IL PESO DELLA GLICEMIA
DIABETE E OBESITÀ TRA RISCHIO CARDIO-RENALE, EPATICO E NEUROLOGICO

Trattamento multifattoriale: dallo Steno 2 ai giorni nostri

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Unità di Diabetologia, Endocrinologia e Malattie Metaboliche

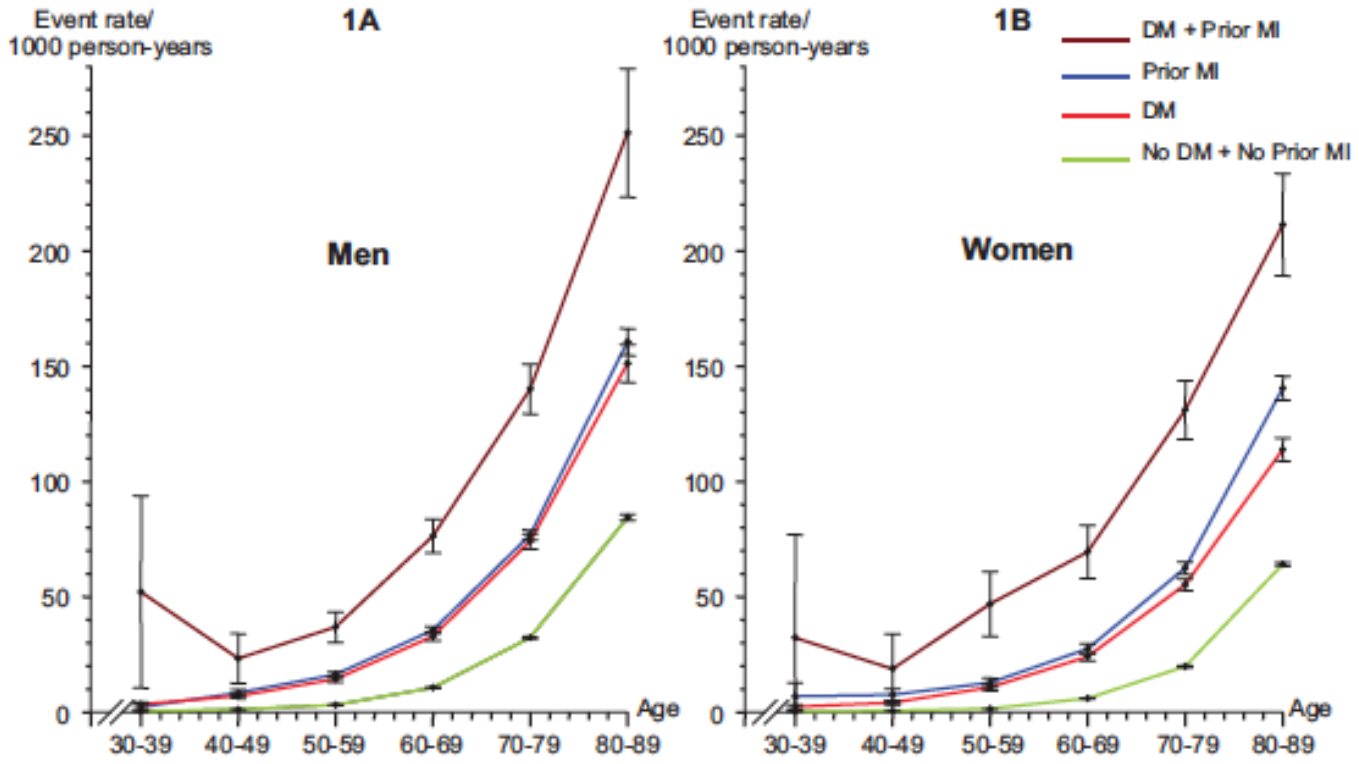
Centro Cardiologico Monzino

Dichiarazione di conflitti di interesse

Stefano Genovese, dichiara di avere ricevuto negli ultimi 2 anni onorari per conferenze e/o consulenze dalle seguenti aziende portatrici di interesse in ambito sanitario:

- Abbott Diabetes Care
- AstraZeneca
- Boehringer Ingelheim
- Daichi Sankyo
- Eli Lilly
- Hikma Pharmaceuticals
- MSD
- Molteni Farmaceutici
- Neopharmed Gentili
- Novo Nordisk
- Sanofi
- SiBionics

Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior MI carry the same cardiovascular risk



Schramm TK eta al. Circulation. 2008;117:1945-1954

Cardiovascular risk categories in patients with diabetes

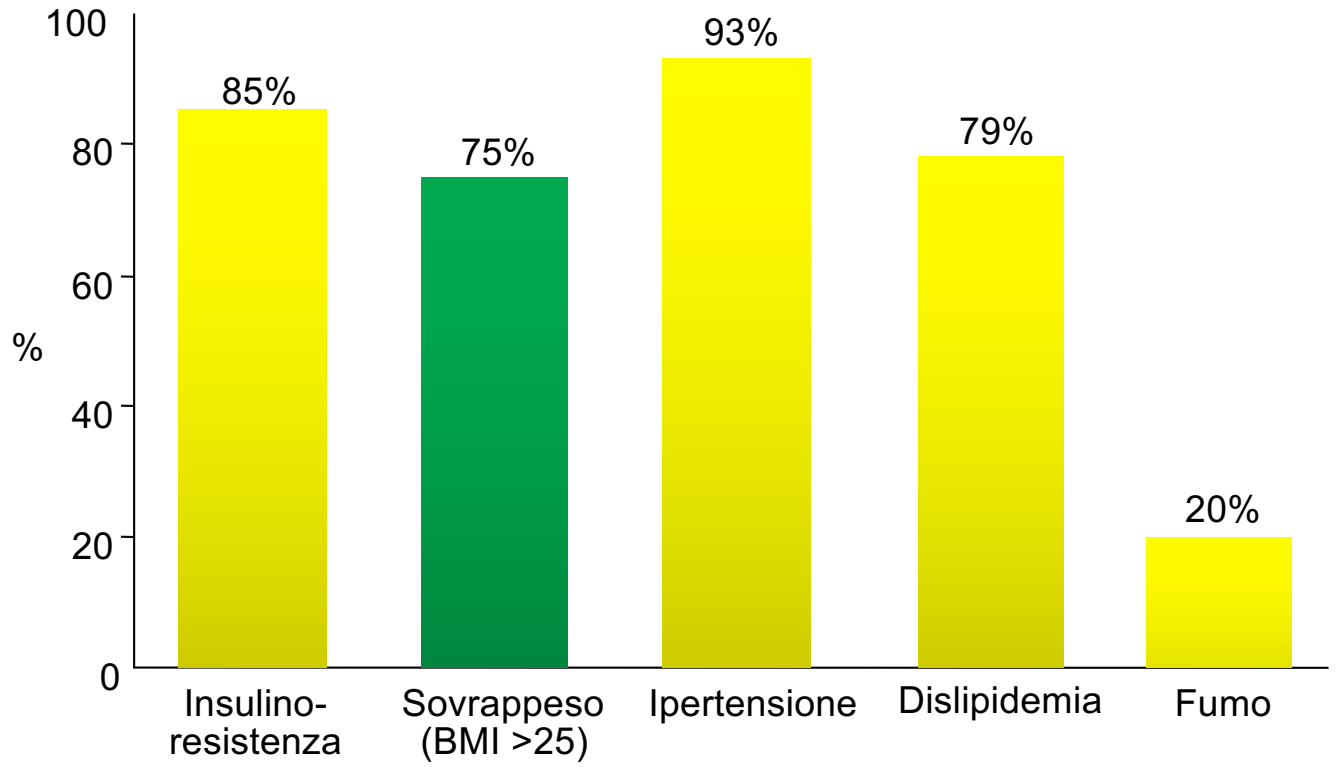
Very high CV risk	Patients with T2DM with: • Clinically established ASCVD or • Severe TOD or • 10-year CVD risk ≥20% using SCORE2-Diabetes
High CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk 10 to <20% using SCORE2-Diabetes
Moderate CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk 5 to <10% using SCORE2-Diabetes
Low CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk <5% using SCORE2-Diabetes

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; SCORE2-Diabetes, type 2 diabetes-specific 10-year CVD risk score; T2DM, type 2 diabetes mellitus; TOD, target-organ damage; UACR, urinary albumin-to-creatinine ratio.
Severe TOD defined as eGFR <45 mL/min/1.73 m^2 irrespective of albuminuria; or eGFR 45–59 mL/min/1.73 m^2 and microalbuminuria (UACR 30–300 mg/g; stage A2); or proteinuria (UACR >300 mg/g; stage A3); or presence of microvascular disease in at least three different sites [e.g. microalbuminuria (stage A2) plus retinopathy plus neuropathy].[43–45]

Eur Heart J. 2023 Oct 14;44(39):4043-4140

Prevalenza di fattori di rischio non glicemici nel diabete mellito di tipo 2

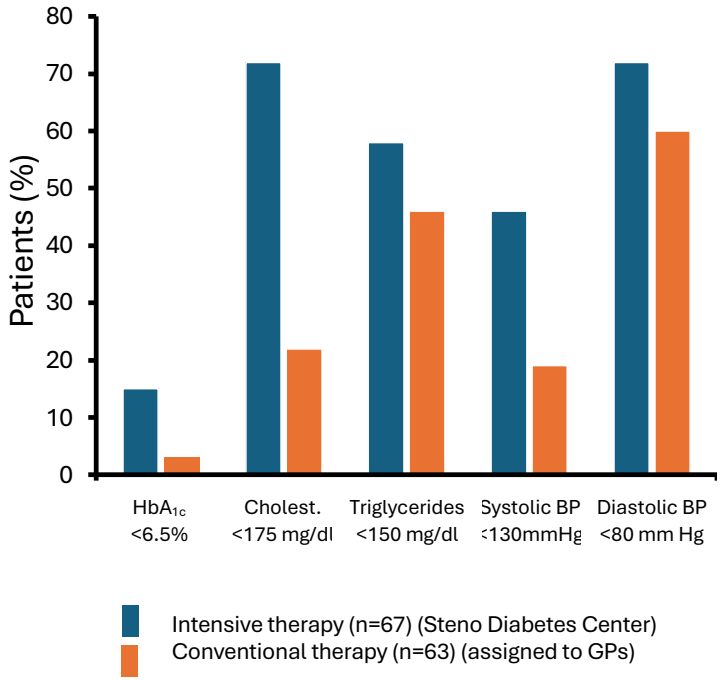
Verona NIDDM Complication Study



Multifactorial Intervention in T2DM

Steno-2: A prospective, randomised, open, blinded endpoint study of patients with T2DM and microalbuminuria

