La prevenzione della malattia cardiovascolare aterosclerotica nel paziente con diabete anche attraverso la gestione del "rischio residuo"

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Università di Ferrara

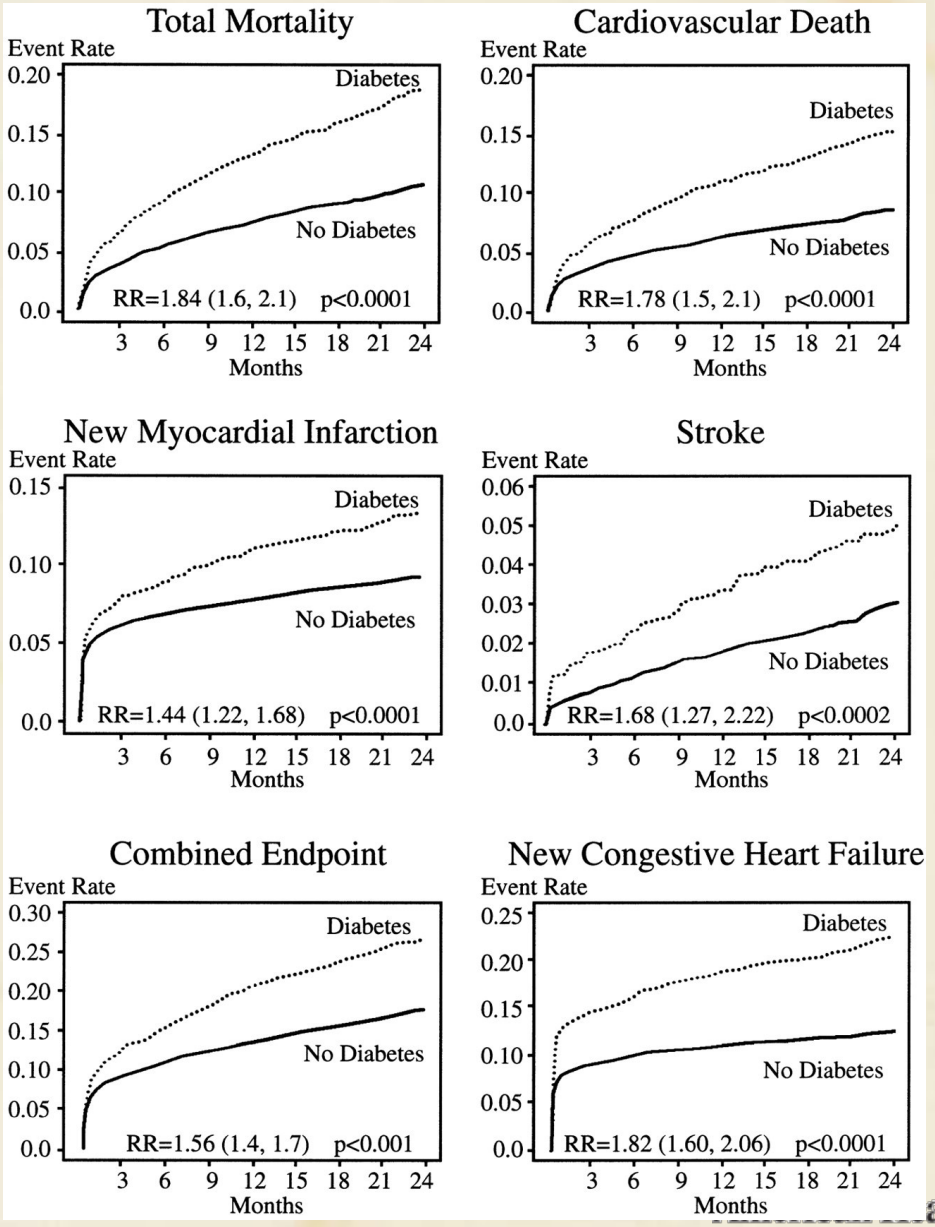
Cumulative event curves for different outcomes in patients with and without diabetes.

American Heart Association®

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

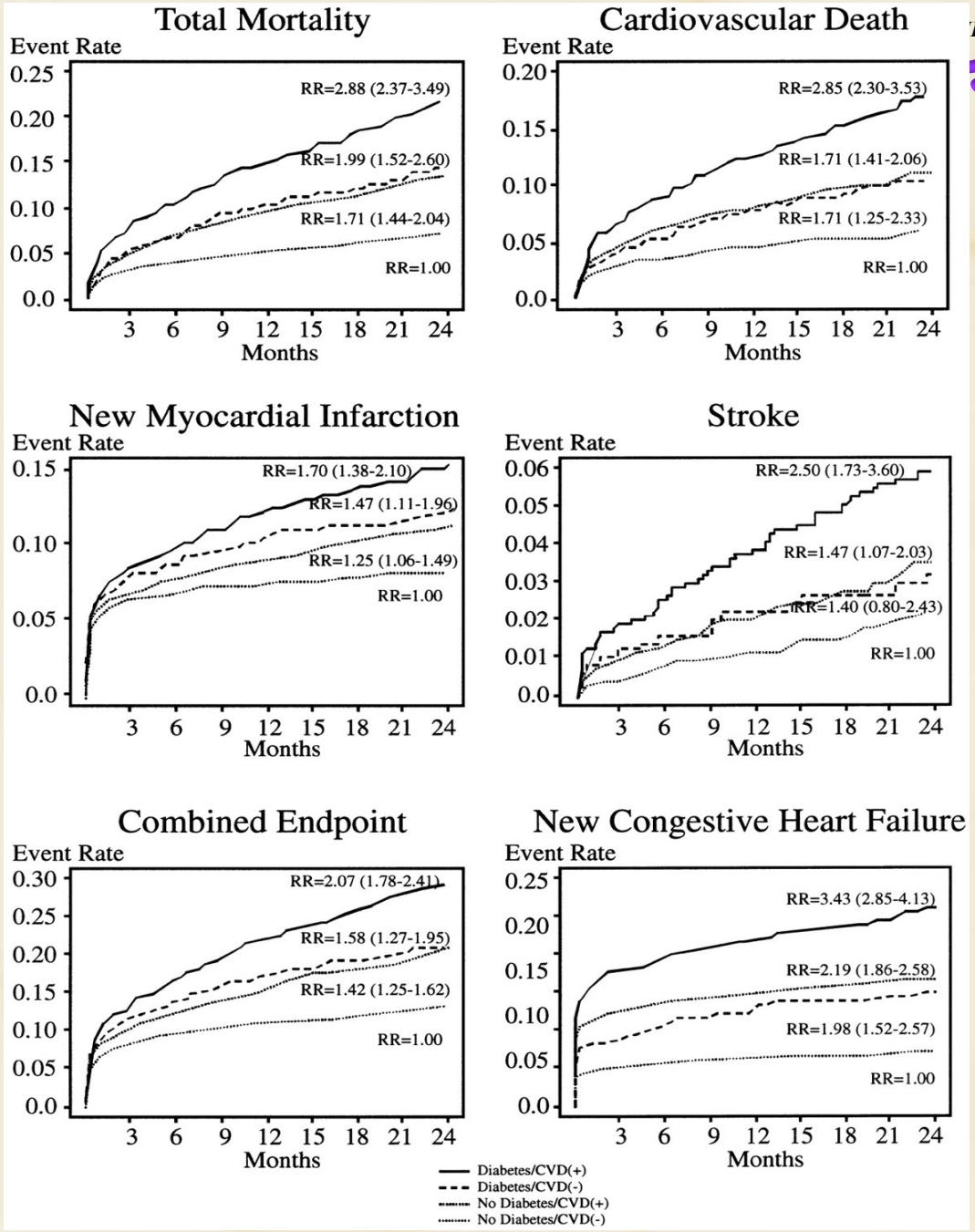
Impact of Diabetes on Long-Term Prognosis in Patients With Unstable Angina and Non–Q-Wave Myocardial Infarction : Results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry

Klas Malmberg, Salim Yusuf, Hertzel C. Gerstein, Joanne Brown, Feng Zhao, David Hunt, Leopoldo Piegas, James Calvin, Matyas Keltai, Andrzej Budaj and for the OASIS Registry Investigators

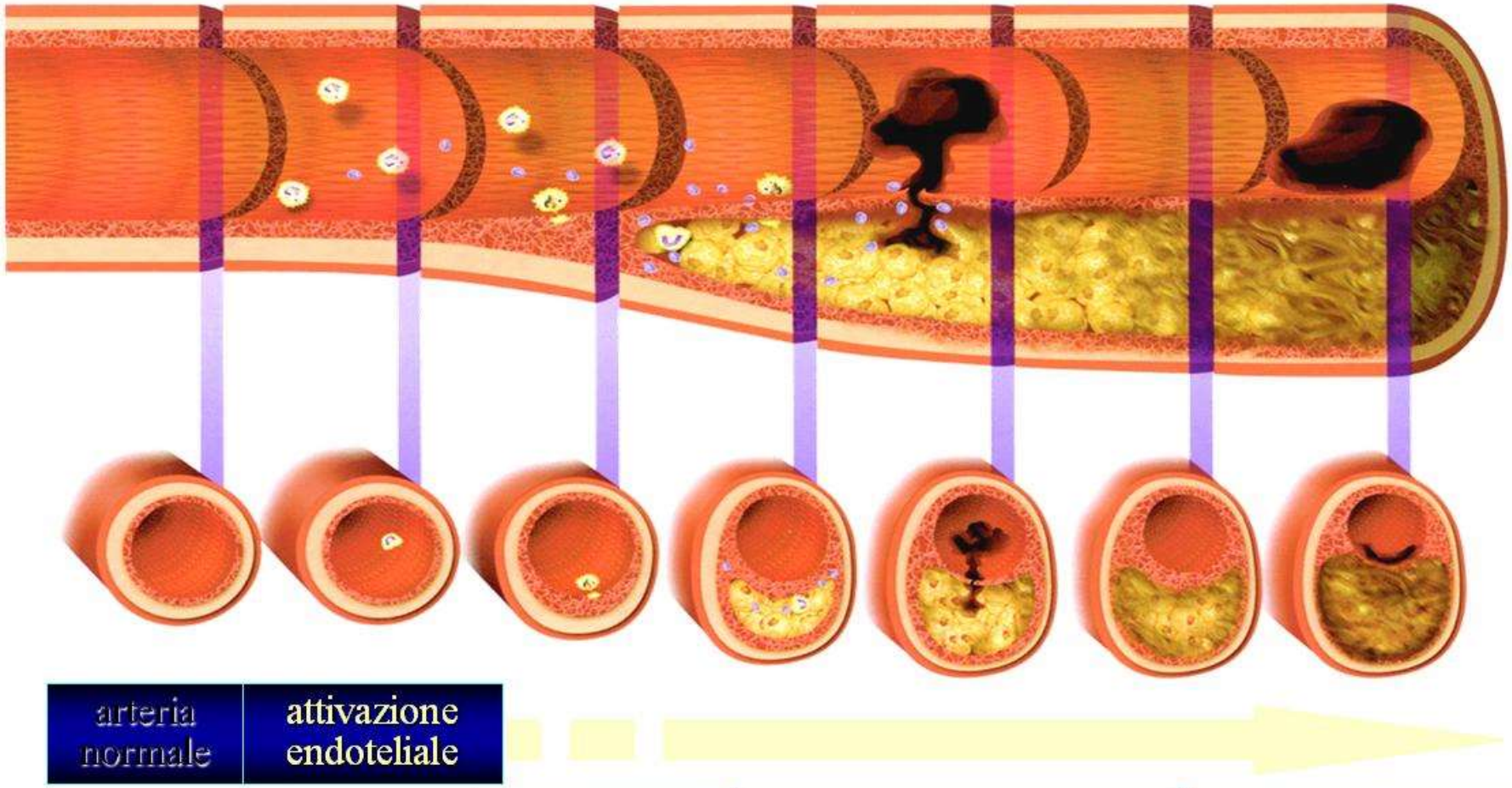


Malmberg K et al. Circulation 2000;102:1014-1019

Cumulative event curves for patients with and without diabetes in relation to previously known CVD. Age- and sex-adjusted RRs (by Cox model) between nondiabetic patients without prior cardiovascular disease [(No Diabetes/CVD(−)] and other strata are given.



