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Guidelines

ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with EASD. Summary of the document prepared by the Czech Society of Cardiology☆

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1. Preamble

This is the second iteration of the European Society of Cardiology (ESC) and European Association for the Study of Diabetes (EASD) joining forces to write guidelines on the management of the combination of diabetes mellitus (DM), pre-diabetes, and cardiovascular disease (CVD), designed to assist clinicians and other healthcare workers to make evidence based management decisions [1].

2. Introduction

The increasing prevalence of DM worldwide has led to a situation where approximately 360 million people had DM in 2011 (60 million in Europe), of whom more than 95% would have had type 2 DM (T2DM); another 300 million individuals had features indicating future risk of developing T2DM, including fasting hyperglycaemia, impaired glucose tolerance (IGT), gestational DM and euglycaemic insulin resistance (IR).

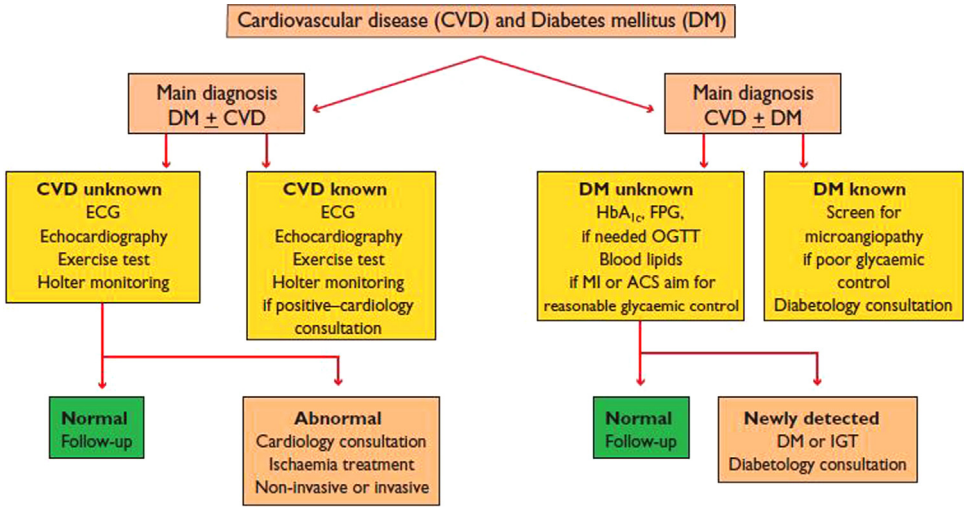

Fig. 1 – Investigational algorithm outlining the principles for the diagnosis and management of cardiovascular disease (CVD) in diabetes mellitus (DM) patients with a primary diagnosis of DM or a primary diagnosis of CVD. The recommended investigations should be considered according to individual needs and clinical judgement and are not meant as a general recommendation to be undertaken by all patients. ACS = acute coronary syndrome; ECG = electrocardiogram; FPG = fasting plasma glucose; HbA1c = glycated haemoglobin A1c; IGT = impaired glucose tolerance; MI = myocardial infarction; OGTT = oral glucose tolerance test.

More than half the mortality and a vast amount of morbidity in people with DM are related to CVD, which caused physicians in the fields of DM and cardiovascular medicine to join forces to research and manage these conditions (Fig. 1).

3. Abnormalities of glucose metabolism and cardiovascular disease

3.1. *Definition, classification and diagnosis*

Definition, classification and diagnosis of impaired glucose metabolism are presented in Tables 1 and 2. To standardize glucose determinations, venous plasma measures have been recommended.

3.2. *Epidemiology*

The International Diabetes Federation's global burden of DM in 2011 and predictions for 2030 are summarized in Table 3.

3.3. *Screening for disorders of glucose metabolism*

Population testing of blood glucose to determine CV risk is not recommended. Screening of hyperglycaemia for CV risk purposes should therefore be targeted to high-risk individuals. Several DM risk scores for DM have been developed; ***the FINnish Diabetes RIsk SCore*** is the most commonly used in Europe (Fig. 2). It is recommended in the general population and people with assumed abnormalities (obesity, hypertension, family history of DM). In CVD patients, no diabetes risk score is needed but an OGTT is indicated if HbA1c and/or fasting plasma glucose (FPG) are inconclusive.

Table 1 – Comparison of 2006 World Health Organization (WHO) and 2003/2011 and 2012 American Diabetes Association (ADA) diagnostic criteria.

Diagnose/ measurement	WHO 2006/2011	ADA 2003 and 2012
Diabetes		
HbA1c	**Can be used** If measured ≥ 48 mmol/mol **Recommended** ≥7.0 mmol/L (≥126 mg/dL)	**Recommended** ≥48 mmol/mol
FPG	**or** ≥11.1 mmol/L (≥200 mg/dL)	≥7.0 mmol/L (≥126 mg/dL) **or**
2hPG		≥11.1 mmol/L (≥200 mg/dL)
IGT		<7.0 mmol/L (<126 mg/dL)
FPG	<7.0 mmol/L (<126 mg/dL)	
2hPG	≥7.8.–<11.1 mmol/L (≥140–<200 mg/dL)	**Not required** If measured 7.8–11.0 mmol/L (140–198 mg/dL)
IFG		
FPG	6.1–6.9 mmol/L (110–125 mg/dL) **If measured**	5.6–6.9 mmol/L (100–125 mg/dL)
2hPG	<7.8 mmol/L (<140 mg/dL)	

FPG = fasting plasma glucose; IGT = impaired glucose tolerance; IFG = impaired fasting glucose; 2hPG = 2-h post-load plasma glucose.

Table 2 – Cut-points for diagnosing DM, impaired glucose tolerance, and impaired fasting glucose based on other blood specimens than the recommended standard, venous plasma.

Diagnosis	Venous plasma* mmol/L (mg/dL)	Venous blood mmol/L (mg/dL)	Capillary blood mmol/L (mg/dL)
IFG-FG	6.1 (110)	5.0 (90)	5.6 (101)
IGT-2hG	7.8 (140)	6.5 (117)	7.2 (130)
Diabetes-FG	7.0 (126)	5.8 (104)	6.5 (117)
Diabetes-2hG	11.1 (200)	9.4 (169)	10.3 (185)

FPG = fasting plasma glucose; FG = fasting glucose; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; 2hG = 2-h post-load glucose; 2hPG = 2-h post-load plasma glucose.
* Standard.

Table 3 – Burden of DM in Europe in 2011 and predictions for 2030.

Variable	2011	2030
Total population (millions)	896	927
Adults (20–79 years; millions)	651	670
DM (20–79 years)		
European prevalence (%)	8.1	9.5
Number with DM (millions)	52.6	64.0
IGT (20–79 years)		
Regional prevalence (%)	9.6	10.6
Number with IGT (millions)	62.8	71.3
Type I DM in children (0–14 years)		
Number with type I DM (thousands)	115.7	–
Number newly diagnosed/year (thousands)	17.8	–
DM mortality (20–79 years)		
Number of deaths; men (thousands)	281.3	–
Number of deaths; women (thousands)	316.5	–
Healthcare expenditure due to DM (20–79 years, Europe)		
Total expenditure (billions of €)	75.1	90.2

DM = diabetes mellitus; IGT = impaired glucose tolerance.

3.4. *Disorders of glucose metabolism and cardiovascular disease*

Several studies have shown that increasing HbA1c is associated with increasing CVD risk. Comparing all three glycaemic parameters: FPG, 2hPG and HbA1c simultaneously for mortality and CVD risk revealed that the association is strongest for 2hPG. Women with newly diagnosed T2DM have a higher relative risk for CVD mortality than their male counterparts. The overall relative risk (the ratio of risk in women to risk in men) was 1.46 (1.21–1.95) in people with DM and 2.29 (2.05–2.55) in those without, suggesting that the well-known gender differential in CAD is reduced in DM.

3.5. *Delaying conversion to type 2 diabetes mellitus*

Modest weight loss and increased physical activity prevent or delay progression in high-risk individuals with IGT. Thus, those at high risk for T2DM and those with established IGT should be given appropriate lifestyle counselling (Tables 4 and 5).

