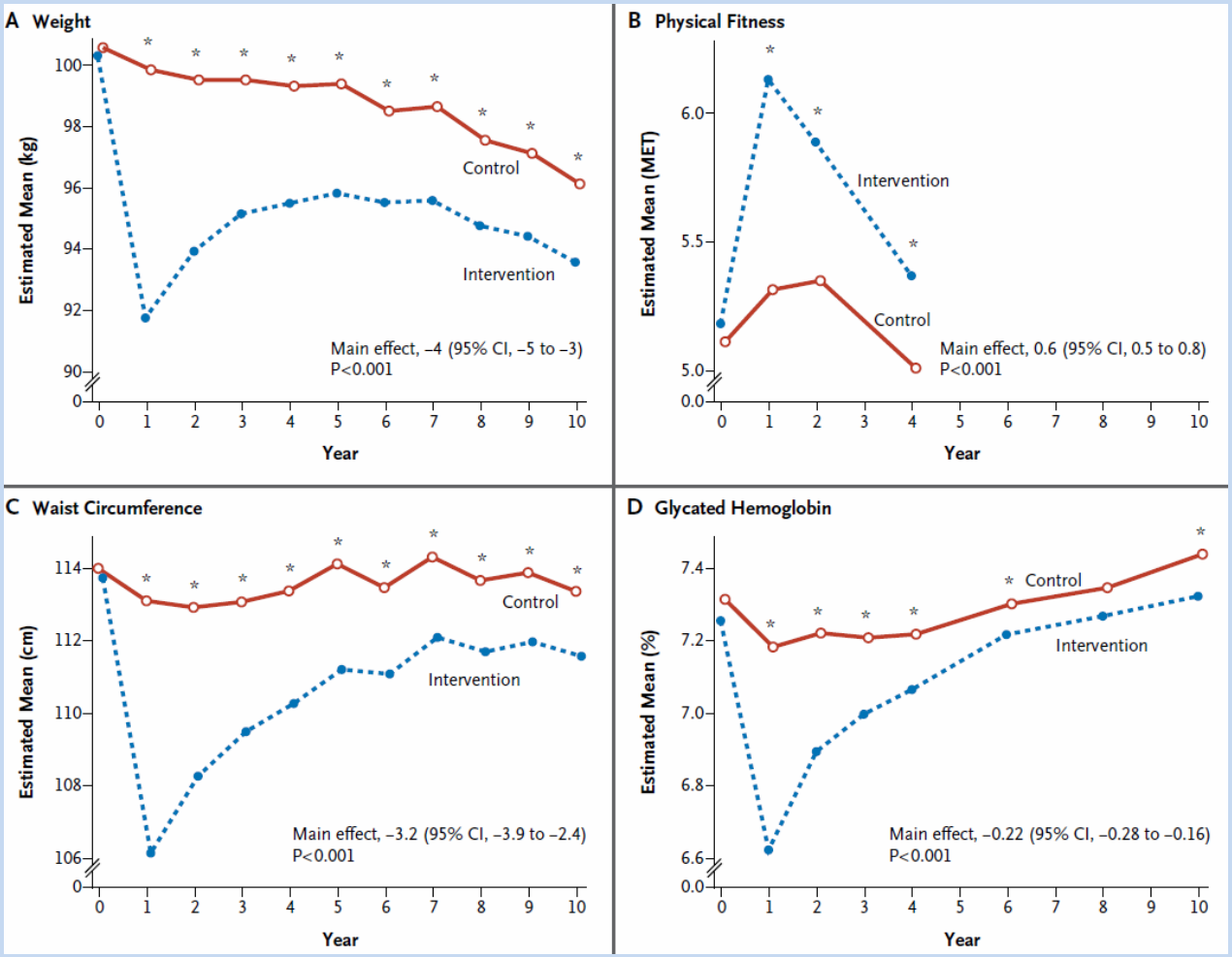
No. at Risk

Control	2575	2425	2296	2156	2019	688
Intervention	2570	2447	2326	2192	2049	505

N Engl J Med 2013;369:145-54.

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*



N Engl J Med 2013;369:145-54.

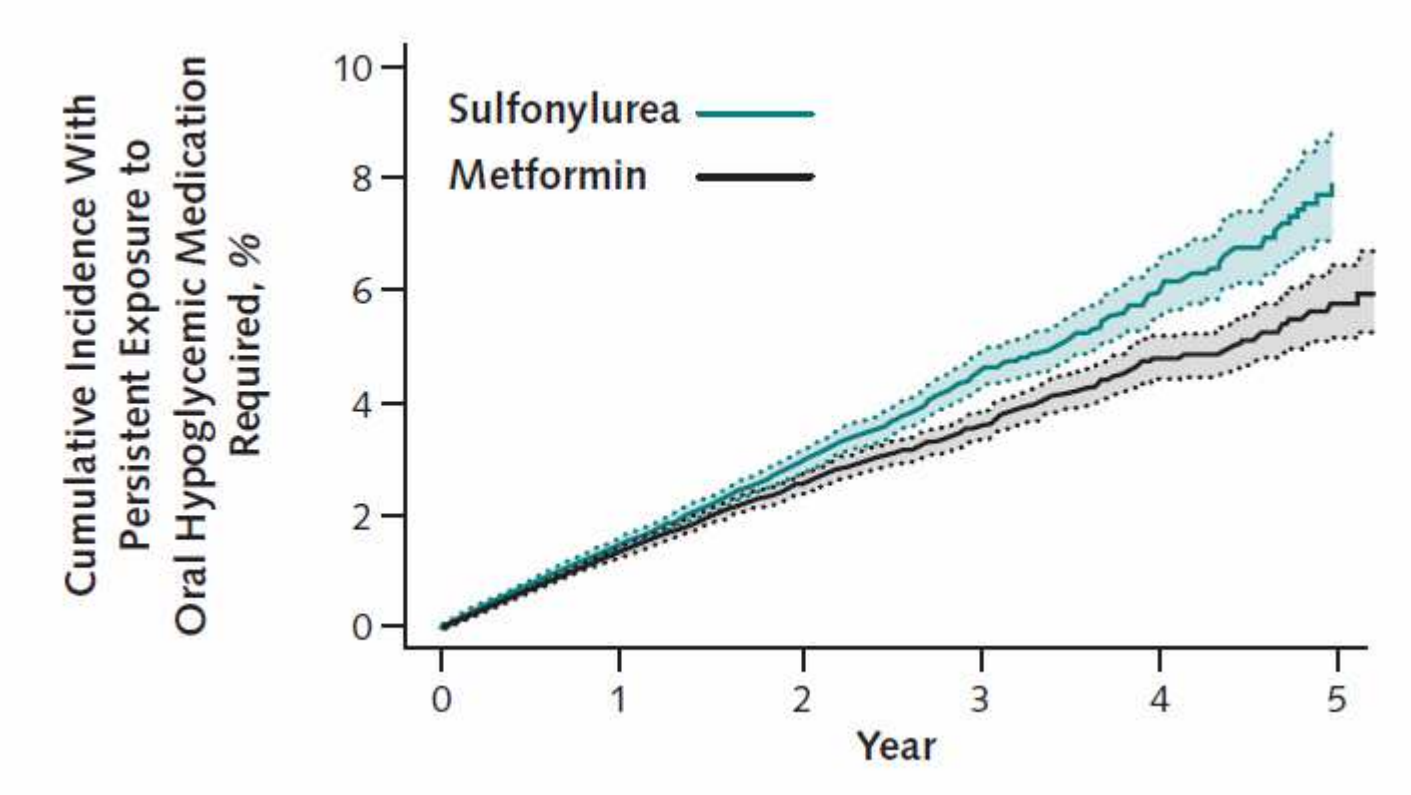
ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

Glycaemic control in diabetes		
Recommendations	**Class** [a]	**Level** [b]
It is recommended that glucose lowering is instituted in an individualized manner taking duration of DM, co-morbidities and age into account.	I	C
It is recommended to apply tight glucose control, targeting a near-normal HbA_{1c} (<7.0% or <53 mmol/mol) to decrease microvascular complications in T1DM and T2DM.	I	A
A HbA_{1c} target of ≤7.0% (≤53 mmol/mol) should be considered for the prevention of CVD in T1 and T2 DM.	IIa	C