Percentage of patients who achieved intensive-treatment goals in each group at 7.8 years



BP, blood pressure; CV, cardiovascular; GP, general practitioner; MI, myocardial infarction; T2DM, Type 2 diabetes mellitus

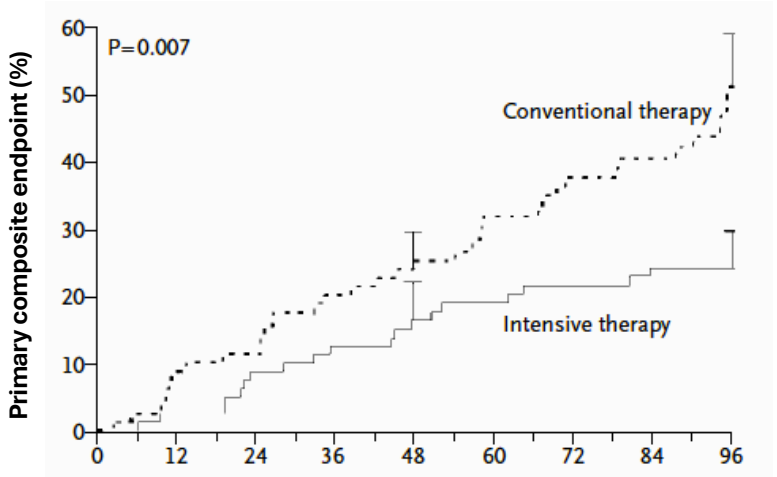
Gaede P, et al. *N Engl J Med* 2008;348:383–393

Multifactorial Intervention in T2DM

Steno-2: A prospective, randomised, open, blinded endpoint study of patients with T2DM and microalbuminuria

Primary composite endpoint:

- Death from CV causes
- Non-fatal MI
- Non-fatal stroke
- Coronary artery bypass
- Grafting
- Percutaneous coronary intervention
- Amputation
- Surgery for peripheral atherosclerotic artery disease

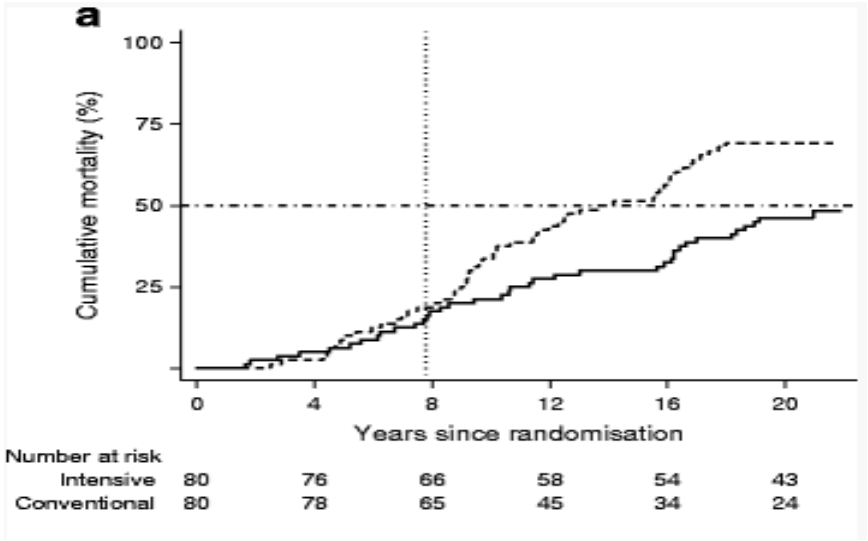


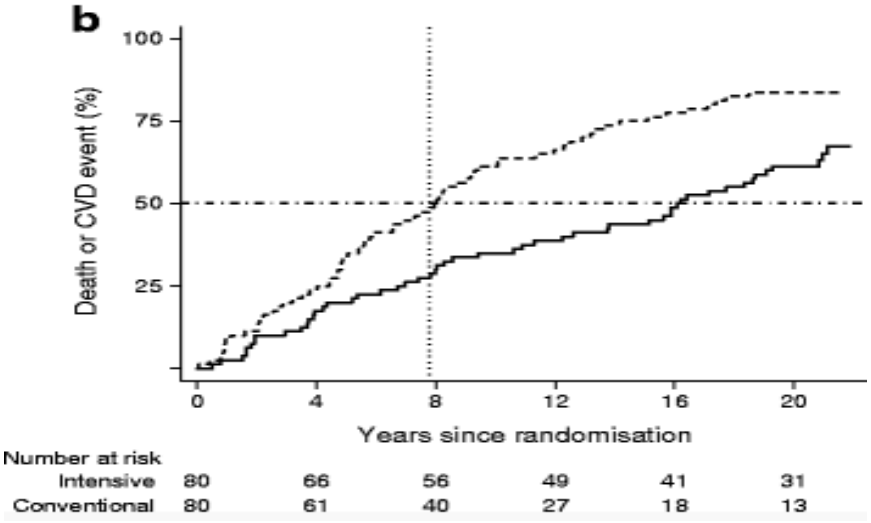
Number at risk:	Months of follow up								
Intensive therapy	80	78	74	71	66	63	61	59	19
Conventional therapy	80	72	71	63	59	50	44	41	13

BP, blood pressure; CV, cardiovascular; MI, myocardial infarction; T2DM, Type 2 diabetes mellitus

Gaede P, et al. *N Engl J Med* 2008;348:383–393

STENO-2: Years of Life Gained by Multifactorial Intervention





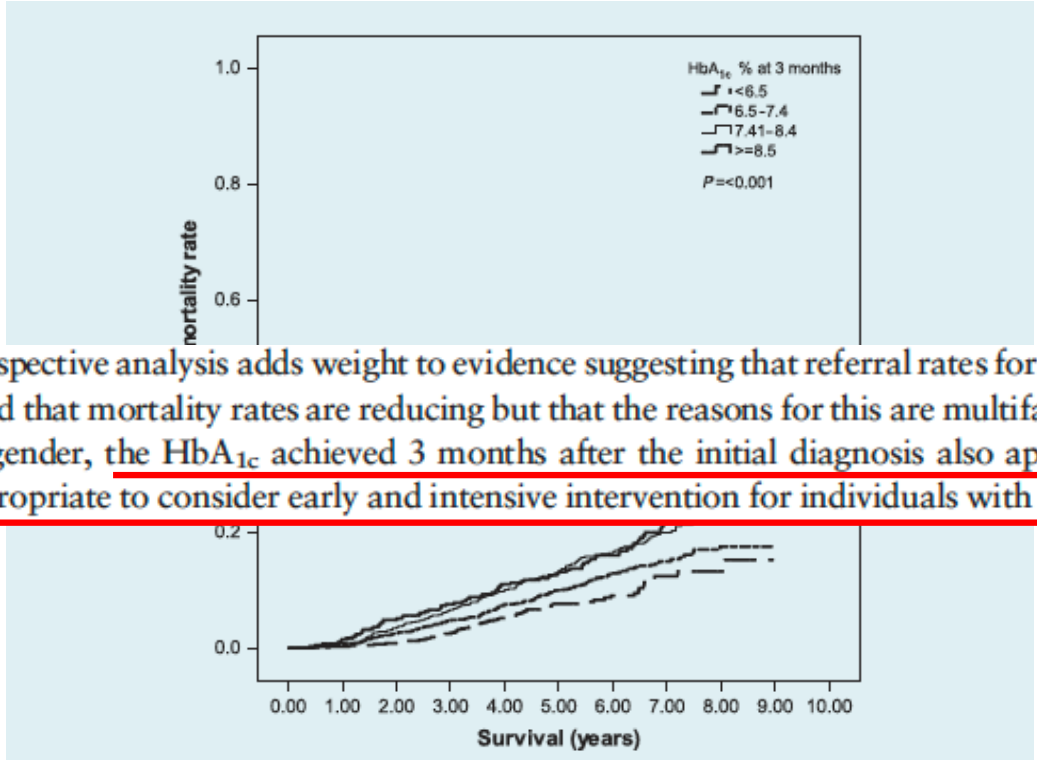
- Increased median life length by 7.9 years over 21.2 years of intensified, multifactorial target-driven follow up of T2DM patients
- Increase in lifespan matched by time free from incident CV disease

CV, cardiovascular; T2DM, Type 2 diabetes mellitus

Gæde P, et al. *Diabetologia* 2016;59:2298–2307

La glicemia

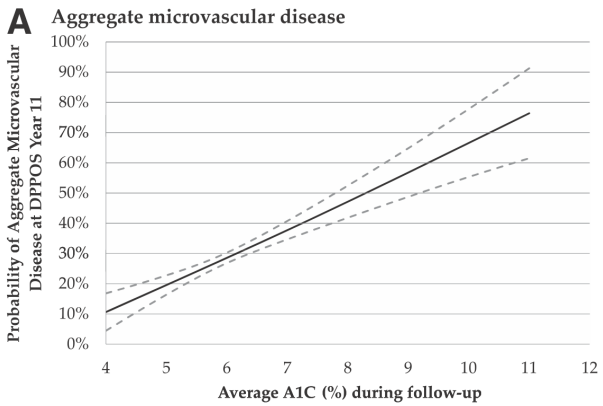
HbA1c 3 months after diagnosis predicts premature mortality in patients with new onset type 2 diabetes

