



EUROPEAN SOCIETY OF CARDIOLOGY®

# Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary

The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD)

**Authors/Task Force Members, Lars Rydén, Co-Chairperson (Sweden)\*, Eberhard Standl, Co-Chairperson (Germany)\*, Małgorzata Bartnik (Poland), Greet Van den Berghe (Belgium), John Betteridge (UK), Menko-Jan de Boer (The Netherlands), Francesco Cosentino (Italy), Bengt Jönsson (Sweden), Markku Laakso (Finland), Klas Malmberg (Sweden), Silvia Priori (Italy), Jan Östergren (Sweden), Jaakko Tuomilehto (Finland), Inga Thrainsdottir (Iceland)**

**Other Contributors, Ilse Vanhorebeek (Belgium), Marco Stramba-Badiale (Italy), Peter Lindgren (Sweden), Qing Qiao (Finland)**

**ESC Committee for Practice Guidelines (CPG), Silvia G. Priori (Chairperson) (Italy), Jean-Jacques Blanc (France), Andrzej Budaj (Poland), John Camm (UK), Veronica Dean (France), Jaap Deckers (The Netherlands), Kenneth Dickstein (Norway), John Lekakis (Greece), Keith McGregor (France), Marco Metra (Italy), João Morais (Portugal), Ady Osterspey (Germany), Juan Tamargo (Spain), José Luis Zamorano (Spain)**


**Document Reviewers, Jaap W. Deckers (CPG Review Coordinator) (The Netherlands), Michel Bertrand (France), Bernard Charbonnel (France), Erland Erdmann (Germany), Ele Ferrannini (Italy), Allan Flyvbjerg (Denmark), Helmut Gohlke (Germany), Jose Ramon Gonzalez Juanatey (Spain), Ian Graham (Ireland), Pedro Filipe Monteiro (Portugal), Klaus Parhofer (Germany), Kalevi Pyörälä (Finland), Itamar Raz (Israel), Guntram Schernthaner (Austria), Massimo Volpe (Italy), David Wood (UK)**

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\*Corresponding author. Lars Rydén, Department of Cardiology, Karolinska University Hospital Solna, SE-171 76 Stockholm, Sweden. Tel.: +46 8 5177 2171; fax: +46 8 34 49 64. Eberhard Standl, Department of Endocrinology, Munich Schwabing Hospital, D-80804 Munich, Germany. Tel: +49 89 3068 2523; Fax: +49 89 3068 3906. E-mail address: lars.ryden@ki.se; eberhard.standl@lrz.uni-muenchen.de



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**Preamble**

Guidelines and Expert Consensus documents aim to present management and recommendations based on all of the relevant evidence on a particular subject in order to help physicians to select the best possible management strategies for the individual patient, suffering from a specific condition, taking into account not only the impact on outcome, but also the risk benefit ratio of a particular diagnostic or therapeutic procedure. The ESC recommendations for guidelines production can be found on the ESC website<sup>†</sup>.

In brief, the ESC appoints experts in the field to carry out a comprehensive and critical evaluation of the use of diagnostic and therapeutic procedures and to assess the risk-benefit ratio of the therapies recommended for management and/or prevention of a given condition. The strength of evidence for or against particular procedures or treatments is weighed according to predefined scales for grading recommendations and levels of evidence, as outlined below. Once the document has been finalized and approved by all the experts involved in the Task Force, it is submitted to outside specialists for review. If necessary, the document is revised once more to be finally approved by the Committee for Practice Guidelines and selected members of the Board of the ESC.

The *ESC Committee for Practice Guidelines (CPG)* supervises and coordinates the preparation of new *Guidelines* and *Expert Consensus Documents* produced by Task Forces, expert groups, or consensus panels. The chosen experts in these writing panels are asked to provide disclosure statements of all relationships they may have, which might be perceived as real or potential conflicts of interest. These disclosure forms are kept on file at the European Heart House, headquarters of the ESC. The Committee is also responsible for the endorsement of these Guidelines and Expert Consensus Documents or statements.

Classes of recommendations	
Class I	Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful, and effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment or procedure
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Evidence or general agreement that the treatment or procedure is not useful/effective and, in some cases, may be harmful

**Introduction**

Diabetes and cardiovascular diseases (CVD) often appear as two sides of a coin: diabetes mellitus (DM) has been rated

Levels of evidence	
A	Data derived from multiple randomized clinical trials or meta-analyses
B	Data derived from a single randomized clinical trial or large non-randomized studies
C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

as an equivalent of coronary heart disease, and conversely, many patients with established coronary heart disease suffer from diabetes or its pre-states. Thus, it is high time that diabetologists and cardiologists join their forces to improve the quality management in diagnosis and care for the millions of patients who have both cardiovascular and metabolic diseases in common. The cardio-diabetological approach not only is of utmost importance for the sake of those patients, but also instrumental for further progress in the fields of cardiology and diabetology and prevention.

The ESC and the EASD accepted this challenge and have developed joint, evidence-based guidelines for diabetes and CVD. Experts from both sides were asked to form a Task Force. The core approach of the group is depicted in *Figure 1*. An algorithm was developed to help discover CVD in patients with diabetes, and vice versa, the metabolic diseases in patients with coronary heart disease, setting the basis for appropriate joint therapy.

This executive summary, an abridged version of the full document, is intended for the practising physician. It focuses on the background and the most relevant references behind the given recommendations. More detailed information is to be found in the full text document. The numbering of references is the same in the executive summary as in this document. Figures and tables are, however, numbered in numerical order in the executive summary and do therefore not necessarily have the same numbers in the full-text document. The latter also contains a detailed chapter on the pathophysiological connections between glucose abnormalities and CVD and much more information on the economical aspects on diabetes and CVD. The full text guidelines will be available from the ESC/EASD web pages ([www.escardio.org](http://www.escardio.org) and [www.easd.org](http://www.easd.org)).

It is a privilege for the co-chairmen having been able to work with the best reputed experts in the field and to give these guidelines now to the community of cardiologists and diabetologists. We wish to thank all members of the task force, who so generously shared their knowledge, as well as the referees for their tremendous input. Special thanks go to Professor Carl Erik Mogensen for his advice on the diabetic renal disease and microalbuminuria sections. We would also like to thank the ESC and the EASD for making these guidelines possible. Finally, we want to express our appreciation of the guideline team at the Heart House, especially Veronica Dean, for extremely helpful support.

*Stockholm and Munich September 2006*  
 Professor Lars Rydén, Past-President ESC  
 Professor Eberhard Standl, Vice President EASD

<sup>†</sup> Recommendations for ESC Guidelines Production at [www.escardio.org](http://www.escardio.org)

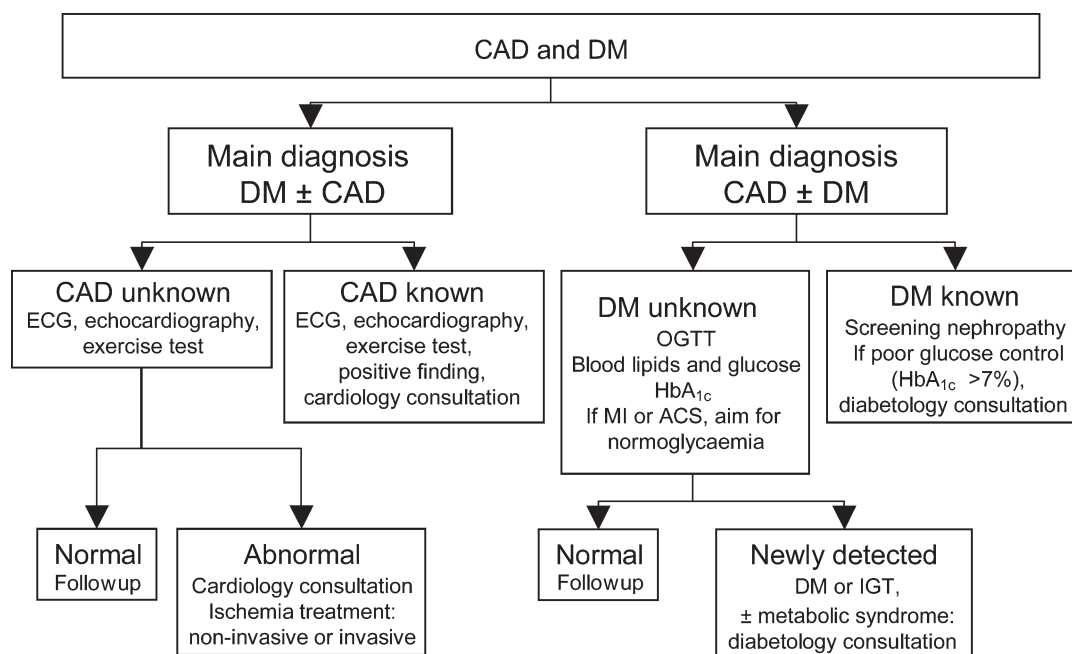


Figure 1 Investigational algorithm for patients with coronary artery disease and diabetes mellitus.

## Definition, classification, and screening of diabetes and pre-diabetic glucose abnormalities

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
The definition and diagnostic classification of diabetes and its pre-states should be based on the level of the subsequent risk of cardiovascular complications	I	B
Early stages of hyperglycaemia and asymptomatic type 2 diabetes are best diagnosed by an oral glucose tolerance test (OGTT) that gives both fasting and 2 h post-load glucose values	I	B
Primary screening for the potential type 2 diabetes can be done most efficiently by using a non-invasive risk score, combined with a diagnostic OGTT in people with high score values	I	A

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

DM is a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects of insulin secretion, insulin action, or a combination of both.<sup>1</sup> Type 1 diabetes is due to a virtually complete lack of endogenous pancreatic insulin production, whereas in type 2 diabetes, the rising blood glucose results from a combination of genetic predisposition, unhealthy diet, physical inactivity, and increasing weight with a central distribution resulting in complex pathophysiological processes. DM is associated with the development of specific long-term

organ damage due to microvascular disease (diabetes complications). Patients with diabetes are also at a particularly high risk for cardiovascular, cerebrovascular, and peripheral artery disease.

## Definition and classification of diabetes

Criteria for glucometabolic disturbances as established by the World Health Organization (WHO)<sup>4,5</sup> and the American Diabetes Association (ADA)<sup>6,7</sup> are outlined in *Table 1*.

Classification of diabetes (*Table 2*) includes aetiological types and different clinical stages of hyperglycaemia.<sup>8</sup> Four main aetiological categories have been identified as diabetes type 1, type 2, other specific types, and gestational diabetes, as detailed in the WHO document.<sup>4</sup>

**Type 1 diabetes.** It is characterized by deficiency of insulin due to destructive lesions of pancreatic  $\beta$ -cells, typically occurs in young subjects, but may occur at any age.<sup>9</sup> People who have antibodies to pancreatic  $\beta$ -cells, such as glutamic acid decarboxylase antibodies, are likely to develop either typical acute onset or slow-progressive insulin-dependent diabetes.<sup>10,11</sup>

**Type 2 diabetes.** It is caused by a combination of decreased insulin secretion and decreased insulin sensitivity. Early stages of type 2 diabetes is characterized by insulin resistance causing excessive post-prandial hyperglycaemia. This is followed by a deteriorating first-phase insulin response to increased blood glucose concentrations.<sup>12</sup> Type 2 diabetes, comprising over 90% of adults with diabetes, typically develops after middle age. The patients are often obese and physically inactive.

**Gestational Diabetes.** This constitutes any glucose perturbation that develops during pregnancy and disappears after delivery. Approximately 70% of females with gestational diabetes will develop diabetes over time.<sup>13</sup>

The currently valid clinical classification criteria, issued by the WHO<sup>4</sup> and ADA,<sup>7</sup> are currently under review by the

**Table 1** Criteria used for glucometabolic classification according to the WHO (1999) and ADA (1997 and 2003) (values are expressed as venous plasma glucose)

Glucometabolic category	Source	Classification criteria [mmol/L (mg/dL)]
Normal glucose regulation (NGR)	WHO	FPG < 6.1 (110) + 2 h PG < 7.8 (140)
	ADA (1997)	FPG < 6.1 (110)
	ADA (2003)	FPG < 5.6 (100)
Impaired fasting glucose (IFG)	WHO	FPG ≥ 6.1 (110) and < 7.0 (126) + 2 h PG < 7.8 (140)
	ADA (1997)	FPG ≥ 6.1 (110) and < 7.0 (126)
	ADA (2003)	FPG ≥ 5.6 (100) and < 7.0 (126)
Impaired glucose tolerance (IGT)	WHO	FPG < 7.0 (126) + 2 h PG ≥ 7.8 and < 11.1 (200)
Impaired glucose homeostasis (IGH)	WHO	IFG or IGT
Diabetes mellitus (DM)	WHO	FPG ≥ 7.0 (126) or 2 h PG ≥ 11.1 (200)
	ADA (1997)	FPG ≥ 7.0 (126)
	ADA (2003)	FPG ≥ 7.0 (126)

FPG = fasting plasma glucose; 2-h PG = two-hour post-load plasma glucose (1 mmol/L = 18 mg/dL).

IGT can only be diagnosed by OGTT. OGTT is performed in the morning, after 8–14 h fast; one blood sample is taken before and one 120 min after intake of 75 g glucose dissolved in 250–300 mL water for 5 min (timing is from the beginning of the drink).

WHO. Updated criteria will be introduced soon. The WHO recommendations for glucometabolic classification are based on measuring both fasting and 2 h post-load glucose concentrations and recommend that a standardized 75 g OGTT should be performed in the absence of overt hyperglycaemia.<sup>4</sup> The cutpoints for diabetes on fasting and 2 h post-load glucose values were primarily determined by the values where the prevalence of diabetic retinopathy, which is a specific complication of hyperglycaemia, starts to increase. Even though macrovascular diseases are major causes of death in patients with type 2 diabetes and IGT, macrovascular disease has not been considered in the classification. The National Diabetes Data Group<sup>2</sup> and the WHO<sup>3</sup> coined the term IGT, an intermediate category between normal glucose tolerance and diabetes. The ADA<sup>6</sup> and the WHO Consultation<sup>4</sup> proposed some changes to the diagnostic criteria for diabetes and introduced a new category called impaired fasting glucose/glycaemia (IFG). The ADA recently decreased the lower cutoff point for IFG from 6.1 to 5.6 mmol/L,<sup>7</sup> but this has been criticized and has not yet been adopted by the WHO expert group, which recommends keeping the previous cutpoints as shown in the WHO consultation report in 1999. These criteria were reviewed by a new WHO expert group in 2005.

In order to standardize glucose determinations, plasma has been recommended as the primary specimen. Many equipment uses either whole blood or venous or capillary blood. Cutoff points for these vehicles have been given<sup>15</sup> as outlined in Table 3.

Glucometabolic categorization based on FPG may differ from that based on a 2 h post-load glucose. Having a normal FPG requires the ability to maintain an adequate

**Table 2** Aetiological classification of glycaemia disorders<sup>a</sup>

Type 1 (β-cell destruction, usually leading to absolute insulin deficiency)
Autoimmune
Idiopathic
Type 2 (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance)
Other specific types
Genetic defects of β-cell function
Genetic defects in insulin action
Diseases of the exocrine pancreas
Endocrinopathies
Drug- or chemical-induced (e.g. cortisone, anti-depressant drugs, BBs, thiazide, etc.)
Infections
Uncommon forms of immune-mediated diabetes
Other genetic syndromes sometimes associated with diabetes (e.g. Down's syndrome, Friedreich's ataxia, Klinefelter's syndrome, Wolfram's syndrome)
Gestational diabetes <sup>b</sup>

<sup>a</sup>As additional subtypes are discovered, it is anticipated that they will be reclassified within their own specific category.

<sup>b</sup>Includes the former categories of gestational impaired glucose tolerance (IGT) and gestational diabetes.

**Table 3** Conversion factors between plasma and other vehicles for glucose values

Plasma glucose (mmol/L) = 0.558 + 1.119 × whole blood glucose (mmol/L)
Plasma glucose (mmol/L) = 0.102 + 1.066 × capillary blood glucose (mmol/L)
Plasma glucose (mmol/L) = -0.137 + 1.047 × serum glucose (mmol/L)

basal insulin secretion and an appropriate hepatic insulin sensitivity to control hepatic glucose output. During an OGTT, the normal response to the absorption of the glucose load is both to suppress hepatic glucose output and to enhance hepatic and skeletal muscle glucose uptake. To keep a post-load glucose level within the normal range requires appropriate dynamics of the β-cell secretory response, amount, and timing, in combination with adequate hepatic and muscular insulin sensitivity.<sup>1,16,17</sup>

### Glycated haemoglobin

Glycated haemoglobin (HbA<sub>1c</sub>), a useful measure of the efficacy of glucose-lowering treatment, is an integrated summary of circadian blood glucose during the preceding 6–8 weeks, equivalent to the lifespan of erythrocytes.<sup>18</sup> HbA<sub>1c</sub> has never been recommended as a diagnostic test for diabetes. HbA<sub>1c</sub> is insensitive in the low range. A normal HbA<sub>1c</sub> cannot exclude the presence of diabetes or IGT.