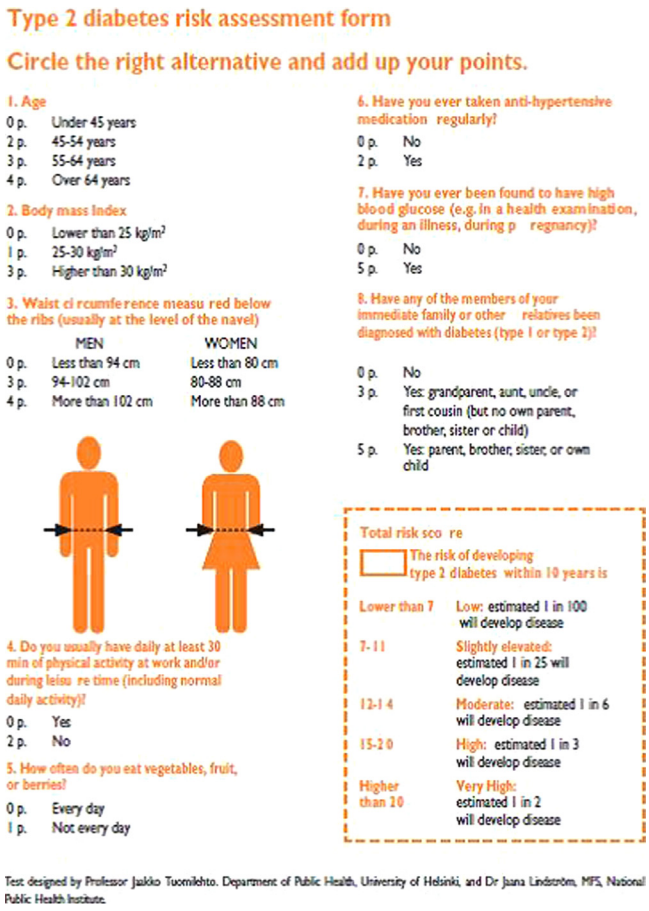

Fig. 2 – FINnish Diabetes RIsk SCore (FINDRISC) to assess the 10-year risk of type 2 diabetes in adults.

4. Molecular basis of cardiovascular disease in diabetes mellitus

4.1. *The cardiovascular continuum in diabetes mellitus*

See Fig. 3.

4.2. *Pathophysiology of insulin resistance in type 2 diabetes mellitus*

Insulin resistance has an important role in the pathophysiology of T2DM and CVD and both genetic and environmental factors facilitate its development. More than 90% of people with T2DM are obese, and the release of free fatty acids (FFAs) and cytokines from adipose tissue directly impairs insulin sensitivity.

4.3. *Endothelial dysfunction, oxidative stress and vascular inflammation*

See Fig. 4.

4.4. *Macrophage dysfunction*

It seems that macrophage abnormalities provide a cellular link between DM and CVD by both enhancing IR and by

Table 4 – Prevention of T2DM by lifestyle intervention – the evidence.

Study	Intervention	Patients (n)	Follow-up (years)	RRR (%)
Da-Qing Study China	Diet Exercise Diet+ exercise Control	130 141 126 133	6	**31** **46** **42**
Diabetes Prevention Study Finland	Diet + physical activity Control	265 257	3.2	**58**
US Diabetes Prevention Program Outcomes Study USA	diet + physical activity metformin placebo	1079 1073 1082	2.8	**58** **31**
Indian Diabetes Prevention Program India	Lifestyle Metformin Lifestyle + metformin control	133 133 129 136	2.5	**29** **26** **28**
Japanese trial in men with IGT Japan	Diet + exercise control	102 356	4	**67**
Study on lifestyle-intervention and IGT Maastricht study The Netherlands	Diet + physical activity control	74 73	3	**58**
European Diabetes Prevention Study Newcastle, UK	Diet + physical activity control	51 51	3.1	**55**
Zensharen Study Japan	Diet + physical activity control	330 311	3	**44**

IGT = impaired glucose tolerance; RRR = relative risk reduction; SLIM = study on lifestyle-intervention and IGT Maastricht.
Absolute risk reduction numbers would have added value but could not be reported since such information is lacking in several of the studies.
The Zensharen study recruited people with IFG, while other studies recruited people with IGT.

Table 5 – Recommendations for diagnosis of disorders of glucose metabolism.

Diagnosis of disorders of glucose metabolism			
Recommendations	**Class a**	**Level b**	**Ref. c**
It is recommended that the diagnosis of diabetes is based on HbA_{1c} and FPG combined or on an OGTT if still in doubt.	I	B	2-5,8,10
It is recommended that an OGTT is used for diagnosing IGT.	I	B	2-5,8,10
It is recommended that screening for potential T2DM in people with CVD is initiated with HbA_{1c} and FPG and that OGTT is added if HbA_{1c} and FPG are inconclusive	I	A	36-41
Special attention should be considered to the application of preventive measures in women with disorders of glucose metabolism	IIa	C	-
It is recommended that people at high risk for T2DM receive appropriate lifestyle counselling to reduce their risk of developing DM.	I	A	59,60

CVD = cardiovascular disease; DM = diabetes mellitus; FPG = fasting plasma glucose; HbA1c = glycated haemoglobin A1c; IGT = impaired glucose tolerance; OGTT = oral glucose tolerance test; T2DM = type 2 diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence (see original paper).

Table 6 – Characteristics of dyslipidaemia in type 2 diabetes mellitus.

Dyslipidaemia is a major risk factor for CVD

Dyslipidaemia represents a cluster of lipid and lipoprotein abnormalities including elevation of both fasting and post-prandial TG
Apo B, small dense LDL particles, low HDL-C and Apo A

Increased waist circumference and elevation of TG sis a simple tool to capture high-risk subjects with metabolic syndrome

Apo = apolipoprotein; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL = low-density lipoprotein; TG = triglyceride; TRL = triglyceride-rich lipoprotein.

contributing to the development of fatty streaks and vascular damage.

4.5. *Atherogenic dyslipidaemia*

See Table 6. It is an independent predictor of CV risk, stronger than isolated high triglycerides or a low HDL cholesterol.

4.6. *Coagulation and platelet function*

IR and hyperglycaemia participate in the pathogenesis of a prothrombotic state: increased plasminogen activator

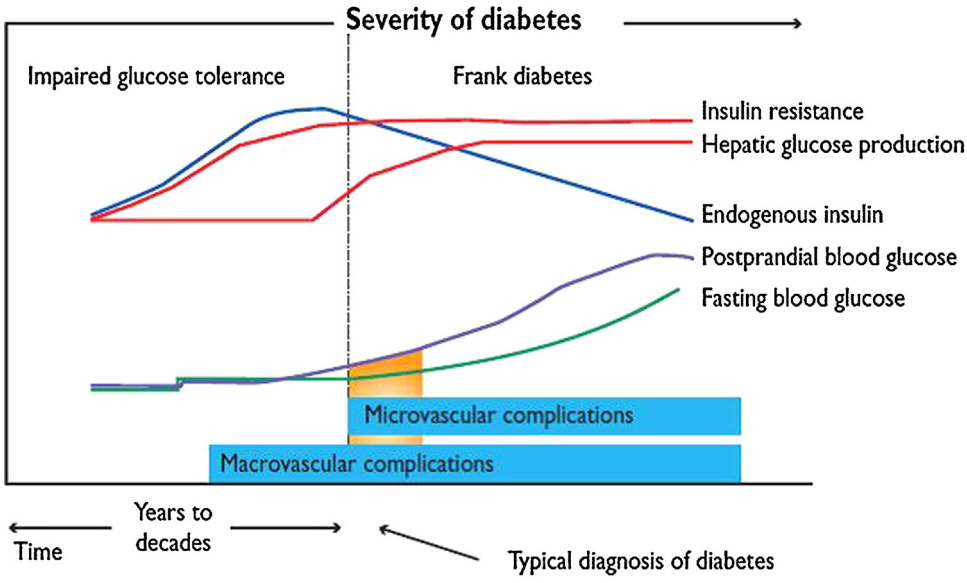

Fig. 3 – Glycaemic continuum and cardiovascular disease.

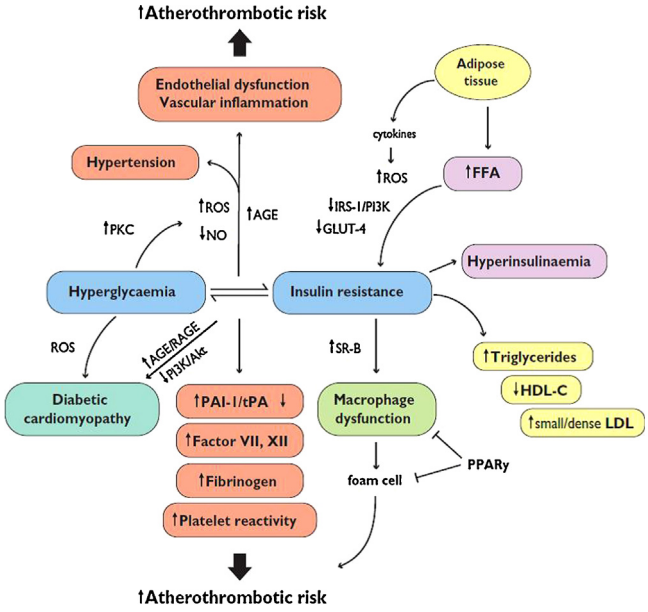

Fig. 4 – Hyperglycaemia, insulin resistance, and cardiovascular disease. AGE = advanced glycated end-products; FFA = free fatty acids; GLUT-4 = glucose transporter 4; HDL-C = high-density lipoprotein cholesterol; LDL = low-density lipoprotein particles; NO = nitric oxide; PAI-1 = plasminogen activator inhibitor-1; PKC = protein kinase C; PPARγ = peroxisome proliferator-activated receptor γ; PI3K = phosphatidylinositide 3-kinase; RAGE = AGE receptor; ROS = reactive oxygen species; SR-B = scavenger receptor B; tPA = tissue plasminogen activator.

inhibitor-1 (PAI-1), factor VII, XII and fibrinogen, reduced tissue plasminogen activator (tPA) levels, platelet hyper-reactivity.