European Heart Journal
doi:10.1093/eurheartj/eht108

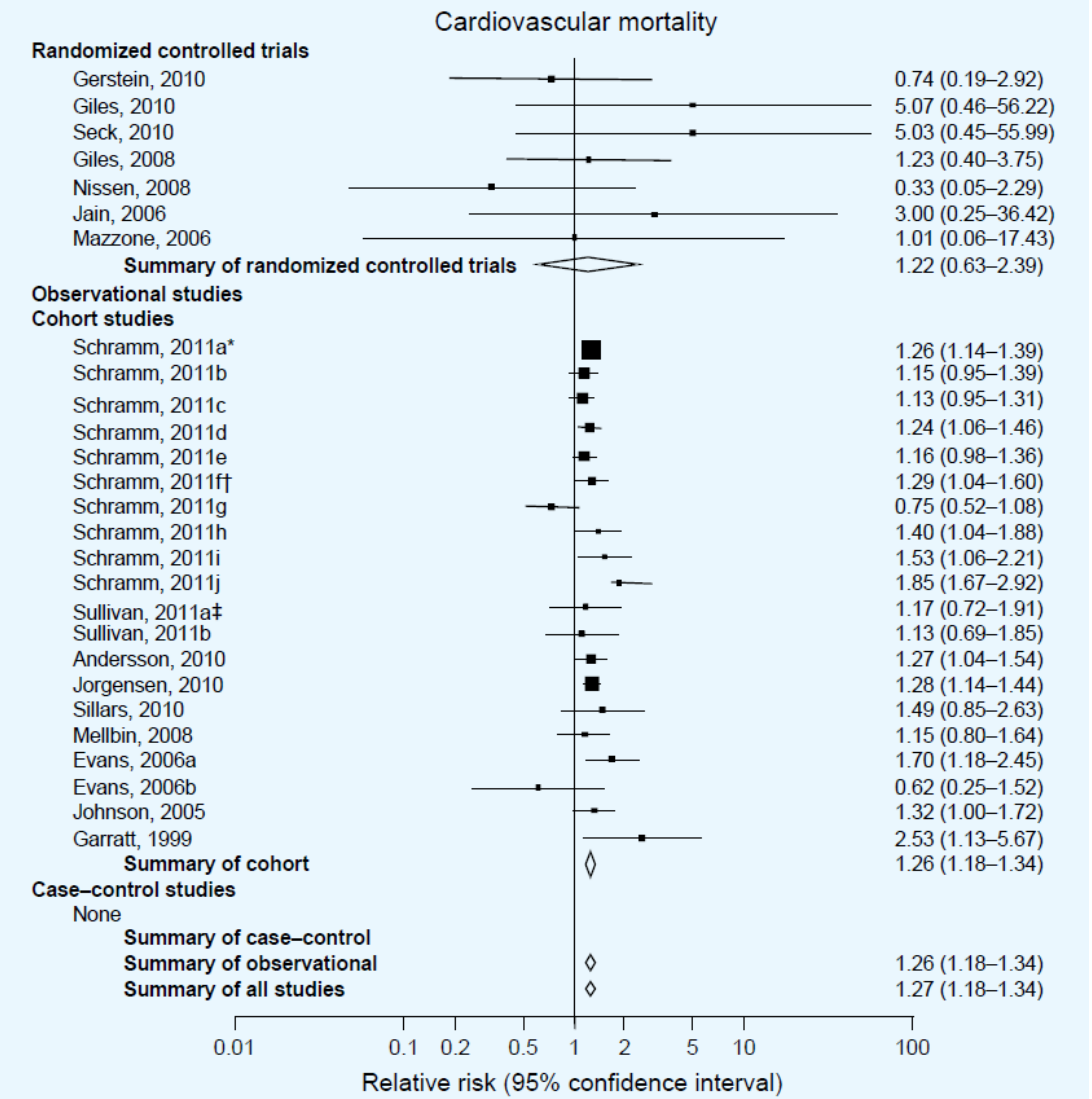
Comparative Effectiveness of Sulfonylurea and Metformin Monotherapy on Cardiovascular Events in Type 2 Diabetes Mellitus

A Cohort Study



Ann Intern Med. 2012;157:601-610.

Sulphonylureas and risk of cardiovascular disease: systematic review and meta-analysis



Meta-analysis results of studies comparing sulphonylureas to non-sulphonylurea on cardiovascular mortality

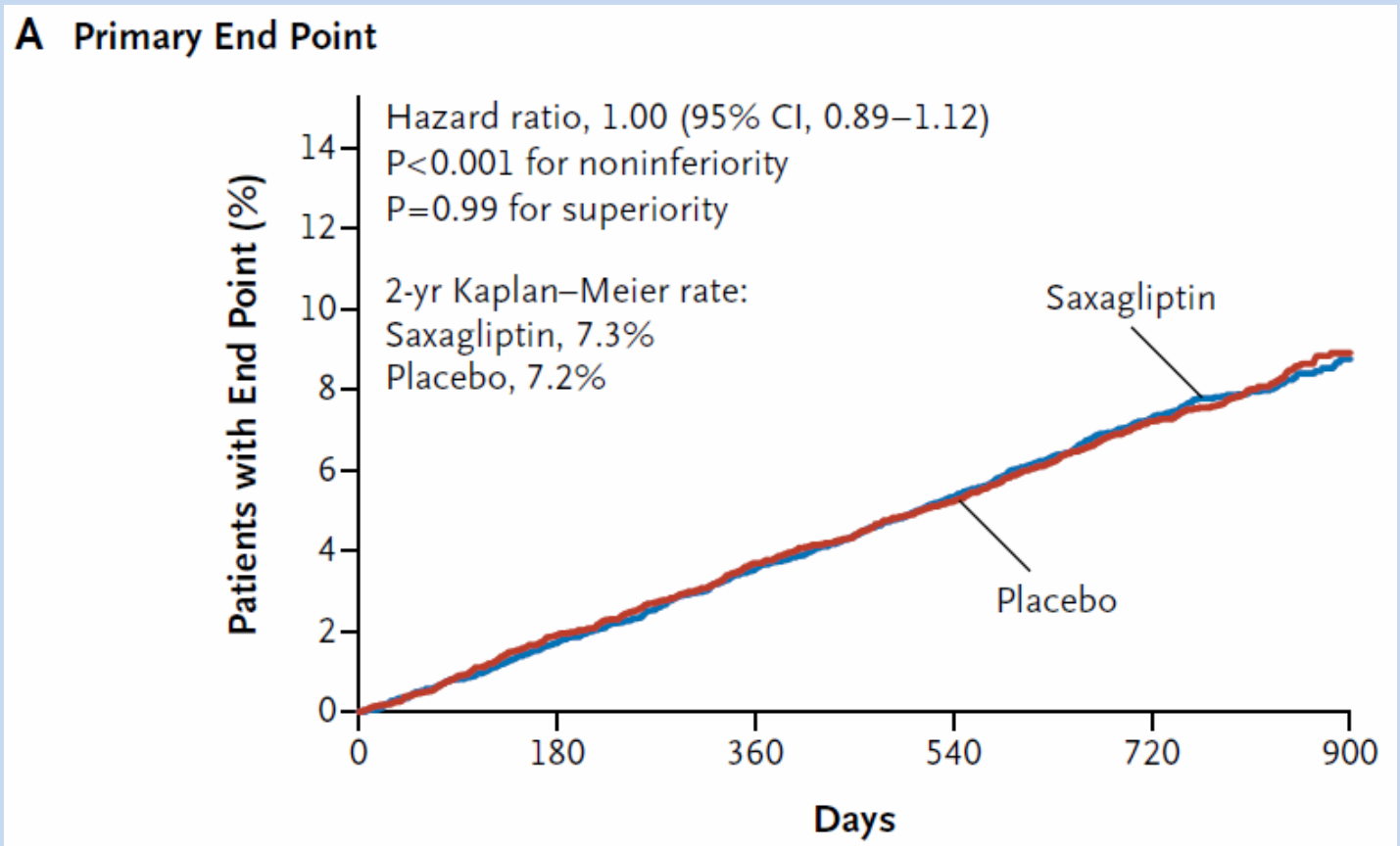
Diabet. Med. 30, 1160–1171 (2013)

Ongoing, prospective clinical trials of DPP-4 inhibitors with cardiovascular outcomes

DPP-4 inhibitor	Trial name	Trial design	Patient characteristics	Primary end point
Alogliptin	EXamination of cArdiovascular outcoMes: alogliptIN vs standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE)[117]	*n* = 5,400 6.25 mg, 12.5 mg, or 25.0 mg vs placebo Superiority trial	HbA1c 6.5–11.0% Acute coronary syndrome 15–90 days before randomization	Time from randomization to the first occurrence of a primary major adverse cardiac event (nonfatal MI, nonfatal stroke, or cardiovascular death)
Linagliptin	CARdiOvascular outcome study of LINAagliptin versus glimepiride in patients with type 2 diabetes (CAROLINA)[118]	*n* = 6,000 5 mg vs glimepiride 1–4 mg Noninferiority and superiority trial	HbA1c 6.5–8.5% High cardiovascular risk	Time to the first occurrence of nonfatal MI, nonfatal stroke, hospitalization for unstable angina, or cardiovascular death
Saxagliptin	Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus (SAVOR-TIMI 53) trial[116]	*n* = 16,500 2.5 mg or 5.0 mg vs placebo Noninferiority and superiority trial	HbA1c ≥6.5% High cardiovascular risk	Time to first confirmed cardiovascular event (nonfatal MI, nonfatal ischaemic stroke, or cardiovascular death)
Sitagliptin	Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)[119]	*n* = 14,000 50 mg or 100 mg vs placebo Noninferiority trial	HbA1c 6.5–8.0% History of cardiovascular disease	Time to first confirmed cardiovascular event (nonfatal MI, nonfatal stroke, or hospitalization for unstable angina)

Scheen, A. J. *Nat. Rev. Cardiol.* **10**, 73–84 (2013)

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus



N Engl J Med 2013;369:1317-26.

ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

Dyslipidaemia in diabetes		
Recommendations	**Class** [a]	**Level** [b]
Statin therapy is recommended in patients with T1DM and T2DM at very high-risk (i.e. if combined with documented CVD, severe CKD or with one or more CV risk factors and/or target organ damage) with an LDL-C target of <1.8 mmol/L (<70 mg/dL) or at least a ≥50% LDL-C reduction if this target goal cannot be reached.	I	A
Statin therapy is recommended in patients with T2DM at high risk (without any other CV risk factor and free of target organ damage) with an LDL-C target of <2.5 mmol/L (<100 mg/dL).	I	A
Statins may be considered in T1DM patients at high risk for cardiovascular events irrespective of the basal LDL-C concentration.	IIb	C
It may be considered to have a secondary goal of non–HDL-C <2.6 mmol/L (<100 mg/dL) in patients with DM at very high risk and of <3.3 mmol/L (<130 mg/dL) in patients at high risk.	IIb	C
Intensification of statin therapy should be considered before the introduction of combination therapy with the addition of ezetimibe.	IIa	C
The use of drugs that increase HDL-C to prevent CVD in T2DM is not recommended.	III	A

European Heart Journal
doi:10.1093/eurheartj/eht108

Standards of Medical Care in Diabetes—2013

Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients:

- With overt CVD (A)
- Without CVD who are over the age of 40 years and have one or more other CVD risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria) (A)

For lower-risk patients than the above (e.g., without overt CVD and under the age of 40 years), statin therapy should be considered in addition to lifestyle therapy if LDL cholesterol remains above 100 mg/dL or in those with multiple CVD risk factors. (C)

In individuals with overt CVD, a lowerLDL cholesterol goal of <70 mg/dL (1.8 mmol/L), using a high dose of a statin, is an option. (B) In individuals without overt CVD, the goal is LDL cholesterol <100 mg/dL (2.6 mmol/L). (B)

If drug-treated patients do not reach the above targets on maximal tolerated statin therapy, a reduction in LDL cholesterol of ~30–40% from baseline is an alternative therapeutic goal. (B)

DIABETES CARE, VOLUME 36, SUPPLEMENT 1, JANUARY 2013

Standards of Medical Care in Diabetes—2013

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

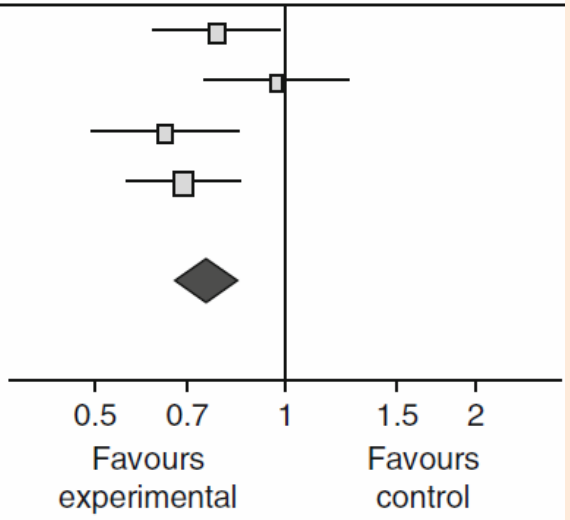
Combination therapy has been shown not to provide additional cardiovascular benefit above statin therapy alone and is not generally recommended. (A)

DIABETES CARE, VOLUME 36, SUPPLEMENT 1, JANUARY 2013

Results for the primary prevention of major cardiovascular and cerebrovascular events wtih statins in diabetic patients

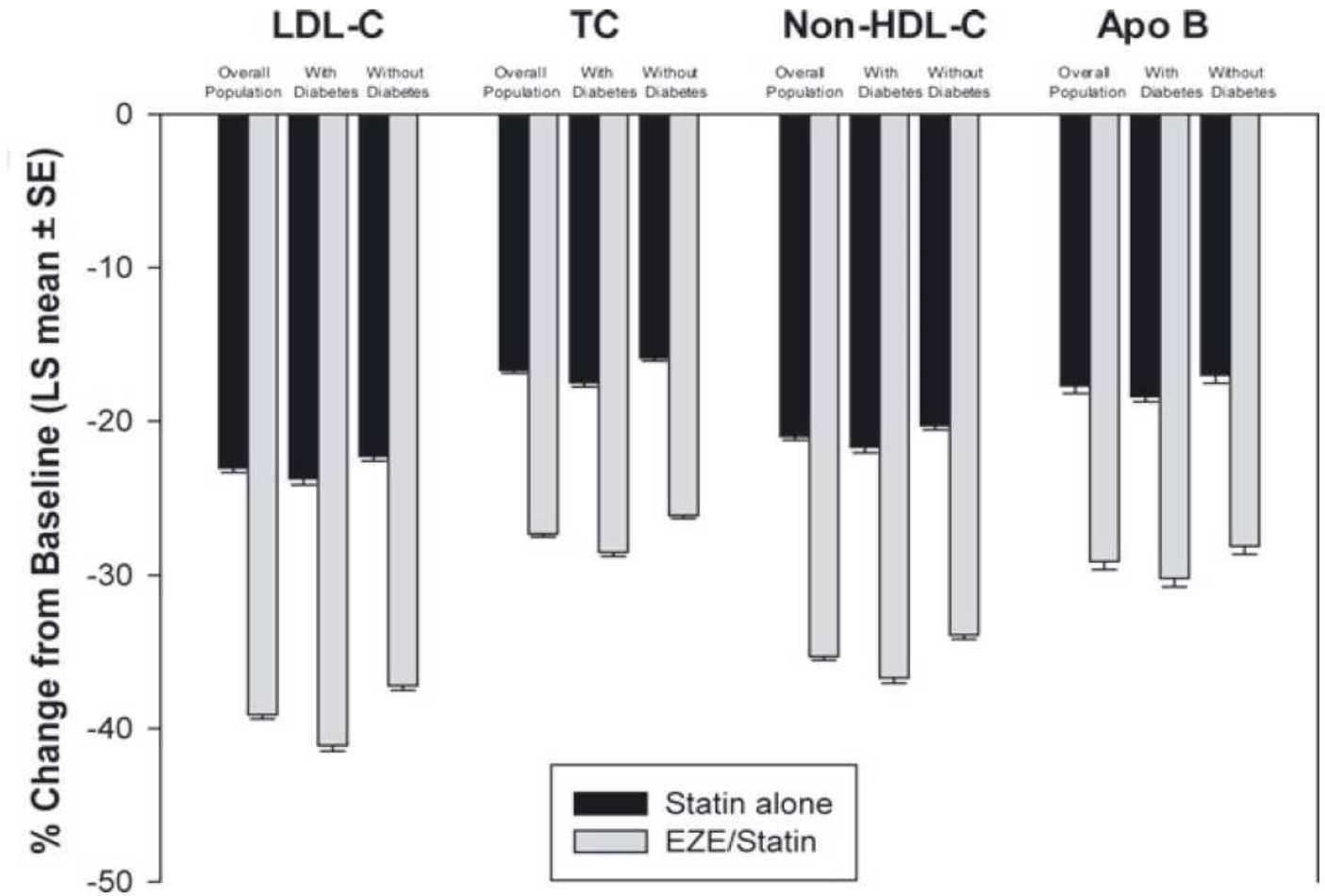
Study or subgroup	Experimental Events	Total	Placebo Events	Total	Weight	Risk ratio M-H, Fixed (95% CI)
ASCOT-LLA 2005	116	1258	151	1274	26.0%	0.78 (0.62–0.98)
ASPEN 2006	100	959	102	946	17.8%	0.97 (0.75–1.26)
CARDS 2004	83	1428	127	1410	22.2%	0.65 (0.49–0.84)
HPS 2003	135	1455	196	1457	34.0%	0.69 (0.56–0.85)
Total (95% CI)		**5100**		**5087**	**100.0%**	**0.75 (0.67, 0.85)**
Total events	434		576			

Heterogeneity: $Chi^2 = 5.59$, $df = 3$ ($p = 0.13$); $I^2 = 46\%$
Test for overall effect: $Z = 4.72$ ($p < 0.00001$)