### Markers of glucometabolic perturbations

A difficulty in the diagnosis of diabetes is the lack of an identified, unique biological marker that would separate people with IFG, IGT, or diabetes from people with normal glucose metabolism. The use of diabetic retinopathy has been discussed. The limitation is that this condition

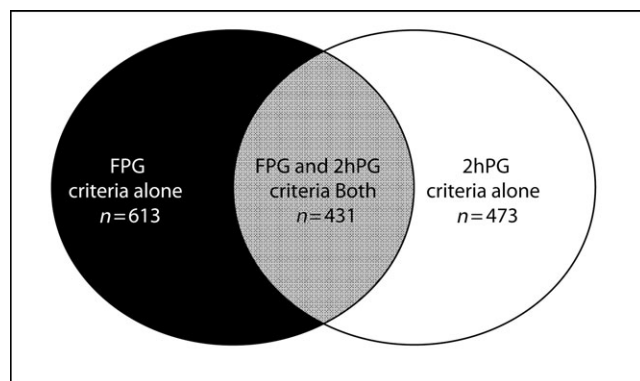
usually becomes evident only after several years of hyperglycaemic exposure.<sup>1,5-10</sup> Thus far, total mortality and CVD have not been considered for defining those glucose categories that carry a significant risk. Nevertheless, the vast majority of people with diabetes die from CVD, and asymptomatic glucometabolic perturbations more than double mortality and the risk for myocardial infarction (MI) and stroke. Since the majority of type 2 diabetic patients develop CVD, which is a more severe and costly complication of diabetes than retinopathy, CVD should be considered when defining cutpoints for glucose.

### Comparisons between FPG and 2 h post-load glucose

The DECODE study has shown that any mortality risk in people with elevated FPG is related to a concomitant elevated 2 h post-load glucose.<sup>15,19,20</sup> Thus, the current cutoff point for diabetes based on a 2 h post-load glucose level of  $\geq 11.1$  mmol/L may be too high. It has been noted that, although an FPG level  $\geq 7.0$  mmol/L and a 2 h post-load glucose level of  $\geq 11.1$  mmol/L sometimes identify the same individuals, often they may not coincide. In the DECODE study<sup>21</sup> recruiting patients with diabetes by either criterion alone or their combination, only 28% met both, 40% met the fasting, and 31% the 2 h post-load glucose criterion only. Among those who met the 2 h post-load glucose criterion, 52% did not meet the fasting criterion, and 59% of those who met the fasting criterion did not meet the 2 h post-load glucose criterion.

### Screening for undiagnosed diabetes

Recent estimates suggest that 195 million people throughout the world have diabetes. This number will increase to 330, maybe even to 500 million, by 2030.<sup>23,24</sup> Up to 50% of all patients with type 2 diabetes are undiagnosed<sup>21,22,34</sup> since they remain asymptomatic for many years. Detecting these patients is important for public health and everyday clinical practice. Mass screening for asymptomatic diabetes has not been recommended pending evidence that the prognosis of such patients will improve by early detection and treatment.<sup>25,26</sup> Indirect evidence suggests that screening might be beneficial, improving possibilities for the prevention of cardiovascular complications. In addition, people with IGT



**Figure 2** Fasting and post-load glucose levels identify different individuals with asymptomatic diabetes. FPG, fasting plasma glucose; 2hPG, 2 h post-load plasma glucose (adapted from the DECODE Study Group<sup>21</sup>).

might benefit from lifestyle or pharmacological intervention to reduce or delay the progression to diabetes.<sup>27</sup>

### Detection of people at high risk for diabetes

Typically, persons at high risk for developing diabetes and those with asymptomatic diabetes are unaware of their high-risk status. Although much attention has been directed at detecting undiagnosed type 2 diabetes, only recently attention has turned to those with lesser degrees of glucometabolic abnormalities, which tend to share the same risk factors with type 2 diabetes. Three general approaches for early detection exist: (i) measuring blood glucose to explicitly determine prevalent impaired glucose homeostasis (IGH), a strategy that will detect undiagnosed diabetes as well; (ii) using demographic and clinical characteristics and previous laboratory tests to determine the likelihood of future incident diabetes, a strategy that leaves current glycaemic state ambiguous; (iii) collecting questionnaire-based information on factors that provide information about the presence and extent of a number of aetiological factors for type 2 diabetes, a strategy that also leaves the current glycaemic state ambiguous. The two latter approaches can serve as primary and cost-efficient screening tools, identifying a subgroup of the population in whom glycaemic testing may be targeted with a particular yield. The second option is particularly suited for certain groups, including those with pre-existing CVD and women who have had gestational diabetes, whereas the third option is better suited for the general population (*Figure 3*). Glycaemic testing is necessary as a secondary step in all three approaches to accurately define IGH, since the initial screening step is not diagnostic.

There will be a trade-off between sensitivity and specificity among the strategies. False labelling may be a problem in the first approach only, since the two other deal with elevated risk factors that are less sensitive to misclassification, and by their own right already should lead to lifestyle advice.<sup>25</sup> Including more glycaemic tests will contribute more explicit information on the glycaemic status, whereas fewer tests result in more uncertainty. If a strategy does not incorporate an OGTT at any stage, individual glucose tolerance cannot be determined. Fasting glucose and HbA<sub>1c</sub> will not reveal information about glucose excursions after meals or a glucose load.

It is necessary to separate three different scenarios: (i) general population; (ii) subjects with assumed metabolic abnormalities, including those who are obese, hypertensive, or who have a family history of diabetes; and (iii) patients with prevalent CVD. When patients with prevalent CVD have glucometabolic abnormalities, in most cases, it is the 2 h post-load glucose value which is elevated, whereas fasting glucose is often normal.<sup>30</sup> Thus, the measurement of fasting glucose alone should be avoided in such patients. Since patients with CVD by definition can be considered at high risk, there is no need to carry out a separate diabetes risk assessment, but an OGTT should be carried out in them. In the general population, the appropriate strategy is to start with risk assessment as the primary screening tool combined with subsequent glucose testing of individuals identified to be at a high risk.<sup>31</sup> This tool predicts the 10 year risk of type 2 diabetes with 85% accuracy, and in addition, it detects current asymptomatic diabetes and abnormal glucose tolerance.<sup>32,33</sup>

**Finland Diabetes Association**

Type 2 diabetes risk assessment form

Circle the right alternative and add up your points.

- Age
  - 0 p. Under 45 years
  - 2 p. 45–54 years
  - 3 p. 55–64 years
  - 4 p. Over 64 years
- Body mass index (See reverse of form)
  - 0 p. Lower than 25 kg/m<sup>2</sup>
  - 1 p. 25–30 kg/m<sup>2</sup>
  - 3 p. Higher than 30 kg/m<sup>2</sup>
- Waist circumference measured below the ribs (usually at the level of the navel)
 

MEN		WOMEN	
0 p.	Less than 94 cm	0 p.	Less than 80 cm
3 p.	94–102 cm	3 p.	80–88 cm
4 p.	More than 102 cm	5 p.	More than 88 cm
- Do you usually have daily at least 30 min of physical activity at work and/or during leisure time (including normal daily activity)?
  - 0 p. Yes
  - 2 p. No
- How often do you eat vegetables, fruit, or berries?
  - 0 p. Every day
  - 1 p. Not every day
- Have you ever taken antihypertensive medication regularly?
  - 0 p. No
  - 2 p. Yes
- Have you ever been found to have high blood glucose (e.g. in a health examination, during an illness, during pregnancy)?
  - 0 p. No
  - 5 p. Yes
- 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 one in 100 will develop disease
- 7–11 Slightly elevated: estimated one in 25 will develop disease
- 12–14 Moderate: estimated one in 6 will develop disease
- 15–20 High: estimated one in three will develop disease
- Higher than 20 Very high: estimated one in 2 two will develop disease

Please turn over

Figure 3 FINnish Diabetes Risk Score (FINDRISC) to assess the 10 year risk of type 2 diabetes in adults. (modified from Lindstrom and Tuomilehto<sup>31</sup>) available at [www.diabetes.fi/english](http://www.diabetes.fi/english)

### Epidemiology of diabetes, IGH, and cardiovascular risk

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
The relationship between hyperglycaemia and CVD should be seen as a continuum. For each 1% increase of HbA1c, there is a defined increased risk for CVD	I	A
The risk of CVD for people with overt diabetes is increased by two to three times for men and three to five times for women compared with people without diabetes	I	A
Information on post-prandial (post-load) glucose provides better information about the future risk for CVD than fasting glucose, and elevated post-prandial (post-load) glucose also predicts increased cardiovascular risk in subjects with normal fasting glucose levels	I	A
Glucometabolic perturbations carry a particularly high risk for cardiovascular morbidity and mortality in women, who in this respect need special attention	IIa	B

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.

### Prevalence of disease categories and age

#### Plasma glucose age and gender

The mean 2 h plasma glucose concentration rises with age in European populations, particularly after the age of 50. Women have significantly higher mean 2 h plasma glucose concentrations than men, in particular, after the age of 70 years, probably due to survival disadvantage in men compared with women. Mean fasting plasma glucose (FPG) concentration increases only slightly with age. It is higher in men than in women during the age period 30–69 years and becomes higher in women after 70 years.

#### Prevalence of diabetes and IGH

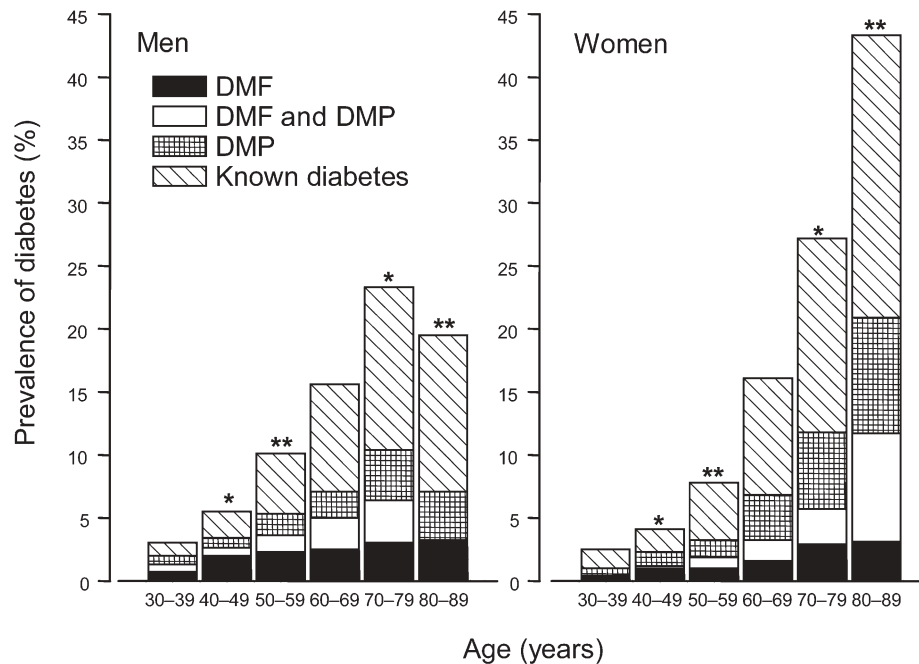
The age-specific prevalence of diabetes rises with age up to the seventh to eighth decades in both men and women (Figure 4).<sup>14</sup> The prevalence is less than 10% in subjects below the age of 60 and 10–20% between 60 and 69 years; 15–20% in the oldest age groups have previously known diabetes, and a similar proportion have screen-detected asymptomatic diabetes. This suggests that the lifetime risk of diabetes in European people is 30–40%.

The prevalence of IGT increases linearly with age, but the prevalence of impaired fasting glycaemia does not. In middle-aged people, the prevalence of IGH is ~15%, whereas in the elderly, 35–40% of European people have IGH. The prevalence of diabetes and IGT defined by isolated post-load hyperglycaemia is higher in women than in men, but the prevalence of diabetes and IFG diagnosed by isolated fasting hyperglycaemia is higher in men than in women.<sup>14</sup>

### Diabetes and coronary artery disease

The most common cause of death in European adults with diabetes is coronary artery disease (CAD). Several studies have demonstrated they have a risk that is two to three times higher than that among people without diabetes.<sup>39</sup> There are wide differences in the prevalence of CAD in patients with type 1<sup>40</sup> or 2 diabetes and also between different populations. In the EURODIAB IDDM Complication Study, involving 3250 type 1 diabetic patients from 16 European countries, the prevalence of CVD was 9% in men and 10% in women,<sup>43</sup> increasing with age, from 6% in the age group of 15–29 years to 25% in the age group of 45–59 years, and with the duration of diabetes. In type 1 diabetic patients, the risk of CAD increases dramatically with the onset of diabetic nephropathy. Up to 29% of patients with childhood-onset type 1 diabetes and nephropathy will, after 20 years with diabetes, have CAD compared with only 2–3% in similar patients without nephropathy.<sup>44</sup>

Several studies compared the magnitude of risk for CAD associated with the history of type 2 diabetes or the presence of previous CAD. In 51 735 Finnish men and women, aged 25–74 years, who were followed for an average of 17 years, and comprising 9201 deaths, the combined hazard ratios for coronary mortality, adjusted for other risk factors,<sup>49</sup> among men with diabetes only, with MI only, and with both diseases, were 2.1, 4.0, and 6.4, respectively, compared with men without either disease. The corresponding hazards ratios for women were 4.9, 2.5, and 9.4. Hazards ratios for total mortality were 1.8, 2.3, and 3.7 in men and 3.2, 1.7, and 4.4 in women. Diabetic men and women had comparable mortality rates, whereas coronary mortality among men was markedly higher. Thus, a history of diabetes



**Figure 4** Age- and gender-specific prevalence of diabetes in 13 European population-based cohorts included in the DECODE study.<sup>14</sup> DMF, diabetes determined by FPG  $\geq 7.0$  mmol/L and 2 h plasma glucose  $< 11.1$  mmol/L; DMP, diabetes determined by 2 h plasma glucose  $\geq 11.1$  mmol/L, and FPG  $< 7.0$  mmol/L; DMF and DMP, diabetes determined by FPG  $\geq 7.0$  mmol/L and 2 h plasma glucose  $\geq 11.1$  mmol/L; Known diabetes, previously diagnosed diabetes. \* $P < 0.05$  and \*\* $P < 0.001$  for the difference in prevalence between men and women, respectively.

and MI markedly increased CVD and all-cause mortality. The relative effect of diabetes was larger in women, whereas the relative effect of the history of MI was more substantial among men. The increased risk of CAD in subjects with diabetes was only partly explained by concomitant risk factors including hypertension, obesity, dyslipidaemia, and smoking. Thus, the diabetic state or hyperglycaemia itself and its consequences are very important for the increased risk for CAD and related mortality. Further support to the important relation between diabetes and MI was obtained from the Interheart study.<sup>160</sup> Diabetes increased the risk by more than two times in men and women, independent of ethnicity.

## IGH and CAD

### Cardiovascular risk and post-prandial hyperglycaemia

The major disagreement in the classification of glucose homeostasis between the criteria issued by the WHO and ADA focuses on whether diabetes should be diagnosed by means of a fasting or a 2 h post-load plasma glucose. Hence it is clinically important to know how these two entities relate to mortality and the risk for CVD. In the Japanese Funagata Diabetes Study, survival analysis concluded that IGT, but not IFG, was a risk factor for CVD.<sup>63</sup> In a recent Finnish study, IGT at baseline was an independent risk predictor of incident CVD and premature all-cause and cardiovascular mortality, a finding not confounded by the development of clinically diagnosed diabetes during follow-up.<sup>29</sup> The Chicago Heart Study of approximately 12 000 men without a history of diabetes showed that white men with asymptomatic hyperglycaemia [1 h glucose  $\geq 11.1$  mmol/L (200 mg/dL)] had an increased risk of CVD mortality compared with men with a low post-load glucose  $< 8.9$  mmol/L (160 mg/dL).<sup>58</sup> Several studies assessed the association of CVD with fasting and 2 h post-load plasma

glucose. On the basis of longitudinal studies in Mauritius, Shaw *et al.*<sup>62</sup> reported that people with isolated post-challenge hyperglycaemia doubled their CVD mortality compared with non-diabetic persons, whereas there was no significant increase in mortality related to isolated fasting hyperglycaemia [FPG  $\geq 7.0$  mmol/L (126 mg/dL) and 2 h post-load plasma glucose  $< 11.1$  mmol/L (200 mg/dL)]. The most convincing evidence for a relation between abnormal glucose tolerance and an increased CAD risk has been provided by the DECODE study, jointly analysing data from more than 10 prospective European cohort studies including more than 22 000 subjects.<sup>68,69</sup> Death rates from all causes, CVD, and CAD were higher in diabetic subjects diagnosed by 2 h post-load plasma glucose than in those not meeting this criterion. Significantly increased mortality was also observed in subjects with IGT, whereas there was no difference in mortality between subjects with impaired and normal fasting glucose. Multivariate analyses showed that high 2 h post-load plasma glucose predicted mortality from all causes, CVD, and CAD, after adjustment for other major cardiovascular risk factors, but high fasting glucose alone did not. High 2 h post-load plasma glucose was a predictor for death, independent of FPG, whereas increased mortality in people with elevated FPG largely related to the simultaneous elevation of the 2 h post-load glucose. The largest absolute number of excess CVD mortality was observed in subjects with IGT, especially those with normal FPG. The relation between 2 h post-load plasma glucose and mortality was linear, but such a relation was not seen with FPG.