4.7. *Diabetic cardiomyopathy*

Diabetic cardiomyopathy is a clinical condition diagnosed when ventricular dysfunction occurs in the absence of coronary atherosclerosis and hypertension.

4.8. *The metabolic syndrome (MetS)*

MetS represents the combination of multiple risk factors. Patients with MetS have a 2-fold increase of CVD risk and a 5-fold increase in development of T2DM.

4.9. *Endothelial progenitor cells and vascular repair*

Impaired function and reduced endothelial progenitor cells are features of T1DM and T2DM.

4.10. *Conclusions*

Oxidative stress plays a major role in the development of micro- and macrovascular complications. Accumulation of free radicals in the vasculature of patients with DM is responsible for the activation of detrimental biochemical pathways, leading to vascular inflammation and reactive oxygen species generation.

5. Cardiovascular risk assessment in patients with dysglycaemia

5.1. *Risk scores developed for people without diabetes*

The European Systematic Coronary Risk Evaluation (SCORE) for fatal CVD was not developed for application in patients with DM. The 2012 Joint European Society guidelines on CVD prevention recommended that patients with DM, and at least one other CV risk factor or target organ damage, should be considered to be at *very high risk* and all other patients with DM to be at *high risk*. There are other scoring systems in Europe.

5.2. *Evaluation of cardiovascular risk in people with pre-diabetes*

High 2hPG, but not FPG, predicted all-cause mortality, CVD and coronary artery disease (CAD).

5.3. *Risk engines developed for people with diabetes*

Many risk scores were developed. There was little evidence to suggest that using risk scores specific to DM provides a more accurate estimate of CVD risk. Risk scores for the evaluation of DM have good results in the populations in which they were developed, but validation is needed in other populations.

5.4. *Risk assessment based on biomarkers and imaging*

Albuminuria and elevated circulating NT-proBNP are strong predictors of excess overall and CV mortality. Cardiovascular target organ damage: low ankle-brachial index, increased carotid intima-media thickness, artery stiffness or coronary artery calcium score, cardiac autonomic neuropathy and silent cardial ischaemia may account for a part of the cardiovascular residual risk that remains, even after control of conventional risk factors. The detection of these biomarkers and disorders contributes to a more accurate risk estimate and should lead to a more intensive control of modifiable risk factors. However the cost-effectiveness of this strategy needs to be evaluated.

5.5. *Gaps in knowledge*

*How to prevent or delay T1DM. *Biomarkers and diagnostic strategies useful for the early detection of CAD in asymptomatic patients. *Prediction of CV risk in people with pre-diabetes (Table 7).

6. Prevention of cardiovascular disease in patients with diabetes

6.1. *Lifestyle*

Healthy eating, regular physical activity and cessation of smoking are first measures for the prevention and/or

Table 7 – Recommendations for cardiovascular risk assessment in diabetes.

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	113
Screening for silent myocardial ischaemia may be considered in selected high risk patients with DM	IIb	C	-

CVD = cardiovascular disease; DM = diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence (see original paper).

management of T2DM, with targets of weight loss and reduction of CV risk. An individualized approach to T2DM is also recommended. Smoking increases the risk of T2DM, CVD and premature death, and should be avoided. For detailed instruction on smoking cessation principles, see Table 8. For recommendations on life style modifications in diabetes, see Table 9.

Gaps in knowledge: *Lifestyles that influence the risk of CVD among people with DM are constantly changing and need to be followed. *The CVD risk, caused by the increasing prevalence of T2DM in young people due to unhealthy lifestyles. *The remission in T2DM seen after bariatric surgery and CVD risk.

Table 8 – 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.

Table 9 – Recommendations on life style modifications in diabetes.

Life style modifications in diabetes			
Recommendations	**Class a**	**Level b**	**Ref. c**
Smoking cessation guided by structured advice is recommended in all subjects with DM and IGT	I	A	148
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	57,129,132,134
It is recommended that dietary fibre intake should be >40 g/day (or 20g/1000 Kcal/day) in the prevention of T2DM and control of DM	I	A	57,129,132,134
Any diet with reduced energy intake can be recommended in lowering excessive body weight in DM.	I	B	129,132
Vitamin or micronutrient supplementation to reduce the risk of T2DM or CVD in DM is not recommended	III	B	129,135
Moderate to vigorous physical aktivity of ≥150 min/week is recommended for the prevention and control of T2DM and prevention of CVD in DM	I	A	141,142
Aerobic exercise and resistance training are recommended in the prevention of T2DM and control of DM, but best when combined.	I	A	144

CVD = cardiovascular disease, DM = diabetes mellitus, T2DM = type 2 diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence (see original paper).

6.2. *Glucose control*

Microvascular complications of DM are reduced by *tight glycaemic control* (42–53 mmol/mol), which also exerts a favourable influence on CVD. A meta-analysis of CV outcomes suggested that an HbA1c reduction of 1% was associated with a 15% relative risk reduction in nonfatal MI but without benefits on stroke or all-cause mortality.

Patients with a short duration of T2DM and without a history of CVD, without trend to hypoglycaemia seemed to benefit from more-intensive glucose-lowering strategies. In T1DM and T2DM: (i) glycaemic control is important for reducing long-term macrovascular complications; (ii) a very long follow-up period is required to demonstrate an effect and (iii) early glucose control is important (metabolic memory). An HbA1c target of <53 mmol/mol to reduce microvascular disease is a generally accepted level. More stringent targets, e.g. HbA1c 42–48 mmol/mol might be considered in selected patients. It is important to individualize treatment targets.

The choice of agent, the conditions of their use and the role of combination therapy have been extensively reviewed in the joint ADA/EASD guidelines (Table 10).

Gaps in knowledge: *Long-term CVD outcomes for most glucose-lowering treatments.

*The consequences of polypharmacy for quality of life and the most appropriate choice of treatment in DM-patients with comorbidities, particularly in the elderly. *The level of glycaemia (FPG, 2hPG, HbA1c) at which CV benefits can be seen in T2DM (Table 11).

6.3. *Blood pressure*

The prevalence of hypertension is higher in patients with T1DM than in the general population (up to 49%) and more than 60% of patients diagnosed with T2DM. This is related to: (i) hyperinsulinaemia linked to increased renal reabsorption of sodium; (ii) increased sympathetic tone and (iii) increased renin–angiotensin–aldosterone system activity. Obesity, ageing and the appearance of renal disease further increase the prevalence of hypertension. Hypertension causes a 4-fold increase in cardiovascular risk in people with DM. Present evidence makes it reasonable to reduce blood pressure (BP) in patients with DM to <140/85 mmHg; further reduction might be associated with an increased risk of serious adverse events, especially in patients of advanced age and with longer duration of T2DM. Thus the risks and benefits of more intensive BP management need to be carefully considered on an individual basis, e.g. in patients with nephropathy with overt proteinuria an even lower BP (SBP <130 mm Hg) may be considered.

To achieve BP goal, a combination of BP-lowering drugs is needed in most patients. All available BP-lowering drugs can be used, but evidence strongly supports the inclusion of an inhibitor of the RAAS (ACE-I/ARB) in the presence of proteinuria. It should be borne in mind that many DM patients do not reach the recommended BP target.

Gaps in knowledge: *The consequences of blood pressure-lowering multi-drug combinations in the elderly. *The evidence

Table 10 – Pharmacological treatment options for T2DM.