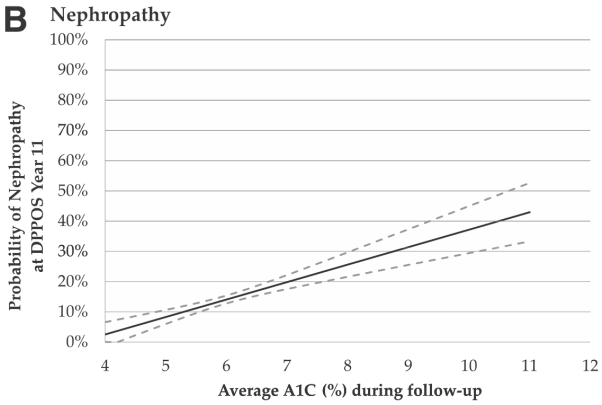


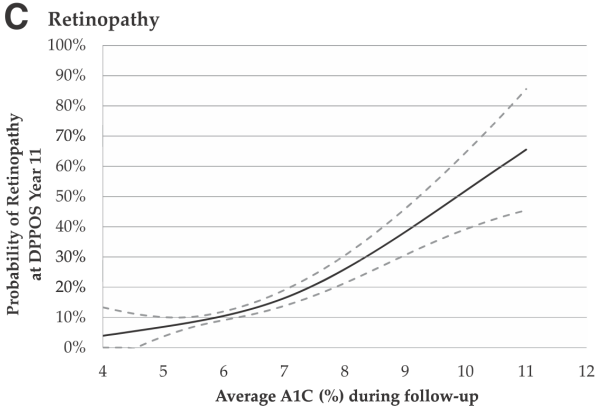
Conclusions Our retrospective analysis adds weight to evidence suggesting that referral rates for people with Type 2 diabetes are increasing rapidly and that mortality rates are reducing but that the reasons for this are multifactorial. In addition to blood pressure, smoking and gender, the HbA_{1c} achieved 3 months after the initial diagnosis also appears to predict subsequent mortality. It may be appropriate to consider early and intensive intervention for individuals with new onset type 2 diabetes.

Kerr D et al Diabet. Med. 2011; 28, 1520–1524

Regression to normal glucose regulation is associated with a lower prevalence of microvascolar disease