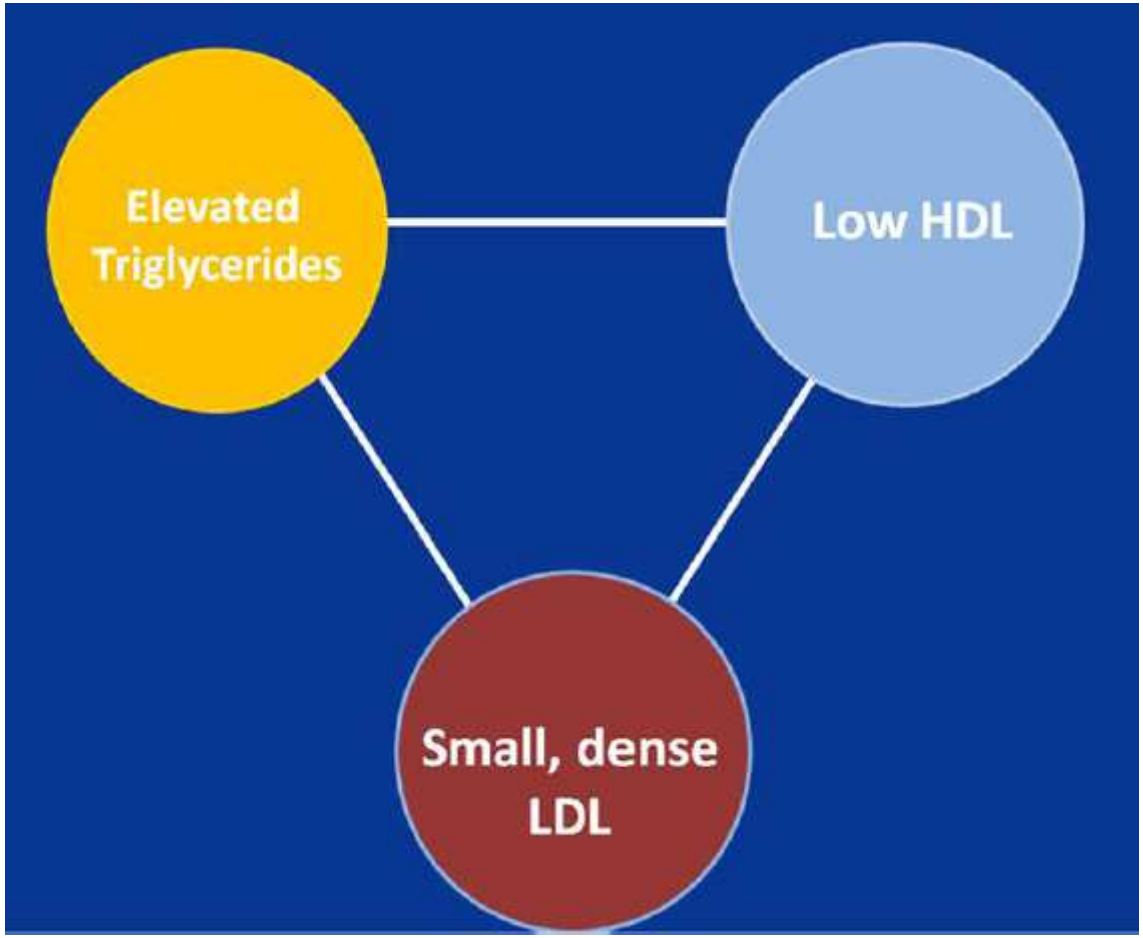
Drugs 2012; 72 (18): 2365-2373

Lipid-altering efficacy and safety profile of combination therapy with ezetimibe/statin vs. statin monotherapy in patients with and without diabetes: an analysis of pooled data from 27 clinical trials



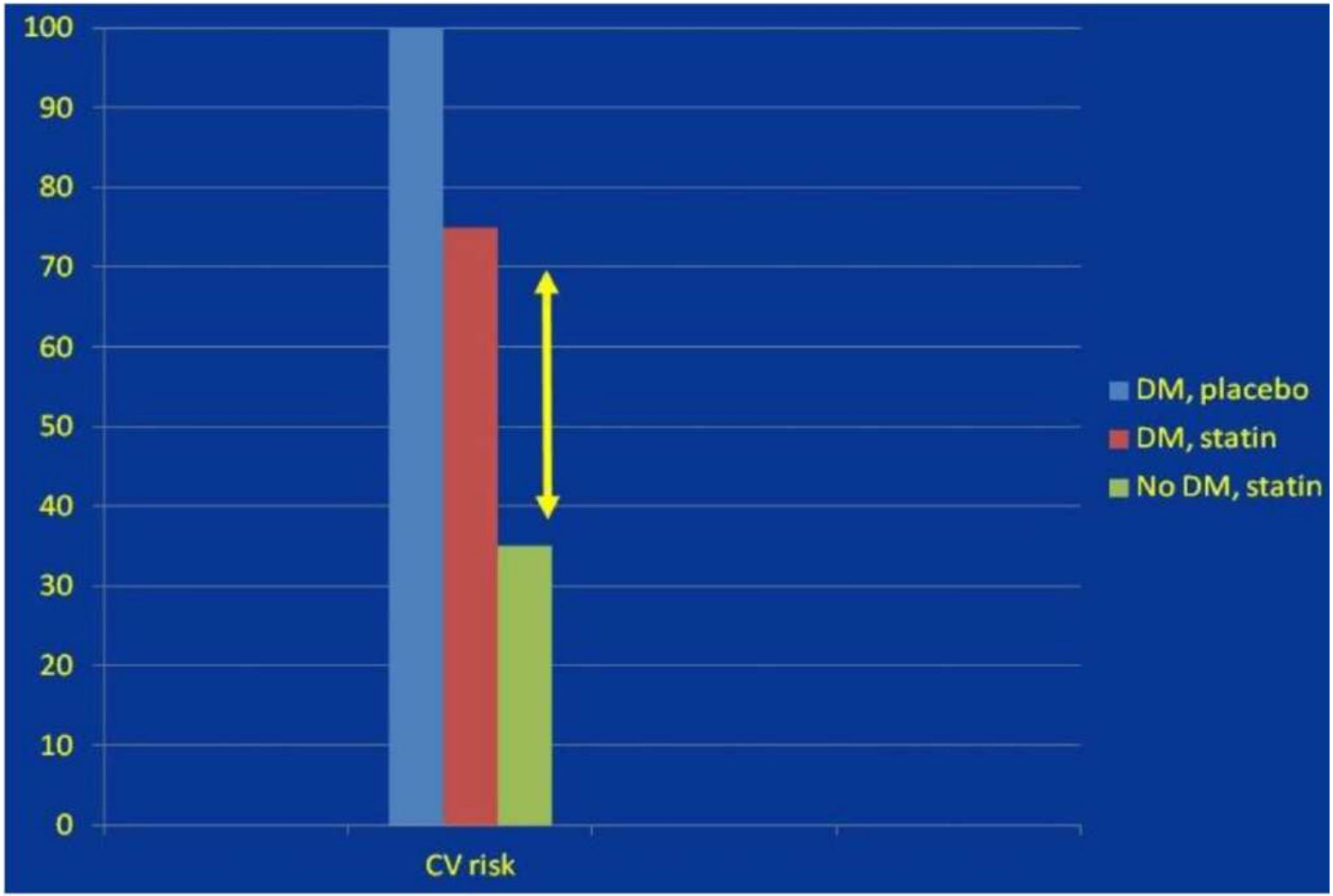
Diabetes, Obesity and Metabolism 13: 615–628, 2011.

Atherogenic dyslipidemia: typical lipid profile of patients with type 2 diabetes



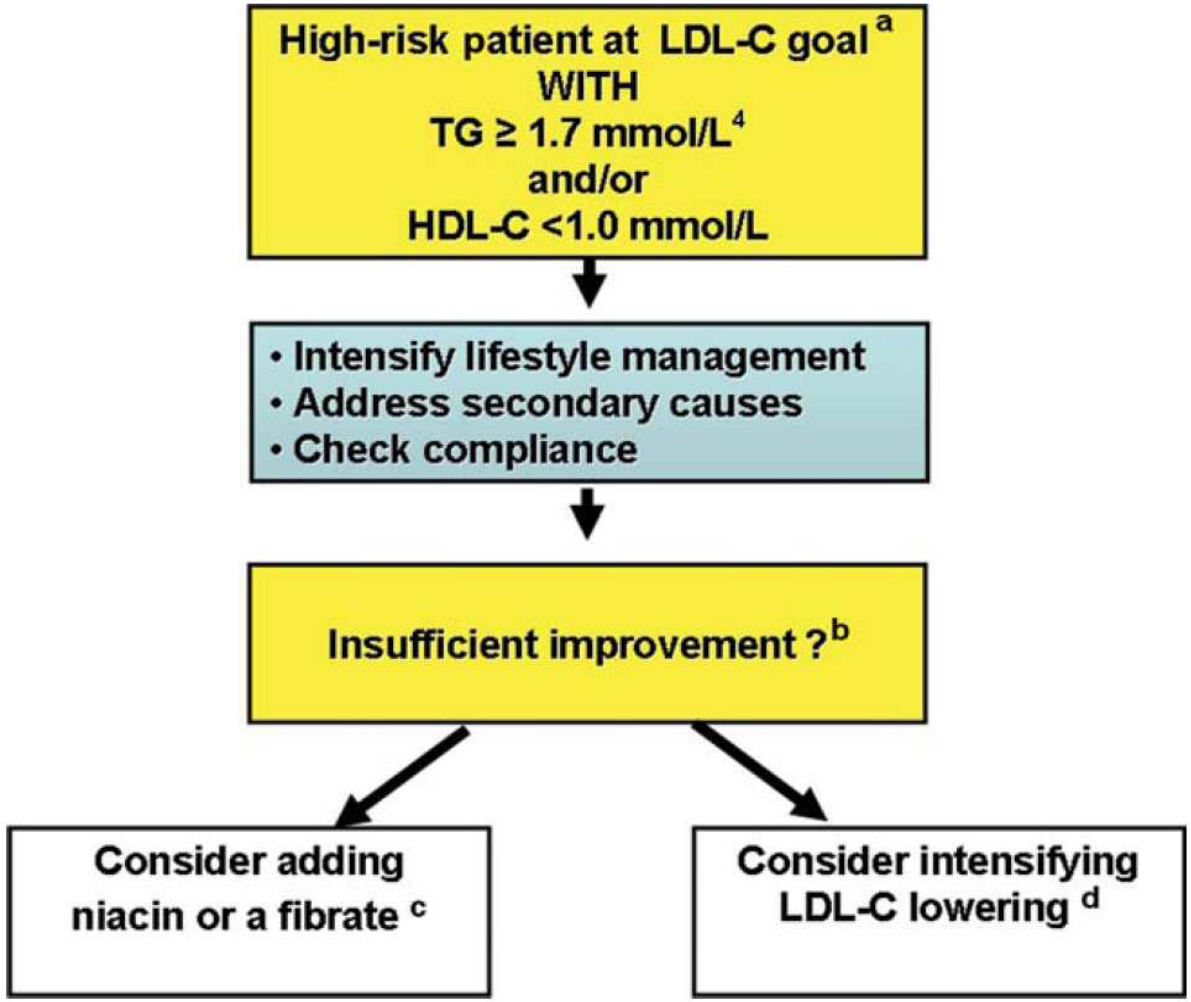
Cardiovascular Diabetology 2012, **11**:125