Drug class	Effect	Weight change	Hypoglycaemia (monotherapy)	Comments
Metformin	Insulin sensitizer	Neutral/ loss	No	Gastrointestinal side-effects, lactic acidosis, B12 deficiency. Contraindications, low eGFR, hypoxia, dehydration
Sulphonylurea	Insulin provider	Increase	Yes	Allergy Risk for hypoglycaemia and weight gain
Meglitinides	Insulin provider	Increase	Yes	Frequent dosing Risk for hypoglycaemia
Alfa-glucosidase inhibitor	Glucose absorption inhibitor	Neutral	No	Gastrointestinal side-effects Frequent dosing
Pioglitazone	Insulin sensitizer	Increase	No	Heart failure, oedema, fractures, urinary bladder cancer
GLP-I agonist	Insulin provider	Decrease	No	Gastrointestinal side-effects Pancreatitis injectable
DPP-4 inhibitor	Insulin provider	Neutral	No	Pancreatitis
Insulin	Insulin provider	Increase	Yes	Injectable Risk for hypoglycaemia and weight gain
SGLT2 inhibitors	Blocks renal glucose absorption in the proximal tubuli	Decrease	No	Urinary tract infections

eGFR = estimated glomerular filtration rate; GLP-1 = glucagon- like peptide-1; DPP = Diabetes Prevention Program; SGLT2 = sodium glucose co-transporter 2.

base for efficacy or harm for microvascular complications for both individual blood pressure-lowering drugs alone or in combination. *The role of arterial stiffness in predicting CV risk in patients with DM, over and above the role of conventional risk factors. *Optimal blood pressure targets. *Metabolic side-effects of beta-blockers or diuretics clinically (Table 12).

6.4. *Dyslipidaemia*

In individuals with T1DM and good glycaemic control, the pattern of lipid abnormalities contrasts with that of T2DM: serum TG is normal and HDL-chol is within the upper normal range or slightly elevated. A cluster of lipid and apoprotein abnormalities accompanies T2DM, affecting all lipoprotein classes (Table 6).

Comprehensive and consistent data exist on the mechanism of action and efficacy of statins in the primary and secondary prevention of CVD events in T2DM. A 9% reduction in all-cause mortality and a 21% reduction in the incidence of major vascular outcomes per mmol/l of LDL-cholesterol lowering ($p < 0.0001$) was reported. High dose statin therapy was associated with risk of new-onset T2DM (OR 1.09; 1.0–1.2), which increased with age. The small risk of developing DM is clearly outweighed by the reduction of cardiovascular events.

T2DM patients at the LDL-C target remain at high CV risk, and this residual risk is linked to many factors including atherogenic dyslipidemia (Table 6). It has been suggested that targeting elevated TG (>2.2 mmol/l) and/or low HDL-C (<1.0 mmol/l) may provide further benefits. Meta-analyses

Table 11 – Recommendations for glycaemic control in diabetes.

Glycaemic control in diabetes			
Recommendations	**Class a**	**Level b**	**Ref. c**
It is recommended that glucose lowering in 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} <53 mmol/mol to decrease microvascular complications in T1DM and T2DM.	I	A	151-153,155 159
A HbA_{1c} target of ≤53 mmol/mol should be considered for the prevention of CVD in T1 and T2DM.	IIa	C	-
Basal bolus insulin regimen, combined with frequent glucose monitoring, is recommended for optimizing glucose control in T1DM.	I	A	151,154
Metformin should be considered as first-line therapy in subjects with T2DM following evaluation of renal function.	IIa	B	153

CVD = cardiovascular disease; DM = diabetes mellitus; HbA1c = glycated haemoglobin A1c; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence (see original paper).

Table 12 – Recommendations for blood pressure control in diabetes.

Blood pressure control in diabetes			
Recommendations	**Class a**	**Level b**	**Ref. c**
Blood pressure control is recommended in patients with DM and hypertension to lower the risk of cardiovascular events.	I	A	189-191, 193-195
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	191-193,195
It is recommended that a combination of blood pressure lowering agents is used to achieve blood pressure control.	I	A	192-195,205-207
A RAAS blocker (ACE-I or ARB) is recommended in the treatment of hypertension in DM, particularly in the presence of proteinuria or microalbuminuria.	I	A	200,205-207
Simultaneous administration of two RAAS blockers should be avoided in patients with DM	III	B	209,210

ACE-I = angiotensin converting enzyme-inhibitors; ARB = angiotensin receptor blockers; DM = diabetes mellitus; RAAS = renin angiotensin aldosterone system.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence (see original paper).

Table 13 – Recommendations on management of dyslipidaemia in diabetes.

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 CV 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/dL (<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

CV = cardiovascular; CVD = cardiovascular disease; CKD = chronic kidney disease; DM = diabetes mellitus; HDL-C = high density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence (see original paper).

have confirmed the clinical benefits of fibrates on major CVD events but not on cardiovascular mortality.

Gaps in knowledge: *The role of HDL particles in the regulation of insulin secretion in beta-cells. *Efficiency and safety of drugs increasing or improving HDL-C particles. *The relative contributions of HDL function and plasma HDL concentration in the pathogenesis of CVD (Table 13).

6.5. *Platelet function*

Persistent hyperglycaemia have been identified as major determinants of in vivo platelet activation in the early and late phases of the natural history of T2DM. For recommendation for antiplatelet therapy, see Table 14.

Gaps in knowledge: *The optimal antithrombotic regimen for the primary prevention of CVD in DM.

Table 14 – Recommendations for antiplatelet therapy in patients with diabetes.

Antiplatelet therapy in patients with diabetes			
Recommendations	**Class a**	**Level b**	**Ref. c**
Antiplatelet therapy with aspirin in DM-patients at low CVD risk is not recommended.	III	A	272-274
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	270
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	276,277, 280,282, 284
Clopidogrel is recommended as an alternative antiplatelet therapy in case of aspirin intolerance.	I	B	280,285

ACS = acute coronary syndrome; CVD = cardiovascular disease; DM = diabetes mellitus; PCI = percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence (see original paper).

Table 15 – Recommendations for multifactorial risk management in diabetes.

Multifactorial risk management in diabetes			
Recommendations	**Class a**	**Level b**	**Ref. c**
Risk stratification should be considered as part of the evaluation of patients with DM and IGT.	IIa	C	-
Cardiovascular risk assessment is recommended in people with DM and IGT as a basis for multifactorial management.	I	B	156,213
Treatment targets, as listed in Table 10, should be considered in patients with DM and IGT with CVD.	IIa	B	156,213

CVD = cardiovascular disease; DM = diabetes mellitus; HbA1c = glycated haemoglobin A1c; IGT = impaired glucose tolerance; LDL = low density lipoprotein; T2DM = type 2 diabetes mellitus.
[c]Reference(s) supporting levels of evidence (see original paper).

6.6. *Multifactorial approaches*

Data from the Euro Heart Survey on Diabetes and the Heart support a multifactorial approach as a cornerstone of patient management (Table 15). Treatment targets are summarized in Table 16.

Gaps in knowledge: Pleiotropic effects of glucose-lowering therapies on CVD outcomes.

Table 16 – Summary of treatment targets for managing patients with diabetes mellitus or impaired glucose tolerance and coronary artery disease.

Blood pressure (mmHg)	<140/85
In case of nephropathy	<130
Glycaemic control	Generally < 53 mmol/mol
HbA1c	On an individual basis 48–52 mmol/mol
Lipid profile (mmol/l/mg/dL)	Very high risk patients < 1.8 mmol/L (<70 mg/dL) or reduced by at least 50%
LDL-cholesterol	High risk patients < 2.5 mmol/L (<100 mg/dL)
Platelet 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	<35%
Saturated	<10%
Monounsaturated fatty acids	>10%
Dietary fibre intake	>40 g/day (or 20 g/1000 kcal/day)

CVD = cardiovascular disease; DM = diabetes mellitus; HbA1c = glycated haemoglobin A1c; IGT = impaired glucose tolerance; LDL = low density lipoprotein; T2DM = type 2 diabetes mellitus.

7. Management of stable and unstable coronary artery disease in patients with diabetes

7.1. Optimal medical treatment

DM is associated with a poorer prognosis in patients with acute and stable CAD. All patients with CAD should have their glycaemic state evaluated. The appropriate screening method is an OGTT, which should be performed, but not earlier than 4–5 days after an acute coronary syndrome (ACS) to minimize false positive results. In-hospital and long-term mortality after MI has declined, but the outcome is still poor among patients with DM. The reasons are not fully explained but a higher prevalence of complications, in combination with lack of appropriate evidence-based treatment, contributes.

Beta-blockers are advocated for the whole spectrum of CAD. However they improve prognosis in post-MI patients with DM, may have negative metabolic effects (increasing IR, masking hypoglycaemia, etc.). There are some differences between non-vasodilating metoprolol, atenolol, and vasodilating carvedilol or labetalol; on the other hand β1-blockers with modulation synthesis of NO (nebivolol) have a better glucometabolic profile. Overall the positive effects of beta-blockade on prognosis outweigh the negative glucometabolic effects.