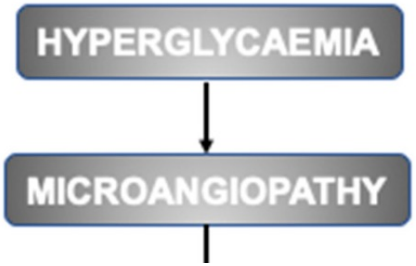




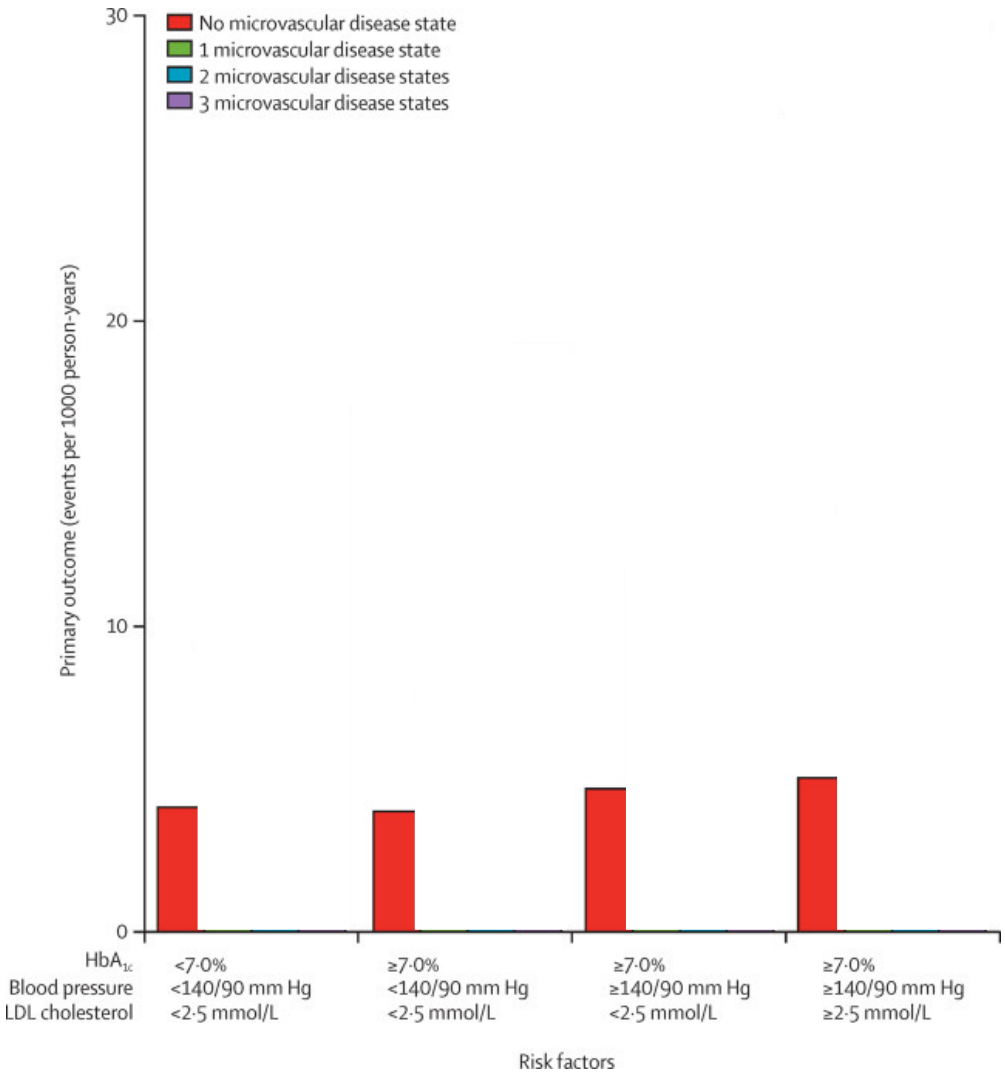


Perreault L et al Diabetes Care 2019;42:1809–1815

The systemic consequences of microvascular disease

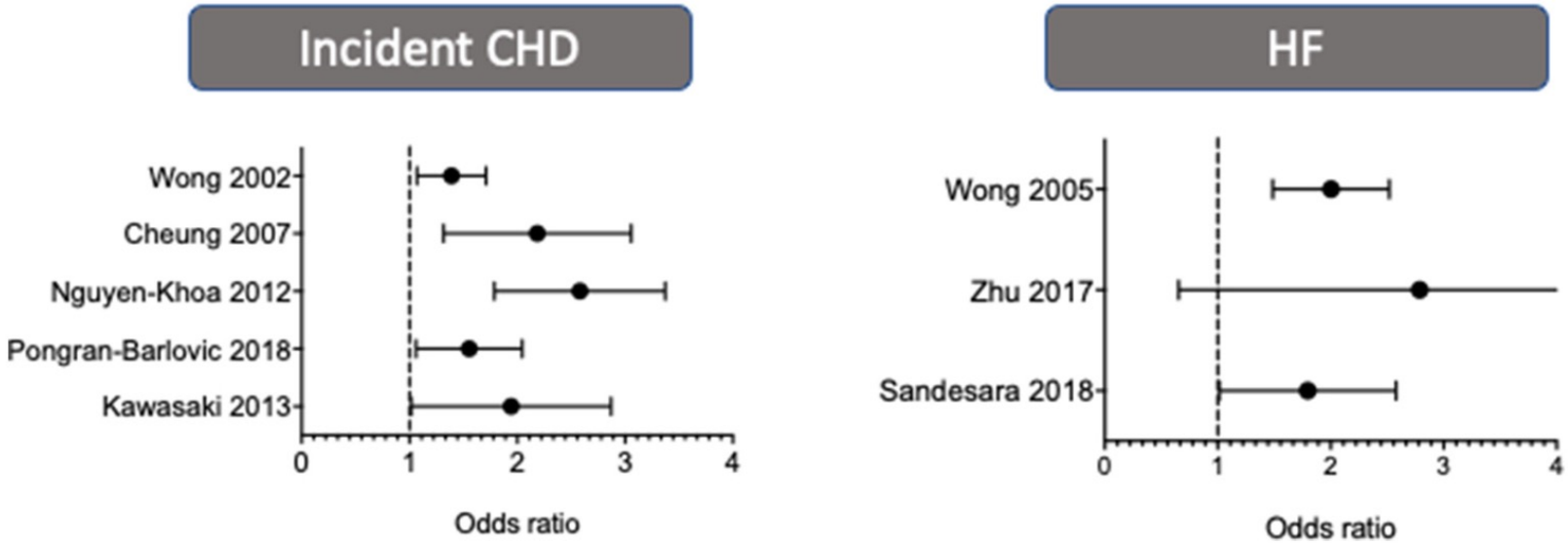


A. Avogaro, G.P. Fadini International Journal of Cardiology 291 (2019) 29–35



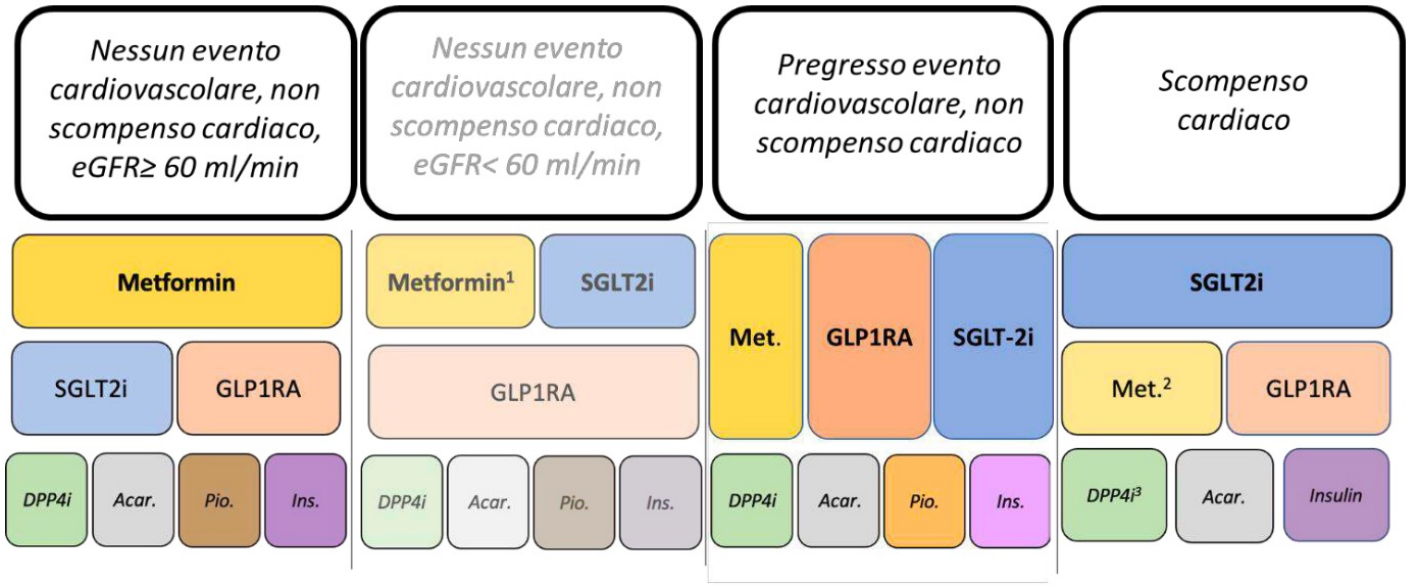
Brownrigg JRW et al. Lancet Diabetes Endocrinol, Volume 4, Issue 7, 2016, 588–597

The prediction of diabetic rethinopaty on incident CHD and HF



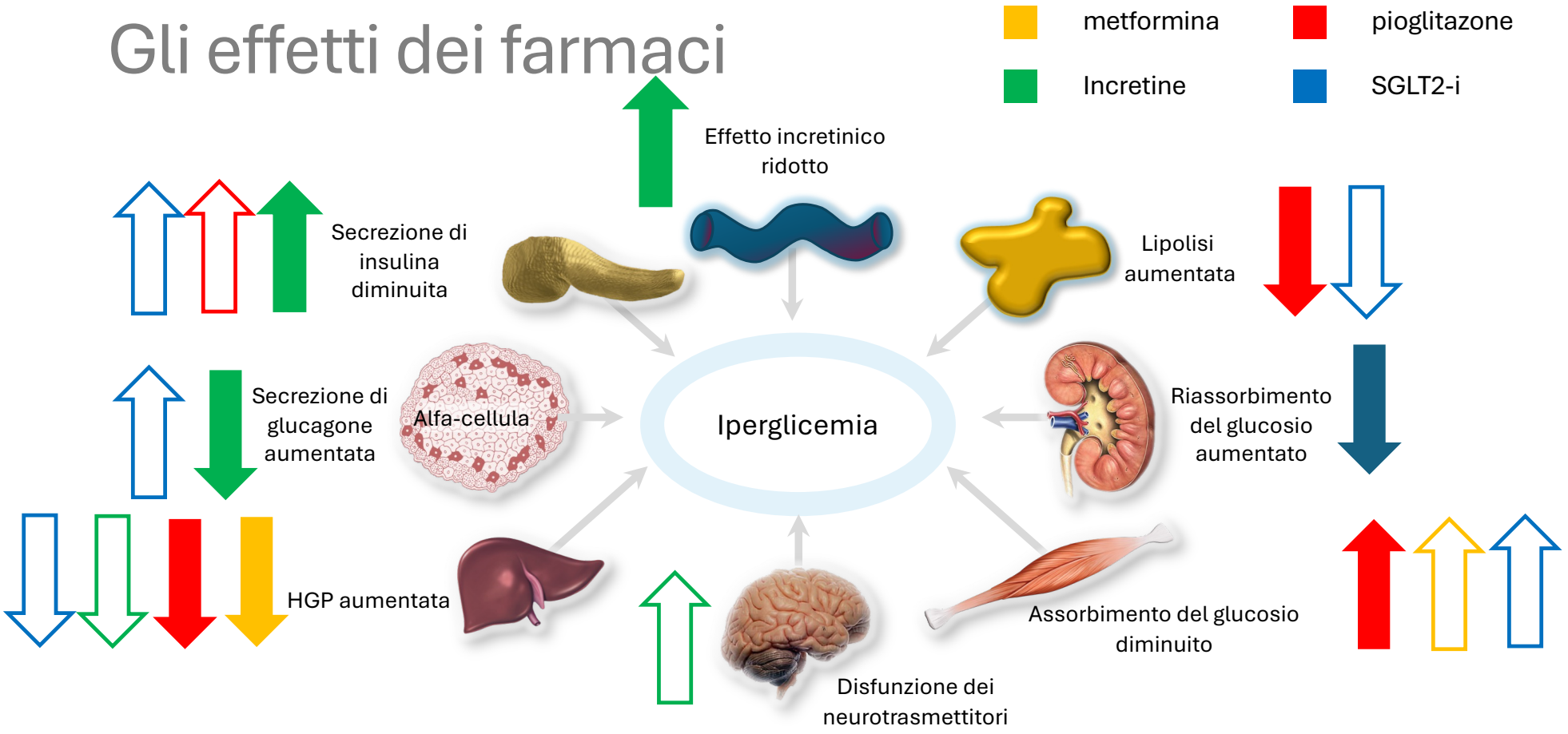
A. Avogaro, G.P. Fadini International Journal of Cardiology 291 (2019) 29–35

Linea Guida della Società Italiana di Diabetologia (SID) e dell'Associazione dei Medici Diabetologi (AMD)



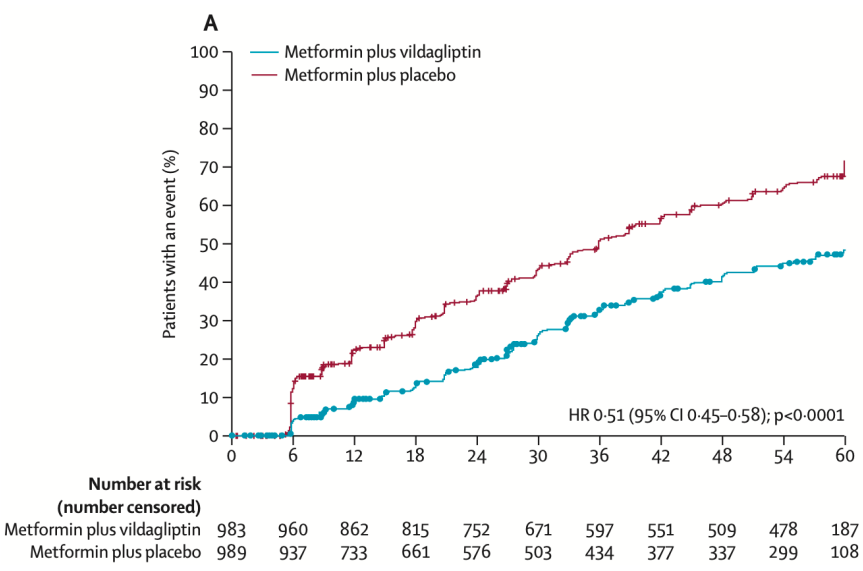
[1]Se la metformina non è controindicata per ridotto eGFR.
[2]Se la metformina non è controindicata per ridotta funzione cardiaca.
[3]Eccetto saxagliptin che non è indicato in caso di scompenso cardiaco.
La raccomandazione sui pazienti con eGFR< 60ml/min è debole per carenza di studi clinici effettuati su questa popolazione
Si raccomanda la deprescrizione di sulfanilurre e glinidi

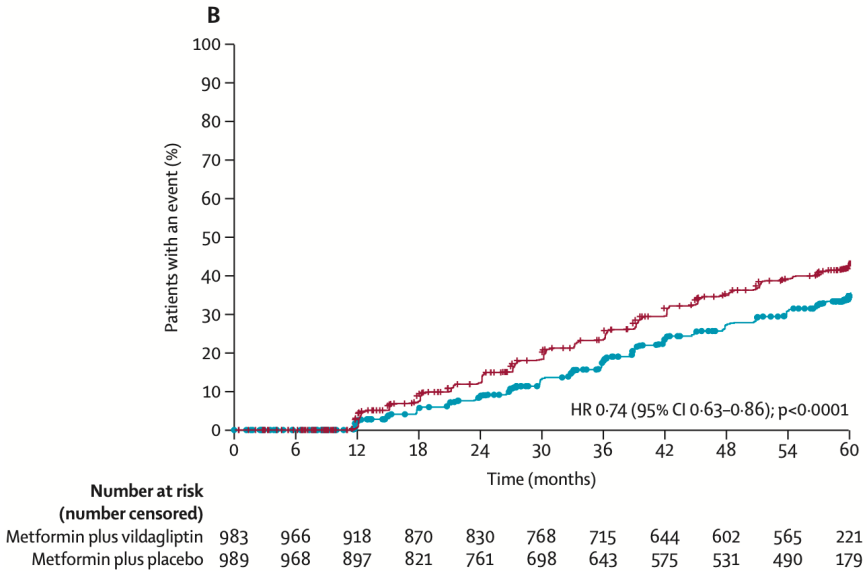
Gli effetti dei farmaci



Modified from De Fronzo RA. Diabetes 2009;58:773-795

Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial





Conlusions

Early intervention with a combination therapy of vildagliptin plus metformin provides greater and durable long-term benefits compared with the current standard-of-care initial metformin monotherapy for patients with newly diagnosed type 2 diabetes.