### Glycaemic control and cardiovascular risk

Although several prospective studies have unequivocally confirmed that post-load hyperglycaemia increases CVD

morbidity and mortality, it still remains to be demonstrated that lowering a high 2 h post-load plasma glucose will reduce this risk. Studies are underway but thus far data are scarce. A secondary endpoint analysis of the STOP-NIDDM (Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus) revealed statistically significant reductions in CVD event rates in IGT subjects receiving acarbose compared with placebo.<sup>70</sup> Since acarbose specifically reduces post-prandial glucose excursions, this is the first demonstration that lowering post-prandial glucose may lead to a reduction in CVD events. It should, however, be noted that the power in this analysis is low due to a very small number of events.

The largest trial in type 2 diabetic patients so far, the United Kingdom Prospective Diabetes Study (UKPDS),<sup>71</sup> was not powered to test the hypothesis that lowering blood glucose by intensive treatment can reduce the risk of MI, although there was a 16% (marginally significant) reduction in intensively treated patients compared with conventionally treated patients. In this study, post-load glucose excursions were not measured, and over the 10 years of follow-up, the difference in the HbA<sub>1c</sub> concentrations between the intensive and conventional groups was only 0.9% (7.0 vs. 7.9%). Moreover, the drugs used for intensive treatment, sulphonylureas, long-acting insulin, and metformin, mainly influence FPG, but not post-prandial glucose excursions. The German Diabetes Intervention Study, recruiting newly diagnosed type 2 diabetic patients, is so far the only intervention study that has demonstrated that controlling post-prandial hyperglycaemia (blood glucose measured 1 h after breakfast) had a greater impact on CVD and all-cause mortality than controlling fasting blood glucose.<sup>72</sup> During the 11 year follow-up, poor control of fasting glycaemia did not significantly increase the risk of MI or mortality, whereas poor vs. good control of post-prandial glucose was associated with a significantly higher mortality. Additional support is obtained from a meta-analysis of seven long-term studies using acarbose in type 2 diabetic patients. The risk for MI was significantly lower in patients receiving acarbose compared with those on placebo.<sup>73</sup>

### Gender difference in CAD related to diabetes

In the middle-aged general population, men have a two to five times higher risk for CAD than women.<sup>74,75</sup> The Framingham Study was the first to underline that women with diabetes seem to lose their relative protection against CAD compared with men.<sup>76</sup> The reason for the higher relative risk of CAD in diabetic women than diabetic men is still unclear. A meta-analysis of 37 prospective cohort studies, including 447 064 diabetic patients estimated the diabetes associated, gender-related risk of fatal CAD.<sup>81</sup> CAD mortality was higher in patients with diabetes than in those without (5.4 vs. 1.6%). The overall relative risk among people with and without diabetes was significantly greater among women with diabetes 3.50 (95% CI 2.70–4.53) than among men with diabetes 2.06 (1.81–2.34).

### Glucose homeostasis and cerebrovascular disease

#### Diabetes and stroke

Cerebrovascular disease is a predominant long-term cause of morbidity and mortality in patients with both type 1 and type 2 diabetes. Since the first observations, presented by the Framingham investigators, several large population-based

studies have verified an increased frequency of stroke in the diabetic population.<sup>85,88</sup> Diabetes was the strongest single risk factor for stroke (relative risk for men 3.4 and for women 4.9) in a prospective study from Finland with a follow-up of 15 years.<sup>82</sup> DM may also cause microatheromas in small vessels, leading to lacunar stroke, one of most common subtypes of ischaemic stroke. Stroke patients with diabetes, or with hyperglycaemia in the acute stage of stroke, have a higher mortality, worse neurological outcome, and more severe disability than those without.<sup>82,90–101</sup>

There is much less information concerning the risk of stroke in type 1 than type 2 diabetes. The World Health Organization Multinational Study of Vascular Disease in Diabetes indicated increased cerebrovascular mortality in type 1 diabetic patients, however, with considerable variations among countries.<sup>103</sup> The data from the nationwide cohort of more than 5000 Finnish childhood-onset type 1 diabetic patients showed that, by the age of 50 years (i.e. after 20–40 years with diabetes), the risk for an acute stroke was equal to that of an acute coronary event without any gender-related difference.<sup>44</sup> Presence of diabetic nephropathy was the strongest predictor of stroke, causing a 10-fold increase of risk.

#### IGT and stroke

Considerably less is known about the frequency of asymptomatic diabetes and IGT in patients with stroke. In a recent Austrian study<sup>104</sup> involving 238 patients, 20% had previously known diabetes, 16% newly diagnosed diabetes, 23% IGT, but only 0.8% had IFG. Thus, as few as 20% had a normal glucose homeostasis. Another 20% of the patients had hyperglycaemic values, which could not be fully classified owing to missing data in the OGTT. In an Italian study, 106 patients were recruited with acute ischaemic stroke and without any history of diabetes, 81 patients (84%) had abnormal glucose metabolism at discharge (39% IGT and 27% newly detected diabetes) and 62 (66%) after three months.<sup>105</sup>

### Prevention of CVD in people with IGH

Although overall trends in CVD mortality have shown a significant downward trend in developed countries during the last decades, it has been suggested that the decline has been smaller or not existent at all in diabetic subjects.<sup>106</sup> A more recent study reports on a 50% reduction in the rate of incident CVD events among adults with diabetes. The absolute risk of CVD was, however, two-fold greater than among persons without diabetes.<sup>161</sup> More data are needed to judge this issue in European populations.

An imminent issue is to prove that prevention and control of post-prandial hyperglycaemia will cause a reduction in mortality, CVD, and other late complications of type 2 diabetes. There is also a need to reconsider the thresholds used to diagnose hyperglycaemia.<sup>20</sup> The majority of premature deaths related to IGH occur in people with IGT,<sup>15,19</sup> obviating the need for increased attention to people with a high 2 h post-load plasma glucose. A first step would be to detect such people through systematic screening of high-risk groups (see chapter on definition, classification, and screening of diabetes and pre-diabetic glucose abnormalities). The best way to prevent the negative health consequences of hyperglycaemia may be to prevent the development of type 2



diabetes. Controlled clinical outcome trials among asymptomatic subjects with hyperglycaemia are underway, but results will only be available after some years. Meanwhile, the only way to make clinical treatment decisions in such subjects is to make inferences from the observational epidemiological data and pathophysiological studies.

## Identification of subjects at high risk for CVD or diabetes

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
The metabolic syndrome identifies people at a higher risk of CVD than the general population, although it may not provide a better or even equally good prediction of cardiovascular risk than scores based on the major cardiovascular risk factors (blood pressure, smoking, and serum cholesterol)	II	B
Several cardiovascular risk assessment tools exist and they can be applied to both non-diabetic and diabetic subjects	I	A
An assessment of predicted type 2 diabetes risk should be part of the routine health care using the risk assessment tools available	II	A
Patients without known diabetes but with established CVD should be investigated with an OGTT	I	B
People at high risk for type 2 diabetes should receive appropriate lifestyle counselling and, if needed, pharmacological therapy to reduce or delay their risk of developing diabetes. This may also decrease their risk to develop CVD	I	A
Diabetic patients should be advised to be physically active in order to decrease their cardiovascular risk	I	A

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.

## Metabolic syndrome

In 1988, Reaven<sup>118</sup> described a syndrome on the basis of the clustering of the following abnormalities: resistance to insulin-stimulated glucose uptake, hyperinsulinemia, hyperglycaemia, increased very low density lipoprotein triglycerides, decreased high-density lipoprotein (HDL) cholesterol, and high blood pressure. Subsequently, this syndrome became referred to as the 'metabolic syndrome'.<sup>120</sup> More recently, several new components have been proposed as belonging to the syndrome, including markers of inflammation, microalbuminuria, hyperuricaemia, and fibrinolytic and coagulation abnormalities.<sup>121</sup>

### Definitions

Currently, there are at least five definitions of the metabolic syndrome proposed by the WHO in 1998<sup>122</sup> (revised in 1999<sup>4</sup>); the European Group for Study of Insulin Resistance (EGIR) in 1999<sup>124,125</sup>; the National Cholesterol Education

Programme (NCEP) Adult Treatment Expert Panel III in 2001<sup>126,127</sup>; the American Association of Clinical Endocrinologists (AAACE) in 2003<sup>128,129</sup>; and the International Diabetes Federation (IDF) Consensus Panel.<sup>130</sup> The WHO and EGIR definitions were primarily proposed for research purposes and the NCEP and AAACE definitions for clinical use. The 2005 IDF definition aims at worldwide clinical practice. Tables listing the various definitions are presented in the chapter on pathophysiology in the full-text version of these guidelines ([www.escardio.org](http://www.escardio.org)).

Studies on the relationship between the presence of metabolic syndrome and the risk of mortality and morbidity are still scarce, particularly the comparison of risk by different definitions of the syndrome. Several studies in Europe revealed that the presence of the metabolic syndrome increased CVD and all-cause mortality,<sup>131-134</sup> but a couple of reports from the USA have shown inconsistent evidence. On the basis of the data of 2431 US adults aged 30-75 years participating in the second National Health and Nutrition Examination Survey (NHANES II), it was found that the metabolic syndrome was associated with a moderately increased risk of mortality from CVD but not significantly associated with mortality from all-causes, coronary heart disease, or stroke.<sup>136</sup> In the San Antonio Heart Study, after excluding subjects with diabetes, the corresponding relative risk for all-cause mortality decreased substantially from 1.45 (1.07-1.96) to 1.06 (0.71-1.58) for the NCEP definition and from 1.23 (0.90-1.66) to 0.81 (0.53-1.24) for a modified WHO syndrome.<sup>137</sup> A recent study revealed that the NCEP metabolic syndrome is inferior to established predictive models for either type 2 diabetes or CVD.<sup>138</sup> Lawlor *et al.*<sup>139</sup> recently showed that point estimates of the effect for each definition of the syndrome were similar or even weaker than those for individual factors, suggesting there is little additional prognostic value in defining the individual factors as a syndrome for predicting CVD mortality. Although each definition of the metabolic syndrome includes several risk factors, they are defined dichotomously. Thus, such a prognostic formula cannot predict CVD as accurately as a risk model on the basis of continuous variables.

## Risk charts

The first of risk chart, the Framingham risk score, has been available since 1967, comprising the major risk factors known by that time: gender, age, systolic blood pressure, total cholesterol, cigarette smoking, and diabetes. The most recent Framingham score added HDL-cholesterol and deleted left ventricular hypertrophy.<sup>140</sup> The Framingham and other risk scores have been tested in different populations,<sup>141-149</sup> and the conclusion from the comparative studies is that, although the absolute risk may differ from population to population, the proportionate risk ranking provided by these scores is consistent across populations. The definition of the NCEP metabolic syndrome and the Framingham cardiovascular risk score were compared for the prediction of cardiovascular events. Data from the population-based San Antonio Study<sup>138</sup> showed that the Framingham risk score predicted CVD better than the metabolic syndrome. This is not surprising considering that the Framingham score, in contrast to the metabolic syndrome, was specifically developed to predict cardiovascular events and that it differs by including smoking as a risk factor.

More recently a European Heart Score, based on fatal events, has been generated from pooled data from more than 200 000 men and women,<sup>150</sup> taking the overall CVD risk profile into account. Diabetes was not uniformly defined in these cohorts and, because of that, not taken into account in the risk chart. It is, however, stated that the presence of diabetes positions the person at a high risk level. Results from a number of cohort studies, particularly the large European DECODE study, do, however, indicate that either fasting or 2 h post-load plasma glucose is an independent risk factor for all-cause and cardiovascular morbidity and mortality even in people without diagnosed diabetes.<sup>15,19,20,69</sup> The DECODE group developed a CVD risk score, which is presently the only one of its kind including IGT or IFG in the risk function determination.<sup>157</sup>

A population strategy for altering lifestyle and environmental factors, the underlying causes of the mass occurrence of CAD, has been considered since 1982 in a report of the WHO Expert Committee on Prevention of Coronary Heart Disease. This is in accordance with the notion that even small decreases in the risk factor pattern at a population level, through the large number of individuals involved, will affect the health of many people.<sup>158</sup> Such an approach has proved successful in Finland.<sup>158</sup> For public health purposes, there is a need to develop a CVD risk assessment tool on the basis of easily available information similar to the one developed to predict the development of type 2 diabetes in Finland.<sup>32</sup> This Finnish Diabetes Risk Score (FINDRISC) predicts the 10 year risk for developing type 2 diabetes with 85% accuracy. It also detects asymptomatic diabetes and abnormal glucose tolerance with high reliability in other populations.<sup>32,111</sup> In addition, FINDRISC predicts the incidence of MI and stroke.<sup>163</sup> Such high-risk individuals identified by a simple scoring system can be a target for proper management, not only for diabetes prevention, but also for CVD prevention.

### Preventing progression to diabetes

The development of type 2 diabetes is often preceded by a variety of altered metabolic states, including IGT, dyslipidaemia, and insulin resistance.<sup>170</sup> Although not all patients with such metabolic abnormalities progress to diabetes, their risk of developing the disease is significantly enhanced. Carefully conducted clinical studies<sup>174-178</sup> have demonstrated that effective lifestyle intervention strategies and drug treatments can prevent or at least delay the progression to type 2 diabetes in high-risk individuals.

In the Swedish Malmö study, increased physical exercise and weight loss prevented or delayed type 2 diabetes in subjects with IGT to less than half the risk in the control group, during 5 years of follow-up.<sup>174</sup>

In a Chinese study from Da Qing, 577 individuals with IGT were randomized into one of four groups: exercise only, diet only, diet plus exercise, and a control group.<sup>175</sup> The cumulative incidence of type 2 diabetes during 6 years was significantly lower in the three intervention groups than in the control group (41% in the exercise group, 44% in the diet group, 46% in the diet plus exercise group, and 68% in the control group).

In the Finnish Diabetes Prevention Study, a  $\geq 5\%$  reduction in bodyweight, achieved through an intensive diet and exercise programme, was associated with a 58% reduction in the risk of developing type 2 diabetes ( $P < 0.001$ ) in overweight middle-aged men and women with IGT.<sup>176</sup> The reduction in

the risk of progression to diabetes was directly related to the magnitude of the changes in lifestyle; none of the patients who had achieved at least four of the intervention goals by 1 year developed type 2 diabetes during follow-up.<sup>108,179</sup>

The US Diabetes Prevention Programme, comparing active lifestyle modification or metformin to standard lifestyle advice combined with placebo, found that lifestyle modification reduced the incidence of type 2 diabetes by 58% in overweight American adults with IGT.<sup>109</sup> The goal of the programme was to achieve  $\geq 7\%$  reduction in body weight and physical activity of moderate intensity for at least 150 min per week. The cumulative incidence of diabetes was 4.8, 7.8, and 11.0 cases per 100 person-years in the lifestyle, metformin, and control groups, respectively. This reduction in incidence equated to one case of diabetes prevented for every seven people with IGT treated for 3 years in the lifestyle intervention group, compared with 14 for the metformin group.