Malmberg K et al. Circulation 2000;102:1014-1019



European Heart Journal

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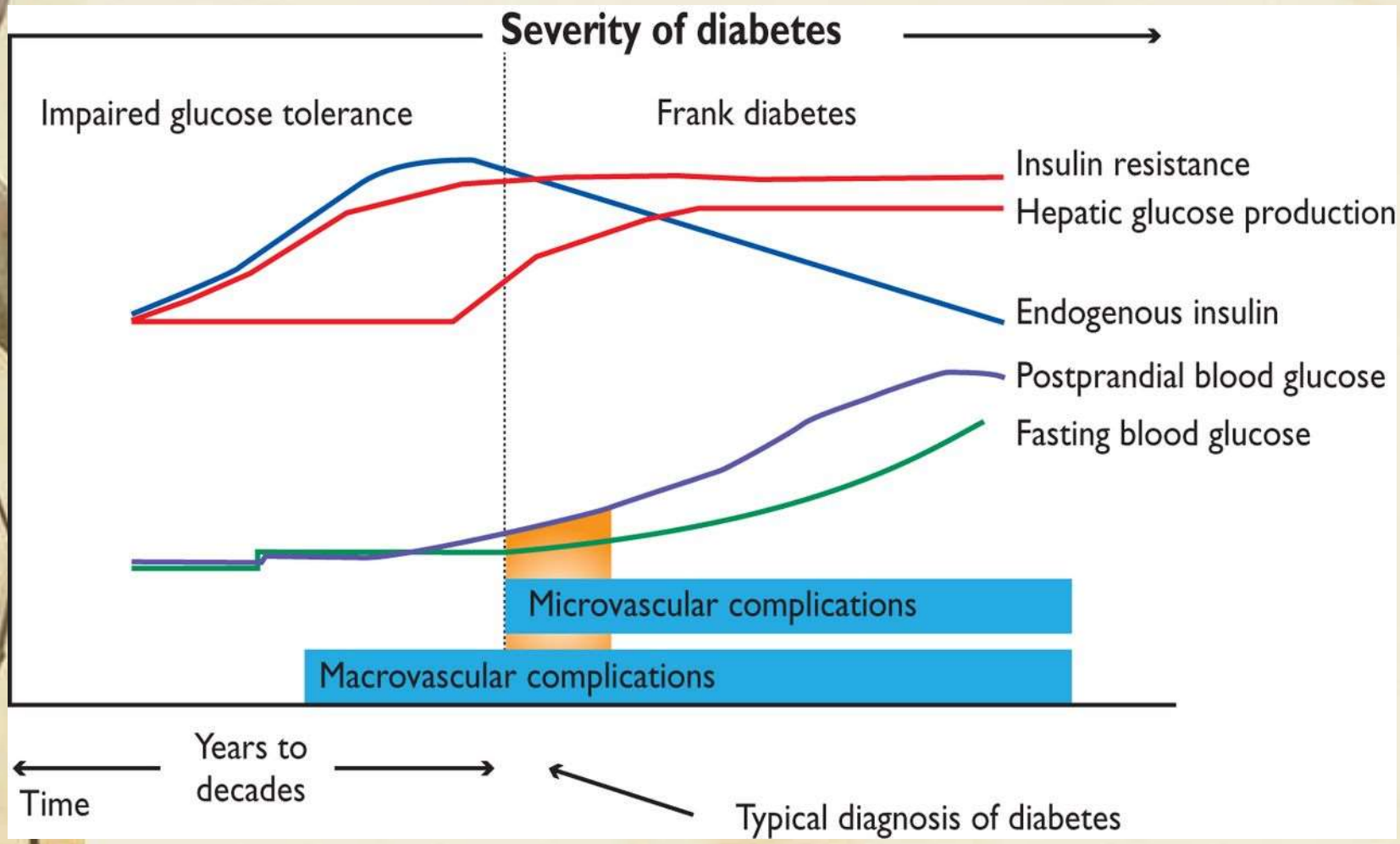
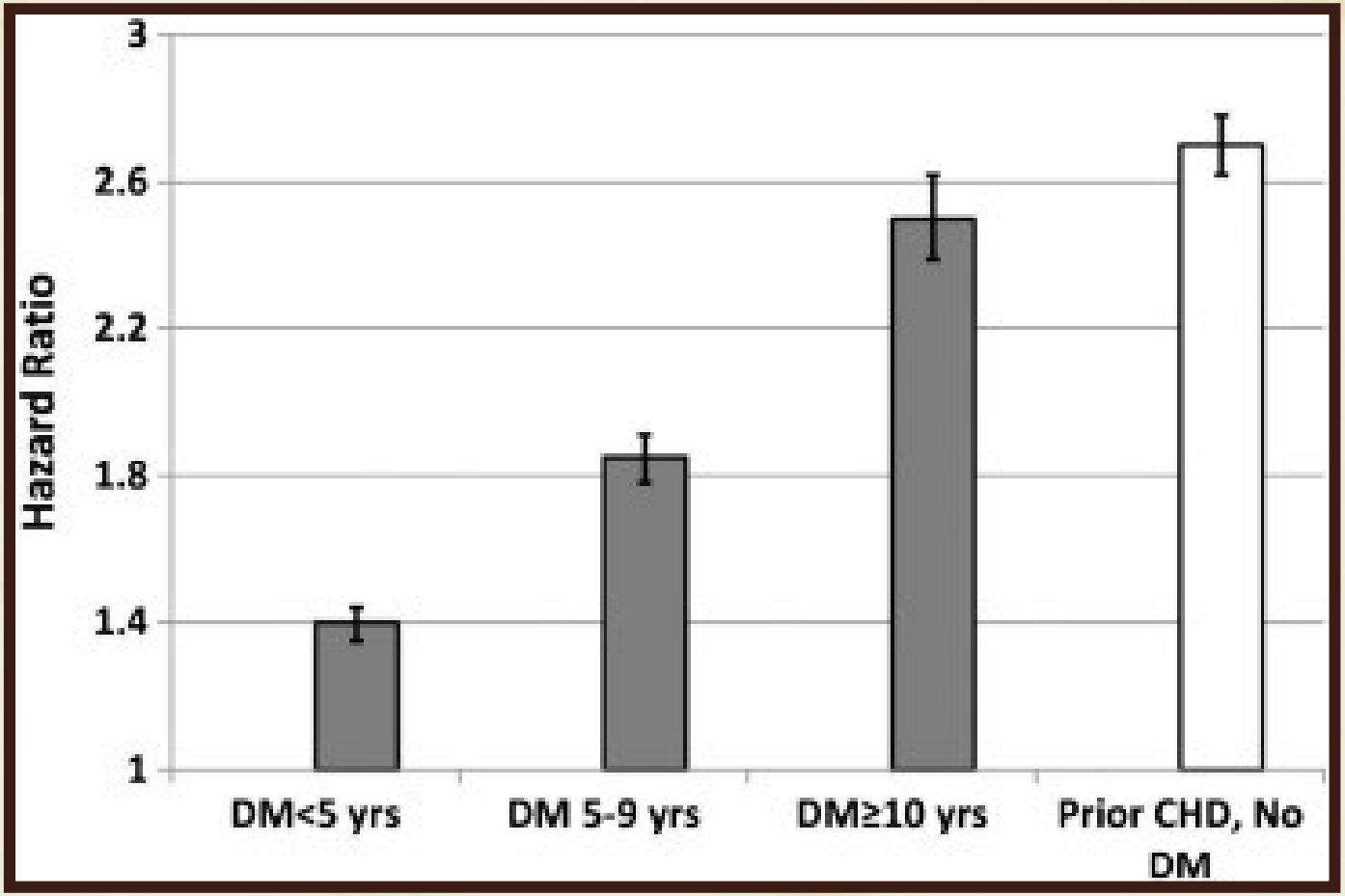
Glycaemic continuum and cardiovascular disease.



Authors/Task Force Members et al. Eur Heart J 2013;34:3035-3087

European Heart Journal



. Risk of coronary heart disease (CHD) by duration of diabetes versus prior CHD. CHD risk among individuals with diabetes alone (DM) by duration of diabetes, versus prior CHD alone. Hazard ratios adjusted for age by 10 years, sex, ethnicity, smoking stat...

Sina Kianoush, Mahmoud Al Rifai, Seamus P. Whelton, Gabriel E. Shaya, Aaron L. Bush, Garth Graham, Nathan D. Wong, Michael J. Blaha

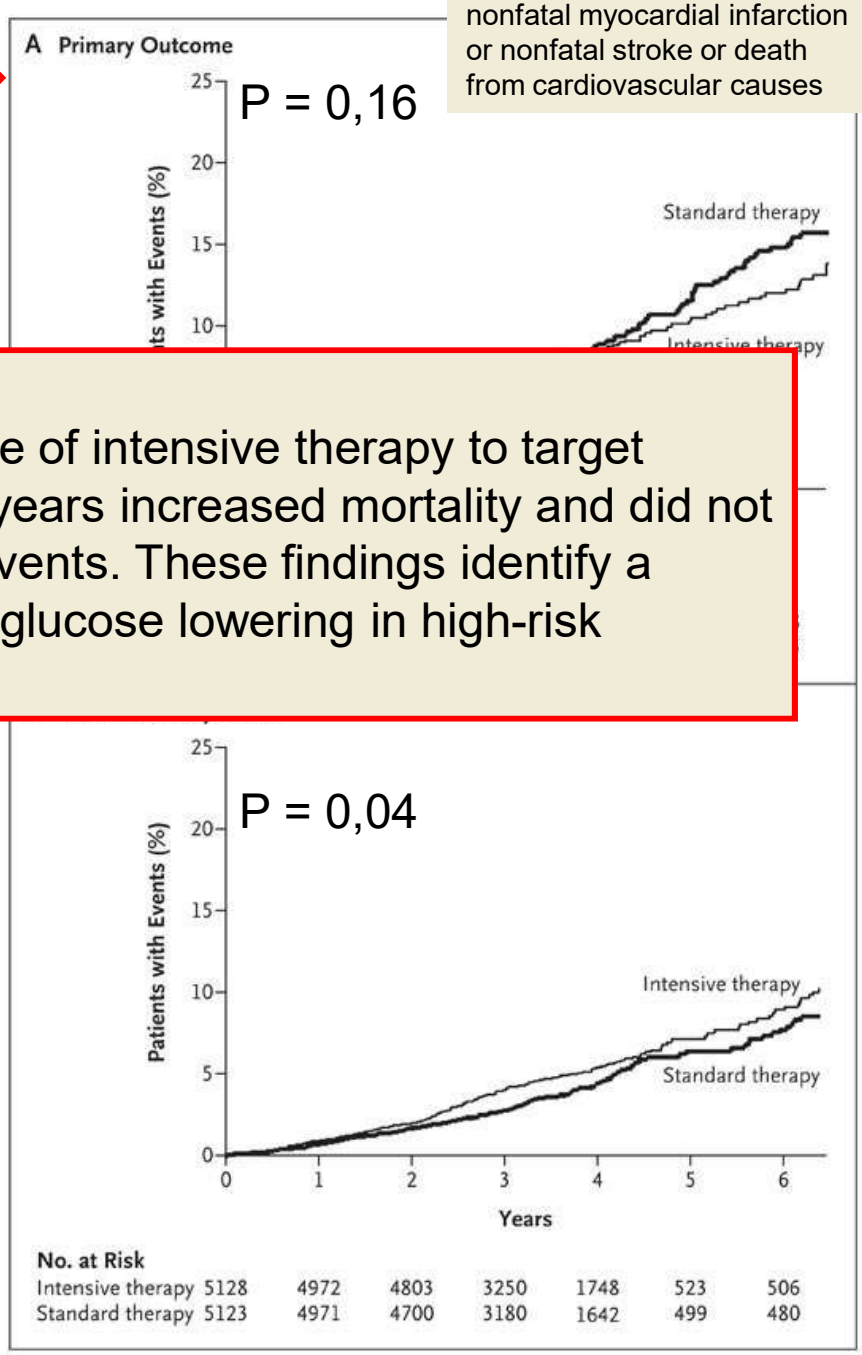
Stratifying cardiovascular risk in diabetes: The role of diabetes-related clinical characteristics and imaging

Journal of Diabetes and its Complications, 2016, Available online 30 April 2016

Kaplan–Meier Curves for the Primary Outcome and Death from Any Cause

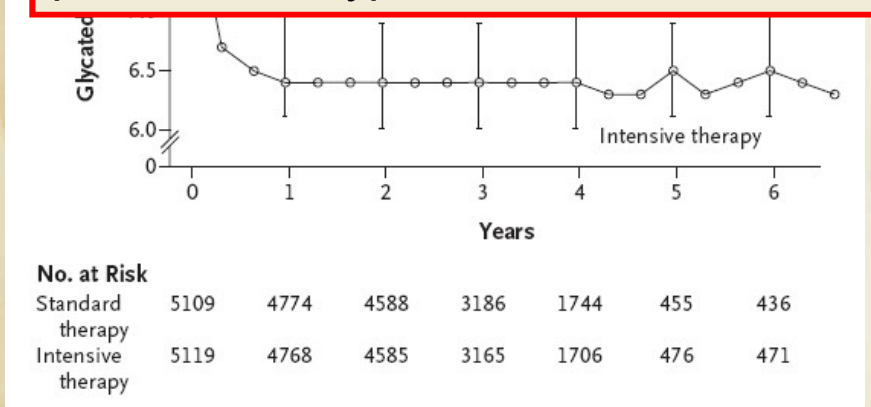
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 12, 2008 VOL. 358 NO. 24

nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes



Conclusions

As compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. These findings identify a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes.