Matthews DR et al. Lancet. 2019 Oct 26;394(10208):1519-1529.

La pressione arteriosa

Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom prospective diabetes study (UKPDS: 23)

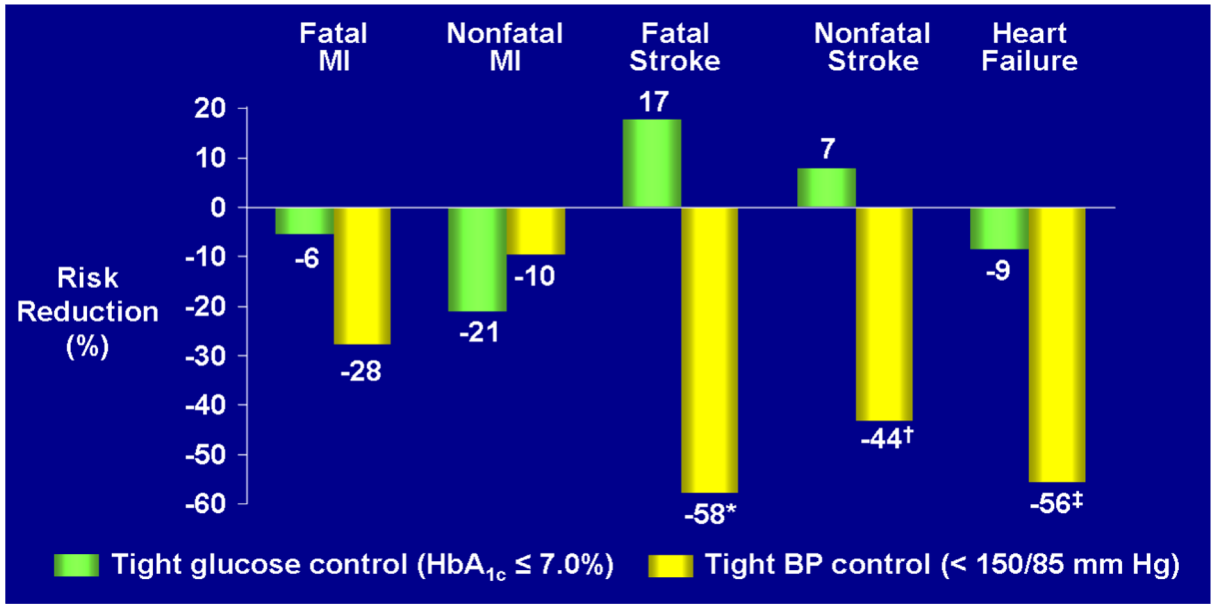
Stepwise selection of risk factors, adjusted for age and sex, in 2693 white patients with non-insulin dependent diabetes mellitus with dependent variable as time to first event. P values are significance of risk factor after accounting for all other risk factors in model

Position in model	Coronary artery disease (n=280)		Non-fatal or fatal myocardial infarction (n=192)		Fatal myocardial infarction (n=79)	
	Variable	P value	Variable	P value	Variable	P value
First	Low density lipoprotein cholesterol	<0.0001	Low density lipoprotein cholesterol	0.0022	Diastolic blood pressure	0.0012
Second	High density lipoprotein cholesterol	0.0001	Diastolic blood pressure	0.0074	Low density lipoprotein cholesterol	0.012
Third	Haemoglobin A_{1c}	0.0022	Smoking	0.025	Haemoglobin A_{1c}	0.024
Fourth	Systolic blood pressure	0.0065	High density lipoprotein cholesterol	0.026		
Fifth	Smoking	0.056	Haemoglobin A_{1c}	0.053		

BMJ. 1998 Mar 14;316(7134):823–828

Effect of Blood Pressure Control on CV risk reduction

United Kingdom Prospective Diabetes Study (UKPDS)



BP control yields greater CV risk reduction than glycemic control

*P=0.04, †P=0.029, ‡P=0.04 vs less tight BP control (<180/105 mm Hg)

UKPDS 38. *BMJ* 1998;317:703-713
UKPDS 33. *Lancet* 1998;352:837-853

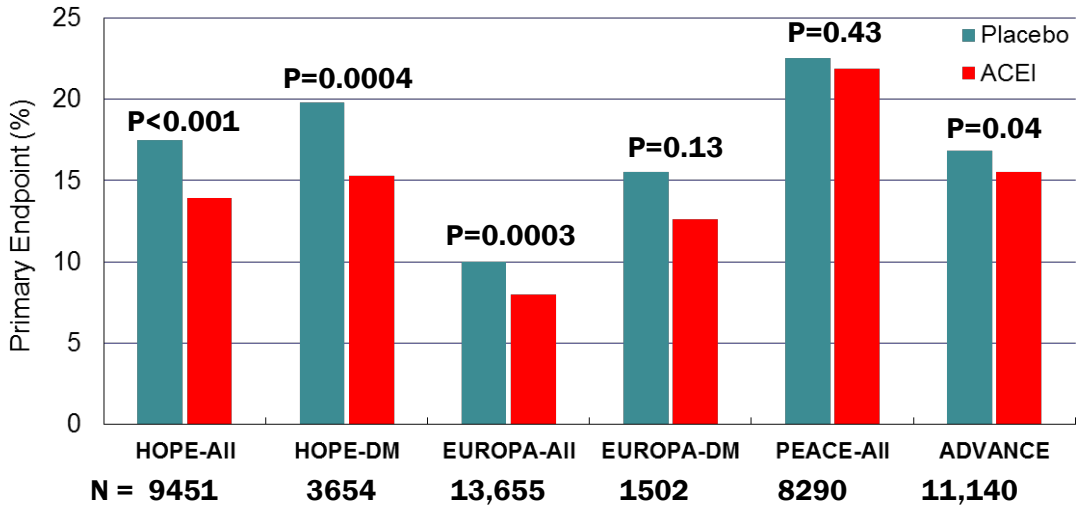
6.3 Blood pressure

Key messages

- The BP goal is to target systolic BP (SBP) to 130 mmHg in patients with DM and <130 mmHg if tolerated, but not <120 mmHg. In older people (aged >65 years), the SBP goal is to a range of 130 - 139 mmHg.
- The diastolic BP (DBP) target is <80 mmHg, but not <70 mmHg.
- Optimal BP control reduces the risk of micro- and macrovascular complications.
- Guidance on lifestyle changes must be provided for patients with DM and hypertension.
- Evidence strongly supports the inclusion of an angiotensin-converting enzyme inhibitor (ACEI), or an angiotensin receptor blocker (ARB) in patients who are intolerant to ACEI.
- BP control often requires multiple drug therapy with a renin–angiotensin–aldosterone system (RAAS) blocker, and a calcium channel blocker or diuretic. Dual therapy is recommended as first-line treatment.
- The combination of an ACEI and an ARB is not recommended.
- In pre-DM, the risk of new-onset DM is lower with RAAS blockers than with beta-blockers or diuretics.
- Patients with DM on combined antihypertensive treatments should be encouraged to self-monitor BP.

European Heart Journal (2020) 41, 255 323

Diabetes Mellitus: effect of ACE inhibitor



Use of an ACE inhibitor in most trials of DM is associated with a reduction in adverse CV events

Heart Outcomes Prevention Evaluation Study Investigators. Lancet 2000
Fox KM, Lancet 2003
Patel A, Lancet 2007
Daly CA, Eur Heart J 2005
The PEACE Trial Investigators. NEJM 2004
ADVANCE Collaborative Group. NEJM 2008

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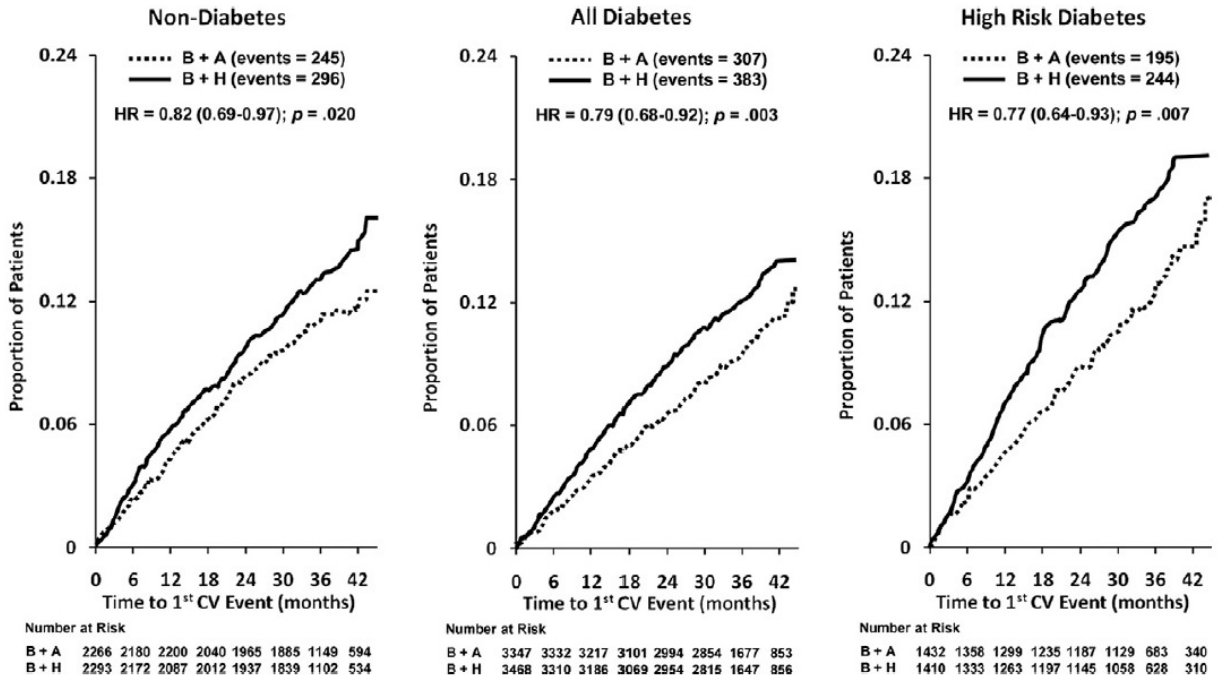
European Heart Journal (2020) 41, 255 323

Cardiovascular events during differing hypertension therapies in patients with diabetes

Primary endpoint: a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for angina, resuscitated arrest, and coronary revascularization.