Treatment with *ACE-I or ARBs* should be started during hospitalization for ACS and continued in patients with left ventricular dysfunction, hypertension, or chronic kidney disease, in all patients with ST-elevation MI or stable CAD. The ONTARGET trial improved, that ACE inhibitor and AT II receptor blockers are equivalent as regards the cardioprotection; combination of the two drugs is not recommended.

The beneficial effect of *statins* in patients with CAD and DM is firmly established (see above).

There is no evidence for a prognostic impact of *nitrates* but they may be used for symptomatic relief. *Calcium channel blockers* are efficacious in relieving ischaemic symptoms. Verapamil and diltiazem may prevent re-infarction and death, they may be appropriate for long-term use in patients without heart failure, as an alternative to beta-blockers. The combination of these drugs and beta-blockers should be avoided. An alternative is the use of a dihydropyridine calcium channel blockers (amlodipine, felodipine or nicardipine). Ivabradine is effective in preventing angina in patients with DM and stable CAD, in patients with heart rate >70 bpm esp. with left ventricular dysfunction.

Antiplatelet and antithrombotic drugs are indicated in the same way as in nondiabetic patients.

Elevated *plasma glucose* during an ACS associated with a more serious prognosis in DM. Glucose-insulin-potassium infusion (GIK), regardless of the presence of DM or PG, improves use of glucose for energy production, endothelial function and fibrinolysis. Randomized controlled trials failed to show mortality or morbidity benefits.

Diabetics with ACS will benefit from glycaemic control if hyperglycaemia is significant (>10 mmol/l). Insulin infusion is the most efficient way to achieve rapid glucose control with less stringent targets in those with severe co-morbidities. There is a J- or U-shaped relationship between glucose and prognosis.

Gaps in knowledge: *The role and optimum level of glycaemic control in the outcome in patients with ACS. *Final infarct size reduction by means of very early GIK administration after MI symptoms (Table 17).

7.2. Revascularization

A quarter of myocardial *revascularization procedures* are performed in patients with DM. Revascularization in these patients is challenged by a more diffuse atherosclerotic involvement of epicardial vessels, a higher propensity to develop re-stenosis after PCI (percutaneous coronary intervention) and saphenous graft occlusion after coronary artery bypass graft surgery (CABG) and unremitting atherosclerotic progression causing new stenosis.

No interaction between the effect of myocardial revascularization and the presence of DM has been documented in trials on non-ST-elevation ACS management. An early invasive strategy improved outcomes in the overall population with a greater benefit in patients with DM. In STEMI patients, a pooled analysis of individual patient comparing primary PCI with fibrinolysis showed that patients with DM treated with reperfusion had an increased mortality compared with those without DM.

CABG is superior and cost-effective strategy compared with PCI for patients with DM and advanced CAD. There was no significant interaction based on SYNTAX (SYNergy between PCI with TAXus and cardiac surgery) score, since the absolute difference in the primary end points between PCI and CABG were similar in patients with low, intermediate and high SYNTAX scores. It can be concluded that a discussion with the patient, explaining the mortality benefit with CABG surgery, and an individualized risk assessment should be mandatory before the type of intervention is decided.

The second-generation everolimus-eluting stents were not superior in terms of target lesion failure after one year of

Table 17 – Recommendations for the management of patients with stable and unstable coronary artery disease and diabetes.

Management of patients with stable and unstable coronary artery disease and diabetes			
Recommendations	**Class a**	**Level b**	**Ref. C**
It is recommended that patients with CVD are investigated for disorders of glucose metabolism.	I	A	294,295
Beta-blockers should be considered to reduce mortality and morbidity in patients with DM and ACS.	IIa	B	309,310
ACE-I or ARBs are indicated in patients with DM and CAD to reduce the risk for cardiovascular events.	I	A	210,312, 313
Statin therapy is indicated in patients with DM and CAD to reduce the risk for cardiovascular events.	I	A	227
Aspirin is indicated in patients with DM and CAD to reduce the risk for cardiovascular events.	I	A	274,316
Platelet P2Y12 receptor inhibition is recommended in patients with DM and ACS in addition to aspirin.	I	A	280,282, 284,285, 304,307
Insulin-based glycaemic control should be considered in ACS patients with significant hyperglycaemia (>10 mmol/L or >180 mg/dL) with the target adapted to possible comorbidities.	IIa	C	-
Glycaemic control, that may be accomplished by different glucose-lowering agents, should be considered in patients with DM and ACS.	IIa	B	326,328, 330

ACE-I = angiotensin converting enzyme inhibitor; ACS = acute coronary syndrome; ADP = adenosine diphosphate; ARB = angiotensin receptor blockers; CAD = coronary artery disease; CVD = cardiovascular disease; DM = diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence (see original paper).

Table 18 – Recommendations for coronary revascularization of patients with diabetes.

Coronary revascularization of patients with diabetes			
Recommendations	**Class a**	**Level b**	**Ref. c**
Optimal medical treatment should be considered as preferred treatment in patient with stable CAD and DM unless there are large areas of ischaemia or significant left main or proximal LAD lesions.	IIa	B	339
CABG is recommended in patients with DM and multivessel or complex (SYNTAX Score >22) CAD to improve survival free from major cardiovascular events.	I	A	337,339,346,350,355,374
PCI for symptom control may be considered as an alternative to CABG in patients with DM and less complex multivessel CAD (SYNTAX score ≤22) in need of revascularization.	IIb	B	347,349, 350
Primary PCI is recommended over fibrinolysis in DM patients presenting with STEMI if performed within recommended time limits.	I	B	343
In DM patients subjected to PCI, DES rather than BMS are recommended to reduce risk of target vessel revascularization.	I	A	351,352
Renal function should be carefully monitored after coronary angiogramy/ PCI in all patients on metformin.	I	C	-
If renal function deteriorates in patients on metformin undergoing coronary angiography / PCI it is recommended to withhold treatment for 48 h or until renal function has returned to its initial level.	I	C	-

BMS = bare-metal stent; CABG = coronary artery bypass grafting; CAD = coronary artery disease; DES = drug-eluting stent; DM = diabetes mellitus; LAD = left anterior descending coronary artery; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence (see original paper).

follow-up in a head-to-head comparison with paclitaxel-eluting stents, while zotarolimus-eluting stents were inferior to sirolimus-eluting stents in patients with DM. Antithrombotic treatment in DM patients undergoing coronary revascularization for stable angina or ACS is no different from those without DM.

There is no randomized evidence regarding the use of one vs. two internal thoracic artery (ITA) conduits in DM. A single-centre non-randomized study comparing CABG with bilateral ITA and PCI in DM reported improved outcomes (freedom from angina, re-intervention, or composite major adverse cardiac events) in the surgical group, but no difference in six-year survival.

More than 50% of patients with moderate-to-poor blood glucose control after cardiac surgery may not have been diagnosed as having DM during pre-operative assessment. This may lead to inadequate peri-operative glycaemic control, which is a predictor of in-hospital mortality and morbidity, although hypoglycaemic medications may influence the safety of coronary angiography, as well as early and late outcomes of revascularization with PCI or CABG (Table 18).

Gaps in knowledge: *The optimal policy on metformin treatment in patients undergoing PCI. *The role and optimum level of glycaemic control in the outcome during and after myocardial revascularization.

8. Heart failure and diabetes

Patients with T2DM were associated with significantly increased risk of developing heart failure (HF). Insulin resistance and dysglycaemia have unfavourable effects on the myocardium and leads to the diabetic cardiomyopathy. Myocardial dysfunction may progress in a time dependent fashion after the onset of diastolic dysfunction, which can worsen during physical exercise, leading to systolic dysfunction and the classical features of HF.

8.1. *Prevalence and incidence of HF in T2DM and T2DM in HF*

The prevalence of HF in a general population is 1–4% and 0.3–0.5% of the patients have both HF and T2DM. There are about 12–30% patients with T2DM in patients with HF. Independent risk factors for the development of HF in T2DM, including high HbA1c, increased BMI, advancing age, associated CAD, retinopathy, nephropathy and insulin use, end-stage renal disease, proteinuria and albuminuria, and duration of T2DM, were associated with HF and its progression.

8.2. *DM and HF morbidity and mortality*

T2DM represents an independent predictor of mortality in all HF patients, mostly in ischaemic aetiology; the combination of T2DM and HF resulted in a 12-fold higher annual mortality than among T2DM without HF.