Action to Control Cardiovascular Risk in Diabetes
ACCORD

The ADVANCE Trial: Major Macrovascular Events

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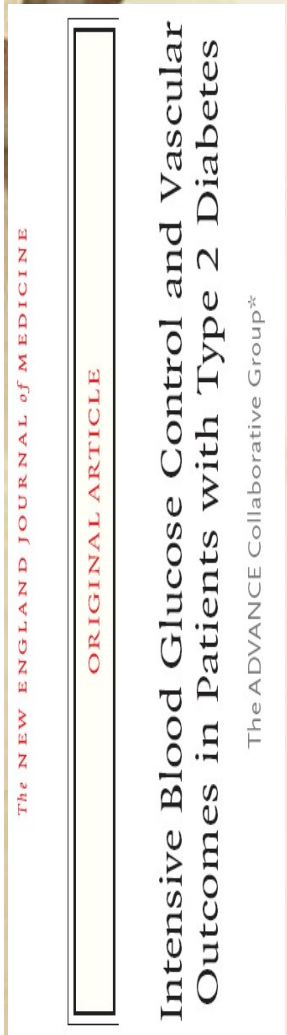
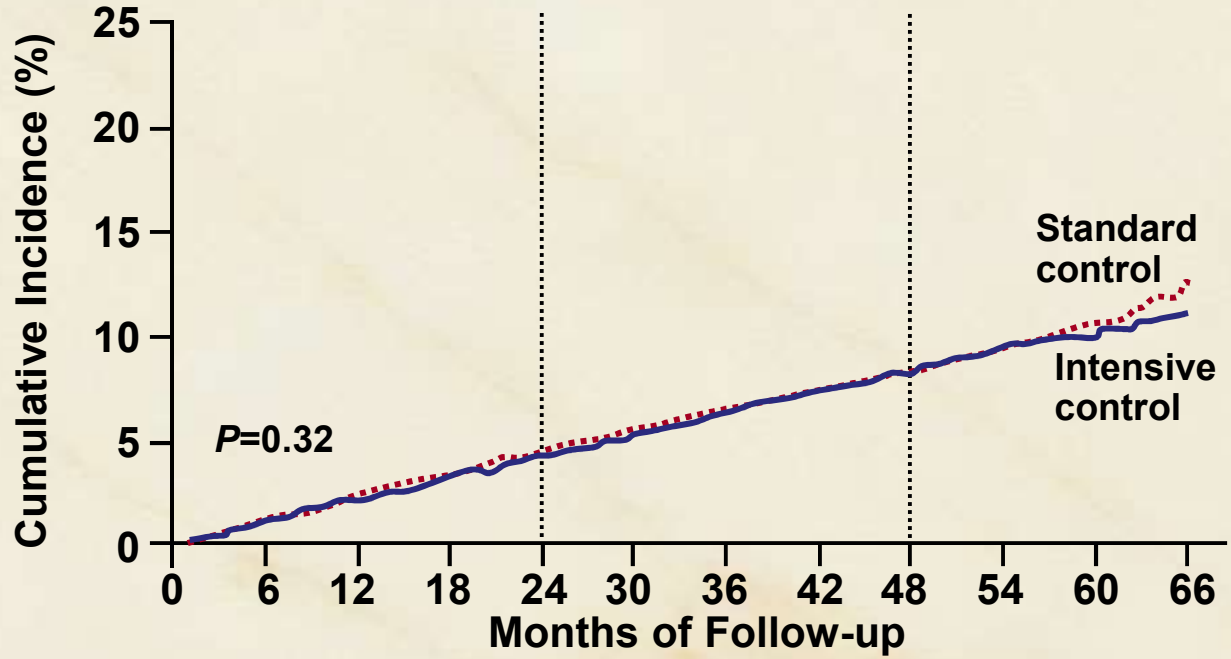


Hazard ratio for intensive control vs standard control was 0.94 (95% CI: 0.84 to 1.06)

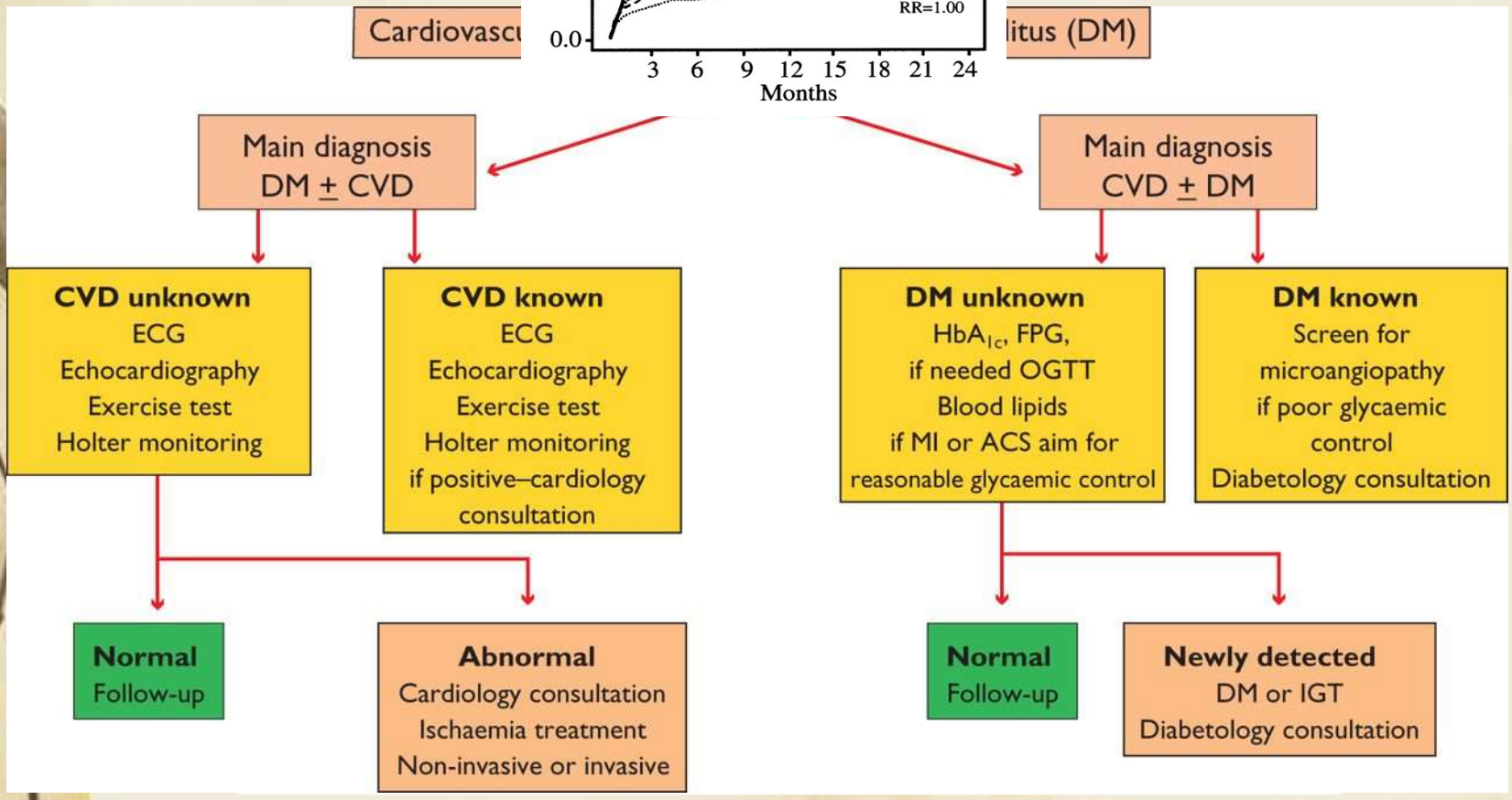


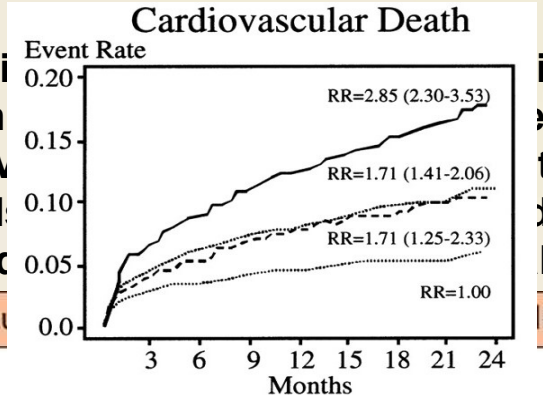
No. at Risk

Intensive	5570	5494	5428	5338	5256	5176	5097	5005	4927	4396	2071	486
Standard	5569	5486	5413	5330	5237	5163	5084	4995	4922	4385	2108	509

The ADVANCE Collaborative Group. *N Engl J Med.* 2008;358(24):2560-2572.

Investigational algorithm outli… iagnosis and management of cardiovascular disease (CVD) in… ents with a primary diagnosis of DM or a primary diagnosis of CV… tigations should be considered according to individual needs… d are not meant as a general recommend… ll patients.

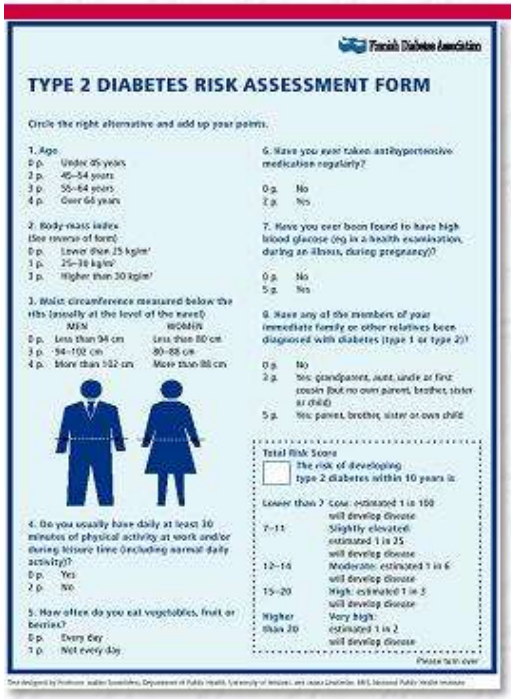




Authors/Task Force Members et al. Eur Heart J 2013;34:3035-3087

European Heart Journal

Screening for disorders of glucose metabolism



Finnish Diabetes Association

TYPE 2 DIABETES RISK ASSESSMENT FORM

Circle the right alternative and add up your points.