B+A = benazepril with amlodipine

B+H = benazepril with hydrochlorothiazide

Weber MA et al. J Am Coll Cardiol 2010;56: 77–85

Cardiovascular events during differing hypertension therapies in patients with diabetes

After 3 years

Table 8 Metabolic and Renal Measurements During Treatment in Patients With Diabetes

Characteristic	B+A		B+H		p Value*
	Baseline	Change	Baseline	Change	
Fasting blood glucose (mg/dl)	145.2 (52.4)	2.0 (61.5)	144.1 (50.6)	−0.11 (59.2)	0.150
Serum potassium (mM)	4.31 (0.42)	0.12 (0.47)	4.30 (0.41)	0.03 (0.48)	<0.001
Serum creatinine (mg/dl)	0.97 (0.28)	0.07 (0.34)	0.97 (0.27)	0.15 (0.32)	<0.001
eGFR (ml/min)	80.3 (22.1)	−2.4 (17.5)	80.9 (22.3)	−9.9 (17.6)	<0.001
Urinary albumin/creatinine ratio (mg/g)	224.8 (484.2)	92.2 (788.0)	232.4 (493.3)	−20.1 (503.6)	<0.001
LDL cholesterol (mg/dl)	101.3 (32.6)	−10.6 (32.8)	100.8 (32.1)	−11.2 (32.9)	0.489
HDL cholesterol (mg/dl)	48.2 (13.0)	−0.06 (8.9)	48.4 (13.4)	−1.2 (9.0)	<0.001
Triglycerides (mg/dl)	178.0 (114.5)	−23.3 (95.8)	177.3 (121.8)	−11.9 (105.4)	<0.001

B+A = benazepril with amlodipine
B+H = benazepril with hydrochlorothiazide

All measurements are mean (SD). *p values are for differences between changes in the 2 treatments.

Weber MA et al. J Am Coll Cardiol 2010;56: 77–85

I lipidi

Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom prospective diabetes study (UKPDS: 23)

Stepwise selection of risk factors, adjusted for age and sex, in 2693 white patients with non-insulin dependent diabetes mellitus with dependent variable as time to first event. P values are significance of risk factor after accounting for all other risk factors in model

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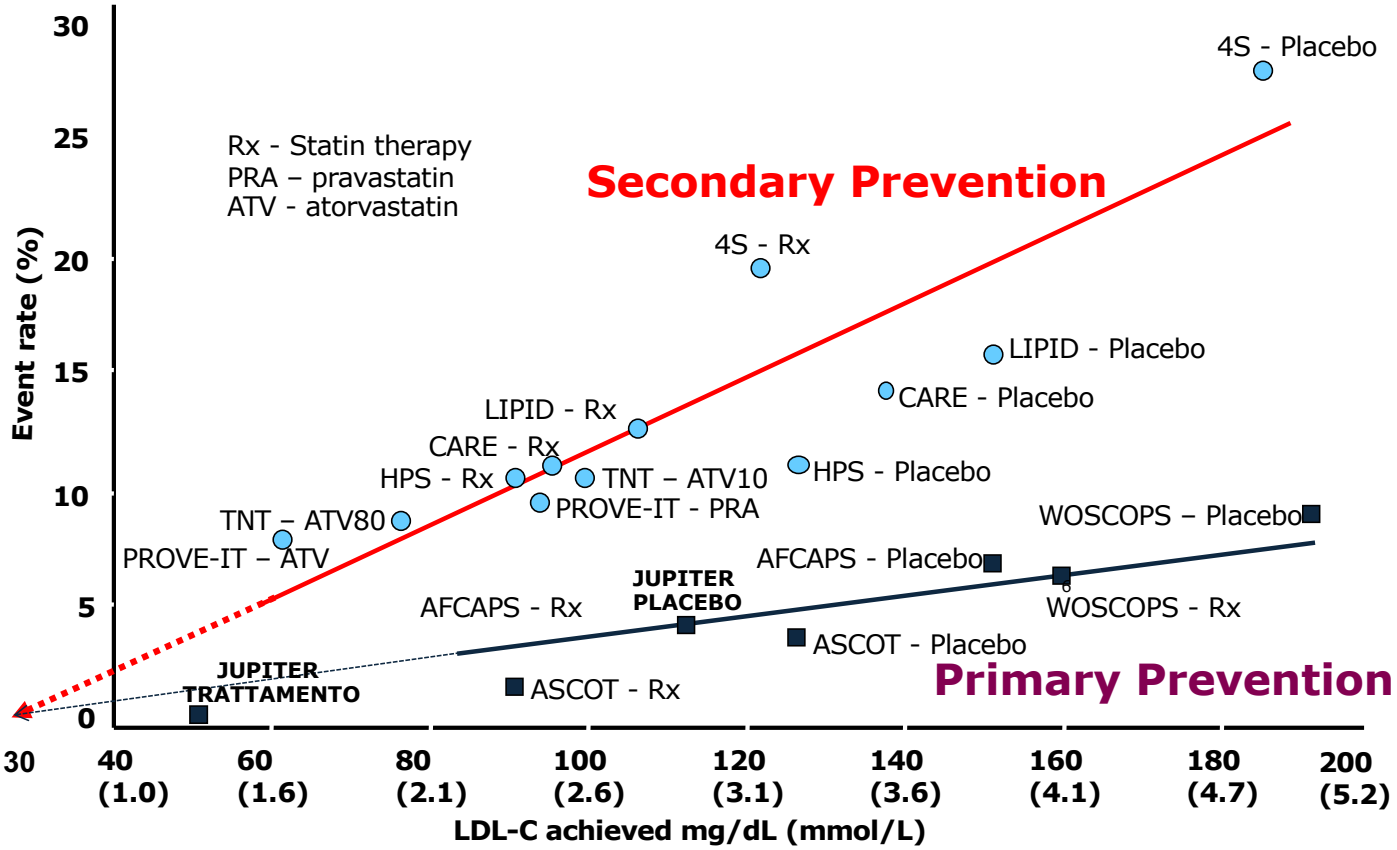
BMJ. 1998 Mar 14;316(7134):823–828

Recommendations for the management of dyslipidaemia with lipid-lowering drugs

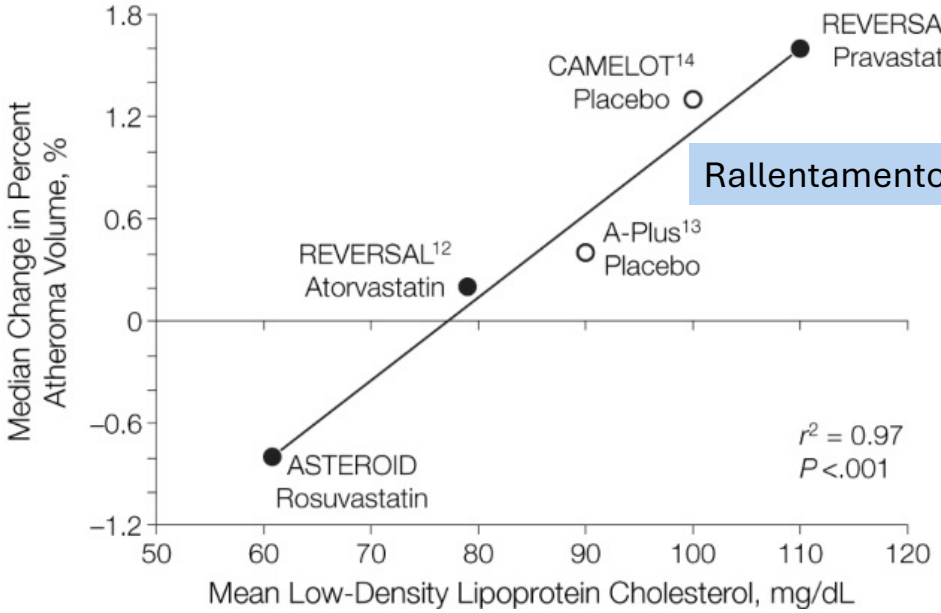
Recommendations	Class[a]	Level[b]
Targets		
In patients with T2DM at moderate CV risk,[c] an LDL-C target of <2.6 mmol/L (<100 mg/dL) is recommended.[210–212]	I	A
In patients with T2DM at high CV risk,[c] an LDL-C target of <1.8 mmol/L (<70 mg/dL) and LDL-C reduction of at least 50% is recommended.[d] [210–212]	I	A
In patients with T2DM at very high CV risk,[c] an LDL-C target of <1.4 mmol/L (<55 mg/dL) and LDL-C reduction of at least 50% is recommended.[d] [200,201,210]	I	B
In patients with T2DM, a secondary goal of a non-HDL-C target of <2.2 mmol/L (<85 mg/dL) in very high CV-risk patients, and <2.6 mmol/L (<100 mg/dL) in high CV-risk patients, is recommended.[d,213,214]	I	B

Every reduction in LDL-C is associated with a corresponding reduction in CVD events



Rosensen RS. Exp Opin Emerg Drugs 2004 LaRosa JC et al. NEJM 2005 Ridker PM et al. NEJM 2008

Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: The ASTEROID Trial

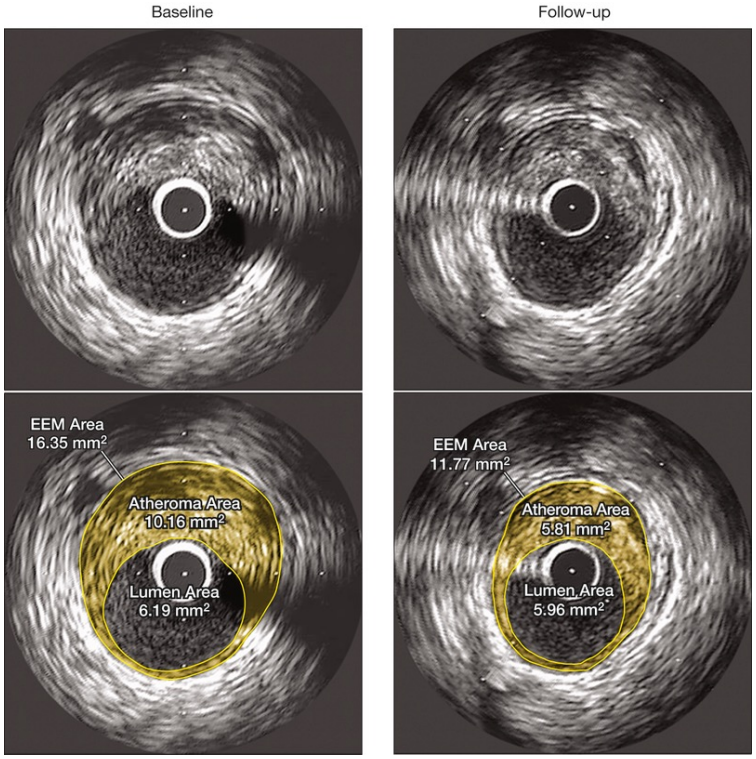


Rallentamento della progressione di placca

Regressione di placca

Nissen S. et al. JAMA; 2006

Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: The ASTEROID Trial



Baseline IVUS 24 months IVUS

Nissen S. et al. JAMA; 2006

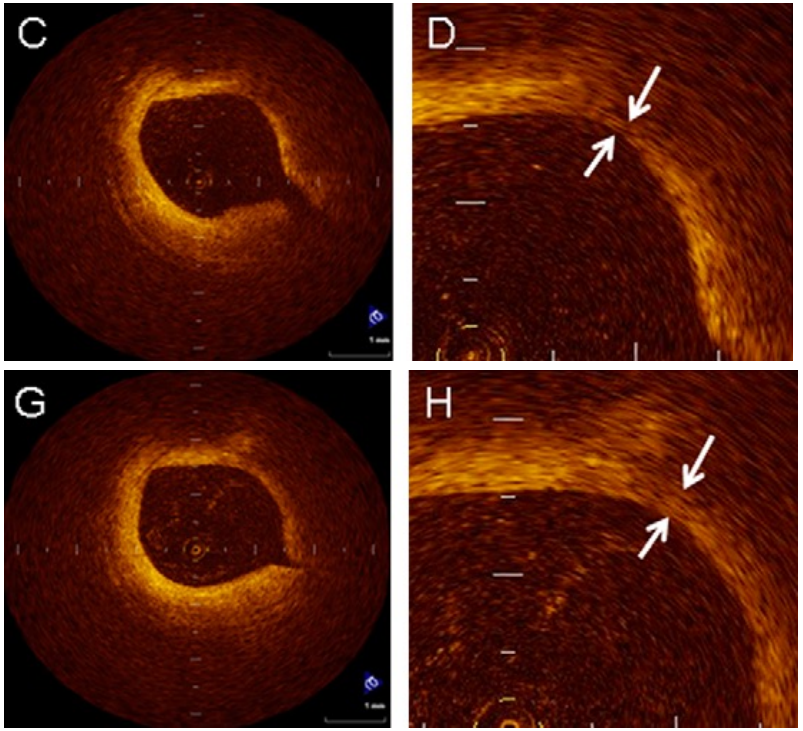
+15%
HDL-C

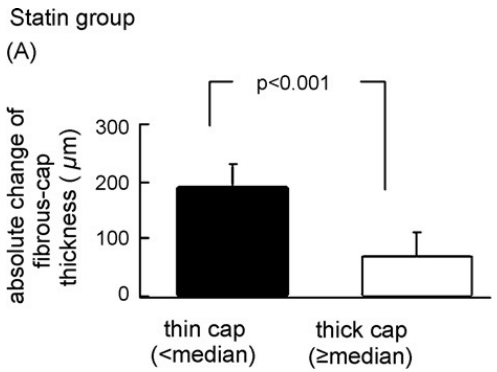
Rosuvastatina 40 mg

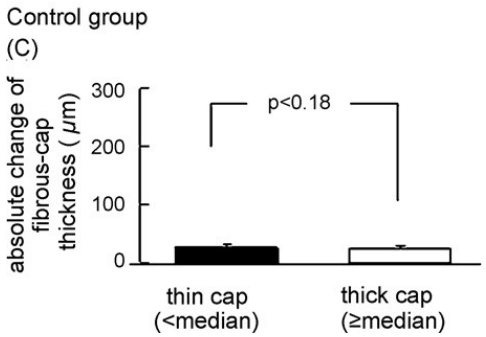
for 24 months

-53%
LDL-C

Effect of statin therapy on coronary fibrous-cap thickness in patients with acute coronary syndrome







Takarada S et al. Atherosclerosis 2009

2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias

2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias
Mach F. et al, European Heart Journal (2025) 00, 1–20

Cardiovascular risk categories

Very high risk	People with any of the following: • Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), chronic coronary syndromes, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan or on carotid or femoral ultrasound or **markedly elevated CAC score by CT.** • DM with target organ damage, or at least three major risk factors, or early onset of T1DM of long duration (>20 years). • Severe CKD (eGFR <30 mL/min/1.73 m^2). • A calculated **SCORE2 or SCORE2-OP ≥20%** for 10-year risk of fatal or non-fatal CVD. • FH with ASCVD or with another major risk factor.

SCORE 2, Systematic Coronary Risk Evaluation 2-Older Persons; **SCORE 2 OP**, Systematic Coronary Risk Evaluation 2-Older Persons; **ACS,** Acute Coronary Syndrome; **ASCVD**, Atherosclerotic Cardiovascular Disease; **PCI**, Percutaneous Coronary Intervention; **CABG**, Coronary Artery Bypass Graft; **DM,** Diabetes Mellitus; **CT,** Computed Tomography ; **CAC,** Coronary Artery Calcium; **T1DM**, Type 1 Diabetes Mellitus; **CKD**, Chronic Kidney Disease

2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias
Mach F. et al, European Heart Journal (2025) 00, 1–20

Cardiovascular risk categories

High risk	People with any of the following: • Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. • Patients with FH without other major risk factors. • Patients with DM without target organ damage, with DM duration ≥10 years or another additional risk factor. • Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). • A calculated **SCORE2 or SCORE2-OP** ≥10% and <20% for 10-year risk of fatal or non-fatal CVD.
Moderate risk	People with any of the following: • Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. • Calculated **SCORE2 or SCORE2-OP** ≥2% and <10% for 10-year risk of fatal or non-fatal CVD.
Low risk	• Calculated **SCORE2 or SCORE2-OP** <2% for 10-year risk of fatal or non-fatal CVD.

SCORE 2, Systematic Coronary Risk Evaluation 2-Older Persons; **SCORE 2 OP**, Systematic Coronary Risk Evaluation 2-Older Persons; **TC**, Triglyceride; **BP**, Blood Pressure **DM,** Diabetes Mellitus;**T1DM,** Type 1 Diabetes Mellitus; **T2DM,** Type 2 Diabetes Mellitus; **CT,** Computed Tomography ; **CAC,** Coronary Artery Calcium; **CKD**, Chronic Kidney Disease; **CVD**, Cardiovascular Disease; **FH,** Familial Hypercholesterolemia

2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias
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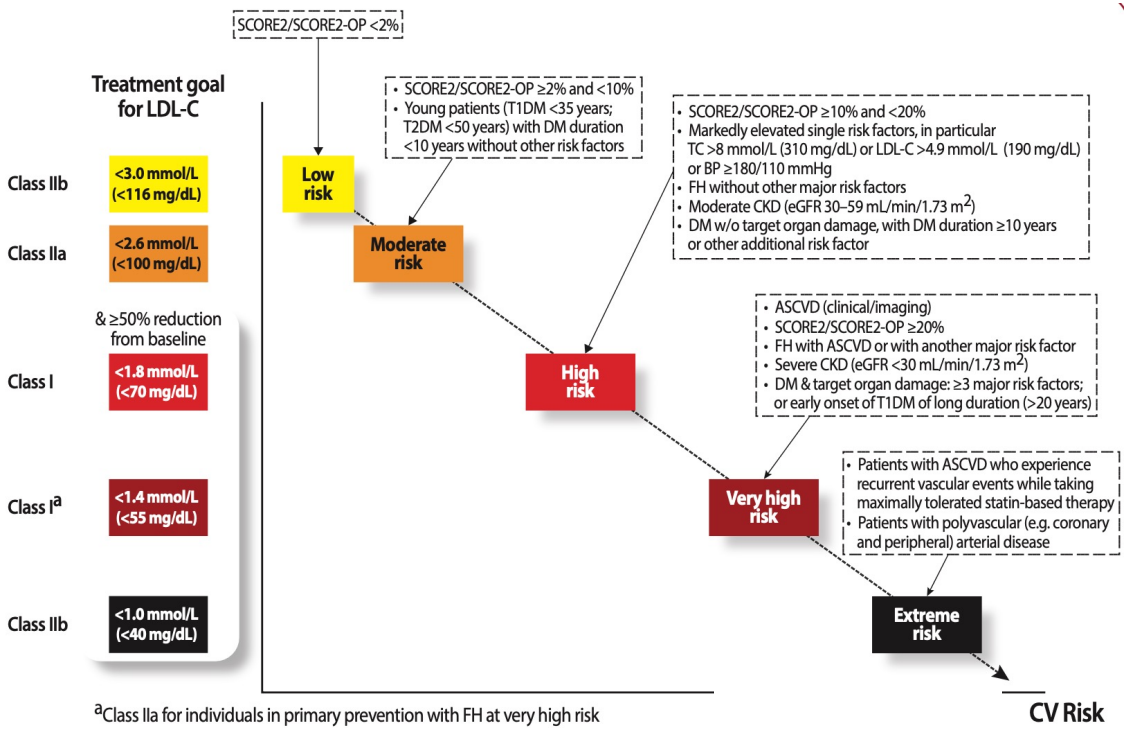
Treatment goals for low-density lipoprotein cholesterol across categories of total cardiovascular risk.