In the light of these impressive results, the ADA and the National Institutes of Diabetes, Digestive and Kidney Diseases (NIDDK) recommend that people over 45 years with BMI  $\geq 25$  kg/m<sup>2</sup> should be screened for evidence of high blood glucose. Those with evidence of a pre-diabetic state should be given appropriate counselling on the importance of weight loss through a programme of dietary modification and exercise.<sup>180</sup> In addition, since patients with the metabolic syndrome have an increased risk of CVD and mortality,<sup>131,132,136</sup> lifestyle interventions in obese patients and those with evidence of obesity or hyperglycaemia are likely to be beneficial in terms of overall health and life expectancy. The numbers needed to treat (NNT) to prevent one case of type 2 diabetes with lifestyle intervention in people with IGT is dramatically low (*Table 4*).

In the recently reported Indian Diabetes Prevention Programme (IDPP), lifestyle and metformin showed similar capability to reduce the incidence of diabetes, but a combination of these two treatment possibilities did not improve the outcome.

The Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM)<sup>268,318</sup> trial investigated prospectively whether these two pharmacological compounds may reduce the onset of diabetes, using a factorial design, in people with impaired glucose tolerance, impaired fasting glucose or both. The primary endpoint was the development of diabetes or death. After a median follow up time of three years, the incidence of this endpoint did not differ significantly between ramipril and placebo (18.1% vs. 19.5%; HR 0.91; 95% CI 0.81–1.03). Rosiglitazone reduced the endpoint significantly ( $n = 306$ ; 11.6%) compared with placebo ( $n = 686$ ; 26.0%; HR 0.40; 0.35–0.46;  $P < 0.0001$ ). Thus the effect of rosiglitazone on the likelihood to develop diabetes in people with impaired glucose homeostasis was as could be expected considering its known glucose lowering property. Overall, total cardiovascular events did not differ significantly between the rosiglitazone and placebo groups. In the rosiglitazone group, however, body weight increased significantly ( $P < 0.0001$ ) and more heart failure cases (0.5 vs. 0.1%;  $P < 0.01$ ) were found. The DREAM trial was neither planned nor powered to evaluate cardiovascular outcomes, which would have demanded a longer trial period. Also, a longer follow-up is needed to see whether the glucometabolic effect of rosiglitazone on glucose only lasts as long as the treatment is continued, or if it is sustained. Thus, rosiglitazone cannot, until further evidence has been gained, be

**Table 4** Summary of the findings of four lifestyle intervention studies that aimed at preventing type 2 diabetes in subjects with IGT

Study	Cohort size	Mean BMI (kg/m <sup>2</sup> )	Duration (years)	RRR (%)	ARR (%)	NNT
Malmö <sup>174</sup>	217	26.6	5	63	18	28
DPS <sup>108</sup>	523	31.0	3	58	12	22
DPP <sup>109</sup>	2161 <sup>a</sup>	34.0	3	58	15	21
Da Qing <sup>175</sup>	500	25.8	6	46	27	25

RRR = relative risk reduction; ARR = absolute risk reduction/1000 person-years; NNT = numbers needed to treat to prevent one case of diabetes over 12 months.

<sup>a</sup>Combined numbers for placebo and diet and exercise groups.

considered appropriate management to reduce the risk of CVD in people with impaired glucose homeostasis. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with IGT (IDPP-1).<sup>37</sup>

The recent data from the STOP-NIDDM trial have for the first time suggested that acute cardiovascular events in people with IGT may be prevented by treatment that reduces post-prandial glucose levels.<sup>70</sup> Furthermore, data based on NHANES III have shown that control of low-density lipoprotein (LDL) cholesterol, HDL-cholesterol, and blood pressure to normal levels in patients with the metabolic syndrome (without diabetes and CAD) would result in preventing 51% of coronary events in men and 43% in women; control of these risk factors to optimal levels would result in preventing 81 and 82% of events, respectively.<sup>183</sup>

### Prevention of CVD by physical activity

Studies assessing the association between physical activity and the risk of cardiovascular mortality among diabetic patients indicate that regular physical activity is associated with reduced CVD and total mortality.<sup>186–191</sup> In the Aerobic Center Longitudinal Study, the low fitness group had a high relative risk for total mortality compared with the fit group.<sup>186</sup> Other types of physical activity, such as occupational and daily commuting physical activities on foot or by bicycle, have also been found to be associated with reduced cardiovascular mortality among diabetic patients<sup>191</sup>; People physically active at their work had a 40% lower cardiovascular mortality compared with people with low physical activity at work. A high level of leisure-time physical activity was associated with a 33% drop in cardiovascular mortality, and moderate activity was linked to a 17% drop in cardiovascular mortality compared with the most sedentary group. Doing one, two, or three types of moderate or high occupational, commuting, and leisure-time physical activity reduced significantly total and CVD mortalities.<sup>190</sup> Thus, the reduction in cardiovascular risk associated with physical activity may be comparable with that of pharmacological treatment prescribed to patients with type 2 diabetes. The ADA, the National Cholesterol Education Programme Expert Panel, and International Diabetes Federation (European Region) have recommended physical activity for the primary and secondary prevention of CVD complications among

diabetic patients.<sup>127,193,194</sup> The level of physical activity can be assessed using simple questionnaires or pedometers. The most important thing is that it is done and that health workers motivate diabetic patients to be physically active.

## Treatment to reduce cardiovascular risk

### Lifestyle and comprehensive management

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
Structured patient education improves metabolic and blood pressure control	I	A
Non-pharmacological life style therapy improves metabolic control	I	A
Self-monitoring improves glycaemic control	I	A
Near normoglycaemic control (HbA <sub>1c</sub> ≤ 6.5% <sup>c</sup> ) reduces microvascular complications	I	A
reduces macrovascular complications	I	A
Intensified insulin therapy in type 1 diabetes reduces morbidity and mortality	I	A
Early escalation of therapy towards predefined treatment targets improves a composite of morbidity and mortality in type 2 diabetes	Ila	B
Early initiation of insulin should be considered in patients with type 2 diabetes failing glucose target	Ilb	C
Metformin is recommended as first line drug in overweight type 2 diabetes	Ila	B

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Diabetes Control and Complication Trial-standardized.

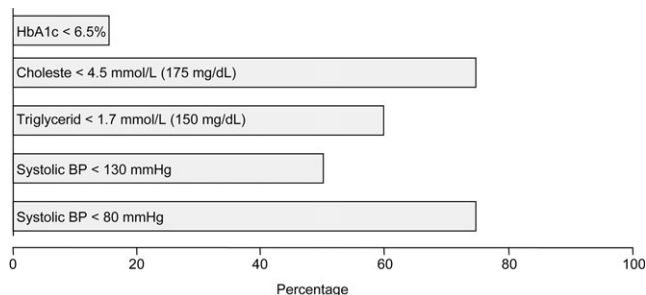
Long-term hyperglycaemia, i.e. DM—both type 1 and type 2, is strongly associated with specific microvascular complications of the retina and the kidneys and with abundant macrovascular disease of the heart, brain, and lower limbs as well as with neuropathy of the autonomic and peripheral nerve system.<sup>286–294</sup> Macrovascular events are about 10 times more common than severe microvascular complications and already occur at excessive rates in patients with glucometabolic disturbances, even before the onset of overt type 2 diabetes.<sup>295–297</sup> Hyperglycaemia is only one of a cluster of vascular risk factors, which is often referred to as the metabolic syndrome.<sup>118,131,135,300</sup> Hence, treatment modalities have to be rather complex and strongly based on non-pharmacological therapy including lifestyle changes and self-monitoring and it requires structured patient education.<sup>301–305</sup> This has to include a heavy emphasis on smoking cessation.

Prior to treatment randomization, patients enrolled into the UKPDS underwent 3 months of non-pharmacological treatment. Along with an average decrease of ~5 kg body weight, HbA<sub>1c</sub> decreased ~2% to an absolute value close to 7%.<sup>303</sup> Hence, non-pharmacological therapy seems to be at least as effective as any glucose-lowering drug therapy, which yields a mean HbA<sub>1c</sub>-lowering effect of 1.0–1.5% in placebo-controlled randomized studies (Table 5).

The specific recommendations include 30 min of physical activity at least five times a week, restriction of calorie intake to ~1500 kcal per day, restriction of fat intake to 30–35% of total daily energy uptake (reservation of 10% for mono-unsaturated fatty acids, e.g. olive oil), avoidance of *trans*-fats,

**Table 5** Mean efficacy of pharmacological treatment options in patients with type 2 diabetes<sup>53,54,331</sup>

Drug	Mean lowering of initial HbA <sub>1c</sub> (%)
Alpha-glucosidase inhibitors	0.5–1.0
Biguanides	1.0–1.5
Glinides	0.5–1.5
Glitazones	1.0–1.5
Insulin	1.0–2.0
Sulphonylurea derivatives	1.0–1.5

**Figure 5** Percentage of patients achieving pre-defined intensive treatment targets in the Steno 2 study (modified from Gaede *et al.*<sup>309</sup>).

increased fibre uptake to 30 g per day, and the avoidance of liquid mono- and disaccharides.<sup>108,109,301,303,307,308</sup>

Risk stratification for concomitant associated hypertension, dyslipidaemia, and microalbuminuria is mandatory for comprehensive management of patients with diabetes.<sup>131,135,275,298–300</sup> The recognition of the underlying insulin resistance with increased visceral adiposity is a key factor for an appropriate therapy, not only of hyperglycaemia, but also of hypertension and dyslipidaemia.<sup>269–300</sup> Using this approach and applying multiple risk factor interventions to high-risk type 2 diabetic patients, as done in the Steno 2 study, are extremely compelling in terms of overall outcome.<sup>309</sup> Targeting hyperglycaemia, hypertension, and dyslipidaemia, together with the administration of acetyl-salicylic acid to high-risk patients with established microalbuminuria, resulted in >50% reduction of major macrovascular events with an NNT of as low as 5 over an 8 year long period ( $P=0.008$ ). This multiple risk factor intervention approach proved highly effective in less than 4 years in terms of microvascular outcomes, thereby confirming the results of UKPDS. Still, the ability to achieve pre-defined targets in Steno 2 was far from complete and strikingly variable. By far, the most difficult target to achieve was HbA<sub>1c</sub> (Figure 5).

This notion was also apparent in the UKPDS,<sup>71,291</sup> fostering the concept of glucose-lowering polypharmacy, like antihypertensive therapy. To reach targets is the crucial objective of comprehensive management. In this context and, in addition, every diabetic patient with some indication of vascular damage, be it macrovascular or microvascular, should be considered for antiplatelet drug therapy, especially acetyl-salicylic acid.<sup>309,310</sup> Further details on target levels are outlined in Table 13. It should be noted that failure to reach the target HbA<sub>1c</sub> level should be avoided and that early escalation of glucose-lowering therapy is essential.

To close the gap between the complex needs of comprehensive management in high-risk and multimorbid individuals with type 2 diabetes and the challenges in daily life, intensive counselling of patients is mandatory.<sup>304,305</sup> These patients are not infrequently prescribed up to 10 different classes of drugs in addition to the counselling of a healthy lifestyle. Structured therapy, including educational classes and training programmes for acquiring the skills for a healthy lifestyle and self-monitoring of blood glucose and blood pressure, is an indispensable prerequisite for successful management and therapy.<sup>304,305,310–312</sup> A mutual reviewing of the self-management protocols at each patient visit allows physicians and patients to become partners in treatment. Paramedical personnel, e.g. certified diabetes educators and nurses play an integrated role in this quality process. Successful comprehensive management of patients with diabetes requires a framework of quality structures with auditing of processes and outcomes. Certified quality management should be reinforced by appropriate incentives both for the patient and the physician.

## Glycaemic control

### Relation to microangiopathy and neuropathy

Randomized, controlled trials have provided compelling evidence that diabetic microangiopathy and neuropathy can be reduced by tight glycaemic control.<sup>71,286,287,291,309,314</sup> This will also exert a favourable influence on CVD.<sup>288–291,295</sup> Nephropathy accelerates CVD, and autonomic neuropathy may mask its symptoms. Annual screening for microalbuminuria and retinopathy is mandatory.

When compared with conventional treatment regimens, intensified treatment options, aimed at lowering haemoglobin HbA<sub>1c</sub> close to the normal range, have consistently been associated with a markedly decreased frequency and extent of microvascular and neuropathic complications in people with type 1 and type 2 diabetes. This applies not only to primary intervention, but also to secondary intervention.<sup>71,286,287,314</sup> Analyses from the Diabetes Control and Complication Trial (DCCT) and the UKPDS demonstrated a continuous relationship between HbA<sub>1c</sub> and microangiopathic complications without any apparent threshold of benefit.<sup>287,295</sup> In the DCCT, a 10% reduction of HbA<sub>1c</sub> was associated with a 40–50% lower risk of retinopathy or its progression, although the absolute reduction in risk was substantially less at lower HbA<sub>1c</sub> levels, e.g. <7.5%. The UKPDS reported a linear relationship with each 1.0% lower HbA<sub>1c</sub> associated with a 25% decline in the risk of microvascular complications, again with a rather low absolute risk at HbA<sub>1c</sub> levels <7.5%. Microvascular complications, both at the kidney and the eye level, warrant meticulous further therapeutic measures, including adequate control of blood pressure with the use of ACE-inhibitors and/or angiotensin receptor 2 blockers and the cessation of smoking.

### Relation to macroangiopathy

Although rather suggestive, the relation between macrovascular disease and hyperglycaemia is less clear than the relation to microangiopathy.<sup>71,286,288,295,309,310,314</sup> The recent DCCT post-study follow-up over 11 years (EDIC Study) demonstrated that a randomly assigned, tight glycaemic control (mean HbA<sub>1c</sub> close to 7% over the first 7–10 years) effectively reduced cardiac and other macrovascular disease

manifestations from 98 events in 52 patients to 46 events in 31 patients, corresponding to a decrease of 42%.<sup>316</sup> The risk for MI and stroke, as well as the mortality risk from CVD, was reduced by 57%. This important finding was based on a 93% follow-up rate of the original cohort of 1441 patients with type 1 diabetes. The only significant confounding factor was a higher rate of microalbuminuria and macroproteinuria in the less well-controlled group (complications that are dependent on glycaemic control on their own). On statistical grounds, the reduction of HbA<sub>1c</sub> was by far the most important factor behind the reduction of CVD with a 21% reduction for each per cent decrease of HbA<sub>1c</sub>. In type 2 diabetes, as shown by the UKPDS, each per cent decline of HbA<sub>1c</sub> caused a 14% lower rate of MI and fewer deaths from diabetes or any cause.<sup>71,295</sup> In the Kumamoto trial, a lower HbA<sub>1c</sub> (7.0 vs. 9.0%) resulted in a cardiovascular event rate over 10 years of less than half in the control group. This difference did not, however, reach statistical significance owing to small absolute numbers.<sup>315</sup>

Nearly all prospective observational studies assessing the risk of macrovascular disease in diabetes have shown that this risk is increased already at glycaemic levels slightly above the normal range or even within the high normal range.<sup>292,295-297</sup> In particular, plasma glucose levels 2 h after the glucose load appear to be highly predictive for cardiovascular events, even more than fasting glucose levels.<sup>15,62,63,178</sup> Reduction of post-prandial glucose concentrations by means of an alpha-glucosidase-inhibitor prevented the onset of overt-type 2 diabetes at the stage of IGT, during the study period, and there was also a reduction of cardiovascular events. The number of events was, however, relatively small, and although significant, these results should be interpreted with great caution.<sup>70,178</sup> *Post hoc* analyses of randomized trials in patients with type 2 diabetes, using the same alpha-glucosidase-inhibitor, and with follow-up periods of at least 1 year confirmed these observations in the context of targeting meal-related hyperglycaemia.<sup>73</sup> Insulin resistance is another strong predictor of CVD.<sup>131,135,300</sup> Moreover, components of the metabolic syndrome such as high blood pressure or lipid abnormalities were also attenuated by the chosen intervention in these studies targeting post-prandial hyperglycaemia.<sup>319</sup> Along this line, reducing both insulin resistance and HbA<sub>1c</sub>, as in the PROACTIVE trial, was associated with a 16% (absolute difference 2.1%; NNT = 49) decrease of cardiovascular endpoints such as death, MI, and stroke.<sup>320</sup>

### Relationship with acute coronary syndromes

A wealth of reports indicate that a random blood sugar on admission for an acute coronary syndrome (ACS) is strongly correlated with the short- and long-term outcome of these patients.<sup>393,321-324</sup> Higher blood sugar concentrations in persons with diabetes, including those previously undiagnosed, are highly predictive for poorer outcome both in the hospital and subsequently.<sup>319-324</sup> The landmark Diabetes Glucose And Myocardial Infarction (DIGAMI) study performed in patients with an ACS targeted acute hyperglycaemia on admission in a randomized fashion by means of an insulin-glucose infusion. Within 24 h, glycaemia was significantly lower in the intervention group, to be maintained at a lower level during the next year. This difference translated into an 11% reduced mortality in absolute terms, indicating an NNT of nine patients for one life saved. The beneficial

effect was still apparent after 3.4 years with a relative mortality reduction of ~30%.<sup>323,325</sup> DIGAMI 2 confirmed that glycaemic control is highly predictive for the 2 year mortality rate but did not show any clinically relevant differences between different blood glucose-lowering regimens.<sup>326</sup> A recently published study, however, with a follow-up of only 3 months confirmed that the mean achieved blood glucose is relevant for mortality in diabetic post-MI patients, whereas insulin therapy *per se* did not lower mortality.<sup>66</sup>

Targeting acute hyperglycaemia in diabetic patients with ACS was also introduced into the Schwabing Myocardial Infarction Registry. Provided that all other potential interventions were equally applied to non-diabetic and diabetic patients, 24 h mortality among the diabetics was normalized and total in-hospital mortality the same for the patients with and without diabetes.<sup>327</sup>

### Current treatment approach to glycaemic control

In type 1 diabetes, the gold standard of therapy is intensified insulin therapy, based on appropriate nutrition and blood glucose self-monitoring, aiming at HbA<sub>1c</sub> <7%. Episodes of hypoglycaemia need to be titrated against this goal, and severe hypoglycaemic episodes should be best below a rate of 15/100 patient-years.<sup>310,328</sup>

In type 2 diabetes, a common pharmacological treatment approach is less well accepted. Various diabetes associations have advocated HbA<sub>1c</sub> targets <7.0 or 6.5%,<sup>310,328,329</sup> (Table 6).