1. Age
0 p. Under 45 years
2 p. 45–54 years
3 p. 55–64 years
4 p. Over 64 years

2. Body-mass index
(See reverse of form)
0 p. Lower than 25 kg/m²
1 p. 25–30 kg/m²
3 p. Higher than 30 kg/m²

3. Waist circumference measured below the ribs (usually at the level of the navel)

	MEN	WOMEN
0 p.	Less than 94 cm	Less than 80 cm
3 p.	94–102 cm	80–88 cm
4 p.	More than 102 cm	More than 88 cm

4. Do you usually have daily at least 30 minutes of physical activity at work and/or during leisure time (including normal daily activity)?
0 p. Yes
2 p. No

5. How often do you eat vegetables, fruit or berries?
0 p. Every day
1 p. Not every day

6. Have you ever taken antihypertensive medication regularly?
0 p. No
2 p. Yes

7. Have you ever been found to have high blood glucose (eg in a health examination, during an illness, during pregnancy)?
0 p. No
5 p. Yes

8. Have any of the members of your immediate family or other relatives been diagnosed with diabetes (type 1 or type 2)?
0 p. No
3 p. Yes: grandparent, aunt, uncle or first cousin (but no own parent, brother, sister or child)
5 p. Yes: parent, brother, sister or own child

Total Risk Score

	The risk of developing type 2 diabetes within 10 years is:
Lower than 7	Low: estimated 1 in 100 will develop disease
7–11	Slightly elevated: estimated 1 in 25 will develop disease
12–14	Moderate: estimated 1 in 6 will develop disease
15–20	High: estimated 1 in 3 will develop disease
Higher than 20	Very high: estimated 1 in 2 will develop disease

Please turn over

Questionnaires

e.g FINDRISC

Symptoms
Random glucose
Fasting glucose
HbA_{1c}

Oral glucose tolerance test

75 g glucose in 200 ml H_2O

P-glucose after 0 and 120 minutes

www.escardio.org/guidelines

Full text: European Heart Journal 2013;34(39):3035-3087
Summary: ESC web site & Diabetologia 2013;56(12)

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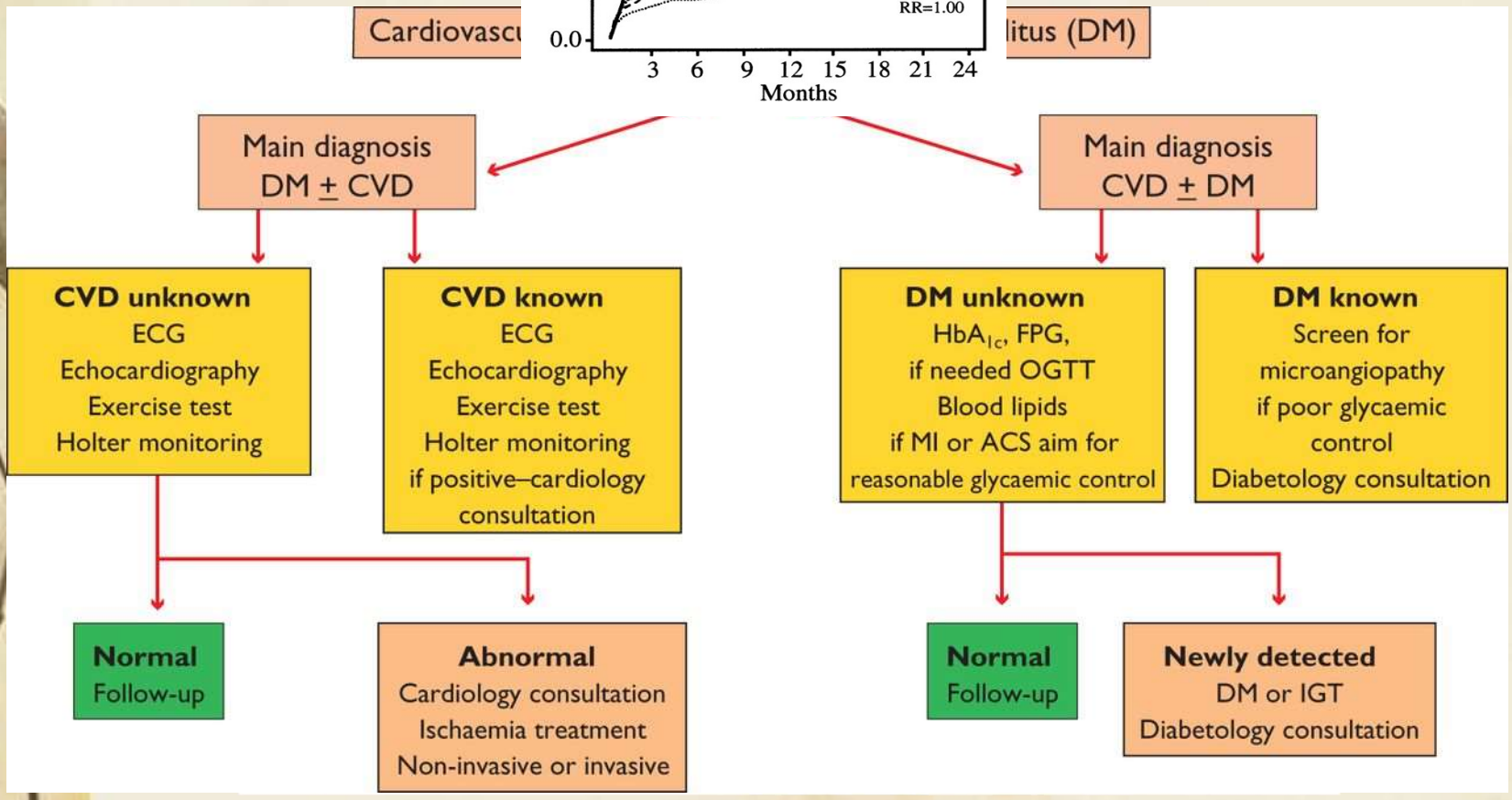
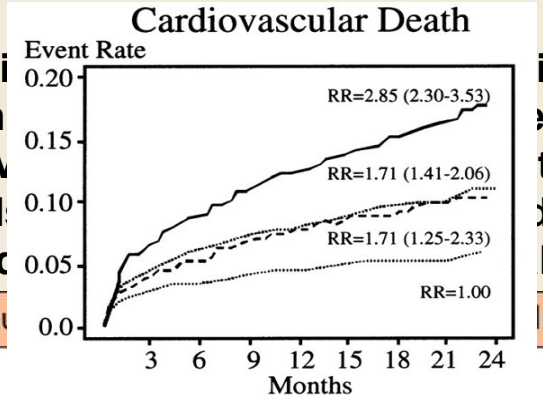
Investigational algorithm outli… iagnosis and management of cardiovascular disease (CVD) in… ents with a primary diagnosis of DM or a primary diagnosis of CV… tigations should be considered according to individual needs… d are not meant as a general recommend… ll patients.





Authors/Task Force Members et al. Eur Heart J 2013;34:3035-3087

European Heart Journal

What is cardiovascular disease prevention?

European Heart Journal Advance Access published May 23, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw106

JOINT ESC GUIDELINES

Definition and rationale

Cardiovascular disease (CVD) prevention is defined as a **coordinated set of actions**, at the population level or targeted at an individual, that are aimed at eliminating or minimizing the impact of CVDs and their related disabilities.

2016 European Guidelines on cardiovascular disease prevention in clinical practice

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)

Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)

When to assess total cardiovascular risk?

Screening is the identification of unrecognized disease or, in this case, of an unknown increased risk of CVD in individuals without symptoms.

CV risk assessment or screening can be done opportunistically or systematically.

Opportunistic screening means without a predefined strategy, but is done when the opportunity arises [e.g. when the individual is consulting his or her general practitioner (GP) for some other reason].

Systematic screening can be done in the general population as part of a screening programme or in targeted subpopulations, such as subjects with a family history of premature CVD or familial hyperlipidaemia.

Recommendations	Class[a]	Level[b]
Systematic CV risk assessment is recommended in individuals at increased CV risk, i.e. with family history of premature CVD, familial hyperlipidaemia, major CV risk factors (such as smoking, high BP, DM or raised lipid levels) or comorbidities increasing CV risk.	I	C
It is recommended to repeat CV risk assessment every 5 years, and more often for individuals with risks close to thresholds mandating treatment.	I	C
Systematic CV risk assessment may be considered in men >40 years of age and in women >50 years of age or post-menopausal with no known CV risk factors.	IIb	C
Systematic CV risk assessment in men <40 of age and women <50 years of age with no known CV risk factors is not recommended.	III	C

How to estimate total cardiovascular risk?

In apparently healthy persons, CV risk in general is the result of multiple, interacting risk factors. This is the basis for the total CV risk approach to prevention.

Ten-year cardiovascular risk

Many CV risk assessment systems are available for use in apparently healthy individuals, including Framingham, SCORE, ASSIGN (CV risk estimation model from the Scottish Intercollegiate Guidelines Network),Q-Risk, PROCAM (Prospective Cardiovascular Munster Study), CUORE, the Pooled Cohort equations, Arriba, ASCVD and Globorisk.

In practice, most risk estimation systems perform rather similarly when applied to populations recognizably comparable to those from which the risk estimation system was derived. **Since 2003, the European Guidelines on CVD prevention in clinical practice recommend use of the SCORE system, because it is based on large, representative European cohort datasets. The SCORE risk function has been externally validated.**[53]

Guidelines for the assessment of

Absolute cardiovascular disease **risk**

In adults without known CVD, a comprehensive assessment of cardiovascular risk includes consideration of the below.

Modifiable risk factors

- Smoking status
- Blood pressure
- Serum lipids
- Waist circumference and body mass index
- Nutrition
- Physical activity level
- Alcohol intake*

Non-modifiable risk factors

- Age and sex
- Family history of premature CVD
- Social history including cultural identity, ethnicity, socioeconomic status and mental health

Related conditions

- Diabetes
- Kidney function (microalbumin ± urine protein, eGFR)
- Familial hypercholesterolaemia
- Evidence of atrial fibrillation (history, examination, electrocardiogram)

* Alcohol is a risk factor for elevated blood pressure (which is itself a major independent determinant of risk of atherosclerotic disease), stroke and cardiomyopathy. For a full discussion of this, please see the NHMRC's *Australian guidelines to reduce health risks from drinking alcohol*.

SCORE chart: 10-year risk of fatal cardiovascular disease in populations of countries at high cardiovascular risk based on the following risk factors: age, sex, smoking, systolic blood pressure, total cholesterol.

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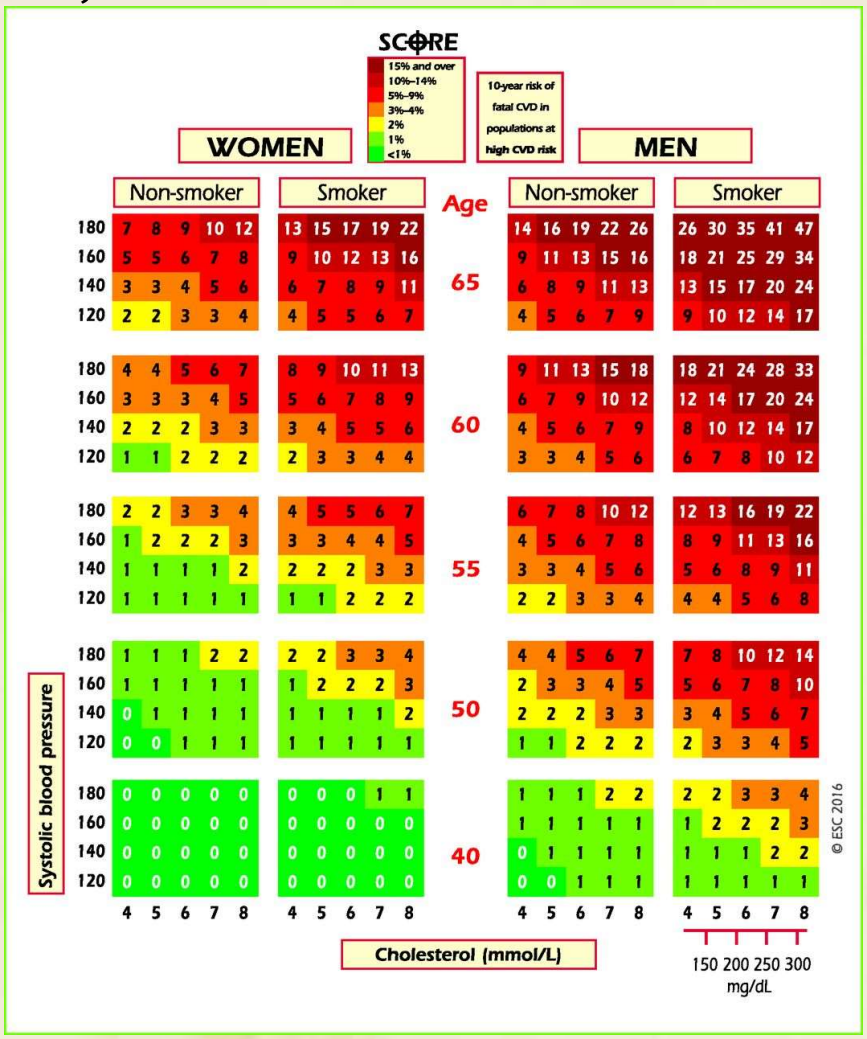
In these guidelines the cut-off points for calling a country 'high risk' are based on age-adjusted 2012 CVD mortality rates in those 45–74 years of age (≥225/100 000 in men and ≥175/100 000 in women).

The very high-risk countries are Albania, Algeria, Armenia, Azerbaijan, Belarus, Bulgaria, Egypt, Georgia, Kazakhstan, Kyrgyzstan, Latvia, former Yugoslav Republic of Macedonia, Moldova, Russian Federation, Syrian Arab Republic, Tajikistan, Turkmenistan, Ukraine and Uzbekistan.