SCORE 2, Systematic Coronary Risk Evaluation 2-Older Persons; **SCORE 2 OP**, Systematic Coronary Risk Evaluation 2-Older Persons; **DM,** Diabetes Mellitus;; **CT,** Computed Tomography ; **CAC,** Coronary Artery Calcium; **CKD**, Chronic Kidney Disease; **eGFR,** Estimated Glomerular Filtration Rate; **ASCVD**, Atherosclerotic Cardiovascular Disease; **TC**, Triglyceride; **FH,** Familial Hypercholesterolemia; **T1DM,** Type 1 Diabetes Mellitus; **T2DM,** Type 2 Diabetes Mellitus; **LDL-C,** low-density lipoprotein cholesterol

2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias
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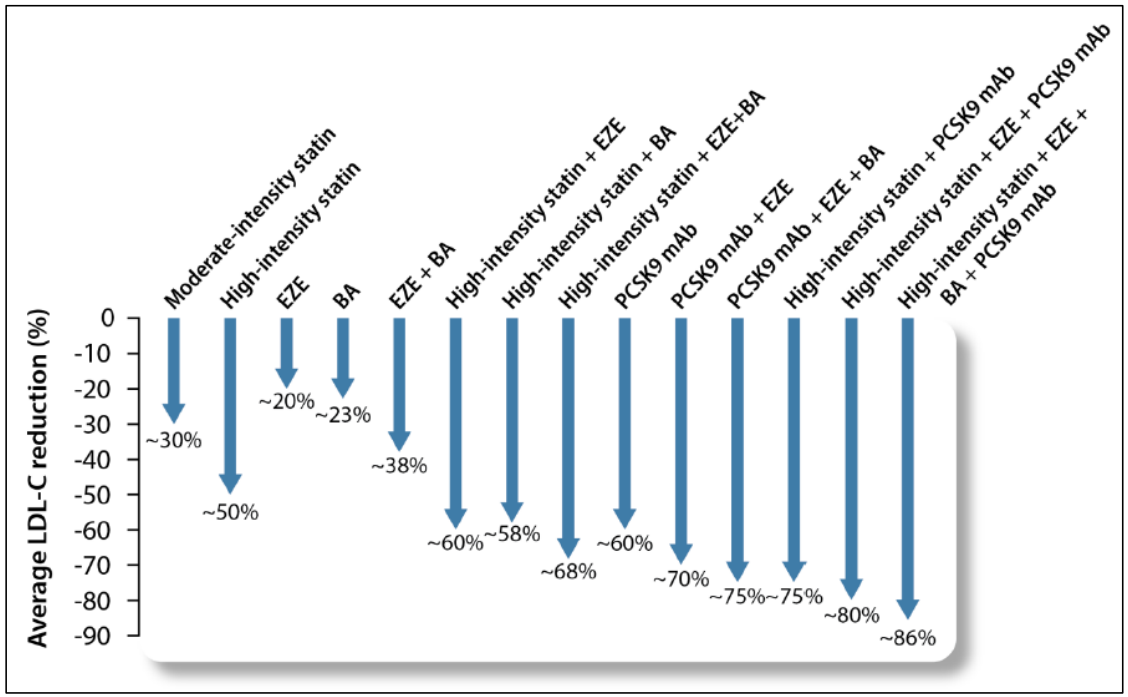
Average reduction in low-density lipoprotein cholesterol levels with different pharmacological therapies with proven cardiovascular benefit.



- As a general concept, this Task Force recommends to add non-statin therapies with proven cardiovascular benefit such as ezetimibe, a PCSK9 mAb, or bempedoic acid, taken alone or in combination, to lower LDL-C if the LDL-C goals are not achieved with the maximum tolerated dose of a statin; the choice should be based on the magnitude of additional LDL-C lowering needed, patient preference, treatment availability, and cost.

- As outlined in the 2019 ESC/EAS Guidelines, LDL-C levels should be measured 4 to 6 weeks after initiation or intensification of lipid-lowering therapy.

EZE, Ezetimibe; **BA**, Bempedoic Acid; **PCSK9 mAB,** Proprotein Convertase Subtilisin/Kexin type 9 Monoclonal Anti Body; **LDL-C,** low-density lipoprotein cholesterol
ESC, European Society of Cardiology; **EAS**, European Society of Lipidology

2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias
Mach F. et al, European Heart Journal (2025) 00, 1–20

New Recommendations

Recommendations	Class	Level
Recommendations for pharmacological low-density lipoprotein cholesterol lowering		
Non-statin therapies with proven cardiovascular benefit, taken alone or in combination, are recommended for **patients who are unable to take statin therapy** to lower LDL-C levels and reduce the risk of CV events. The choice should be based on the magnitude of additional LDL-C lowering needed.	I	A
Bempedoic acid is recommended in patients who are unable to take statin therapy to achieve the LDL-C goal.	I	B
The addition of bempedoic acid to the maximally tolerated dose of statin with or without ezetimibe should be considered in patients at high or very high risk in order to achieve the LDL-C goal.	IIa	C
Evinacumab should be considered in patients with homozygous familial hypercholesterolaemia aged 5 years or older who are not at LDL-C goal despite receiving maximum doses of lipid-lowering therapy to lower LDL-C levels.	IIa	B

LDL-C, low-density lipoprotein cholesterol; **CV**, Cardiovascular

2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias
(European Heart Journal; doi: 10.1093/eurheartj/ehaf190)

Recommendations	Class	Level
Recommendation for measurement of lipoprotein(a)		
Lp(a) levels above 50 mg/dL (105 nmol/L) should be considered in all adults as a CV risk-enhancing factor, with higher Lp(a) levels associated with a greater increase in risk.	**IIa**	**B**

Lp (a); Lipoprotein (a)**; CV,** Cardiovascular

2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias
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Recommendations	Class	Level
Recommendations for drug treatment of patients with hypertriglyceridaemia		
High-dose icosapent ethyl (2 x 2 g/day) should be considered in combination with a statin in high-risk or very high-risk patients with elevated triglyceride levels (fasting triglyceride levels 135–499 mg/dL or 1.52–5.63 mmol/L) to reduce the risk of cardiovascular events.	**IIa**	**B**
Volanesorsen (300 mg/week) should be considered in patients with severe hypertriglyceridaemia (>750 mg/dL or >8.5 mmol/L) due to familial chylomicronaemia syndrome, to lower triglyceride levels and reduce the risk of pancreatitis.	**IIa**	**B**

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Recommendations	Class	Level
Recommendation for dietary supplements		
Dietary supplements or vitamins without documented safety and significant LDL-C-lowering efficacy are not recommended to lower the risk of ASCVD.	III	B

ASCVD, Atherosclerotic Cardiovascular Disease;
LDL-C, low-density lipoprotein cholesterol

2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias
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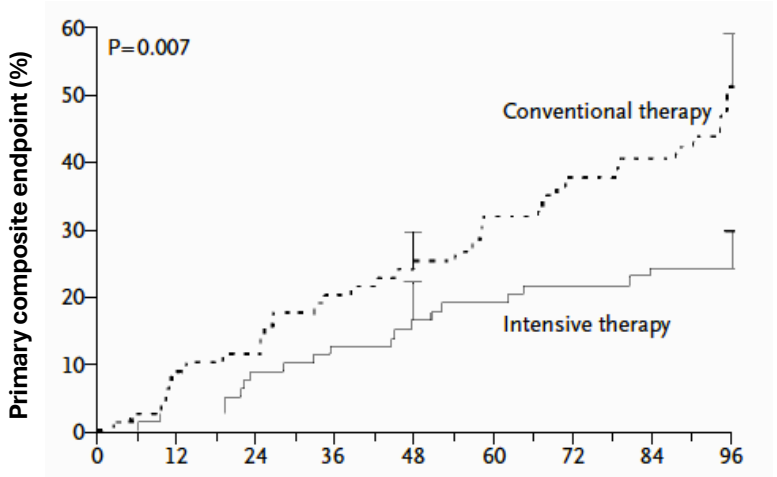
Conclusioni

Multifactorial Intervention in T2DM

Steno-2: A prospective, randomised, open, blinded endpoint study of patients with T2DM and microalbuminuria

Primary composite endpoint:

- Death from CV causes
- Non-fatal MI
- Non-fatal stroke
- Coronary artery bypass
- Grafting
- Percutaneous coronary intervention
- Amputation
- Surgery for peripheral atherosclerotic artery disease



Number at risk:	Months of follow up								
Intensive therapy	80	78	74	71	66	63	61	59	19
Conventional therapy	80	72	71	63	59	50	44	41	13

BP, blood pressure; CV, cardiovascular; MI, myocardial infarction; T2DM, Type 2 diabetes mellitus

Gaede P, et al. *N Engl J Med* 2008;348:383–393

Grazie per la vostra attenzione

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