Residual risk in people with type 2 diabetes and atherogenic dyslipidemia



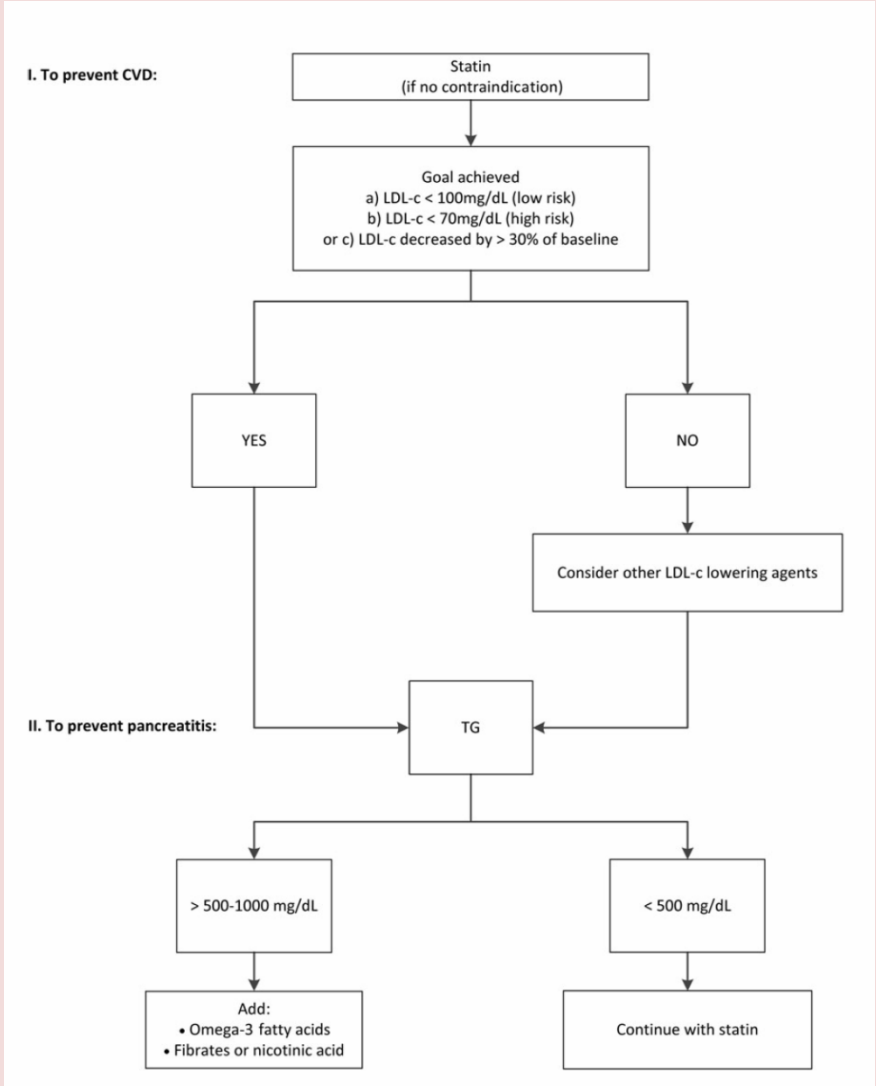
Cardiovascular Diabetology 2012, **11**:125

TRIGLYCERIDE-RICH LIPOPROTEINS AND HIGH-DENSITY LIPOPROTEIN CHOLESTEROL IN PATIENTS AT HIGH RISK OF CARDIOVASCULAR DISEASE: EVIDENCE AND GUIDANCE FOR MANAGEMENT



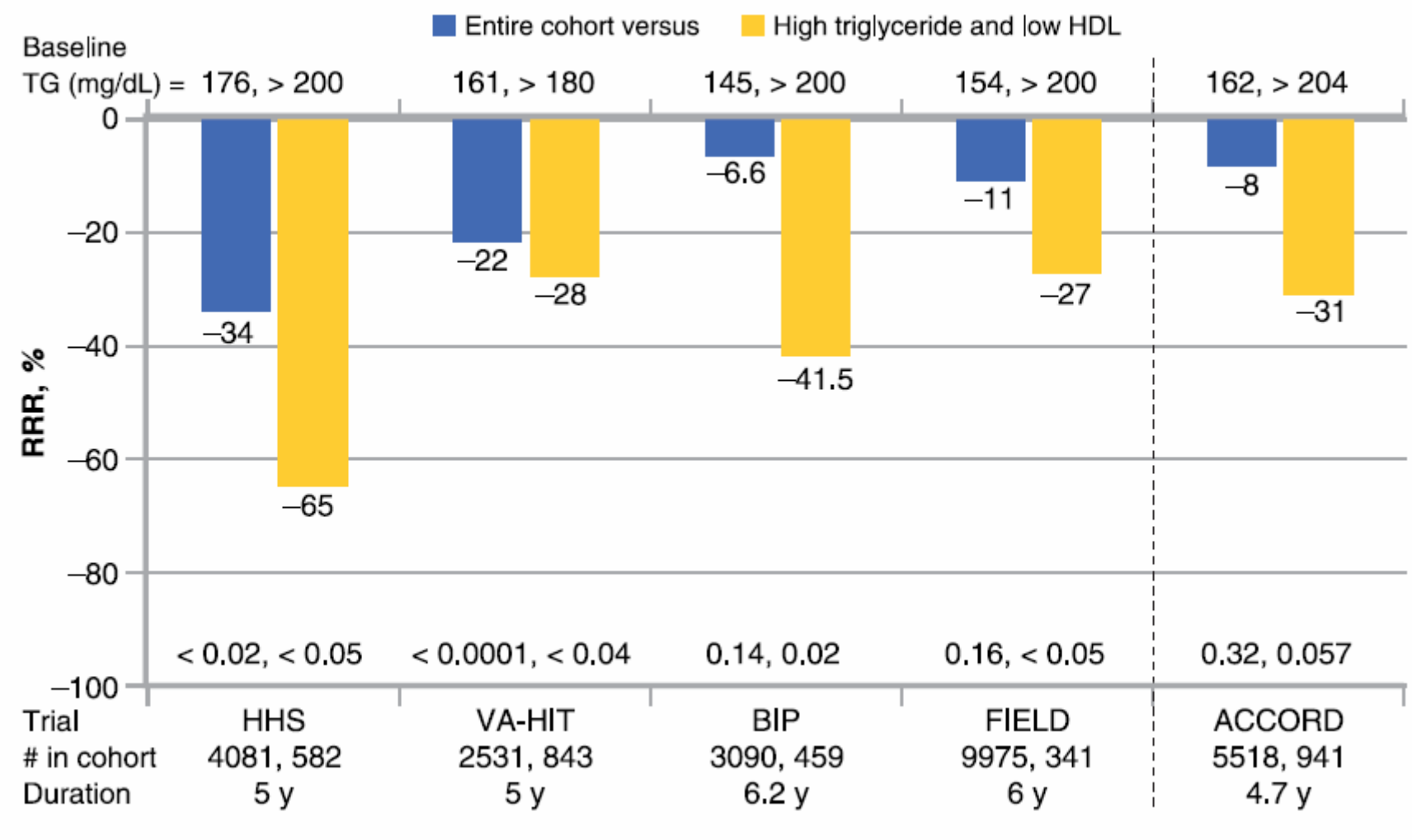
European Heart Journal (2011) **32**, 1345–1361

Evidence-based algorithm from drug therapy of dyslipidemia in patients with diabetes mellitus



Drugs (2013) 73:327–339

Cardiovascular event risk reduction in large monotherapy fibrate clinical trials, relative to the ACCORD study



Curr Cardiol Rep (2012) 14:112–124

ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

Blood pressure control in diabetes		
Recommendations	**Class** [a]	**Level** [b]
Blood pressure control is recommended in patients with DM and hypertension to lower the risk of cardiovascular events.	I	A
It is recommended that a patient with hypertension and DM is treated in an individualized manner, targeting a blood pressure of <140/85 mmHg.	I	A
It is recommended that a combination of blood pressure lowering agents is used to achieve blood pressure control.	I	A
A RAAS blocker (ACE-I or ARB) is recommended in the treatment of hypertension in DM, particularly in the presence of proteinuria or micro-albuminuria.	I	A
Simultaneous administration of two RAAS blockers should be avoided in patients with DM.	III	B