Massimo F. Piepoli et al. Eur Heart J 2016;eurheartj.ehw106

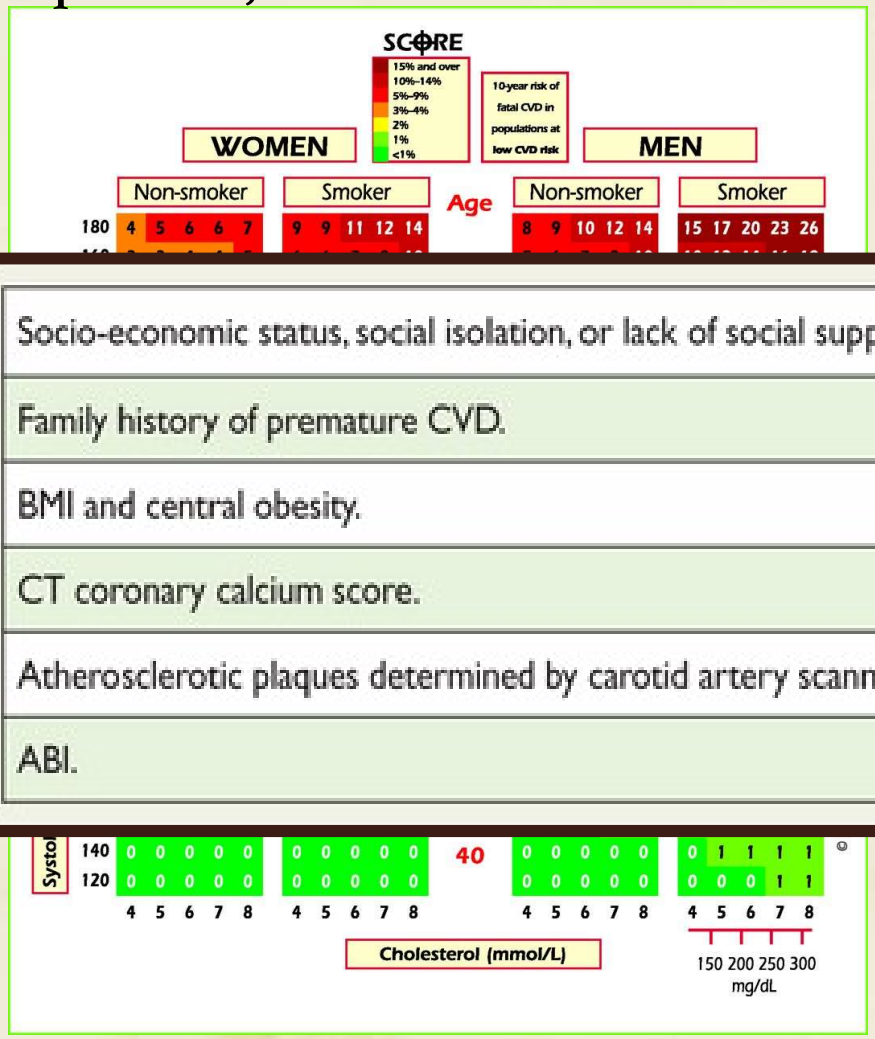
European Heart Journal

SCORE chart: 10-year risk of fatal cardiovascular disease in populations of countries at low cardiovascular risk based on the following risk factors: age, sex, smoking, systolic blood pressure, total cholesterol.

MIGNC,Fe

In these guidelines the cut-off

- Dealing with the impact of additional risk factors such as body weight, family history and newer risk markers is difficult within the constraint of a paper chart. It should be stressed, however, that although many other risk factors have been identified, **their contribution is generally very modest to both absolute CV risk estimations and in terms of reclassification** of an individual to another risk category.



- Socio-economic status, social isolation, or lack of social support.
- Family history of premature CVD.
- BMI and central obesity.
- CT coronary calcium score.
- Atherosclerotic plaques determined by carotid artery scanning.
- ABI.

Massimo F. Piepoli et al. Eur Heart J 2016;eurheartj.ehw106

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Risk categories

ACS = acute coronary syndrome;
AMI = acute myocardial infarction;
BP = blood pressure;
CKD = chronic kidney disease;
DM = diabetes mellitus;
GFR = glomerular filtration rate;
PAD = peripheral artery disease;
SCORE = systematic coronary risk estimation;
TIA = transient ischaemic attack.

Very high-risk	Subjects with any of the following: • Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension. • Severe CKD (GFR <30 mL/min/1.73 m2). • A calculated SCORE ≥10%.
High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m^2). • A calculated SCORE ≥5% and <10%.
Moderate risk	SCORE is ≥1% and <5% at 10 years. Many middle-aged subjects belong to this category.
Low-risk	SCORE <1%.

Cardiovascular risk assessement in people with dysglycaemia (2)

- **Very high risk**
  - Diabetes + ≥1 cardiovascular risk factor or target organ damage.
- **High risk**
  - All other patients with diabetes.

www.escardio.org/guidelines

Full text: European Heart Journal 2013;34(39):3035-3087
Summary: ESC web site & Diabetologia 2013;56(12)

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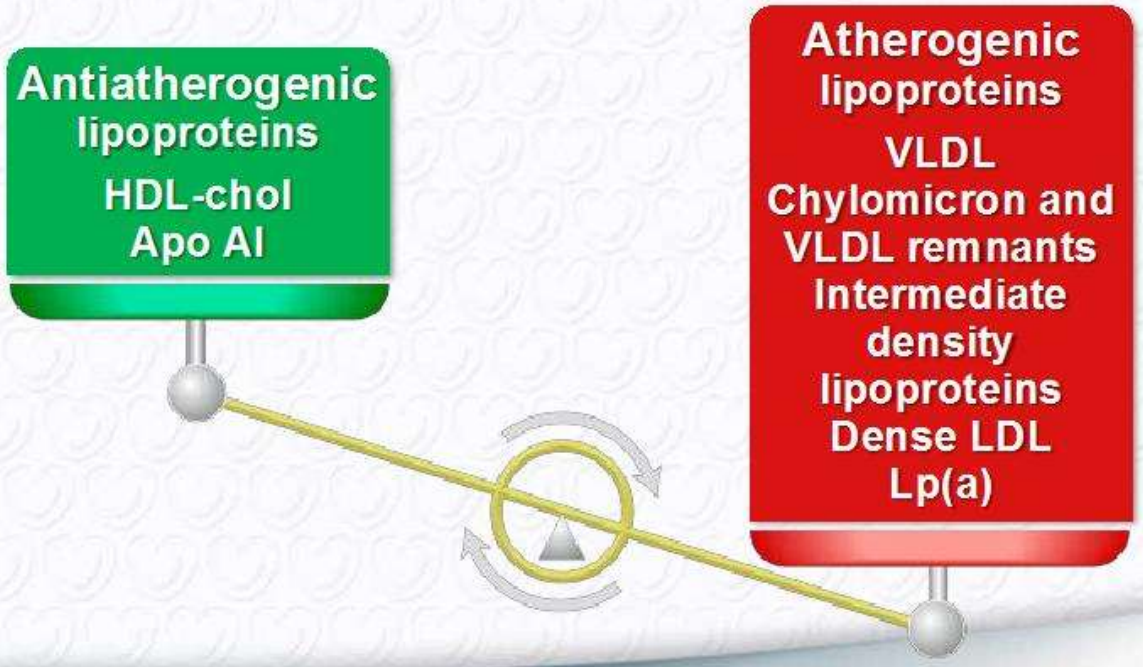
Characteristics of dyslipidaemia in people with type 2 diabetes (2)

Imbalance between atherogenic and antiatherogenic lipoproteins and dysfunctional HDL particles



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Full text: European Heart Journal 2013;34(39):3035-3087
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Stepwise Selection of Risk Factors* in 2693 White Patients with Type 2 Diabetes with Dependent Variable as Time to First Event: UKPDS

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Coronary Artery Disease (n=280)		
Position in Model	Variable	p Value
First	LDL Cholesterol	<0.0001
Second	HDL Cholesterol	0.0001
Third	Hemoglobin A_{1c}	0.0022
Fourth	Systolic Blood Pressure	0.0065
Fifth	Smoking	0.056

*Adjusted for age and sex.

Turner RC et al. BMJ 1998;316:823-828.

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

R C Turner, H Millns, H A W Neil, I M Stratton, S E Manley, D R Matthews, R R Holman for the United Kingdom Prospective Diabetes Study Group

The strategic ‘five As' for smoking cessation

A–ASK:	Systematically inquire about smoking status at every opportunity.
A–ADVISE:	Unequivocally urge all smokers to quit.
A–ASSESS:	Determine the person’s degree of addiction and readiness to quit.
A–ASSIST:	Agree on a smoking cessation strategy, including setting a quit date, behavioural counselling, and pharmacological support.
A–ARRANGE:	Arrange a schedule for follow-up.

Possible intervention strategies as a function of total cardiovascular risk and low-density lipoprotein cholesterol level

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Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.6 mmol/L	100 to <155 mg/dL 2.6 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	≥190 mg/dL ≥4.9 mmol/L
<1	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	Lifestyle advice	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	I/A
≥5 to <10, or high-risk	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice and drug treatment for most	Lifestyle advice and drug treatment	Lifestyle advice and drug treatment
Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A
≥10 or very high-risk	Lifestyle advice, consider drug	Lifestyle advice and concomitant drug treatment	Lifestyle advice and concomitant drug treatment	Lifestyle advice and concomitant drug treatment	Lifestyle advice and concomitant drug treatment
Class[a]/Level[b]	IIa/A	IIa/A	I/A	I/A	I/A

Life-style modification in diabetes

Recommendations	Class	Level
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

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Full text: European Heart Journal 2013;34(39):3035-3087
Summary: ESC web site & Diabetologia 2013;56(12)

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- Three continents (Europe, Asia, Africa), 15 countries
- Dry hot summers and cool pleasant winter
- Staples are wheat and rice
- Olive groves, fig trees, vineyard, almonds, walnuts, lemons, apricots, etc are characteristic of local produce

must be discouraged.

Possible intervention strategies as a function of total cardiovascular risk and low-density lipoprotein cholesterol level

MIGNC,Fe

Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.6 mmol/L	100 to <155 mg/dL 2.6 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	≥190 mg/dL ≥4.9 mmol/L
<1	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	Lifestyle advice	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	I/A
≥5 to <10, or high-risk	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice and drug treatment for most	Lifestyle advice and drug treatment	Lifestyle advice and drug treatment
Class[a]/Level[b]	IIa/A	IIa/A	IIa/A	I/A	I/A
≥10 or very high-risk	Lifestyle advice, consider drug	Lifestyle advice and concomitant drug treatment	Lifestyle advice and concomitant drug treatment	Lifestyle advice and concomitant drug treatment	Lifestyle advice and concomitant drug treatment
Class[a]/Level[b]	IIa/A	IIa/A	I/A	I/A	I/A