Disappointingly, only a minority of patients achieved proposed glucose targets during long-term follow-up in studies like the UKPDS or Steno 2.<sup>71,309</sup> The greatest advance in the treatment of type 2 diabetes in recent years is the advent of polypharmacy, originally suggested by the UKPDS investigators.<sup>330</sup> A concept of early combination therapy has been put forward intended to maximize efficacy and minimize side-effects.

It is based on the fact that a medium dose yields ~80% of the glucose-lowering effect, minimizing potential side-effects such as weight gain, gastrointestinal discomfort, and the risk for hypoglycaemia.<sup>331</sup> This includes early initiation to insulin if oral glucose-lowering drugs in appropriate doses and combinations, backed by appropriate lifestyle therapy, fail to reach target. BMI and the risks of hypoglycaemia, renal insufficiency, and heart failure are major determinants for the choice of treatment<sup>331</sup> (Table 7).

In addition, the stage of the disease and the related preponderant metabolic phenotype<sup>331-334</sup> should be considered when tailoring therapy to individual needs. A strategy for the selection of various glucose-lowering pharmacological

**Table 6** Glycaemic targets for the care of patients with diabetes as recommended by various organizations<sup>107,110,420</sup>

Organization	HbA <sub>1c</sub> (%)	FPG (mmol/L)	Post-prandial PG (mmol/L)
ADA	<7	<6.7 (120) <sup>a</sup>	None
IDF-Europe	≤6.5	≤6.0 (108) <sup>a</sup>	≤7.5 (135) <sup>a</sup>
AACE	≤6.5	<6.0 (108) <sup>a</sup>	<7.8 (140) <sup>a</sup>

ADA = American Diabetes Association; AACE, American Association of Clinical Endocrinology; IDF = International Diabetes Federation.  
<sup>a</sup>mg/dL.

**Table 7** Potential downsides of pharmacological treatment modalities in patients with type 2 diabetes<sup>331</sup>

Potential problem <sup>a</sup>	Avoid or reconsider
Unwanted weight gain	Sulphonylureas, glinides, glitazones, insulin
Gastrointestinal symptoms	Biguanides, alpha-glucosidase inhibitors
Hypoglycaemia	Sulphonylureas, glinides, insulin
Impaired kidney function	Biguanides, sulphonylureas
Impaired liver function	Glinides, glitazones, biguanides, alpha-glucosidase inhibitors
Impaired cardio-pulmonary function	Biguanides, glitazones

See also *Table 5*.

<sup>a</sup>Oedema or lipid disorders may need further considerations.

**Table 8** Suggested policy for the selection of glucose-lowering therapy according to the glucometabolic situation<sup>331</sup>

Post-prandial hyperglycaemia	Alpha-glucosidase inhibitors, short-acting sulphonylureas, glinides, short-acting regular insulin, or insulin analogues
Fasting hyperglycaemia	Biguanides, long acting sulphonylureas, glitazones, long acting insulin or insulin analogues
Insulin resistance	Biguanides, glitazones, alpha-glucosidase inhibitors
Insulin deficiency	Sulphonylureas, glinides, insulin

options on the basis of an assumption or, if available, more detailed knowledge on the glucometabolic situation is outlined in *Table 8*. The use of metformin has emerged as an important option for both mono and combination therapies including insulin, provided that contraindications for this compound are absent.<sup>291</sup>

Successful multicomponent glucose-lowering therapy requires self-monitoring of blood glucose to ensure that metabolic targets are met. Again, the regimen of blood glucose self-monitoring depends on the choice of therapy used and the metabolic phenotype. Obviously, when near-normoglycaemia is the goal, post-prandial glycaemia needs to be taken into account in addition to fasting glycaemia. Monnier and co-workers<sup>313</sup> have shown that to achieve good glycaemic control, HbA1c < 8%, requires measures that lower post-prandial glucose excursion, i.e. treatment that only improves the fasting glucose level will not be sufficient. Blood glucose monitoring is also advantageous in type 2 diabetic patients without insulin treatment, as evidenced by recent meta-analyses.<sup>311,312</sup>

There is an ever increasing body of evidence that a target close to the normal glycaemic levels is advantageous for reducing CVD in people with diabetes. Still, proof of efficacy for primary prevention awaits confirmation. The glycaemic targets recommended for most persons with type 1 and type 2 diabetes are listed in *Table 6*. They should, however, be tailored to individual needs, especially in view of the risk of hypoglycaemia and other compound-specific side-effects of therapy.

## Dyslipidaemia

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
Elevated LDL and low HDL cholesterol are important risk factors in people with diabetes	I	A
Statins are first-line agents for lowering LDL cholesterol in diabetic patients	I	A
In diabetic patients with CVD, statin therapy should be initiated regardless of baseline LDL cholesterol, with a treatment target of <1.8–2.0 mmol/L (<70–77 mg/dL)	I	B
Statin therapy should be considered in adult patients with type 2 diabetes, without CVD, if total cholesterol >3.5 mmol/L (>135 mg/dL), with a treatment targeting an LDL cholesterol reduction of 30–40%	IIb	B
Given the high lifetime risk of CVD, it is suggested that all type 1 patients over the age of 40 years should be considered for statin therapy. In patients 18–39 years (either type 1 or type 2), statin therapy should be considered when other risk factors are present, e.g. nephropathy, poor glycaemic control, retinopathy, hypertension, hypercholesterolaemia, features of the metabolic syndrome, or family history of premature vascular disease	IIb	C
In diabetic patients with hypertriglyceridaemia >2 mmol/L (177 mg/dL) remaining after having reached the LDL cholesterol target with statins, statin therapy should be increased to reduce the secondary target of non-HDL cholesterol. In some cases, combination therapy with the addition of ezetimibe, nicotinic acid, or fibrates may be considered	IIb	B

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## Background and epidemiology

As part of the metabolic syndrome and the pre-diabetic state, dyslipidaemia in type 2 diabetes is often present at the time of diagnosis. It persists despite the use of hypoglycaemic therapy and requires specific therapy with diet, lifestyle, and hypolipidaemic drugs. Typically, there is moderate hypertriglyceridaemia, low HDL cholesterol, and abnormal post-prandial lipaemia. Total and LDL cholesterol levels are similar to those in subjects without diabetes; however, LDL particles are small and dense, which is associated with increased atherogenicity, and there is accumulation of cholesterol-rich remnant particles, which are also atherogenic.

Dyslipidaemia is common in type 2 diabetes. In the Botnia study (4483 men and women aged 35–70 years; 1697 with diabetes and 798 IFG), the prevalence of low HDL cholesterol [<0.9 mmol/L (35 mg/dL) in men and <1.0 mmol/L (39 mg/dL) in women] and/or elevated plasma triglycerides [>1.7 mmol/L (151 mg/dL)] was up to three times higher in those with diabetes and two times higher in those with IFG compared with those with normal glucose tolerance.<sup>131</sup> In this and other studies, the prevalence of dyslipidaemia was more pronounced in women than in men.

## Dyslipidaemia and vascular risk

Although total and LDL cholesterol concentrations in patients with type 2 diabetes are similar to subjects without diabetes, they are important vascular risk factors<sup>335–337</sup> Observational data from the UKPDS demonstrated that a 1 mmol/L (38.7 mg/dL) increase in LDL cholesterol was associated with a 57% increase in CVD endpoints. Low HDL cholesterol was also an important predictor of vascular disease in UKPDS, a 0.1 mmol/L (4 mg/dL) increase being associated with a 15% decrease in CVD endpoints.<sup>336</sup> The independent relationship of elevated plasma triglycerides to vascular risk remains controversial. However, given the complex interactions between triglycerides and other lipoproteins and the inherent variation in triglyceride concentrations, it is clear that determining the independence of the triglyceride/vascular disease relationship by mathematical modelling, such as multivariate regression analyses, is likely to be fraught with problems. In a meta-analysis of population-based cohort studies, average excess risk associated with a 1 mmol/L (89 mg/dL) increase in triglycerides was 32% in men and 76% in women.<sup>338</sup> When adjusted for HDL cholesterol, the excess risk was halved to 37% in women and 14% in men, but remained statistically significant. High triglyceride levels and low HDL cholesterol were significantly related to all coronary heart disease events and to coronary mortality in a large cohort of patients with type 2 diabetes followed for 7 years.<sup>339</sup>

## Treatment benefits of statin therapy

### Secondary prevention

Although no major secondary prevention trial has been performed in a specific diabetic population, there is sufficient evidence from *post hoc* subgroup analysis of over 5000 patients with diabetes, included in the major trials, to

conclude that they show similar benefits in reduction of events (both coronary events and stroke) as patients free from diabetes.

Two *post hoc* analyses involving patients with diabetes have been reported from the Scandinavian Simvastatin Survival Study (4S). In this study, simvastatin was compared with placebo in patients ( $n = 4444$ ) with established CAD and total cholesterol concentrations between 5.5 and 8 mmol/L (193 and 309 mg/dL).<sup>341</sup> At baseline, 202 patients (mean age 60 years, 78% male) were known to have diabetes, a small number and perhaps an atypical diabetic population given that they were hypercholesterolaemic and the triglyceride entry criteria was relatively low at  $<2.5$  mmol/L (220 mg/dL). Lipid changes in this diabetic subgroup were similar to those observed overall. Simvastatin therapy was associated with a 55% reduction in major coronary events ( $P = 0.002$ ). The number of diabetic patients was insufficient to examine the impact of simvastatin on the primary endpoint of overall mortality, although there was a non-significant 43% reduction.<sup>342</sup> A further analysis of 4S identified 483 diabetic patients by baseline plasma glucose. In this cohort, there was a significant 42% reduction in major coronary events and a 48% reduction in revascularizations.<sup>343</sup> These initial results have been supported by subsequent secondary prevention trials, particularly the Heart Protection Study (HPS; *Table 9*). It is clear that patients with diabetes show similar relative risk reductions compared with those without diabetes. Given the higher absolute risk in these patients, the NNT to prevent a CVD event is lower. However, the residual risk in diabetic patients remains high, despite statin treatment underlining the need for a comprehensive management that, as outlined elsewhere in these guidelines, goes beyond lipid lowering.

When the results of the statin trials are related to the degree of LDL reduction, the results show a roughly linear relationship. More recently, the potential-added benefit of

**Table 9** Subgroups of patients with DM in the major secondary prevention trials with statins and the proportionate risk reduction in patients with and without diabetes<sup>112, 123, 153, 154, 341, 342, 344</sup>

Variables			Proportion of events (%)		Relative risk reduction (%)	
Trial	Type of event	Treatment	Diabetes		Patient group	
			No	Yes	All	Diabetes
4S Diabetes $n = 202$	CHD death or non-fatal MI	Simvastatin	19	23	32	55
		Placebo	27	45		
4S Reanalysis Diabetes $n = 483$	CHD death or non-fatal MI	Simvastatin	19	24	32	42
		Placebo	26	38		
HPS Diabetes $n = 3050$	Major coronary event, stroke, or revascularization	Simvastatin	20	31	24	18
		Placebo	25	36		
CARE Diabetes $n = 586$	CHD death or non-fatal MI	Pravastatin	12	19	23	25
		Placebo	15	23		
LIPID Diabetes $n = 782$	CHD death, non-fatal MI, revascularization	Pravastatin	19	29	24	19
		Placebo	25	37		
LIPS Diabetes $n = 202$	CHD death, non-fatal MI, revascularization	Fluvastatin	21	22	22	47
		Placebo	25	38		
GREACE Diabetes $n = 313$	CHD death, non-fatal MI, UAP, CHF, revascularization, stroke	Atorvastatin	12	13	51	58
		Standard care	25	30		

4S, Scandinavian Simvastatin Survival Study; HPS, Heart Protection Study; CARE, Cholesterol and Recurrent Events Trial; LIPID, Long-Term Intervention with Pravastatin in Ischaemic Disease Study; LIPS, Lescol Intervention Prevention Study; GREACE, Greek Atorvastatin and CHD Evaluation Study.

CHD = coronary heart disease; CHF = congestive heart failure; MI = myocardial infarction; revasc = revascularization; UAP = unstable angina pectoris.

achieving LDL cholesterol concentrations lower than levels previously achieved has been tested. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial, standard statin therapy (pravastatin 40 mg/day) was compared with intensive therapy (atorvastatin 80 mg/day) in 4162 patients within 10 days of an ACS, with a mean follow-up of 24 months.<sup>345</sup> More intensive therapy [achieved mean LDL 1.6 mmol/L (62 mg/dL)] was associated with a significant 16% risk reduction in cardiovascular events, compared with standard therapy [mean LDL 2.5 mmol/L (97 mg/dL)]. PROVE-IT included 734 diabetic patients (18%) and there was no heterogeneity of effect in this subgroup.

Treat to New Targets Trial (TNT) has reported on the effects of intensive statin therapy (atorvastatin 80 mg/day) compared with standard therapy (atorvastatin 10 mg/day) in 10 001 patients with stable CAD.<sup>346</sup> Intensive therapy [mean LDL cholesterol 2.0 mmol/L (77 mg/dL)] was associated with a 22% risk reduction, compared with standard therapy [mean LDL cholesterol 2.6 mmol/L (101 mg/dL)], over a median follow-up of 4.9 years. In a recent subgroup analysis of the TNT, the results of intensive, compared with standard, atorvastatin therapy were reported for the 1501 patients with diabetes; 735 received atorvastatin 10 mg/day and 748 atorvastatin 80 mg/day. End-of-treatment mean LDL cholesterol levels were 2.6 mmol/L (99 mg/dL) with atorvastatin 10 mg and 2.0 mmol/L (77 mg/dL) with atorvastatin 80 mg. A primary event occurred in 135 patients (17.9%) receiving atorvastatin 10 mg, compared with 103 patients (13.8%) receiving atorvastatin 80 mg (hazard ratio 0.75;  $P = 0.026$ ). Significant differences between the groups in favour of atorvastatin 80 mg were also observed for time to cerebrovascular event [0.69 (0.48–0.98),  $P = 0.037$ ] and any cardiovascular event [0.85 (0.73–1.00),  $P = 0.044$ ].<sup>181</sup>

### Goals of therapy for secondary prevention

On the basis of evidence from randomized, controlled trials, the Third Joint European Societies Task Force on Cardiovascular Disease Prevention in Clinical Practice<sup>347</sup> recommended treatment goals for patients with established CVD of total cholesterol <4.5 mmol/L (174 mg/dL) and LDL cholesterol <2.5 mmol/L (97 mg/dL). This LDL goal is similar to that of the Adult Treatment Panel III (ATP III) of the Cholesterol Education Programme in the USA.<sup>348</sup> More recently, guidelines have been reviewed by the National Cholesterol Education Programme in the light of recent RCTs.<sup>348</sup> Thus, for very high risk patients, including those with diabetes and symptomatic CVD, a therapeutic option of an LDL goal  $\leq 1.8$  mmol/L (70 mg/dL) is suggested.