European Heart Journal
doi:10.1093/eurheartj/eht108

Standards of Medical Care in Diabetes—2013

Hypertension

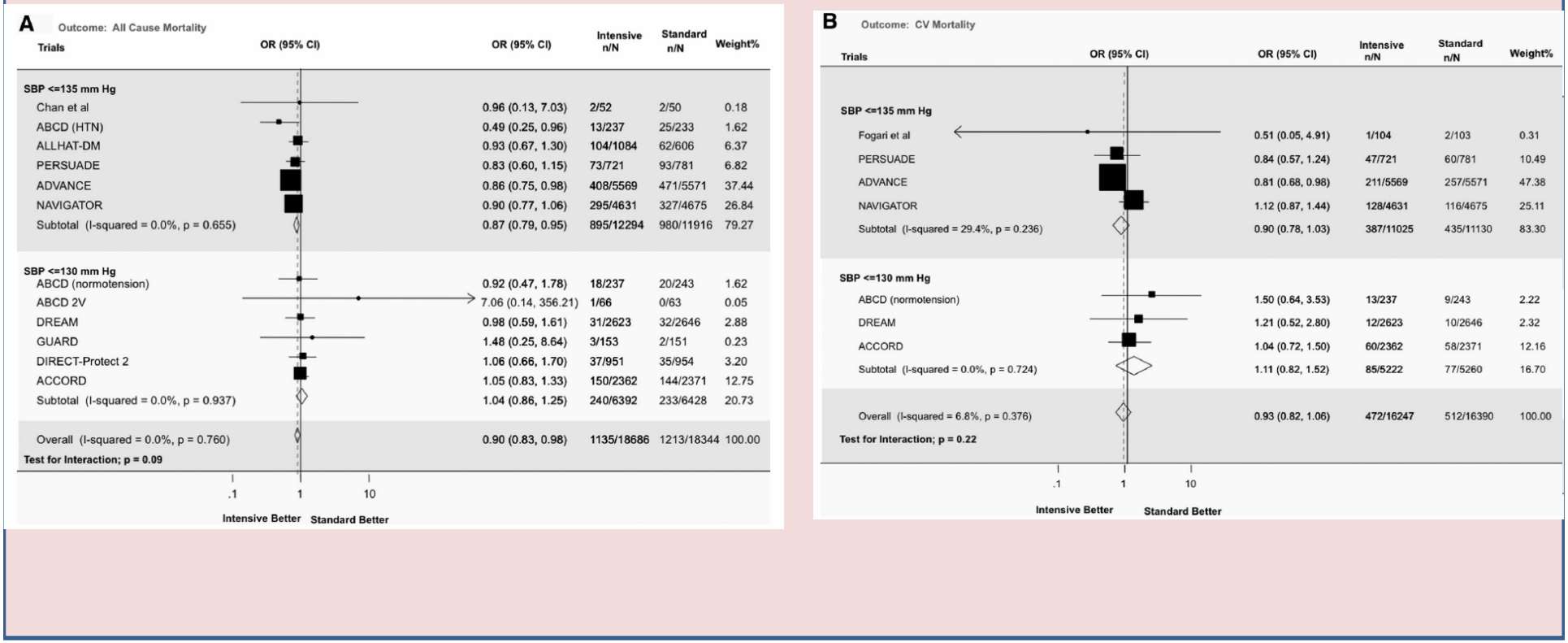
People with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg. (B)

Lower systolic targets, such as <130mmHg, may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden. (C)

Patients with diabetes should be treated to a diastolic blood pressure <80 mmHg.(B)

Blood Pressure Targets in Subjects With Type 2 Diabetes Mellitus/Impaired Fasting Glucose

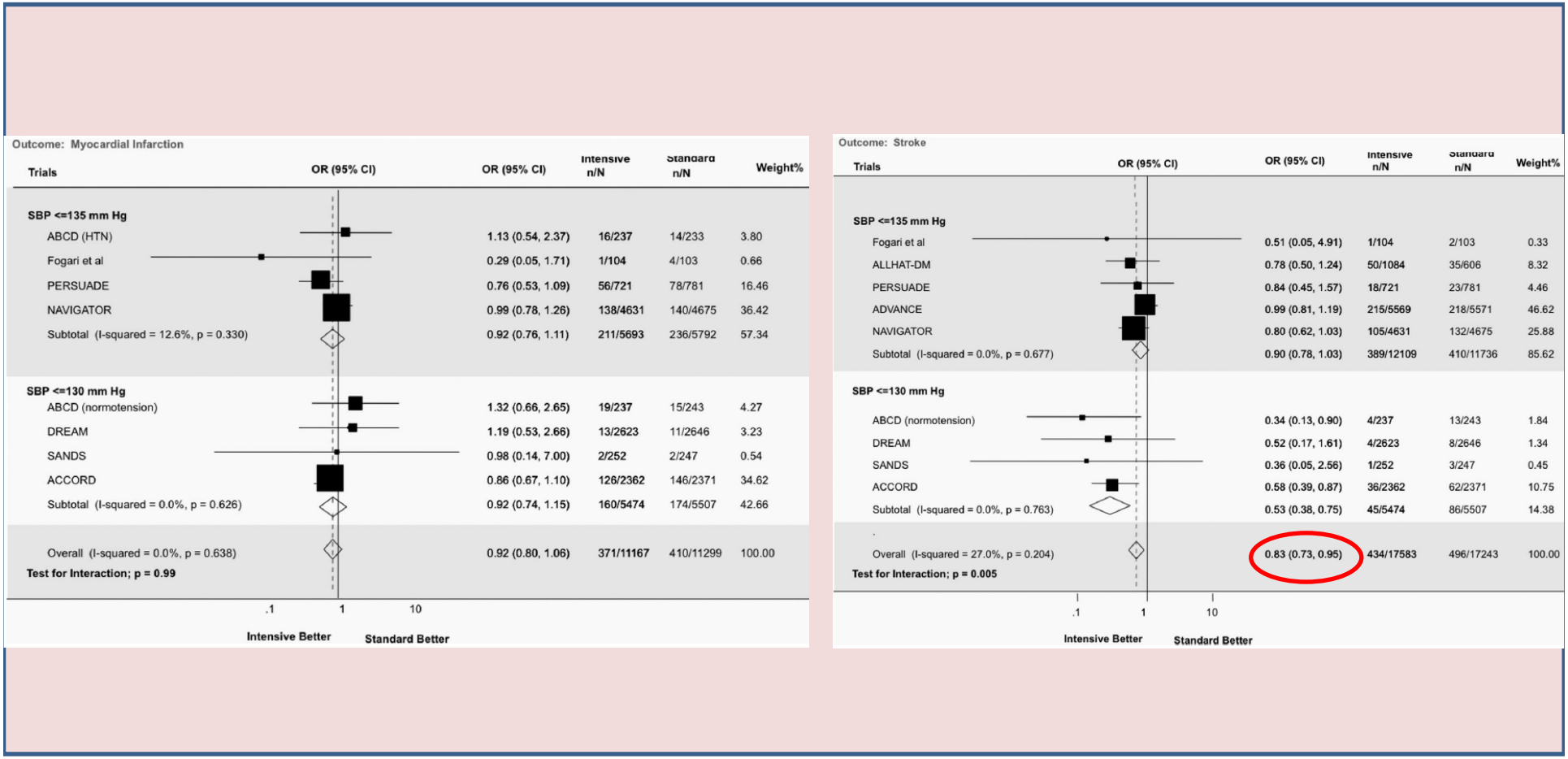
Observations From Traditional and Bayesian Random-Effects Meta-Analyses of Randomized Trials



Circulation. 2011;123:2799-2810.