8.3. *Pharmacological managements of HF in T2DM*

Drug treatment of HF in patients with T2DM is based on the three neurohormonal antagonists: ACE-I or ARB, a beta-blocker and a mineralocorticoid receptor antagonist (MRA) as in patients without DM. They are usually combined with a diuretic for relieving congestion; loop diuretics are recommended, rather than thiazides. Surveillance of kidney function and potassium is mandatory, considering the increased risk of nephropathy in patients with DM. Ivabradine is useful in patients with HF in sinus rhythm and heart rate ≥70 and has the same effects as in non-DM (see Table 19).

8.4. *Non-pharmacological therapies*

Cardiac resynchronization therapy is a guideline-recommended HF treatment in specific groups of patients with or without DM. There is no additional benefit from implantace cardioverter defibrillators in a subgroup of patients with T2DM and HF, compared with patients free from this disease. Cardiac transplantation is an accepted treatment for end-stage HF. The presence of DM is not a contra-indication, but the stringent selection criteria have to be acknowledged. DM was an independent risk factor for decreased 10-year survival in a large registry study of patients with transplanted heart.

8.5. *Glucose-lowering treatment in patients with HF*

The use of metformin is indicated because it is in association with lower mortality rates, lower rates of all-cause hospital admission and fewer adverse events. Discrepancies were seen between sulphonylureas and HF mortality (only observational data). The PPAR gamma-activating thiazolidinediones induce sodium retention and plasma volume expansion and therefore are not recommended in patients with HF. There is a lack of

Table 19 – Recommendations for management of heart failure in diabetes.

Management of heart failure in diabetes			
Recommendations	Class a	Level b	Ref. c
ACE-I is recommended in addition to beta-blockers, in patients with systolic heart failure and T2DM to reduce mortality and hospitalization.	I	A	391,394-396
In patients with systolic heart failure and T2DM, who have a clear ACE-I intolerance due to side effects, an ARB may be used as an alternative to an ACE-I.	I	A	397-399
A beta-blocker is recommended in addition to an ACE-I (or an ARB if an ACE-I is not tolerated) in all patients with systolic heart failure and T2DM to reduce mortality and hospitalization.	I	A	391,401-403,405,406
An MRA is recommended for all patients with persisting symptoms (NYHA class II-IV) and an LVEF ≤35% despite treatment with an ACE-I (or an ARB if an ACE-I is not tolerated) and a beta-blocker, to reduce the risk of heart failure hospitalization and premature death.	I	A	411-413
Addition of ivabradine to an ACE-I, beta-blocker and MRA may be considered in patients in sinus rhythm with T2DM with heart failure and LVEF <40%, who have persisting symptoms (NYHA Class II-IV) and a heart rate >70 b.p.m. despite optimal tolerated dose of beta-blocker in addition to ACE (or ARB) and MRA.	IIb	B	414,428
Thiazolidinediones should not be used in patients with heart failure and T2DM since water retention may worsen or provoke heart failure.	III	B	175,425,426

ACE-I = angiotensin concerting inhibitor; ARB = angiotensin receptor blocker; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; T2DM = type 2 diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence (see original paper).

Table 20 – Recommendations for the management of arrhythmias in patients with diabetes mellitus.

Management of arrhythmias in patients with diabetes mellitus			
recommendations	Class a	Level b	Ref. c
Screening for AF should be considered since it is common in patients with DM and increases morbidity and mortality.	IIa	C	-
Oral anticoagulation with VKAs or a NOAC (e.g. dabigatran, rivaroxaban or apixaban) is recommended in DM patients with AF (paroxysmal and persistent) if not contraindicated.	I	A	439,440,442,443,445-447
Assessment of the risk of bleeding (i.e. HAS-BLED score) should be considered when prescribing antithrombotic therapy in patients with AF and DM.	IIa	C	-
Screening for risk factors for sudden cardiac death should be considered in patients with DM.	IIa	C	-
Implantable cardioverter defibrillators are recommended for patients with DM and ischaemic cardiomyopathy with LVEF <35% and those resuscitated from ventricular fibrillation or sustained ventricular tachycardia.	I	A	459
Beta-blockers are recommended for DM patients with heart failure and after acute MI to prevent sudden cardiac death.	I	A	391,401-403,405,406,449,450

AF = atrial fibrillation, DM = diabetes mellitus, EF = ejection fraction, LV = left ventricular, NOAC = new oral anticoagulants, VKA = -vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence (see original paper).

information on the impact of GLP-1 analogues or DPP-4 inhibitors in patients with HF. Regarding the use of insulin, a retrospective cohort study of patients with DM and a primary diagnosis of HF did not reveal any association between the use of insulin and mortality.

Gaps in knowledge: *The impact of glucose-lowering drugs including metformin, GLP-1 analogues and DPP-IV inhibitors on the prevention of HF.

9. Arrhythmias: atrial fibrillation and sudden cardiac death

9.1. *Diabetes and atrial fibrillation*

Atrial fibrillation (AF) is increasing during the last 2 decades and DM is frequent in patients with AF (about 13% in community studies). The independent role of DM as a risk factor for AF has not been established. When T2DM and AF co-exist, there is a substantially higher risk of all-cause mortality, CV death, stroke and HF. Screening for AF can be recommended in selected patient groups with T2DM with any suspicion of paroxysmal or permanent AF.

Significant factors for stroke risk in patients with AF: age, prior stroke/TIA/thromboembolism, hypertension, DM and structural heart disease. The new scheme is expressed as an acronym CHA_2DS_2-VASc [cardiac failure, hypertension, age $\geq$ 75 (doubled), DM, stroke (doubled)-vascular disease, age 65–74 and sex category (female)]. Oral anticoagulation with vitamin K antagonists (VKAs) or one of the oral direct thrombin inhibitors (e.g. dabigatran etexilate), or oral factor Xa inhibitors (e.g. rivaroxaban, apixaban, edoxiban, betrixiban) are recommended in patients with AF. VKA should be used in all AF patients with DM unless contra-indicated; an international normalized ratio (INR) of 2.0–3.0 is the optimal range for prevention of stroke and systemic embolism in patients with DM. A lower target INR (1.8–2.5) has been proposed for the elderly but this is not based on evidence. Combinations of VKA with antiplatelet therapy do not offer added beneficial effects on ischaemic stroke or vascular events and lead to more bleeding events, and such combinations should be avoided. Aspirin alone is not recommended for the prevention of thromboembolic disease in patients with DM and AF but, in patients unable or unwilling to use anticoagulants, the combination of aspirin and clopidogrel should be considered (Table 20).

9.2. *Sudden cardiac death*

DM was associated with an increased risk of sudden death (almost 4-fold) greater in women than men. There are some risk factors for sudden death in DM (microvascular disease, autonomic neuropathy, nephropathy, hypoglycaemia, etc.).

Gaps in knowledge: *The long-term impact of glycaemic control on the QTc interval. *The role of hypoglycaemia and other predictors in sudden cardiac death.

10. Peripheral- and cerebrovascular disease

10.1. *Peripheral artery disease (PAD)*

The definition of PAD used by the current ESC Guidelines includes atherosclerotic lesions in the extracranial carotid and vertebral, upper and lower extremity, mesenteric and renal arteries. Although abdominal aortic aneurysm is frequent in patients with DM, it is not included in the current PAD definition. Medical history and physical examination are the

Table 21 – History relevant to peripheral artery disease.

– Family history of CVD
– Symptoms suggesting angina
– Any walking impairment, e.g. fatigue, aching, cramping, or pain with localization to buttock, thigh, calf, or foot, particularly when symptoms are quickly relieved at rest
– Any pain at rest localized to the lower legs or feet and its association with the upright or recumbent positions
– Any poorly healing wounds of the extremities
– Exertional pain in the upper extremities particularly if associated with dizziness or vertigo
– Any transistory neurological symptom
– History of abrupt onset hypertension, resistant hypertension (which may result from renal artery stenosis) or renal failure
– Unusual or post-prandial abdominal pain particularly if related to eating and associated with weight loss
– Erectile dysfunction

CVD = cardiovascular disease.

Table 22 – Physical examination relevant to peripheral artery disease.

– Measurement of blood pressure in both arms and notation of asymmetry between the arms
– Auscultation and palpation of the carotid and cervical areas
– Palpation of the pulses at the upper extremities and if necessary, performance of Allen's test. The hands must be carefully inspected
– Abdominal palpation and auscultation at different levels including the flanks and the iliac regions
– Auscultation of the femoral arteries
– Palpation of the femoral, popliteal, dorsalis pedis, and posterior tibial arteries
– Inspection of the feet for colour, temperature, integrity of the skin
– Recording of the presence of ulcerations
– Additional findings suggestive of LEAD, including calf hair loss and skin changes, should be noted
– ABI, calculated by dividing the systolic blood pressure at the tibial or dorsalis pedal level with the brachial pressure. An index of <0.9 is suggestive of LEAD

ABI = ankle-brachial index, LEAD = lower extremity artery disease.

cornerstones of diagnostic workup (Tables 21 and 22) although many patients remain asymptomatic.