### Primary prevention

Given the high risk of CVD in diabetic patients, together with a higher mortality associated with the first event, primary prevention with lipid-lowering is an important component of global preventive strategies in patients with type 2 diabetes. Information from randomized, controlled trials is available from large cohorts of diabetic patients included in HPS<sup>344</sup> and the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA).<sup>349</sup> In ASCOT-LLA, 10 mg of atorvastatin was compared with placebo in 10 305 hypertensive patients with non-fasting total cholesterol of 6.5 mmol/L (251 mg/dL) or less, of whom 2532 had type 2

diabetes. Atorvastatin therapy was associated with a 36% reduction in the primary endpoint of non-fatal MI and fatal CAD, after a median follow-up of 3.3 years. Tests for heterogeneity showed that those with diabetes ( $n = 2532$ ) responded in a similar way, although there were too few events ( $n = 84$ ) to assess reliably the effect in the subgroup alone. In HPS, there were 2912 diabetic patients without symptomatic vascular disease.<sup>344</sup> In this cohort, the risk reduction was 33% ( $P = 0.0003$ ) with simvastatin 40 mg/day. The Collaborative Atorvastatin Diabetes Study (CARDS), compared atorvastatin 10 mg with placebo, in a population of patients with type 2 diabetes (aged 40–75 years) without high cholesterol [baseline LDL 3.0 mmol/L (116 mg/dL)], but with one other risk factors for CVD: hypertension, retinopathy, proteinuria, or cigarette smoking. After a median follow-up of 3.9 years, the risk reduction in first major cardiovascular events was 37% ( $P = 0.001$ ). In all three trials, there was no heterogeneity of effect with regard to baseline LDL cholesterol or other lipid values.<sup>350</sup>

### Goals of therapy for primary prevention

In the Joint European Guidelines, the goals of therapy given for diabetic patients for primary prevention are similar to that given for patients with symptomatic disease: cholesterol <4.5 mmol/L (<174 mg/dL) and LDL <2.5 mmol/L (<97 mg/dL). Patients with type 1 diabetes and proteinuria are included in this guidance.<sup>347</sup> In ATP III, most patients with diabetes without symptomatic disease are considered at high risk and an LDL goal of <2.6 mmol/L (100 mg/dL) is suggested. Given that diabetic patients in HPS and CARDS with low LDL cholesterol levels showed similar relative benefit with statin therapy to those with higher LDL levels, an important clinical question is whether to start statin therapy in patients whose LDL cholesterol is already <2.6 mmol/L (<100 mg/dL). Currently, this decision is left to clinical judgement.<sup>346</sup> In those diabetic patients considered to be at lower risk, drug therapy might not be started if LDL-cholesterol is <3.4 mmol/L (<131 mg/dL). The most recent guidance from the ADA suggests that, in patients with diabetes with a total cholesterol >3.5 mmol/L (>135 mg/dL), statin therapy, to achieve an LDL reduction of 30–40% regardless of baseline LDL levels, is recommended.<sup>351</sup>

In patients with type 1 diabetes, who also have a high lifetime risk of CVD, evidence is still lacking regarding the role of statin therapy for primary prevention.

### Fibrate trials

There is much less information available from randomized controlled trials to determine clinical practice in terms of fibrate therapy compared with statin therapy. In the Veterans Administration HDL Trial (VAHIT), gemfibrozil was compared with placebo in 2531 men with stabilized CAD and low HDL cholesterol [baseline HDL 0.8 mmol/L (31 mg/dL)] and a relatively normal LDL [baseline LDL 2.8 mmol/L (108 mg/dL)]. After a mean follow-up of 5.1 years, gemfibrozil therapy was associated with a 22% risk reduction in the primary endpoint of non-fatal MI or coronary death ( $P = 0.006$ ). In a subgroup of 309 diabetic patients, a composite endpoint of coronary death, stroke, and MI was reduced by 32% (coronary death by 41% and stroke by 40%). This trial suggests benefit beyond LDL-lowering, in that gemfibrozil



therapy did not change LDL cholesterol, but HDL cholesterol increased by 6% and triglycerides fell by 31%.<sup>353,354</sup>

The FIELD study (Fenofibrate Intervention and Event Lowering in Diabetes) assessed the effect of fenofibrate (microzoned preparation 200 mg/day) compared with placebo in type 2 diabetes, with ( $n = 2131$ ) and without ( $n = 7664$ ) previous CVD.<sup>355</sup> After a mean duration of 5 years, fenofibrate therapy was associated with a relative risk reduction of 11% (HR 0.89, 95% CI 0.75–1.05) in the primary endpoint of coronary heart disease death and non-fatal MI, which did not reach statistical significance ( $P = 0.16$ ). Non-fatal MI was reduced significantly (HR 0.76, 95% CI 0.62–0.94;  $P = 0.01$ ), but coronary heart disease mortality showed a non-significant increase (HR 1.19, 95% CI 0.90–1.57;  $P = 0.22$ ). Total cardiovascular events (cardiac death, MI, stroke, coronary, and carotid revascularization) were significantly reduced by fenofibrate therapy ( $P = 0.035$ ). Total mortality was 6.6% in the placebo and 7.3% in the fenofibrate group ( $P = 0.18$ ). In a *post hoc* analysis, fenofibrate therapy was associated with a reduction in coronary events in patients without CVD, but not in those with previous CVD ( $P = 0.03$  for interaction).

There has been much conjecture concerning the conflicting results of FIELD. The degree of baseline dyslipidaemia [total cholesterol 5.0 mmol/L (195 mg/dL), total triglyceride 2.0 mmol/L (173 mg/dL), LDL cholesterol 3.1 mmol/L (119 mg/dL), and HDL cholesterol 1.1 mmol/L (43 mg/dL)] was possibly insufficient to demonstrate the optimal effect of the drug. In the Veterans Administration HDL Trial, a secondary prevention trial which demonstrated a positive outcome with gemfibrozil, baseline HDL cholesterol was 0.8 mmol/L. Other possible confounders include the higher drop-in therapy with statins in the placebo group, the potentially adverse effect of fenofibrate on homocysteine levels (an increase of 3.7  $\mu$ mol/L) and the relatively small impact in reducing LDL cholesterol and increasing HDL cholesterol (only 2% by the end of the study). However, the major conclusion following the results of FIELD trial is that guidance on treatment strategies remains unchanged and statins remain the major treatment choice in the majority of diabetic patients.

#### Guidelines for HDL cholesterol and triglycerides

Given the paucity of information available from controlled trials, guidelines are less specific with regard to goals for HDL cholesterol and triglycerides. However, the joint European guidelines recognize low HDL cholesterol [ $<1$  mmol/L (39 mg/dL) in men and  $<1.2$  mmol/L (46 mg/dL) in women] and fasting triglycerides  $>1.7$  mmol/L (151 mg/dL) as markers of increased vascular risk. In the recent updates of ATP III for patients considered at very high risk, such as diabetic patients with symptomatic vascular disease, high triglyceride, and low HDL cholesterol, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug.<sup>348</sup> When triglycerides are  $>2.3$  mmol/L ( $>189$  mg/dL) but LDL cholesterol levels are to goal following statin therapy, a secondary treatment target of non-HDL cholesterol (total cholesterol minus HDL cholesterol) is suggested with a goal 0.8 mmol/L (31 mg/dL) higher than the identified LDL cholesterol goal.

## Blood pressure

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
In patients with diabetes and hypertension, the recommended target for blood pressure control is $<130/80$ mm Hg	I	B
The cardiovascular risk in patients with diabetes and hypertension is substantially enhanced. The risk can be effectively reduced by blood pressure-lowering treatment	I	A
The diabetic patient usually requires a combination of several anti-hypertensive drugs for satisfactory blood pressure control	I	A
The diabetic patient should be prescribed a renin-angiotensin-system inhibitor as part of the blood pressure-lowering treatment	I	A
Screening for microalbuminuria and adequate blood pressure-lowering therapy including the use of ACE-inhibitors and angiotensin receptor II blockers improves micro- and macrovascular morbidity in type 1 and type 2 diabetes	I	A

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.

### Background

Hypertension is up to three times more common in patients with type 2 DM than in non-diabetic subjects<sup>356,357</sup> and is frequent in patients with type 1 diabetes as well. In the latter condition, nephropathy usually precedes hypertension, which then accelerates the progress of micro- and macrovascular complications. Obesity, increasing age, and onset of renal disease further increase the prevalence of hypertension in diabetic patients.<sup>358</sup>

Diabetes and hypertension are additive risk factors for atherosclerosis and CVD, and hypertension enhances the risk for such disease, more in patients with diabetes than in hypertensive normoglycaemic subjects, as demonstrated, for instance, by the Multiple Risk Factor Intervention Trial<sup>359,360</sup> and the PROspective Cardiovascular Munster (PROCAM) study.<sup>361</sup> There are several possible reasons for this increased risk, one being enhanced susceptibility to pressure-induced vascular wall stress. The diabetic myocardium may also be more sensitive to other risk factors for CVD, increasing the risk for myocardial hypertrophy, ischaemia, and heart failure.<sup>362</sup> Furthermore, diabetic nephropathy is incrementally accelerated by a raised blood pressure creating a vicious cycle once hypertension and nephropathy are present.<sup>363</sup> It should be noted that renal artery stenosis may be responsible for both renal insufficiency and hypertension in the diabetic patient. Screening for this condition is warranted in patients with refractory hypertension and/or renal insufficiency.

### Treatment targets

The UKPDS and the Hypertension Optimal Treatment (HOT) study revealed that an intensive blood pressure-lowering treatment strategy is associated with a lower incidence of cardiovascular complications in patients with diabetes.<sup>364,365</sup> Various manifestations of CVD, including

stroke and renal disease, were markedly reduced in diabetic patients randomized to rigorous blood pressure control in comparison with those randomized to a less tight control. There is a general consensus that recommended blood pressure targets should be lower in patients with diabetes (<130/80 mm Hg) than in those without diabetes (<140/90 mm Hg). If tolerated, diabetic patients with nephropathy should be treated towards even lower blood pressure levels. A vigorous lowering of blood pressure may initially elevate serum creatinine, but will benefit renal function in a long-term perspective.

**How should blood pressure be lowered?**

Lifestyle interventions should form the basis in the treatment of all patients with hypertension. Although important, lifestyle-oriented changes are usually insufficient for adequate blood pressure control. Most patients need pharmacological treatment and often with a combination of several blood pressure-lowering drugs. Registries and clinical trials reveal that many patients with diabetes still do not reach the recommended target of a blood pressure

<130 mm Hg systolic and <80 mm Hg diastolic.<sup>366,367</sup> Thus, there is a considerable potential for improved patient management. Only a few large prospective, randomized clinical trials with antihypertensive agents have specifically been oriented towards patients with diabetes. However, several large placebo-controlled trials with sizeable subgroups of patients with diabetes have reported specifically on the outcome in that subgroup (Table 10). A consistent finding is the marked reduction of the risk for subsequent cardiovascular events among patients on active treatment compared with those on placebo. This finding is consistent for all types of blood pressure-lowering drugs that have been studied.

Chosen as the initial drug, the beneficial effect of diuretics, beta-blockers (BBs), calcium channel blockers, and ACE-inhibitors are well documented.<sup>368-373</sup> More recently, different antihypertensive drugs have been compared with each other (Table 11). It appears that blockade of the renin-angiotensin-aldosterone system seems to be of particular value, especially when treating hypertension in patients with diabetes at particularly high cardiovascular risk.<sup>374-376</sup> Recent evidence supports the efficacy of an ACE-inhibitor

**Table 10** Treatment effects of antihypertensive drugs in comparison with placebo or less intensive treatment as reported in randomized clinical trials

Trial	Treatment comparison	Primary outcome	Risk reduction (%)			
			Absolute diabetes		Relative diabetes	
			Yes	No	Yes	No
HDFP <sup>383</sup>	Diuretic vs. standard therapy	All-cause mortality	27	21	4.2	3.0
SHEP <sup>368</sup>	Diuretic vs. placebo	Stroke	54	23	8.8	3.1
Syst-EUR <sup>370</sup>	CCB vs. placebo	Stroke	69	36	18.3	4.5
HOT <sup>365</sup>	<80 mm Hg DBP vs. <90 mm Hg DBP	MI/stroke/CV mortality	51	11	12.5	1.0
HOPE <sup>372,373</sup>	ACE-I vs. placebo	MI/stroke/CV mortality	25	21	4.5	2.2

ACE-I = angiotensin-converting-enzyme inhibitor; BB = beta-blocker; CCB = calcium channel blocker; DBP = diastolic blood pressure; CV = cardiovascular.

**Table 11** Treatment effects expressed in hazard ratios (95% CI) in randomized clinical trials comparing different antihypertensive treatments in hypertensive patients with type 2 diabetes

Trial	Treatment comparison	n	CAD <sup>a</sup>	Effect on various outcome variables		CV mortality
				Stroke	Mortality	
UKPDS <sup>364</sup>	ACE-I vs. BB	1148	ns	ns	ns	ns
FACET <sup>375</sup>	ACE-I vs. CCB	380	ns	ns	ns	ns
ABCD <sup>374</sup>	ACE-I vs. CCB	470	0.18 (0.07-0.48)	ns	ns	ns
CAPPp <sup>376</sup>	ACE-I vs. BB/Tz	572	0.34 (0.17-0.67)	ns	0.54 (0.31-0.96)	0.48 (0.21-1.10)
STOP-2 <sup>384</sup>	ACE-I vs. BB/Tz	488	0.51 (0.28-0.92)	ns	ns	ns
STOP-2 <sup>384</sup>	CCB vs. BB/Tz	484	ns	ns	ns	ns
NORDIL <sup>385</sup>	CCB vs. BB/Tz	727	ns	ns	ns	ns
INSIGHT <sup>386</sup>	CCB vs. BB/Tz	1302	ns	ns	ns	ns
ALLHAT <sup>380</sup>	ACE-I vs. Tz	6929	ns	ns	ns	nr
ALLHAT <sup>380</sup>	CCB vs. Tz	7162	ns	ns	ns	nr
LIFE <sup>378</sup>	ARB/Tz vs. BB/Tz	1195	ns	0.79 (0.55-1.14)	0.61 (0.45-0.84)	0.63 (0.42-0.95)
ASCOT <sup>387</sup>	CCB/ACE-I vs. BB/Tz	5145	nr	Combined major cardiovascular events 0.86 (0.76-0.98)		

ARB = angiotensin receptor blocker; CAD = coronary artery disease (mainly myocardial infarction); CV = cardiovascular; ACE-I = angiotensin-converting-enzyme inhibitor; BB = beta-blocker; CCB = calcium channel blocker; Tz = thiazide (or thiazide-like) diuretic; ns = not significant; nr = not reported.

<sup>a</sup>Mainly MI.

rather than a calcium channel blocker as initial therapy, when the intention is to prevent or retard the occurrence of microalbuminuria in hypertensive patients with diabetes.<sup>377</sup> In the Losartan Intervention For Endpoint reduction in hypertension study (LIFE), recruiting patients at high risk owing to established left ventricular hypertrophy, blood pressure lowering-therapy initiated with the angiotensin receptor blocker losartan was more effective in reducing the primary composite cardiovascular endpoint than the selective beta-blocker atenolol. In this study, the beneficial effect of losartan was even more apparent in the diabetic subpopulation, with a statistically significant difference also in all-cause mortality.<sup>378</sup> It should be noted that the vast majority of patients in both groups received hydrochlorothiazide in addition to the angiotensin receptor blocker or beta-blocker.

As outlined in *Table 10*, the absolute risk reduction caused by treatment of hypertension in patients with diabetes is consistently greater than in those without. The main aim when treating hypertension in diabetic patients is, therefore, to reduce blood pressure, although it seems less important by means of which drug or combination of drugs this is accomplished.

An inhibitor of the renin-angiotensin-aldosterone system should, however, be part of the pharmacological combination. It is important to monitor renal function when instituting an ACE-inhibitor or an angiotensin blocker, especially considering the risk of deterioration of renal function in the presence of renal artery stenosis.<sup>182</sup>

A matter that has been intensively discussed over the last decades is whether the metabolic actions of various blood pressure-lowering drugs are important for long-term cardiovascular outcome. It is well established that the use of thiazides and BBs is associated with an increased risk of developing type 2 diabetes compared with treatment with calcium channel blockers and inhibitors of the renin-angiotensin-aldosterone system.<sup>379,380</sup> It is, however, not known whether treatment with BBs and/or thiazides in patients with established type 2 diabetes has any metabolic adverse events of clinical importance, including an increased risk for cardiovascular events. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the outcome was similar in subgroups treated with a diuretic, an ACE-inhibitor, or a calcium channel blocker.<sup>381</sup> However, in that study, the subgroup of patients with IFG was very small in comparison with the diabetic and normoglycaemic subgroups. Thus, although drugs with negative metabolic effects, especially the combination of a thiazide and a beta-blocker, probably should be avoided as first-line treatment when managing hypertensive patients with the metabolic syndrome, the goal of lowering blood pressure seems more important than minor alterations in the metabolic condition in patients with established diabetes.<sup>382</sup> A recent observation, of potential interest in explaining differences between atenolol/thiazide based, compared with amlodipine/perindopril based, blood pressure-lowering therapy was recently suggested in a substudy to ASCOT.<sup>155</sup> The beta-blocker/thiazide-based treatment did not lower central blood pressure to the same extent as the other combination of drugs. It was proposed that this may relate to a diminished cardiovascular protection of the former drug combination.