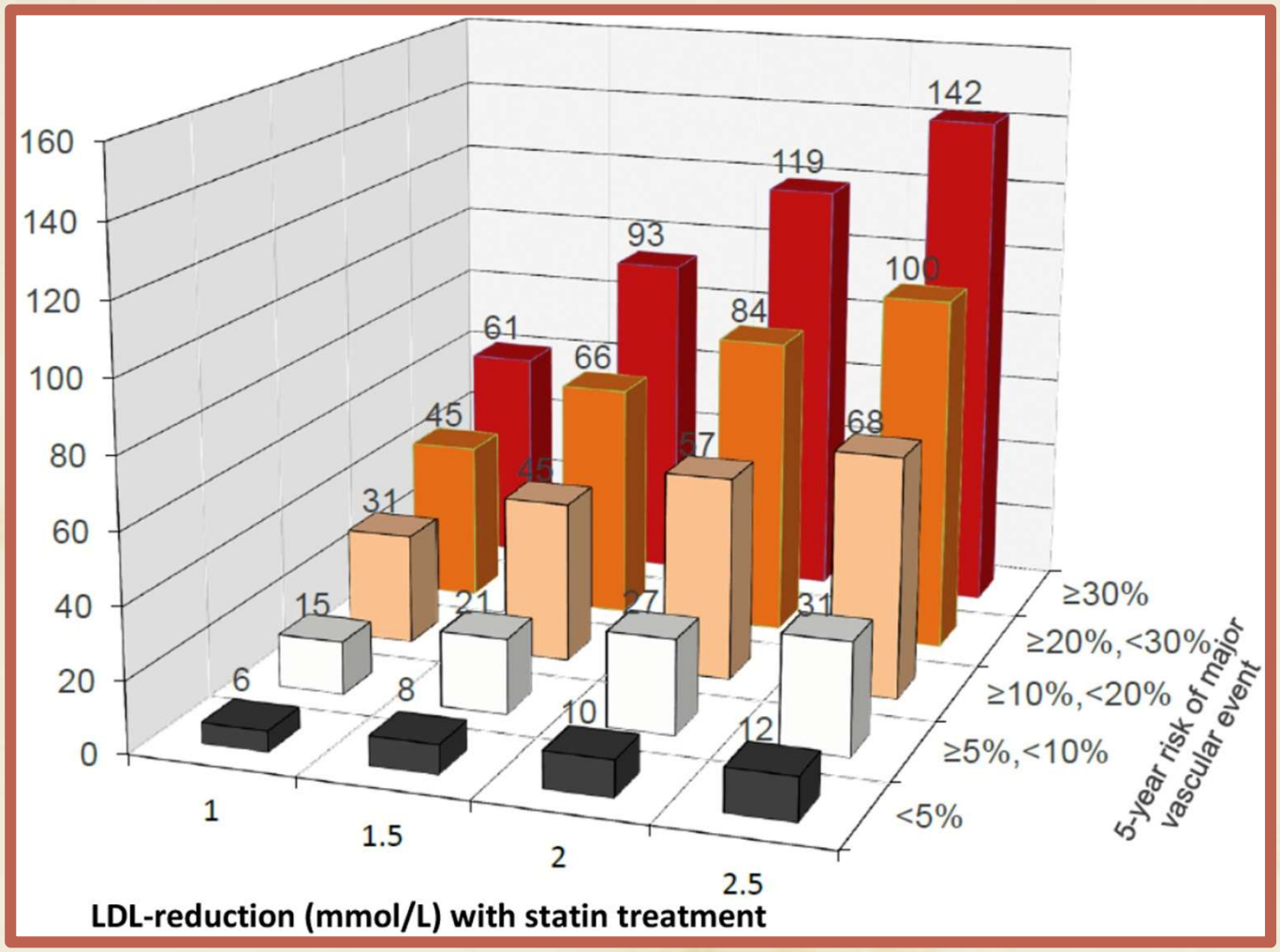
Types of lipid modification agent

Approved drugs

- HMG Co A reductase inhibitors (Statins)
- Cholesterol absorption inhibitors (Ezetimibe)
- PPARα agonists (Fibrates)
- Bile acid sequestrants ('Resins')
- Nicotinic acid (also known as 'niacin')
- Antisense oligonucleotides (Mipomersen)
- Microsomal transfer protein inhibitors (Lomitapide)
- PCSK9 inhibitors (evolocumab and alirocoumab)

In development

- PCSK9 inhibitors (bococizumab)
- CETP inhibitors
- Anti-sense technologies targeting ApoC and lipoprotein (a)



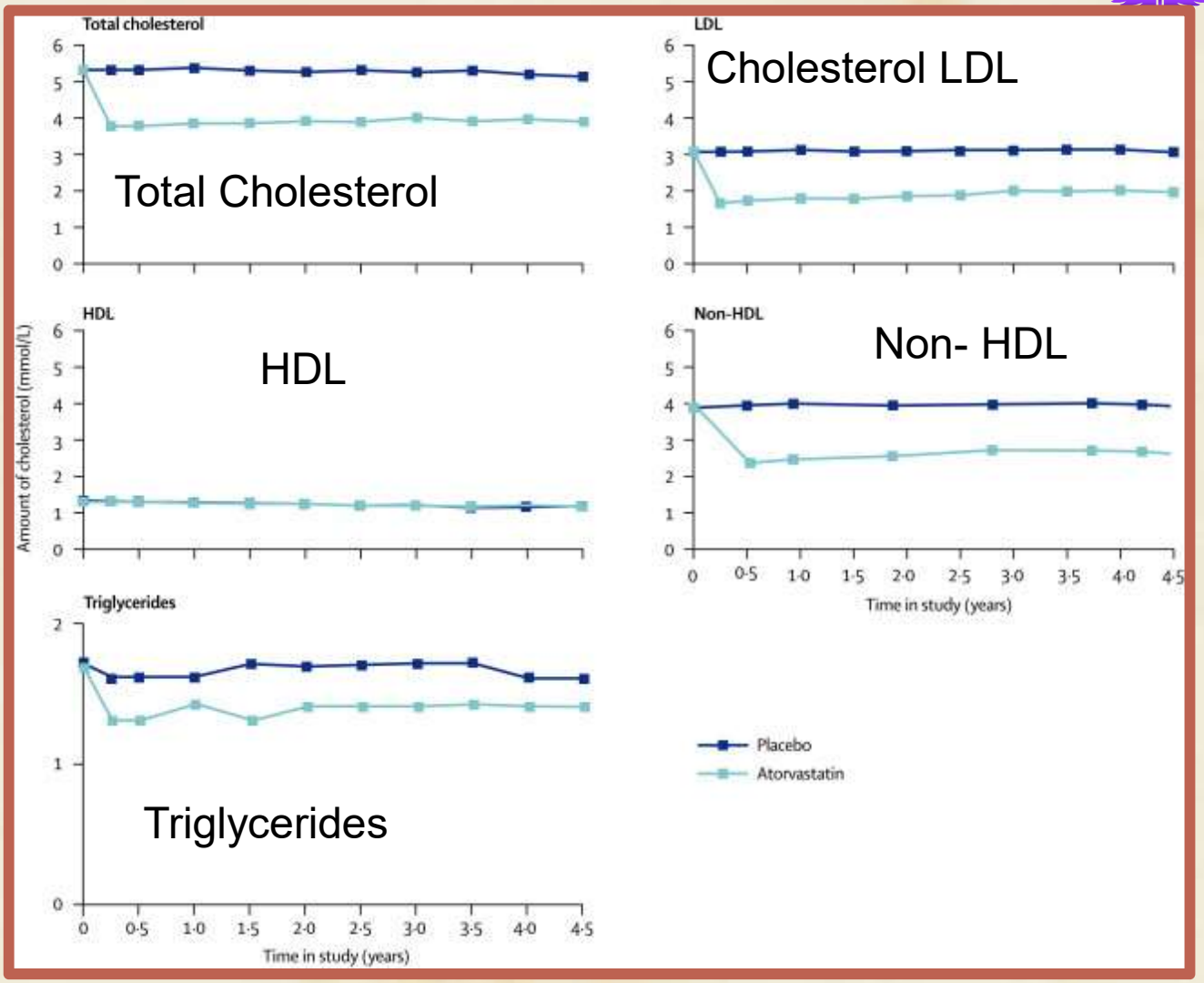
Atherosclerosis 2016 245, 161-170DOI: (10.1016/j.atherosclerosis.2015.12.018)

Median lipid concentrations

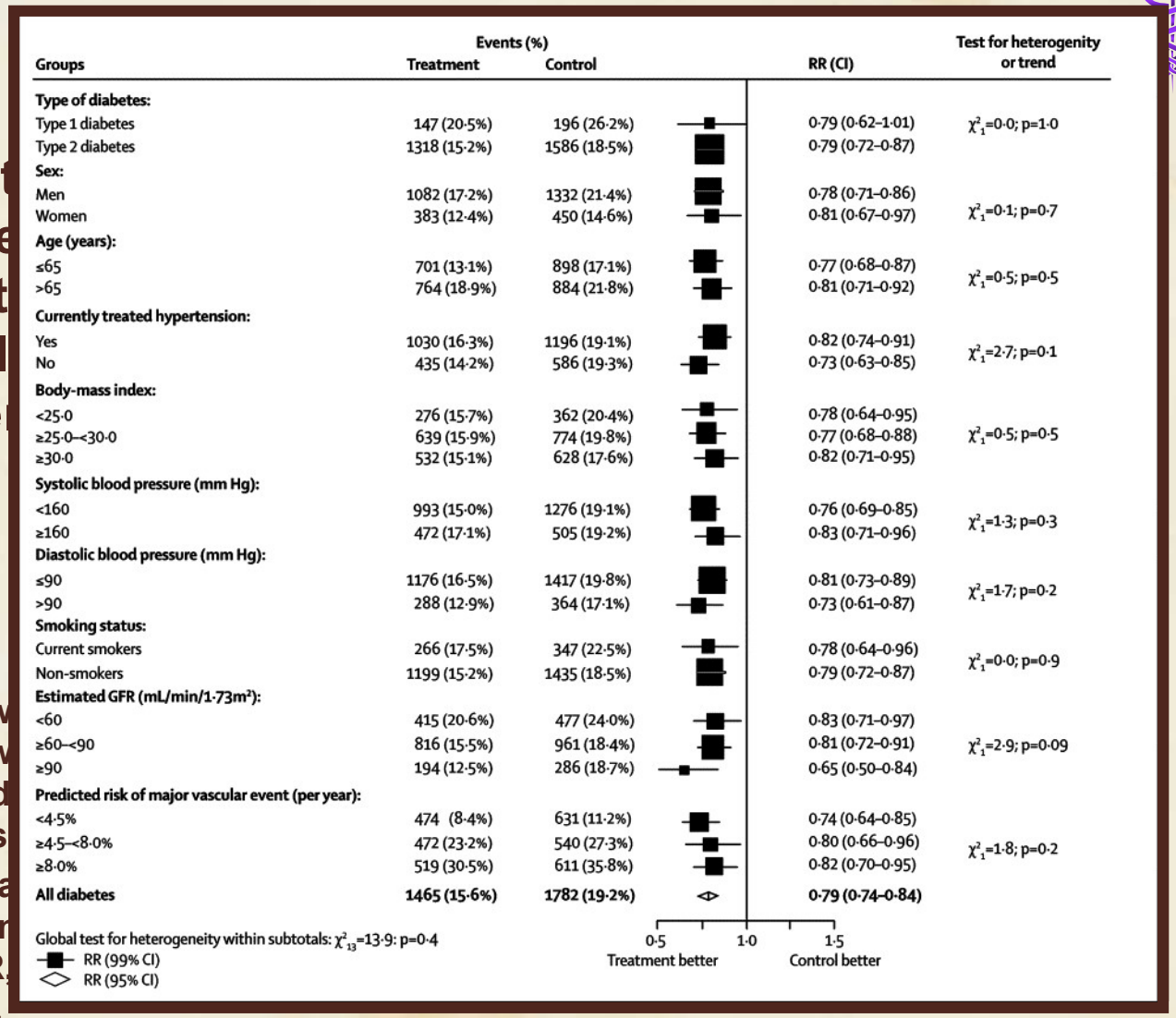
Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial

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

Lancet. 2004 Aug 21-27;364(9435):685-96



Proportional effect
major vascular eve
per mmol/L reduct
in LDL cholesterol
participants prese
with or without
diabetes



Groups	Events (%) Treatment	Control	RR (CI)	Test for heterogenity or trend
Type of diabetes:				
Type 1 diabetes	147 (20·5%)	196 (26·2%)	0·79 (0·62–1·01)	χ^2_1=0·0; p=1·0
Type 2 diabetes	1318 (15·2%)	1586 (18·5%)	0·79 (0·72–0·87)	
Sex:				
Men	1082 (17·2%)	1332 (21·4%)	0·78 (0·71–0·86)	
Women	383 (12·4%)	450 (14·6%)	0·81 (0·67–0·97)	χ^2_1=0·1; p=0·7
Age (years):				
≤65	701 (13·1%)	898 (17·1%)	0·77 (0·68–0·87)	
>65	764 (18·9%)	884 (21·8%)	0·81 (0·71–0·92)	χ^2_1=0·5; p=0·5
Currently treated hypertension:				
Yes	1030 (16·3%)	1196 (19·1%)	0·82 (0·74–0·91)	
No	435 (14·2%)	586 (19·3%)	0·73 (0·63–0·85)	χ^2_1=2·7; p=0·1
Body-mass index:				
<25·0	276 (15·7%)	362 (20·4%)	0·78 (0·64–0·95)	
≥25·0–<30·0	639 (15·9%)	774 (19·8%)	0·77 (0·68–0·88)	χ^2_1=0·5; p=0·5
≥30·0	532 (15·1%)	628 (17·6%)	0·82 (0·71–0·95)	
Systolic blood pressure (mm Hg):				
<160	993 (15·0%)	1276 (19·1%)	0·76 (0·69–0·85)	
≥160	472 (17·1%)	505 (19·2%)	0·83 (0·71–0·96)	χ^2_1=1·3; p=0·3
Diastolic blood pressure (mm Hg):				
≤90	1176 (16·5%)	1417 (19·8%)	0·81 (0·73–0·89)	
>90	288 (12·9%)	364 (17·1%)	0·73 (0·61–0·87)	χ^2_1=1·7; p=0·2
Smoking status:				
Current smokers	266 (17·5%)	347 (22·5%)	0·78 (0·64–0·96)	
Non-smokers	1199 (15·2%)	1435 (18·5%)	0·79 (0·72–0·87)	χ^2_1=0·0; p=0·9
Estimated GFR (mL/min/1·73m²):				
<60	415 (20·6%)	477 (24·0%)	0·83 (0·71–0·97)	
≥60–<90	816 (15·5%)	961 (18·4%)	0·81 (0·72–0·91)	
≥90	194 (12·5%)	286 (18·7%)	0·65 (0·50–0·84)	χ^2_1=2·9; p=0·09
Predicted risk of major vascular event (per year):				
<4·5%	474 (8·4%)	631 (11·2%)	0·74 (0·64–0·85)	
≥4·5–<8·0%	472 (23·2%)	540 (27·3%)	0·80 (0·66–0·96)	
≥8·0%	519 (30·5%)	611 (35·8%)	0·82 (0·70–0·95)	χ^2_1=1·8; p=0·2
All diabetes	**1465 (15·6%)**	**1782 (19·2%)**	**0·79 (0·74–0·84)**	