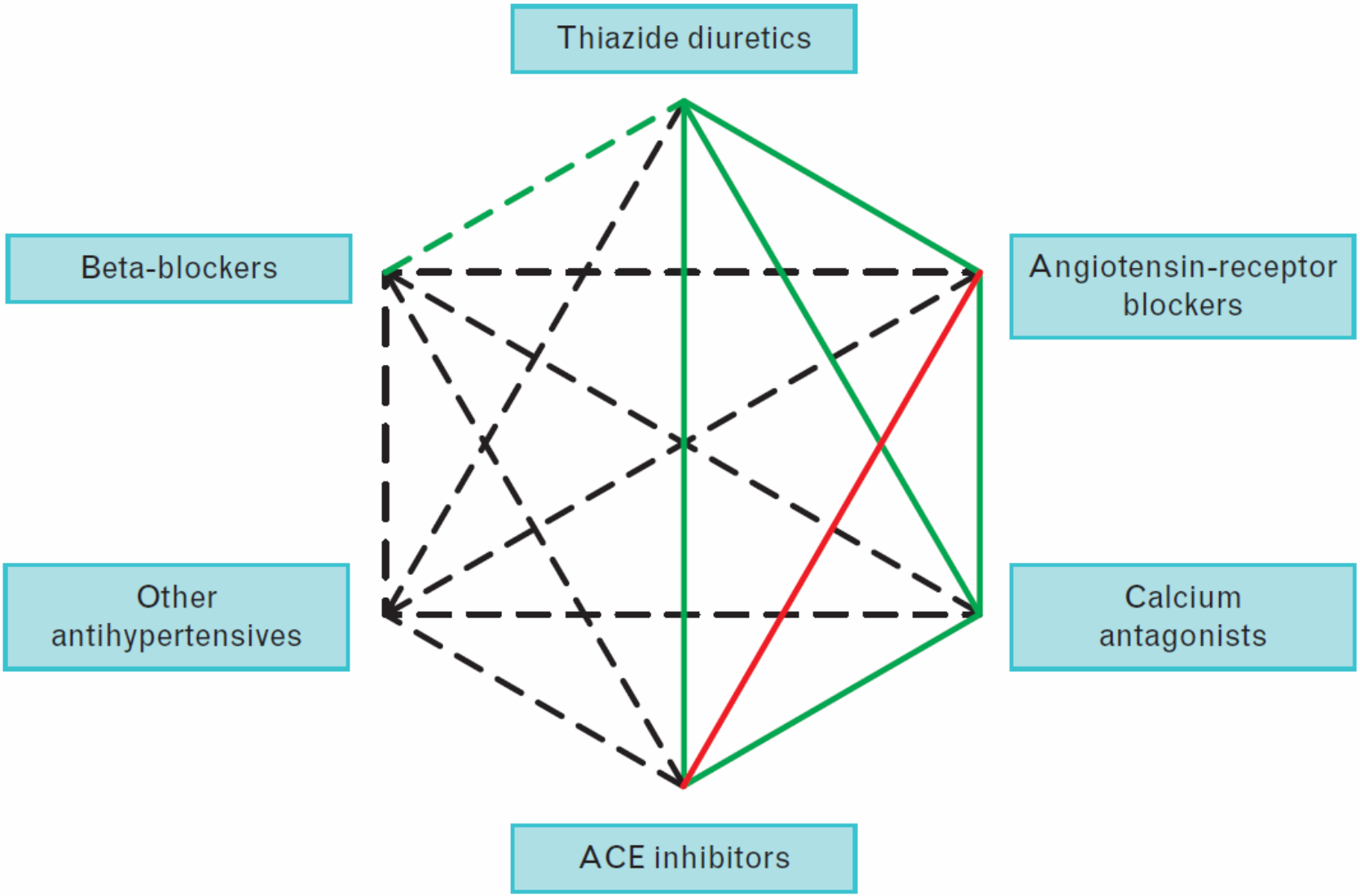
Blood Pressure Targets in Subjects With Type 2 Diabetes Mellitus/Impaired Fasting Glucose

Observations From Traditional and Bayesian Random-Effects Meta-Analyses of Randomized Trials



Circulation. 2011;123:2799-2810.

Possible combinations of classes of antihypertensive drugs



Journal of Hypertension 2013, 31:1281–1357

ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

Antiplatelet therapy in patients with diabetes		
Recommendations	**Class** [a]	**Level** [b]
Antiplatelet therapy with aspirin in DM-patients at low CVD risk is not recommended.	III	A
Antiplatelet therapy for primary prevention may be considered in high risk patients with DM on an individual basis.	IIb	C
Aspirin at a dose of 75–160 mg/day is recommended as secondary prevention in DM.	I	A
A $P2Y_{12}$ receptor blocker is recommended in patients with DM and ACS for 1 year and in those subjected to PCI (duration depending on stent type). In patients with PCI for ACS preferably prasugrel or ticagrelor should be given.	I	A
Clopidogrel is recommended as an alternative antiplatelet therapy in case of aspirin intolerance.	I	B

European Heart Journal
doi:10.1093/eurheartj/eht108

Aspirin for Primary Prevention of Cardiovascular Events in People With Diabetes

A Position Statement of the American Diabetes Association, a Scientific Statement of the American Heart Association, and an Expert Consensus Document of the American College of Cardiology Foundation

-Consider aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk >10%). This includes most men aged >50 years or women aged >60 years who have at least one additional major risk factor (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). (C)

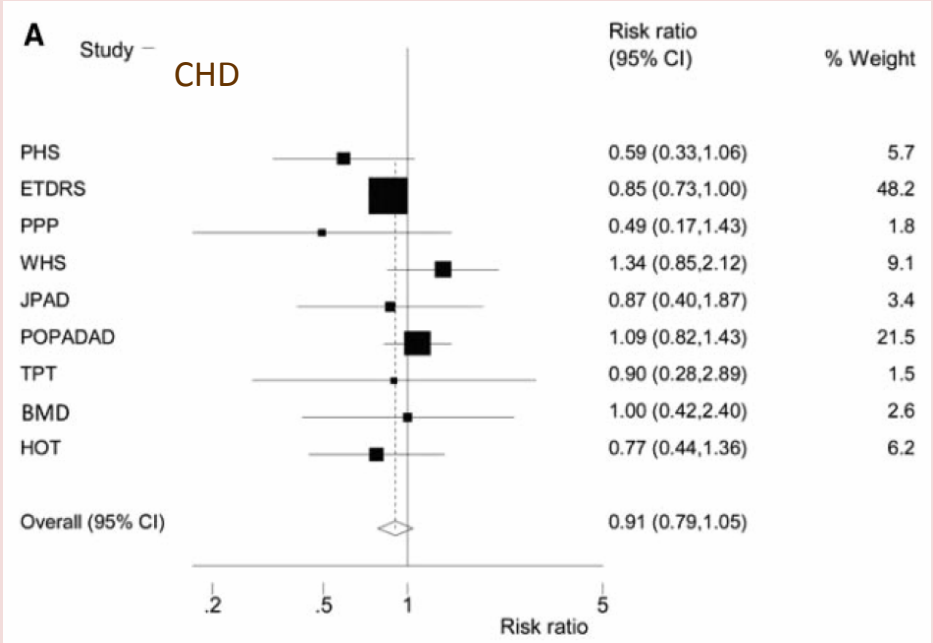
-Aspirin should not be recommended for CVD prevention for adults with diabetes at low CVD risk (10-year CVD risk <5%, such as in men aged <50 years and women aged <60 years with no major additional CVD risk factors), since the potential adverse effects from bleeding likely offset the potential benefits. (C)

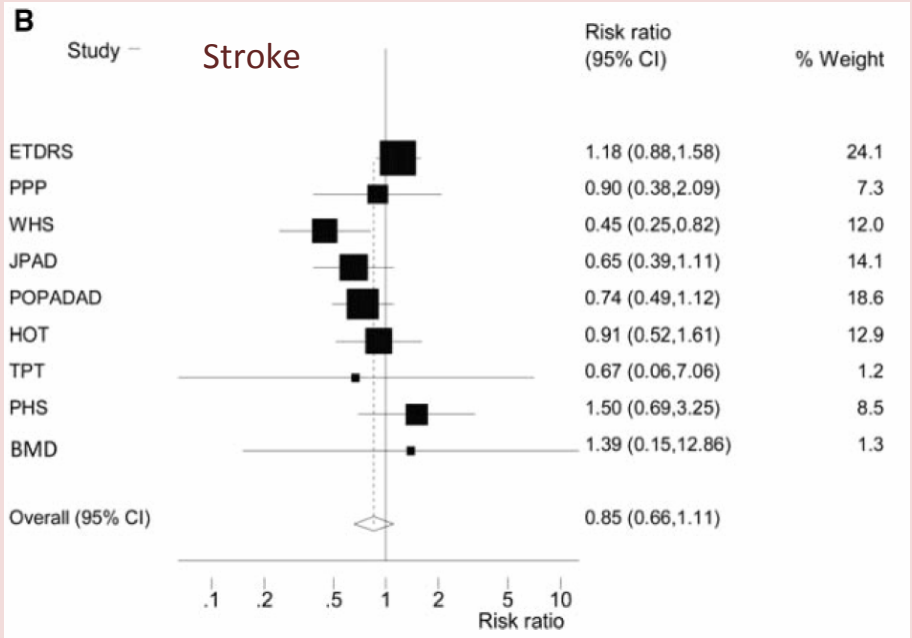
-In patients in these age-groups with multiple other risk factors (e.g., 10-year risk 5–10%), clinical judgment is required. (E)