## Management of CVD

### Coronary artery disease

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
Early risk stratification should be part of the evaluation of the diabetic patient after ACS	Ila	C
Treatment targets, as listed in <i>Table 13</i> , should be outlined and applied in each diabetic patient following an ACS	Ila	C
Patients with acute MI and diabetes should be considered for thrombolytic therapy on the same grounds as their non-diabetic counterparts	Ila	A
Whenever possible, patients with diabetes and ACS should be offered early angiography and mechanical revascularization	Ila	B
BBs reduce morbidity and mortality in patients with diabetes and ACS	Ila	B
Aspirin should be given for the same indications and in similar dosages to diabetic and non-diabetic patients	Ila	B
Adenosine diphosphate (ADP) receptor-dependent platelet aggregation inhibitor (clopidogrel) may be considered in diabetic patients with ACS in addition to aspirin	Ila	C
The addition of an ACE-inhibitor to other therapies reduces the risk for cardiovascular events in patients with diabetes and established CVD	I	A
Diabetic patients with acute MI benefit from a tight glucometabolic control. This may be accomplished by different treatment strategies	Ila	B

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.

### Epidemiology

#### Diabetes and ACS

Diabetes is common among patients with ACS. The proportions range from 19 to 23% in recent multinational registries.<sup>389–391</sup> When patients with acute MI, but without known diabetes, were challenged with an OGTT, 65% had an abnormal glucose regulation (previously undiagnosed diabetes 25% and IGT 40%), a much higher proportion than among age- and gender-matched healthy controls, among whom 65% had a normal glucose regulation (NGR).<sup>392,393</sup> The Euro Heart Survey on Diabetes and the Heart, recruiting patients from 25 countries, disclosed unrecognized diabetes in 22% of patients acutely admitted for CAD when applying an OGTT.<sup>395</sup> Thus, the overall proportion of DM among patients with ACS seems to be about 45%.<sup>396</sup>

#### Prognostic implications

In-hospital and long-term mortality after MI has declined over the years, but patients with diabetes have not benefited to the same extent as those without this disease. Patients with previously known diabetes admitted with

ACS have higher in-hospital mortality (11.7, 6.3, and 3.9% in MI with and without ST-elevation and unstable angina pectoris) than patients without diabetes (6.4, 5.1, and 2.9%) included in the GRACE registry.<sup>389</sup> Diabetes is associated with high long-term mortality, accounting for 15–34% after 1 year and up to 43% after 5 years. The relative risk for overall mortality, following adjustment for differences in baseline characteristics, concomitant diseases, and baseline treatment, which is attributable to diabetes, ranges from 1.3 to 5.4 and is somewhat higher among women than men. Patients with newly detected type 2 diabetes have similar proportions of re-infarction, stroke, and 1 year mortality following an acute MI as patients with previously established diabetes.<sup>406</sup> The main complications in patients with ACS include recurrent myocardial ischaemia, left ventricular dysfunction, severe heart failure, electrical instability, re-infarction, stroke, or death. Most of these complications are significantly more common in patients with diabetes (for a more complete overview, see *Table 17* in the full-text document of these Guidelines, [www.escardio.org](http://www.escardio.org).<sup>388,391,397–406</sup>

The markedly increased adjusted risk of death associated with diabetes beyond the acute phase of coronary events indicates the profound role of the gluco-metabolic derangement. Dysglycaemia at any level causes alterations in energy substrate metabolism, including insulin resistance, increased concentrations of non-esterified fatty acids, and excessive oxidative stress.<sup>201,408</sup> These metabolic factors are further enhanced at the onset of an acute MI when chest pain, breathlessness, and anxiety cause a stress-induced increase in adrenergic tone. Diabetic patients often have widespread and diffuse CAD, decreased vasodilatory reserve, decreased fibrinolytic activity, elevated platelet aggregability, autonomic dysfunction, and possibly diabetic cardiomyopathy (for details, see the chapter on pathophysiology in the full-text version), all factors to be taken into account when choosing therapy. Impaired glucose control may operate in the long-term as well. In type 2 diabetes, metabolic control measured as fasting blood glucose or glycated haemoglobin (HbA<sub>1c</sub>) is a major risk factor for future coronary heart disease. Furthermore, a high blood glucose level at admission is a powerful predictor for in-hospital and long-term mortality, both in patients with and without DM.<sup>327,409,411</sup>

### Treatment principles

Several registry studies show that diabetic patients are not as well treated as non-diabetic patients with regard to evidence-based therapy and coronary interventions.<sup>324,404</sup> In particular, it seems that heparins, thrombolytic agents, and coronary interventions are less frequently administered. One explanation may, as a consequence of autonomic neuropathy, be lack of typical symptoms in diabetic patients with coronary ischaemia. The reported prevalence of silent ischaemia is 10–20% in diabetic, compared with 1–4% in non-diabetic populations.<sup>264</sup> Accordingly, silent infarctions or infarctions with atypical symptoms are more common in diabetic patients, prolonging time to hospital admission as well as to diagnosis, thereby reducing the opportunity to administer adequate treatment. Another possible reason is that the diabetic patient is considered more vulnerable and that this disease has been experienced as a relative

contraindication to some treatment modalities. Nevertheless, evidence-based coronary care treatment, including early coronary angiography and, if possible, revascularization, is at least as effective in the diabetic patient as in the non-diabetic patient and there are no indications for an increased propensity to side-effects.

### Risk stratification

Patients with ACS and concomitant DM, already known or newly recognized, are at high risk for subsequent complications. An extended risk assessment is important to identify specific threats and outline goals for the long-term management strategy.<sup>415,416</sup> This includes (i) a thorough evaluation of history and signs of peripheral, renal, and cerebrovascular disease; (ii) a careful evaluation of risk factors such as blood lipids and blood pressure and of smoking and lifestyle habits; (iii) evaluation of clinical risk predictors including heart failure, hypotension, and risk for arrhythmia, with special focus on autonomic dysfunction; (iv) investigations of inducible ischaemia by means of ST-segment monitoring, exercise testing, stress echocardiography, or myocardial scintigraphy (whatever method is appropriate for the individual patient and clinical setting); (v) assessment of myocardial viability and left ventricular function by means of echo-Doppler and/or magnetic resonance imaging. The reliability (sensitivity/specificity) of exercise testing, stress echocardiography, or myocardial scintigraphy is of a particular concern for the detection of ischaemia in diabetic patients. Confounders are a potentially high threshold for pain owing to autonomic dysfunction, the multivessel nature of the coronary disease, baseline electrocardiographic abnormalities, a commonly poor exercise performance of diabetic patients, coexistence of peripheral artery disease, and use of multiple medications. In this context, a careful clinical evaluation and focused evaluation of laboratory outcomes are of particular importance.

### Treatment targets

Available treatment options, meant to preserve and optimize myocardial function, achieve stabilization of vulnerable plaques, prevent recurrent events by controlling prothrombotic activity, and to counteract progression of atherosclerotic lesions, are summarized in *Table 12*.<sup>417,418</sup> Evidence-based recommendations for secondary prevention are, in general terms, valid for patients with as well as without diabetes. The management strategy should, if anything, be even more ambitious in the former category of patients. For an equal risk reduction, the number of patients

**Table 12** Treatment options based on accumulated evidence

Revascularization
Anti-ischaemic medication
Anti-platelet agents
Anti-thrombin agents
Secondary prevention by means of
Lifestyle habits including food and physical activity
Smoking cessation
Blocking the renin–angiotensin system
Blood pressure control
Lipid-lowering medication
Blood glucose control

**Table 13** Recommended treatment targets for patients with diabetes and CAD (modified from the European Guidelines for Cardiovascular Disease Prevention<sup>419</sup>)

Blood pressure (systolic/diastolic; mm Hg)	< 130/80
In case of renal impairment, proteinuria > 1 g/24 h	< 125/75
Glycaemic control <sup>445</sup>	
HbA <sub>1c</sub> (%) <sup>a</sup>	≤ 6.5
Glucose expressed as venous plasma mmol/L (mg/dL)	
Fasting	< 6.0 (108)
Post-prandial (peak)	< 7.5 (135) diabetes type 2 7.5–9.0 (135–160) diabetes type 1
Lipid profile expressed in mmol/L (mg/dL)	
Total cholesterol	< 4.5 (175)
LDL cholesterol	≤ 1.8 (70)
HDL cholesterol	
Men	> 1.0 (40)
Women	> 1.2 (>46)
Triglycerides <sup>b</sup>	< 1.7 (<150)
TC/HDL <sup>b</sup>	< 3
Smoking cessation	Obligatory
Regular physical activity (min/day)	> 30–45
Weight control	
BMI (kg/m <sup>2</sup> )	< 25
In case of overweight weight reduction (%)	10
Waist (optimum; ethnic specific; cm)	
Men	< 94
Women	< 80
Dietary habits	
Salt intake (g/day)	< 6
Fat intake (% of dietary energy)	
Saturated	< 10
Trans-fat	< 2
Polyunsaturated n-6	4–8
Polyunsaturated n-3	2 g/day of linolenic acid and 200 mg/day of very long chain fatty acids

TC, total cholesterol.

<sup>a</sup>DCCT-standardized, for recalculation formula for some national standards in Europe.<sup>156</sup>

<sup>b</sup>Not recommended for guiding treatment, but recommended for metabolic/risk assessment.

needed to treat to save one life or prevent one defined endpoint is lower among diabetic patients owing to the higher absolute risk.

Important treatment targets are outlined in *Table 13*, summarizing recommendations for secondary prevention on the basis of accumulated evidence, including data from recent guidelines and consensus documents.<sup>130,419–421</sup>

## Specific treatment

### Thrombolysis

A meta-analysis of 43 343 MI patients, 10% of whom had a history of diabetes, revealed that the number of lives saved by thrombolytic therapy was 37 per 1000 treated patients in the diabetic cohort, compared with 15 among

those without DM.<sup>422</sup> Thus, because of their higher risk, fewer numbers are needed to treat to save one life in the diabetic cohort, corresponding to a greater absolute benefit for thrombolytic treatment in diabetics than in non-diabetic patients. It is a myth that thrombolysis is contraindicated in diabetic patients because of an increased risk of eye or cerebral bleeding.

### Early revascularization

Revascularization within 14 days following an acute MI, ST-elevation, as well as non-ST-elevation caused a 53% reduction in 1 year mortality in patients without diabetes and 64% among those with diabetes (15 vs. 5%; RR 0.36; 95% CI 0.22–0.61).<sup>424,425</sup> The early invasive reperfusion strategy among diabetic patients with unstable angina or non-ST-elevation infarctions in the FRISC-II trial resulted in significant reduction of the composite endpoint of death or myocardial re-infarction from 29.9 to 20.6% (OR 0.61; 95% CI: 0.36–0.54).<sup>405</sup> The relative impact of the early invasive strategy was of the same magnitude in both diabetic and non-diabetic patients. This means that, owing to the significantly higher absolute risk, the relative benefit was substantially larger in diabetic patients than in non-diabetic patients. The NNT to save one death or MI was 11 for diabetic and 32 for non-diabetic patients.

The choice between percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) is discussed later in this chapter.

## Anti-ischaemic medication

### Beta-blockade

Although to a large extent based on subgroup analyses, a liberal use of BBs in diabetic patients with MI is advocated, since the beneficial effects have a solid basis in pathophysiology. Post-myocardial treatment with beta-blockade results in a general mortality reduction, as reflected by a systematic overview of scientific reports published during 1966–97 by Freemantle *et al.*<sup>426</sup> In this meta-analysis, the overall mortality reduction was 23% (CI: 15–31%), which can be translated to a number of 42 patients needed to treat during 2 years to save one life. BBs are particularly effective in decreasing post-infarction mortality and new infarcts in patients with a history of DM.<sup>427–432</sup> Thus, oral BBs are, in the absence of contraindications, recommended for all diabetic patients with ACS.<sup>427,428,433</sup> Furthermore, such patients are more prone to develop heart failure and recent trials have documented the beneficial effects of beta-blockade in heart failure patients.<sup>541,543,544</sup>

It seems reasonable to make individualized drug choices among different BBs bearing in mind concomitant conditions and type of diabetes treatment. Selective beta-1-antagonists may be preferred in case of insulin treatment, and alpha-1-beta-adrenergic antagonists such as carvedilol may offer additional benefits for patients with peripheral artery disease or substantial insulin resistance.<sup>434</sup> Still, contemporary data report that diabetic patients with CAD are deprived of this life-saving treatment.<sup>394,397,404</sup>

### Other drugs

Nitrates and calcium antagonists belong to anti-ischaemic drugs. Recent meta-analyses do not reveal survival benefits

for any of them, although favourable effects have been reported for diltiazem in patients with non-ST-elevation infarctions.<sup>418,435</sup> Long-acting calcium channel antagonists and nitrates are therefore not generally recommended, but they may be of value for symptomatic relief in patients already treated with BBs or with contraindications for their use.

#### *Anti-platelet and anti-thrombotic agents*

It has been claimed, but not verified, that diabetic patients need particularly high doses of aspirin for efficient suppression of platelet-derived thromboxane A<sub>2</sub>. A systematic analysis of 195 trials including more than 135 000 patients (4961 with diabetes) at high risk for arterial disease, given antiplatelet therapy in the form of aspirin, clopidogrel, dipyridamol, and glycoprotein IIb/IIIa antagonists (separately or in combination), revealed that the risk of stroke, MI, or vascular death was reduced by ~25%.<sup>436</sup> The benefits experienced among diabetic patients were somewhat lower. The Antithrombotic Trialists concluded that the optimal effective aspirin dose is 75–150 mg daily, with a loading dose of 150–300 mg to be introduced when an immediate effect is needed.

When added to aspirin, the effect of thienopyridines (Ticlopidine, Clopidogrel), which block the adenosine diphosphate (ADP) receptor-dependent platelet activation, is favourable in patients with unstable angina and non-ST-elevation infarctions, lowering the incidence of cardiovascular death, MI, or stroke from 11.4 to 9.3%; (RR 0.80; CI: 0.72–0.90).<sup>437</sup> The outcome of the CURE trial resulted in the recommendation to use clopidogrel (75 mg daily) combined with aspirin (75–100 mg daily) to be continued for 9–12 months following an acute coronary event.<sup>418,438</sup> Among patients with diabetes and vascular disease, clopidogrel provides better protection from serious events (vascular death, re-infarctions, stroke, or recurrent hospitalization for ischaemia) than aspirin (RR 0.87; CI: 0.77–0.88; CAPRIE).<sup>439,440</sup>

#### *ACE-inhibitors*

Blockers of the renin-angiotensin system (ACE-inhibitors) have not been shown to offer any particular advantage in diabetic patients compared with non-diabetic patients in connection with an MI, except from a report from the GISSI-3 trial. In a subgroup analysis from this study, early institution of lisinopril reduced mortality in patients with diabetes, but not in their non-diabetic counterparts.<sup>441</sup> The possibility that the ACE-inhibitor ramipril may prevent cardiovascular events in people with diabetes was tested in the Heart Outcomes Prevention Evaluation (HOPE) Study. A total of 3654 patients with diabetes and previous CVD or one or more risk factors for such disease were recruited to a subgroup in which diabetes was a pre-specified study question.<sup>372</sup> There was a 25% reduction in the composite endpoint of MI, stroke, or cardiovascular death and a clear reduction in each of the component outcomes. More recently, the EUROPE trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) study extended these findings to a population that, in absolute terms, had a lower cardiovascular risk than that in HOPE. Reduction of cardiovascular morbidity and mortality with perindopril was observed irrespective of a relatively high use of other secondary prevention therapies. The proportionate benefit for patients with diabetes

was similar to those in the overall population. The absolute benefit was, however, greater because of the higher event rate among diabetic subjects.<sup>442,443</sup>

Details on blood pressure control and the use of various drugs, including ACE-inhibitors, alone or in combination are given elsewhere in the chapter on treatment to reduce cardiovascular risk.

#### *Lipid-lowering drugs*

The use of lipid-lowering therapy is discussed elsewhere in these guidelines.