10.2. *Lower extremity artery diseases (LEAD)*

Diabetes is a risk factor particularly for LEAD, for which it increases risk 2- to 4-fold, and for carotid artery disease. All patients with PAD should change their life-style and receive adequate lipid-lowering, antihypertensive and antiplatelet treatment, with optimal glycaemic control. Beta-blockers are not contra-indicated in patients with LEAD and DM. An algorithm for the treatment of intermittent claudication is shown in Fig. 5. Early diagnosis of LEAD in patients with DM is important for the prediction of the overall CV risk.

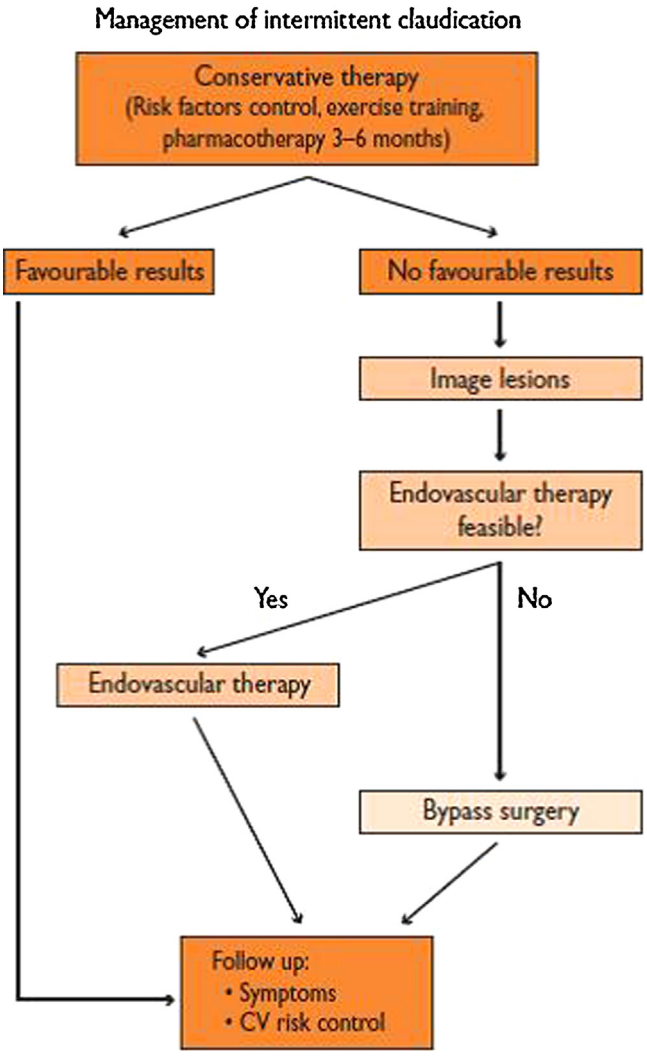

Fig. 5 – Algorithm for treatment of intermittent claudication. CV = cardiovascular.

Critical limb ischaemia (CLI) is defined by the presence of ischaemic pain at rest and ischaemic lesions or gangrene attributable to arterial occlusive disease that is chronic and distinguishable from acute limb ischaemia. An algorithm for the management of CLI is provided in Fig. 6.

The diabetic foot is a specific clinical entity that may involve neuropathy, trauma, arterial disease, infection and inflammation, often in combination. The serious consequences are ulceration, gangrene and high rates of amputation. Follow-up should include patient education, smoking cessation, protective shoes, periodic foot care and reconstructive foot surgery as needed. The management of risk factors including glycaemic control and revascularization surveillance is mandatory.

10.3. *Carotid artery disease*

DM is an independent risk factor for ischaemic stroke with an incidence 2.5–3.5 times higher than in people without DM. Carotid bruits are common in patients with carotid artery

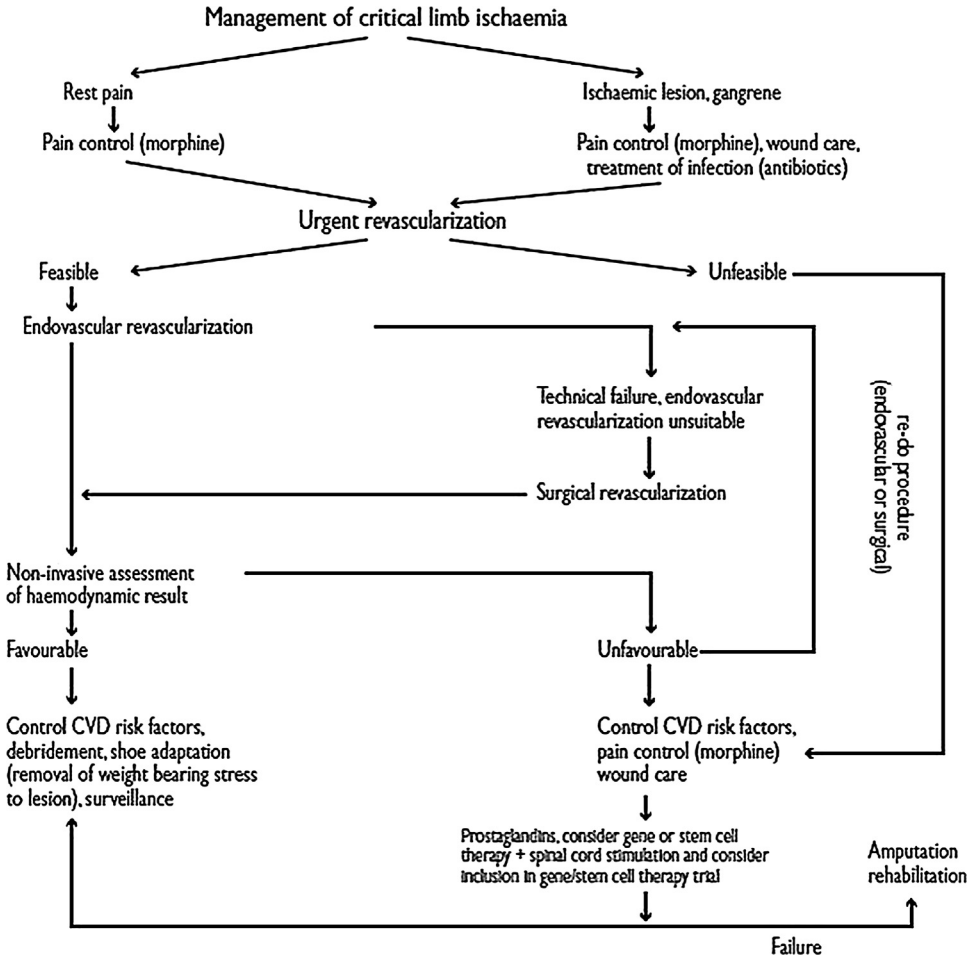

Fig. 6 – Algorithm for the management of critical limb ischaemia. CVD = cardiovascular disease.

stenosis. The spectrum of symptoms is wide, only those who have suffered a stroke or TIA within the past six months are regarded as symptomatic. Urgent imaging of the brain and supra-aortic vessels is mandatory in patients presenting with TIA or stroke. Duplex ultrasonography, computed tomography angiography and magnetic resonance imaging are indicated to evaluate carotid artery stenosis. Management depends on symptoms, severity of the lesion, prognosis for 5-year survival and the outcome of revascularization procedures. A management algorithm is shown in Fig. 7.

Gaps in knowledge: *In comparison with aspirin and clopidogrel, the efficacy of new antiplatelet drugs in patients with DM and PAD. *There is a need for comparisons of endovascular and surgical interventions in different subsets of patients with DM and concomitant carotid or LEAD (Table 23).

11. Microvascular disease in the eyes and kidneys

Renal impairment, i.e. elevated urinary albumin excretion and/or impaired glomerular filtration rate (GFR), is itself an independent predictor of CV outcomes. Retinopathy is the most frequent microvascular complication in DM; vision-threatening proliferative retinopathy affects 50% of patients with T1DM. About 29% patients with T2DM develop vision-threatening macular oedema. The combination of retinopathy and nephropathy predicts excess CV morbidity and mortality.

Table 23 – Recommendations for management of peripheral artery disease in diabetes.