Global test for heterogeneity within subtotals: χ^2_{13}=13·9: p=0·4

RR (99% CI)

RR (95% CI)

0·5 Treatment better

1·0

1·5 Control better

Efficacy of cholesterol-lov
therapy in 18 686 people w
diabetes in 14 randomised
of statins: a meta-analysis

Cholesterol Treatment Tria
(CTT) Collaborators, Kearn
PM, Blackwell L, Collins R,
Keech A, Simes J, Peto R,
Armitage J, Baigent C.

Lancet. 2008 Jan
12;371(9607):117-25.

Percentage reduction of LDL-C required to achieve goals as a function of the starting value

A systematic review and meta-analysis on the therapeutic equivalence of statins

Dyslipidaemia in diabetes			
Recommendations	**Class** [a]	**Level** [b]	**Ref.** [c]
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	227, 234, 238
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	227, 234
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	251, 252, 256

Weng TC, et al. J Clin Pharm Ther. 2010;35;139-151
Mukhtar RY, et al. Int J Clin Pract. 2005;59(2):239-252

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European Heart Journal 2011;32 (14):1769–1818
Atherosclerosis 2011 Jul;217(1):3-46

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Summary of recommendations for monitoring lipids and enzymes in patients on lipid-lowering therapy (1)

Testing lipids
How often should lipids be tested? • Before starting lipid-lowering drug treatment, at least two measurements should be made, with an interval of 1-12 weeeks, with the exception of conditions where immediate drug treatment is suggested such as in ACS.
How often should patients's lipids be tested after starting lipid-lowering treatment? • 8 (± 4) week after starting drug treatment. • 8 (± 4)weeks after adjustements to treatment until within the target range.
How often should cholesterol or lipids be tested once a patient has reached target or optimal cholesterol? • Annually (unless there is adherence problems or another specific reason for more frequent reviews).

European Heart Journal 2011;32 (14):1769–1818
Atherosclerosis 2011 Jul;217(1):3-46

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Summary of recommendations for monitoring lipids and enzymes in patients on lipid-lowering therapy (2)

Monitoring liver and muscle enzymes

How often should liver enzymes (ALT) be routinely mesured in patients taking lipid lowering drug?

- Before treatment.
- 8 weeks after starting drug treatment or after any dose increase.
- Annually thereafter if liver enzymes are <3 x ULN.

What if liver enzymes becomes raised in a person taking lipid-lowering drugs?

If < 3 x ULN:

- Continuous therapy
- Recheck liver enzymes in 4-6 weeks.

If values rise to ≥ 3 x ULN:

- Stop statin or reduce dose, recheck liver enzymes within 4-6 weeks.
- Cautious reintroduction of therapy may be considered after ALT has returned to normal.

ACS = acute coronary syndrome
ALT = alanine aminotransferase
CK = creatine phosphokinase
ULN = upper limit of normal

How often should CK be measured in patients taking lipid-lowering drugs?

Pre-treatment

- Before starting treatment.
- If baseline CK level > 5 x ULN, do not start drug therapy; recheck.

Monitoring

- Routine monitoring of CK is not necessary.
- Check CK if patient develops myalgia.

Increase alertness regarding myopathy and CK elevation in patients at risk such as: elderly patients, concomitant interfering therapy, multiple medications, liver or renal disease.

What if CK becomes raised in a person taking lipid-lowering drugs?

If > 5 x ULN:

- Stop treatment, check renal function and monitor CK every 2 weeks.
- Consider the possibility of transient CK elevation for other reasons such as muscle exertion.
- Consider secondary causes of myopathy if CK remains elevated.

If ≤ 5 x ULN:

- If no muscle symptoms, continue statin (patients should be alerted to report symptoms; consider further checks of CK).
- If muscle symptoms, monitor symptoms and CK regularly.

European Heart Journal 2011;32 (14):1769–1818
Atherosclerosis 2011 Jul;217(1):3-46

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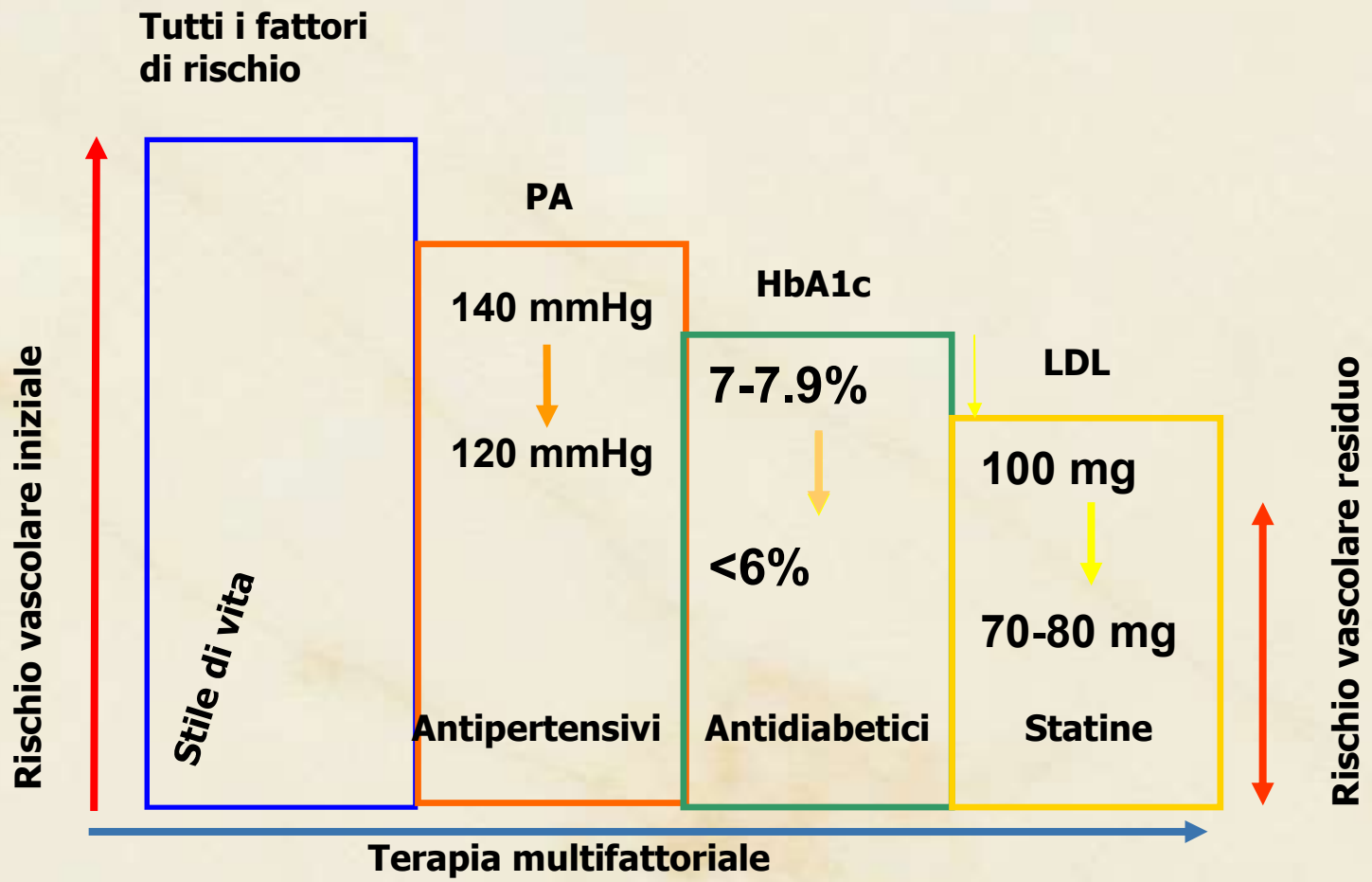
Gli standard terapeutici attuali lasciano i pazienti con un importante rischio vascolare residuo