Circulation. 2010;121:2694-2701

Aspirin for Primary Prevention of Cardiovascular Events in People With Diabetes

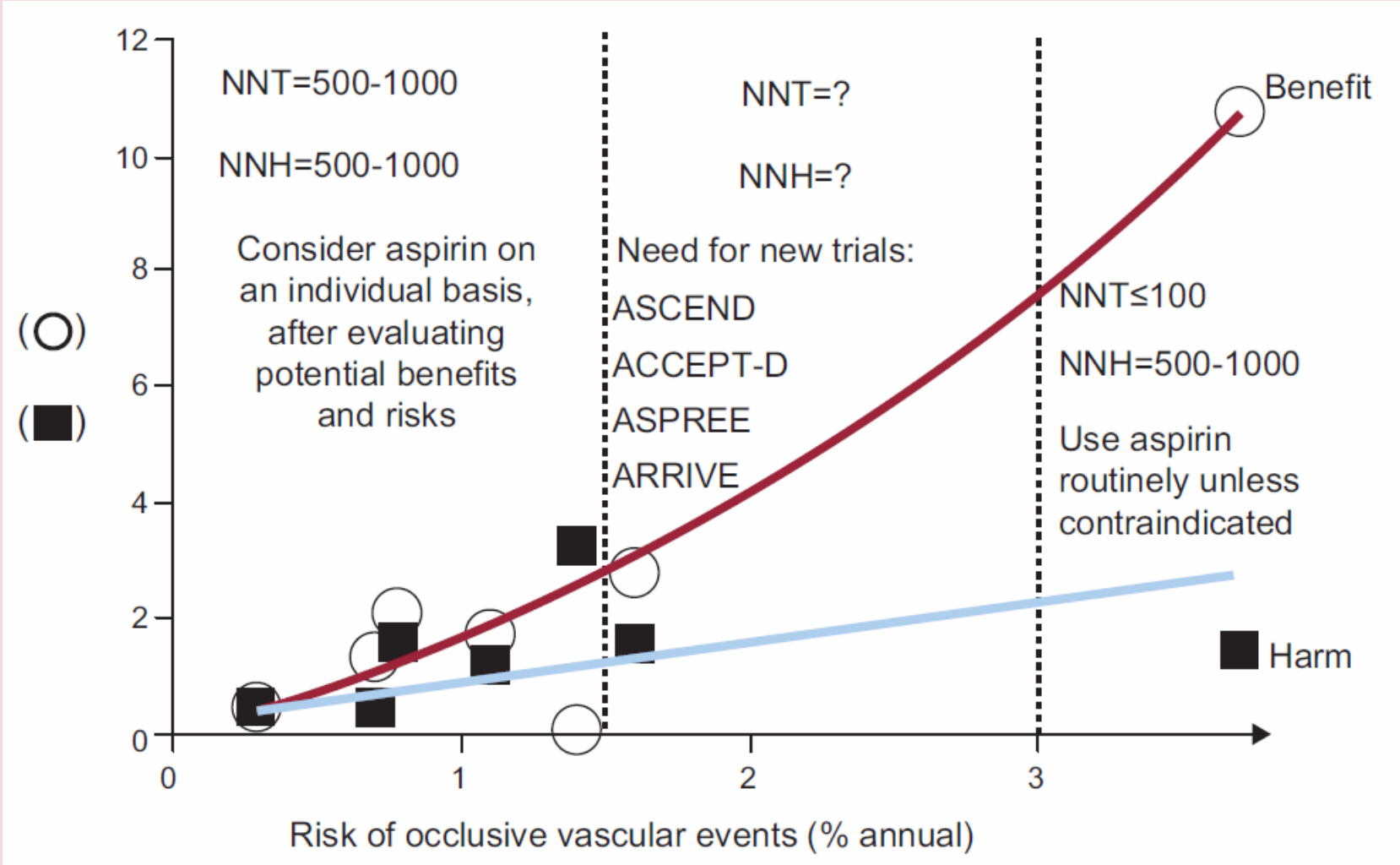
A Position Statement of the American Diabetes Association, a Scientific Statement of the American Heart Association, and an Expert Consensus Document of the American College of Cardiology Foundation





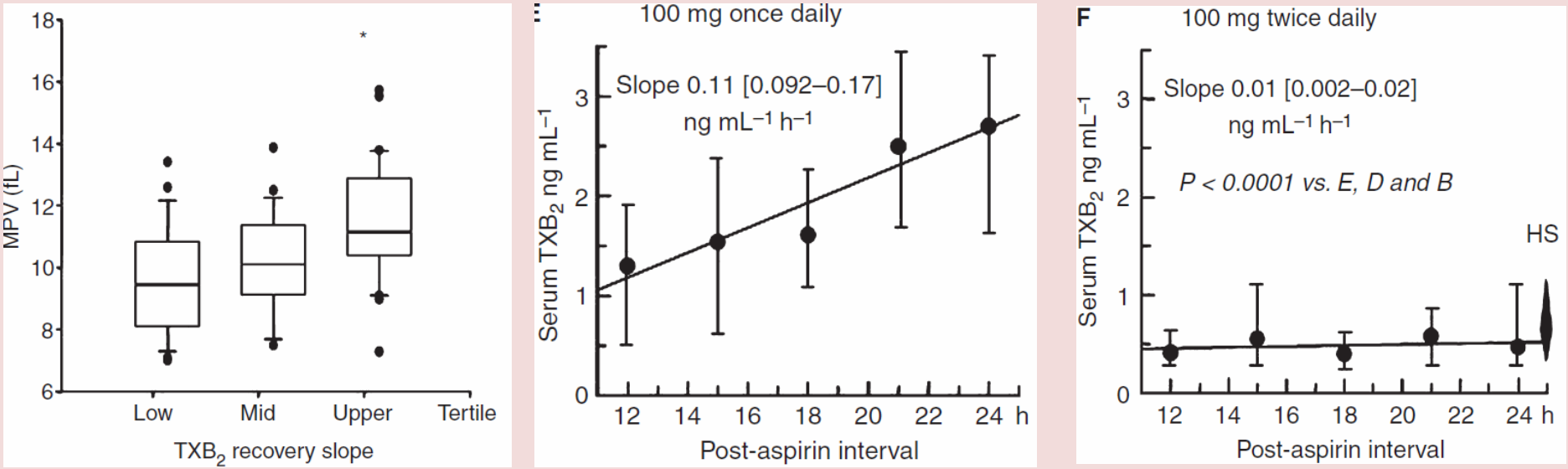
Circulation. 2010;121:2694-2701

Benefits and risks of low-dose aspirin in primary-prevention trials

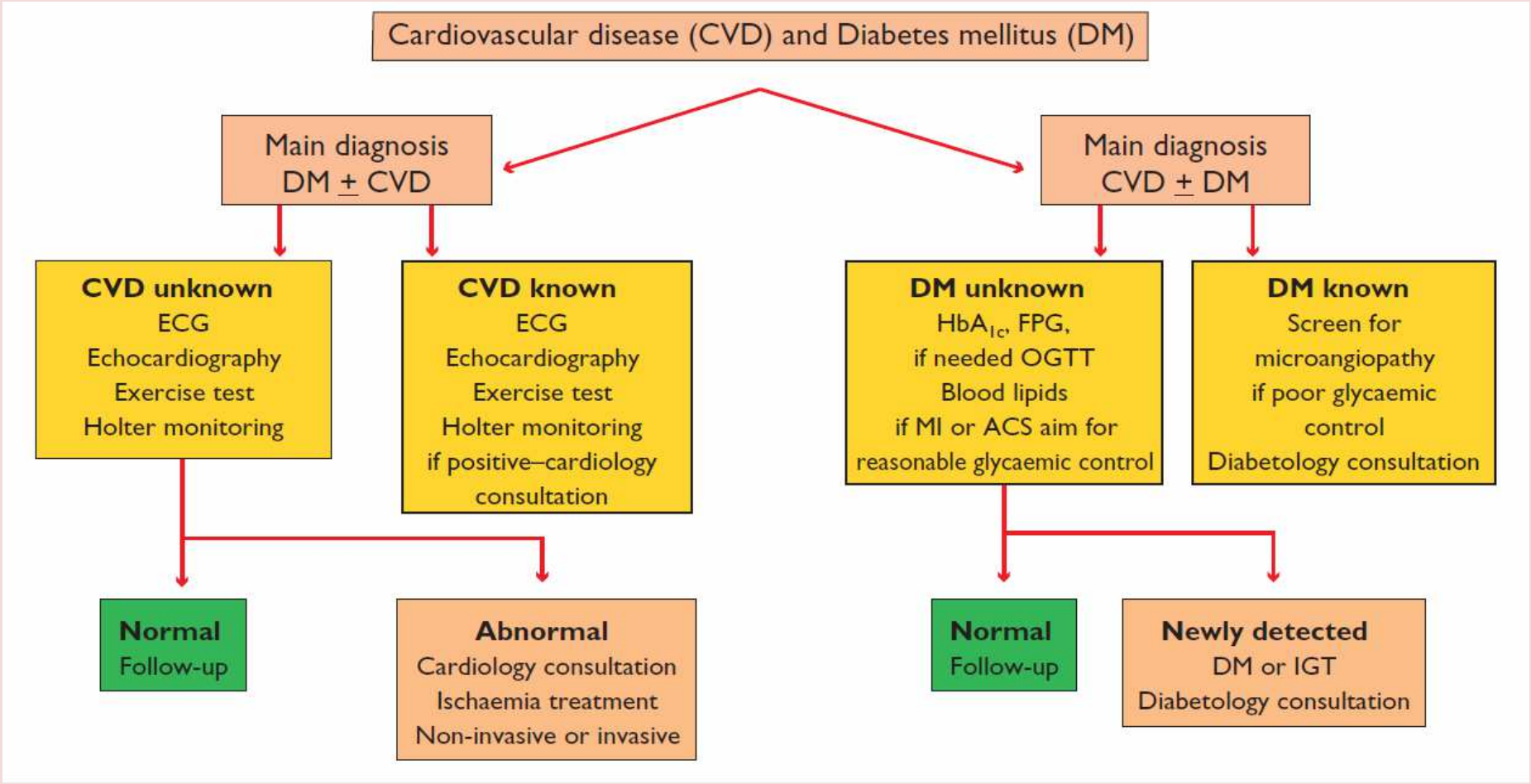


C. Patrono / Rev Esp Cardiol. 2013;66(4):251–254

The recovery of platelet cyclooxygenase activity explains interindividual variability in responsiveness to low-dose aspirin in patients with and without diabetes



ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD



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