Management of peripheral artery disease in diabetes			
Recommendations	Class [a]	Level [b]	Ref. [c]
It is recommended that patients with DM have annual screening to detect PAD and measurement of the ABI to detect LEAD.	I	C	-
It is recommended that all patients with PAD and diabetes who smoke are advised to stop smoking.	I	B	483
It is recommended that patients with PAD and DM have LDL-C lowered to <1.8 mmol/L (<70mg/dL) or by ≥50% when the target level cannot be reached.	I	A	125
It is recommended that patients with PAD and DM have their blood pressure controlled to <140/85 mm Hg.	I	C	-
Antiplatelet therapy is recommended in all patients with symptomatic PAD and DM without contraindications.	I	A	274

ABI = ankle-brachial index; DM = diabetes mellitus; LDL-C = low-density lipoprotein cholesterol; LEAD = lower extremity artery disease; PAD = peripheral artery disease.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence (see original paper).

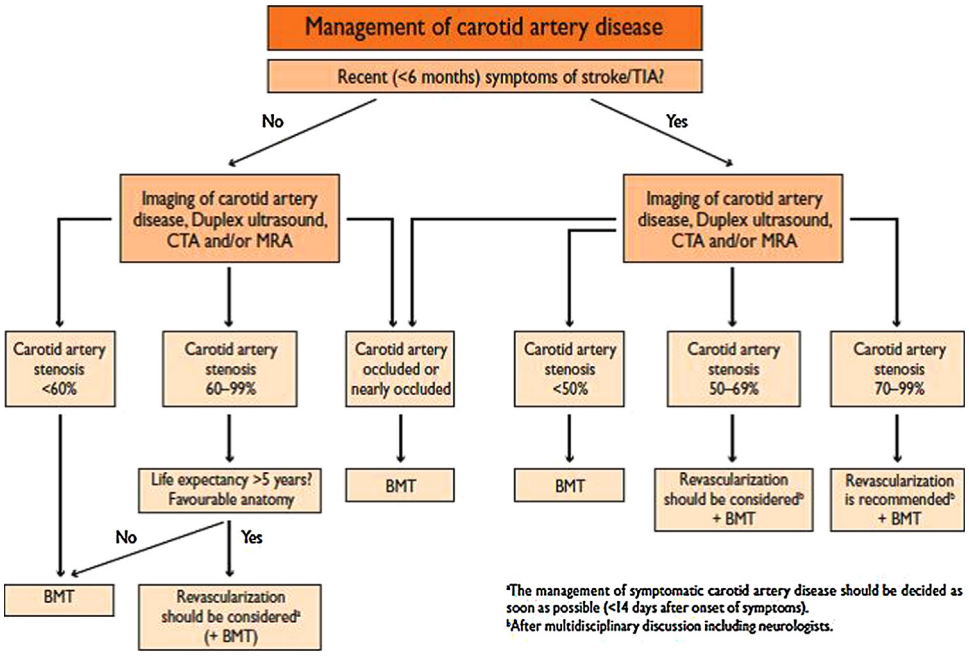

Fig. 7 – Algorithm for the management of extra cranial carotid artery. BMT = best medical therapy; CTA = computed tomography angiography; MRA = magnetic resonance angiography; TIA = transient ischaemic attack.

11.1. *Pathophysiology of microvascular disease*

Chronic hyperglycaemia induces protein glycation and overproduction of reactive oxygen species leading to vascular damage and responsive activation of tissue specific growth/repair systems. The phenotypic characteristics of microvascular damage are progressive vascular occlusion and increased vascular permeability.

11.2. *Treatment and treatment targets*

Lifestyle intervention. There are no trials proving that lifestyle interventions alone have an effect on the prevention of nephropathy, neuropathy or retinopathy.

Strict *glycaemic control* prevents both microvascular and CV outcomes and progression of renal impairment both in T1DM and T2DM.

Retinopathy: The recommended target for HbA1c in bothT1DM and T2DM is <53 mmol/mol. Beyond a certain level of retinal damage, euglycaemia no longer provides a benefit against progression of retinopathy. The good glycaemic control brings the long-term benefit for T1DM. In T2DM, progressing retinopathy benefits from multifactorial treatment.

Blood pressure (BP): Intensified BP control (using RAAS blockers) prevents the onset of microalbuminuria in T2DM, but not in T1DM. Using ACE-I slowed progression of kidney disease in T1DM and reduced end-stage renal failure. In T2DM, high doses of ramipril prevented both renal and cardiovascular events. ARBs reduced progression from microalbuminuria to proteinuria and prevented renal events but not CV death. The currently recommended BP target is <140/85 mmHg, in patients with hypertension and nephropathy with overt proteinuria and even lower SBP (<130 mmHg) may be considered if tolerated by the patient. BP control has beneficial effects on the progression of retinopathy. The recommended threshold is <140/85 mmHg.

Lipid-lowering and antiplatelet therapy: Fibrates and PPARα agonists may reduce kidney function; fenofibrate reduces albuminuria and slowed eGFR loss. Statin-plus-ezetimibe provided CV protection in people with reduced kidney function and DM. There are no clear target levels of lipids (cholesterol, triglycerides) for the prevention or retardation of *retinopathy*. Patients with T2DM require *antiplatelet agents* for secondary prevention of CVD. There is no specific contraindication against the use of aspirin or other antiplatelet agents, as they do not increase the incidence of intravitreal haemorrhages.

Vision-threatening retinopathy: Severe non-proliferative or proliferative *retinopathy* or any level of DM-related macular oedema should immediately be referred to an experienced ophthalmologist (Table 24).

Gaps in knowledge: *The balance between the benefit to microvascular risk associated with tightening of glycaemic control and the risk of adverse CV outcomes.

12. Patient-centred care

12.1. *General aspects*

Patient-centred care emphasizes the person, their experiences, priorities and goals in managing various conditions, and the partnership between providers and patients. When this approach is used by a multidisciplinary team with skills in cognitive behavioural strategies, there will be increased

Table 24 – Recommendations for management of microvascular disease in diabetes.

Management of microvascular disease in diabetes			
Recommendations	**Class a**	**Level b**	**Ref. c**
Screening for the presence of retinopathy should be considered on annual basis in patients with T2DM	IIa	B	530
Multifactorial therapy is recommended when retinopathy is progressing rapidly.	I	B	156
An HbA_{1c} <53 mmol/mol and a blood pressure <140/85 mmHg are recommended for primary prevention of retinopathy related to DM.	I	A	152,161, 191,512-514,524
Lipid lowering should be considered to reduce the progression of retinopathy, the need for laser treatment, and the need for vitrectomy.	IIa	B	513
It is recommended that proliferative DM retinopathy is treated by pan retinal laser photocoagulation.	I	A	530
Grid laser photocoagulation should be considered in clinically significant macular oedema.	IIa	B	532
Iintravitreal anti-vascular endothelial growth factor therapy should be considered in patients with vision impairment and clinically significant macular oedema involving the fovea.	IIa	B	531,532

BP = blood pressure; DM = diabetes mellitus; HbA1c = glycated haemoglobin A1c; T2DM = type 2 diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting levels of evidence (see original paper).

Table 25 – Recommendations for patient-centred care in diabetes.

Patient-centred care in diabetes			
Recommendations	**Class a**	**Level b**	**Ref. C**
Patient-centred care is recommended to facilitate shared control and decision-making within the context of patient priorities and goals.	I	C	-
Patient- centred cognitive behavioural strategies are recommended to help patients achieve lifestyle changes and practise self-management.	I	B	536-538,544
Patient-centred cognitive behavioural strategies combined with simplification of dosing regimens should be considered to improve medication adherence.	IIa	B	539-541
Multidisciplinary teams and nurse-led programmes should be considered to support lifestyle change and self-management.	IIa	B	536,537, 544,545

[a]Class of recommendation.
[b]Levels of evidence.
[c]Reference(s) supporting levels of evidence (see original paper).

success in supporting patients in achieving lifestyle changes and effectively self-managing their conditions. The ongoing support and booster sessions will be necessary for sustained change (Table 25).

12.2. *Gaps in knowledge*

Effects of patient-centred interventions on outcome measures, including micro- and macrovascular complications.

REFERENCES *

[1] ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with EASD. Authors/ Task Force Members: Lars Rydén, Peter J. Grant, Stefan D. Anker, Christian Berne, Francesco Cosentino, Nicolas Danchin, Christi Deaton, Javier Escaned, Hans-Peter Hammes, Heikki Huikuri, Michel Marre, Nikolaus Marx, Linda Mellbin, Jan Ostergren, Carlo Patrono, Petar Seferovic, Miguel Sousa Uva, Marja-Riita Taskinen, Michal Tendera, Jaakko Tuomilehto, Paul Valensi, Jose Luis Zamorano. The original text is available free on the website: http://eurheartj.oxfordjournals.org/content/34/39/3035.full.pdf and was originally published in European Heart Journal 34 (2013) 3035-3087.

* All references supporting the recommendations in this document can be found in the original full text.