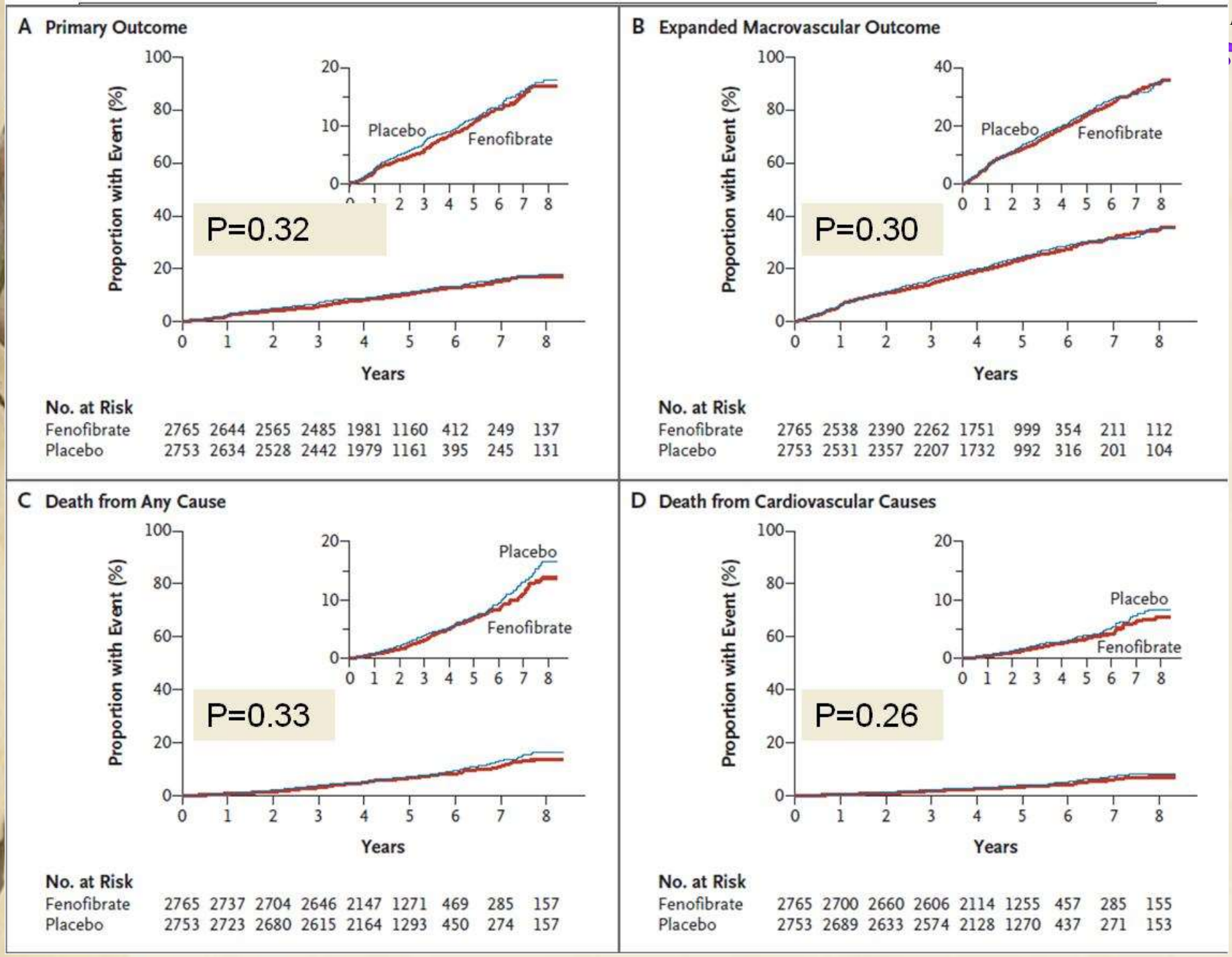
Types of lipid modification agent

Approved drugs

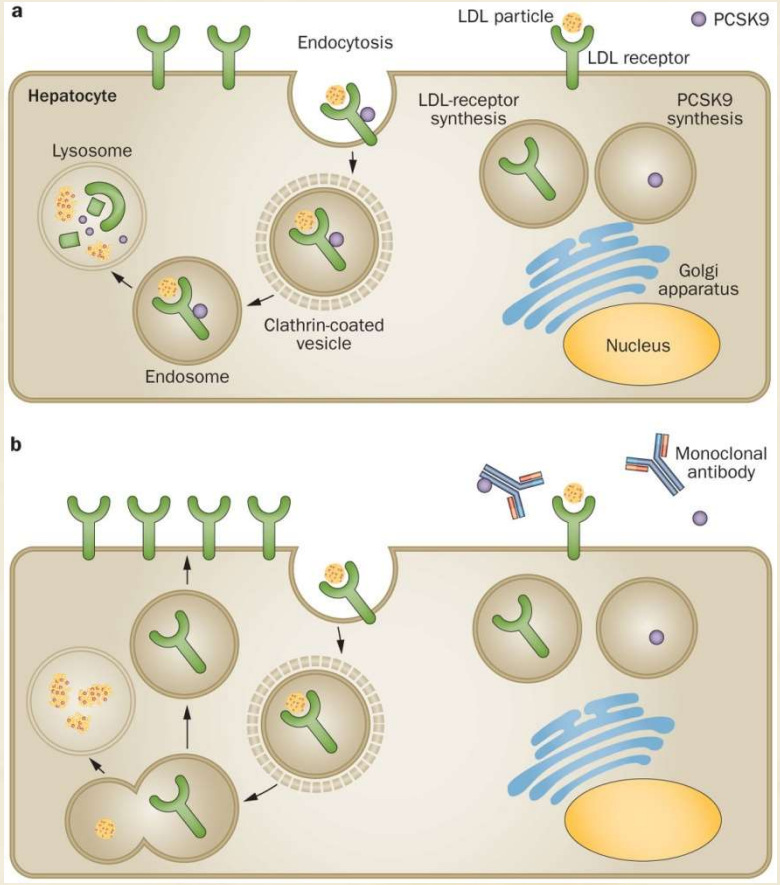
- HMG Co A reductase inhibitors (Statins)
- Cholesterol absorption inhibitors (Ezetimibe)
- PPARα agonists (Fibrates)
- Bile acid sequestrants ('Resins')
- Nicotinic acid (also known as 'niacin')
- Antisense oligonucleotides (Mipomersen)
- Microsomal transfer protein inhibitors (Lomitapide)
- PCSK9 inhibitors (evolocumab and alirocoumab)

In development

- PCSK9 inhibitors (bococizumab)
- CETP inhibitors
- Anti-sense technologies targeting ApoC and lipoprotein (a)


A Primary Outcome
Proportion with Event (%)
Placebo
Fenofibrate
P=0.32
Years
No. at Risk
Fenofibrate 2765 2644 2565 2485 1981 1160 412 249 137
Placebo 2753 2634 2528 2442 1979 1161 395 245 131
B Expanded Macrovascular Outcome
Proportion with Event (%)
Placebo
Fenofibrate
P=0.30
Years
No. at Risk
Fenofibrate 2765 2538 2390 2262 1751 999 354 211 112
Placebo 2753 2531 2357 2207 1732 992 316 201 104
C Death from Any Cause
Proportion with Event (%)
Placebo
Fenofibrate
P=0.33
Years
No. at Risk
Fenofibrate 2765 2737 2704 2646 2147 1271 469 285 157
Placebo 2753 2723 2680 2615 2164 1293 450 274 157
D Death from Cardiovascular Causes
Proportion with Event (%)
Placebo
Fenofibrate
P=0.26
Years
No. at Risk
Fenofibrate 2765 2700 2660 2606 2114 1255 457 285 155
Placebo 2753 2689 2633 2574 2128 1270 437 271 153

LDL-cholesterol metabolism in the presence or absence of PCSK9



Dadu, R. T. & Ballantyne, C. M. (2014) Lipid lowering with PCSK9 inhibitors
Nat. Rev. Cardiol. doi:10.1038/nrcardio.2014.84

nature REVIEWS CARDIOLOGY

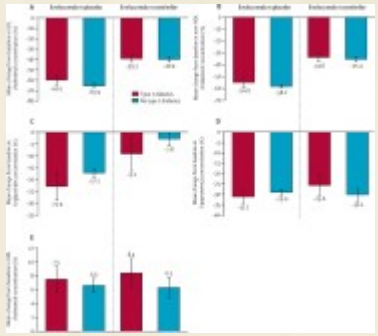
MIGNC,Fe

Lipid-lowering efficacy of the PCSK9 inhibitor evolocumab (AMG 145) in patients with type 2 diabetes: a meta-analysis of individual patient data

Sattar N, Preiss D, Robinson JG, Djedjos CS, Elliott M, Somaratne R, Wasserman SM, Raal FJ.

The Lancet Diabetes & Endocrinology

Volume 4, Issue 5, May 2016, Pages 403–410

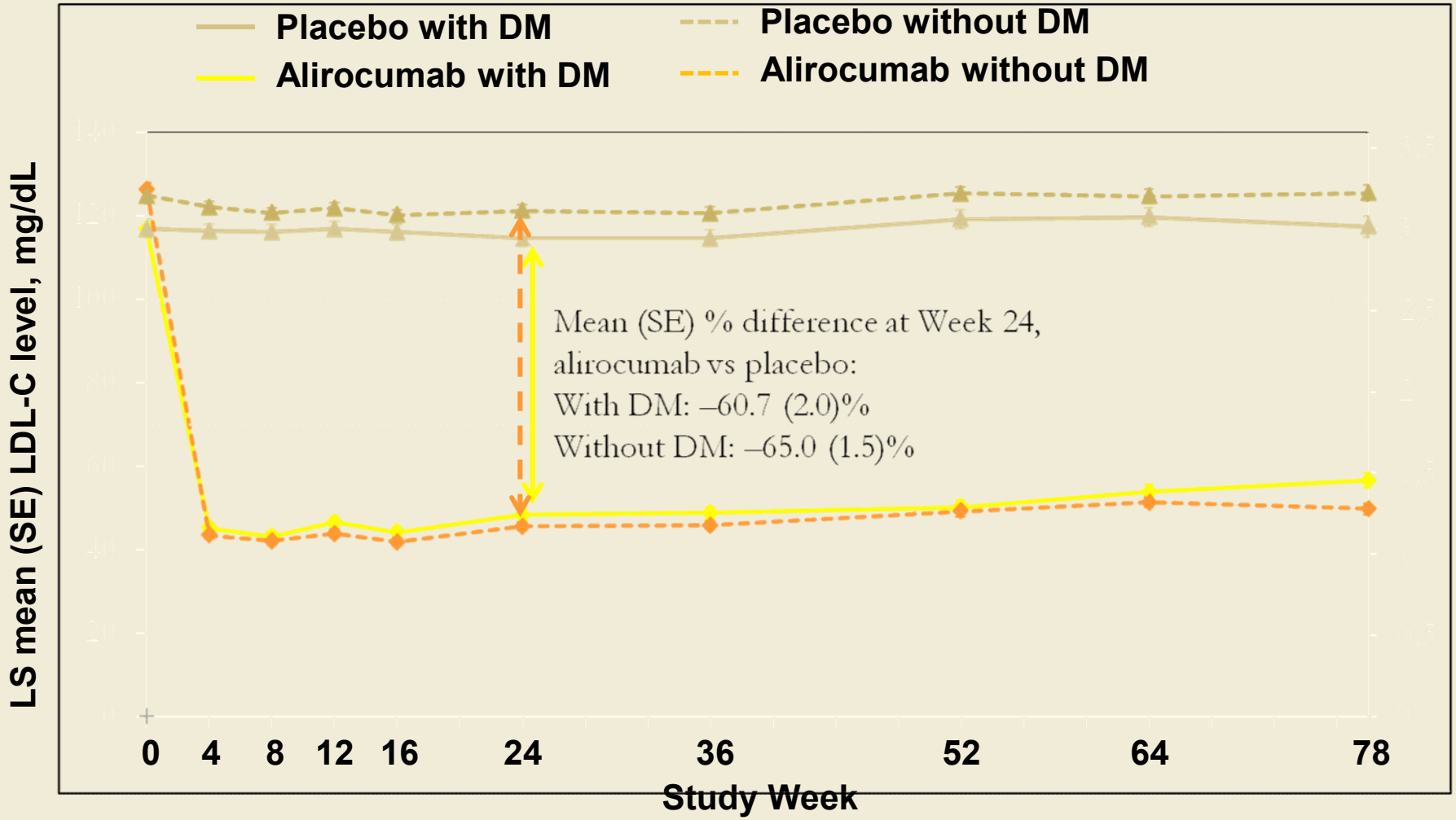


In patients with type 2 diabetes evolocumab caused mean reductions in LDL cholesterol concentration that were **60% (95% CI 51–69) versus placebo and 39% (32–47) versus ezetimibe.**

In patients without type 2 diabetes, evolocumab caused mean reductions in LDL cholesterol that were **66% (62–70) versus placebo and 40% (36–45) versus ezetimibe.**

Repatha

Calculated LDL-C Levels by DM Status (mITT)



Praluent

ODYSSEY

Antiplatelet therapy in people with diabetes

Recommendations	Class	Level
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

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Full text: European Heart Journal 2013;34(39):3035-3087
Summary: ESC web site & Diabetologia 2013;56(12)

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Treatment targets for multifactorial management of people with diabetes

Blood pressure (mmHg) In case of nephropathy	<140/85 Systolic <130
Glycaemic control HbA_{1c} (%)	Generally <7.0 (53 mmol/mol) On an individual basis <6.5-6.9% (48-52 mmol/mol)
Lipid profile mmol/l (mg/dL) LDL-Cholesterol	Very high risk patients <1.8 mmol/L (<70 mg/dL) or reduced by at least 50% High risk patients <2.5 mmol/L (<100 mg/dL)
Patelet stabilization	Patients with CVD and DM ASA 75-160 mg/day
Smoking	Cessation obligatory; passive smoking - none
Physical activity	Moderate to vigorous ≥150 min/week
Weight	Aim for weight stabilization in the overweight or obese DM patients based on calorie balance, and weight reduction in subjects with IGT to prevent development of T2DM
Dietary habits Fat intake (% of dietary energy) Total Saturated Monounsaturated fatty acids Dietary fibre intake	 <35% <10% >10% >40 g/day (or 20 g/1000 Kcal/day)

CVD = cardiovascular disease; DM = diabetes mellitus; HbA_{1c}= glycated haemoglobin A_{14};
IGT = Impaired glucose tolerance; LDL = low density lopoprotein; T2DM = type 2 diabetes mellitus;
??? Diabetes Control and Complication Trial standard.

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Full text: European Heart Journal 2013;34(39):3035-3087
Summary: ESC web site & Diabetologia 2013;56(12)

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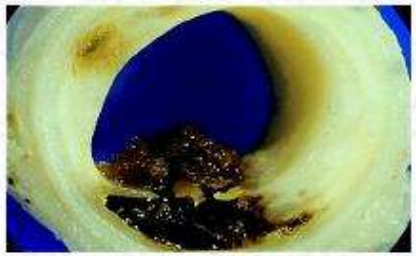
Principles for multifactorial management of people with diabetes

Life style modification

- Glycaemic control
- Antiplatelet therapy
- Blood pressure control
- Lipid control



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Full text: European Heart Journal 2013;34(39):3035-3087
Summary: ESC web site & Diabetologia 2013;56(12)

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28 MAGGIO 2016 CENTO
Hotel Al Castello
LA COMPLESSITÀ ASSISTENZIALE DELLA PERSONA CON DIABETE IN OSPEDALE E SUL TERRITORIO: UN UPDATE SULLE PIÙ RECENTI ACQUISIZIONI DI GOVERNO CLINICO E GESTIONE DELLA TERAPIA
con il Patrocinio di: AMD EMILIA ROMAGNA e SID

Grazie!