#### **Metabolic support and control**

There are several reasons why intensive metabolic control during an acute MI should be of benefit. It would direct myocardial metabolism from beta-oxidation of FFA towards less energy-consuming glucose utilization. One way to achieve this effect is to infuse insulin and glucose. Intense insulin-based glucose control treatment also has the potential to improve platelet function, correct the disturbed lipoprotein pattern, and decrease plasminogen activator inhibitor-1 activity, thereby improving spontaneous fibrinolysis. The concept of acute and/or chronic metabolic control was tested in the two DIGAMI trials. The first DIGAMI trial recruited 620 patients with diabetes and acute MI to be randomly assigned to a control group or to a group receiving intensive insulin treatment, initiated by an insulin-glucose infusion during the first 24 h after MI.<sup>323</sup> In a long-term follow-up over an average of 3.4 years, there was an 11% absolute mortality reduction in the group subjected to intense insulin treatment, implying one saved life for every nine patients treated.<sup>409</sup> Of particular interest was that patients without previous insulin treatment and at a relatively low risk benefited the most. HbA<sub>1c</sub>, used as the measure of improved metabolic control, decreased on average 1.4% in this group of patients. The well established epidemiological relationship between admission glucose level and mortality was seen only among the control patients, indicating that proper metabolic treatment in the peri-infarction period attenuated the harmful effect of a high blood glucose level on admission.<sup>323</sup>

The second DIGAMI trial compared three management protocols, acute insulin-glucose infusion, followed by insulin-based long-term glucose control, insulin-glucose infusion, followed by standard glucose control, and routine metabolic management according to local practice, in 1253 patients with type 2 diabetes and suspected acute MI.<sup>326</sup> This trial did not verify that an acutely introduced long-term intensive insulin treatment strategy improves survival in type 2 diabetic patients following MI and did not demonstrate that initiating treatment with an insulin-glucose infusion is superior to conventional management. However, glucose control was better than in DIGAMI 1 already at the hospital admission, and the three glucose management strategies did not result in a significantly different long-term glucose control. Indeed, target glucose levels were not reached in the intensive insulin group and were better than expected in the two other arms. Given a similar degree of glucose regulation, it seemed as if insulin *per se* did not improve the prognosis more than any other combination of glucose-lowering drugs. The DIGAMI 2 trial confirmed that glucose level is a strong, independent predictor of long-term mortality following MI in patients with type

2 diabetes, with a 20% increase in long-term mortality for an increase in updated plasma glucose by 3 mmol/L.

In the Estudios Cardiológicos Latinoamerica (ECLA) trial, involving 400 patients, there was a trend towards a non-significant reduction in major and minor in-hospital events in patients allocated to glucose–insulin–potassium therapy.<sup>411</sup> The recent CREATE-ECLA trial randomized more than 20 000 patients with acute ST-elevation infarction, out of whom 18% had type 2 diabetes, to high-dose glucose–insulin–potassium or to standard care. The overall outcome was that glucose–insulin–potassium did not influence mortality.<sup>444</sup> It must be emphasized that none of these trials targeted a pure diabetic population or aimed at normalization of blood glucose *per se*. In fact, there was a significant increase in blood glucose levels in the CREATE-ECLA trial, which may have contributed to the neutral result. The very consistent results from this trial strongly suggest that acute metabolic intervention by means of glucose–insulin–potassium has no place in the contemporary treatment of patients with acute MI, if not used to normalize blood glucose. In contrast, and as discussed in detail elsewhere in these guidelines, a Belgian surgical intensive care unit (ICU) study which targeted a ‘normal’ glucose level (4.5–6.1 mmol/L; 80–110 mg/dL) in the actively treated group showed a significant decrease in mortality.<sup>445</sup>

Based on present knowledge, there is reasonable evidence to initiate glucose control by means of insulin infusion in diabetic patients who are admitted for acute MIs with significantly elevated blood glucose levels in order to reach normoglycaemia as soon as possible. Patients admitted with relatively normal glucose levels may be handled with oral glucose-lowering agents. In the follow-up, both epidemiological data and recent trials support that continued strict glucose control is beneficial. The therapeutic regime to accomplish this goal may include diet, lifestyle strategies, oral agents, and insulin. Since there is no definite answer to which pharmacological treatment is the best choice, the final decision can be based on decisions by the physician in charge in collaboration with the patient. Most importantly, the effect on long-term glucose control has to be followed up, and the levels should be targeted to be as normal as possible.

## Diabetes and coronary revascularization

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
Treatment decisions regarding revascularization in patients with diabetes should favour coronary artery bypass surgery over percutaneous intervention	Ila	A
Glycoprotein IIb/IIIa inhibitors are indicated in elective PCI in a diabetic patient	I	B
When PCI with stent implantation is performed in a diabetic patient, drug-eluting stents (DES) should be used	Ila	B
Mechanical reperfusion by means of primary PCI is the revascularization mode of choice in a diabetic patient with acute MI	I	A

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

Revascularization procedures may be indicated in diabetic patients with stable or unstable coronary syndromes, covering the whole spectrum of ischaemic heart disease from asymptomatic patients to ST-elevation MI, ACS, and prevention of sudden cardiac death. Patients with diabetes have a higher mortality and morbidity after CABG compared with non-diabetics, but this is also seen in patients undergoing PCIs.<sup>488–490</sup> The influence of glucometabolic control on the outcome after revascularization (insulin vs. oral agents) is still unclear.

## Surgery vs. percutaneous intervention

The effectiveness of PCI and bypass surgery as a mode of revascularization has been compared in several randomized, controlled trials. Later, when stents became available, studies were conducted, comparing this new percutaneous technology with CABG in multivessel CAD.<sup>474–477</sup>

Major concerns were raised when a *post hoc* subgroup analysis of BARI patients with diabetes and multivessel disease demonstrated a less favourable prognosis among those treated with PCI than those subjected to CABG (Table 14).<sup>458,496</sup> In BARI, the 7 year survival for the total population was 84.4% for surgically treated patients and 80.9% for PCI ( $P=0.043$ ). The corresponding proportions for diabetes patients were 76.4 vs. 55.7% ( $P=0.001$ ).

This suggests that the non-significant treatment difference between the two groups was limited to the PCI patients with diabetes. Furthermore, in BARI, the survival difference was limited to diabetic patients who received at least one arterial internal mammary graft.<sup>459</sup> BARI was not designed to focus on diabetic patients. The suspicion raised by BARI that long-term prognosis after PCI might be worse in patients with diabetes with multivessel disease was, however, confirmed by another large registry of consecutive revascularization procedures.<sup>479</sup> Unrandomized patients, eligible for the BARI study, were included in a registry. Their mode of revascularization was left to the discretion of patients and physicians. In this BARI registry, similar differences in mortality were not observed (Table 14).<sup>456,460</sup> In addition, three other studies, conducted in the balloon angioplasty era, could not confirm the conclusion from BARI with regard to diabetic patients undergoing PCI: RITA-1, CABRI, and EAST (Table 14).<sup>471–473</sup> The Angina with Extreme Serious Operative Mortality Evaluation (AWESOME) trial randomized only patients with unstable angina and high surgical risk. In the PCI group, 54% of the patients received stents and 11% received glycoprotein IIb/IIIa antagonists.<sup>477</sup>

**Table 14** Trials addressing diabetes and revascularization for multivessel disease

Trial	Patients (n)	Follow-up (years)	Mortality (%)		P-value
			CABG	PCI	
BARI <sup>458</sup>	353	7	23.6	44.3	<0.001
CABRI <sup>471</sup>	124	4	12.5	22.6	ns
EAST <sup>472</sup>	59	8	24.5	39.9	ns
BARI registry <sup>460</sup>	339	5	14.9	14.4	ns

**Table 15** Revascularization in diabetes patients with multivessel disease in the stent-era

Trial	Patients (n)	Follow-up (years)	Mortality (%)		Revascularization (%)		Mortality P-value
			CABG	PCI	CABG	PCI	
ARTS <sup>474</sup>	208	3	4.2	7.1	8.4	41.1	0.39
SoS <sup>476</sup>	150	1	0.8	2.5			ns
AWESOME <sup>477</sup>	144	5	34	26			0.27

The combined impression from these studies is that survival does not differ, but that diabetic patients have a significantly higher incidence of repeat revascularization and that restenosis is still a major problem especially in this patient category (Tables 14 and 15).

### Adjunctive therapy

All studies mentioned still raise the question whether revascularization by means of PCI or CABG is to be preferred in patients with diabetes and multivessel disease.

Stents, and later DES, have been hailed to improve the outcome of PCIs in the diabetic patient. Although the results are promising, only one small study did in fact address subacute stent thrombosis, restenosis, and long-term outcome in this patient category, and other available data relate to subsets of patients included in studies on stents and DES.<sup>457,462,480–482</sup> A recent meta-analysis comparing DES with bare metal stents in diabetic subpopulations in several clinical trials revealed that DES were associated with an 80% relative risk reduction for restenosis during the first year of follow-up.<sup>483</sup> Future clinical trials comparing DES with coronary bypass surgery are certainly needed to determine the optimal revascularization strategy in diabetic patients with multivessel disease.

Potent platelet glycoprotein IIb/IIIa inhibitors improve the outcome after PCIs when administered during the procedure in diabetic patients. In three randomized trials with abciximab, there was a 44% reduction of mortality after 1 year, suggesting that these agents are indicated in all diabetic patients undergoing PCI.<sup>482</sup> Adenosine-diphosphate (ADP) receptor antagonists (thienopyridines), like clopidogrel, may prevent early as well as late thrombotic complications after stent implantation, particularly in patients with diabetes.<sup>438</sup>

In patients with diabetes, the progressive nature of the atherosclerotic disease, the marked endothelial dysfunction, and platelet and coagulation abnormalities are responsible for a less favourable outcome after revascularization. Additional treatment should be focused on these specific disease entities, with special attention paid to concomitant disease and risk factors. However, no randomized trials have been conducted to see whether these measures will affect the outcome after revascularization procedures. Furthermore, no data are available regarding whether improved glycaemic control can reduce the incidence of restenosis after PCI or improve patency of bypass grafts after CABG. Whether diabetes in general is associated with an increased physician's preference for either medical or revascularization treatment was addressed in the Euro Heart Survey on coronary revascularization. In a

broad range of European practices, diabetes was not among the factors that determine treatment decisions in stable coronary disease.<sup>490</sup> However, the higher incidence of repeat revascularization in PCI-treated patients should always be taken into consideration. Although patients presenting with ACS have different clinical characteristics than those who present with stable coronary syndromes, the general opinion is that the approach with regard to mode of revascularization has to be identical.<sup>491</sup>

### Revascularization and reperfusion in MI

Patients with diabetes or hyperglycaemia may have a different response to several treatment strategies used for MI.<sup>400,492–494</sup> In patients with ST-segment elevation MI, thrombolysis seems to be less effective in those with diabetes.<sup>495</sup> In general, increasing evidence suggests that primary PCI is preferable to thrombolysis as reperfusion therapy for ST-segment elevation MI.<sup>496–498</sup> Whether this benefit is present in patients with diabetes is less clear. Still, primary PCI has been suggested as the treatment of choice in high-risk patients, among whom are the diabetic patients.<sup>496,497</sup> Although thrombolysis is less beneficial in diabetic patients, revascularization and reperfusion by primary PCI may also be less successful owing to more diffuse CAD, smaller reference diameters, and a tendency for higher restenosis rates.<sup>499,500</sup> Patients with DM have an adverse prognosis after ST-segment elevation MI and myocardial reperfusion as assessed by ST-segment resolution and myocardial blush grade, demonstrating more frequently reduced blush and incomplete ST-segment resolution after primary angioplasty, compared with patients without diabetes.<sup>400</sup>

Identifying the optimal method of reperfusion in diabetic patients is of great clinical importance, as the number of ST-segment elevation MI patients with diabetes is high and their prognosis poor.<sup>395,501</sup> A recent analysis of diabetic patients included in 11 randomized trials demonstrated a survival benefit for those treated with primary PCIs over those with thrombolytic treatment.<sup>497,498</sup> These findings have been confirmed by two other studies.<sup>502,503</sup>

Cardiac surgery in the setting of ST-segment elevation MI is indicated only when the coronary anatomy is not suitable for a percutaneous intervention, after such intervention has failed and the area of myocardium at risk is large, or when mechanical complications occur.

### Unresolved issues

In patients with diabetes and CAD, both PCIs and CABG are treatment options, although it remains to be determined whether one is preferable over the other. The vast majority



of studies includes only subgroups of patients with diabetes and was not dedicated to patients with diabetes in particular. Moreover, only trials randomizing diabetic patients to modern revascularization technology, including DES, will give the answer whether CABG, hybrid revascularization procedures, or PCIs should be the preferred treatment modality. Diffuseness of atherosclerotic involvement, type of diabetes, suitability for percutaneous intervention, clinical presentation, presence of chronic total occlusion, lesion morphology and involvement of proximal left anterior descending coronary artery, co-morbidity, and other factors may define subgroups that may benefit specifically from one or the other revascularization option. Such trials are under way, but until such trials have been completed, an indicative classification remains highly speculative.

## Heart failure and diabetes

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
ACE-inhibitors are recommended as first-line therapy in diabetic patients with reduced left ventricular dysfunction with or without symptoms of heart failure	I	C
Angiotensin-II receptor blockers have similar effects in heart failure as ACE-inhibitors and can be used as an alternative or even as added treatment to ACE-inhibitors	I	C
BBs in the form of metoprolol, bisoprolol, and carvedilol are recommended as first-line therapy in diabetic patients with heart failure	I	C
Diuretics, in particular loop diuretics, are important for symptomatic treatment of diabetic patients with fluid overload owing to heart failure	IIa	C
Aldosterone antagonists may be added to ACE-inhibitors, BBs, and diuretics in diabetic patients with severe heart failure	IIb	C

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.

## Epidemiological aspects

### Prevalence of heart failure and glucose abnormalities

The prevalence of heart failure varies somewhat in different studies. The prevalence of heart failure has been estimated to be 0.6–6.2% in Swedish men and this increases with age. This is similar to the overall prevalence of heart failure among both genders in the Rotterdam population and the Reykjavík Study.<sup>514–516</sup> Considerably less is known about the prevalence of the combination of diabetes and heart failure. The most recent and extensive data on the prevalence of diabetes and heart failure are from the Reykjavík Study, showing that the prevalence of the combination of heart failure and diabetes is 0.5% in men and 0.4% in women, increasing with increasing age. Heart failure was found in 12% of those with diabetes compared with only 3% in individuals without diabetes. Thus, there was a strong association between diabetes and heart failure.<sup>516</sup>

### Incidence of heart failure and glucose abnormalities

Among British outpatients, the incidence of heart failure has been reported to be around 4/1000 person-years, rising with age. Similar data have been reported from Finland.<sup>517,518</sup> Less information is available on the incidence of the combination of diabetes and heart failure. In the Framingham study, the incidence of heart failure was double among males and five times higher in females with diabetes during 18 years of follow-up, compared with patients free from diabetes,<sup>519</sup> and in a general population of elderly Italians, the incidence of diabetes was 9.6% per year in heart failure patients.<sup>520</sup>

### Prognostic implications

In the presence of diabetes and heart failure, the prognosis becomes deleterious.<sup>521</sup> Diabetes is also a serious prognostic factor for cardiovascular mortality in patients with left ventricular dysfunction owing to ischaemic heart disease.<sup>522</sup> In a general population in Reykjavík, the survival decreased significantly with the concomitant presence of both heart failure and glucose abnormalities, even after adjustment for cardiovascular risk factors and ischaemic heart disease.<sup>523</sup> This may be seen as an indicator of the serious implication of the combination of diabetes and heart failure.

### Treatment

There are very few, if any, clinical trials on heart failure treatment specifically addressing diabetic patients. Information on treatment efficacy of various drugs is therefore based on diabetic subgroups included in various heart failure trials. A disadvantage of this is that the subgroups are not always well defined as regards the diabetic state and treatment. Most data favour a proportionately similar efficacy in patients with and without diabetes. Traditional treatment of heart failure in diabetic patients is currently based on diuretics, ACE-inhibitors, and BBs, as outlined in other guidelines.<sup>420,506</sup> Moreover, it is assumed that meticulous metabolic control should be beneficial in heart failure patients with diabetes.<sup>524</sup>

### ACE-inhibitors

The use of ACE-inhibitors is indicated both in asymptomatic myocardial dysfunction and symptomatic heart failure, since they improve the symptoms and reduce mortality. ACE-inhibitors are beneficial in moderate-to-severe heart failure with and without diabetes.

The Studies of Left Ventricular Dysfunction (SOLVD) study showed a similar effect of enalapril treatment in patients with compromised left ventricular function with and without diabetes,<sup>530</sup> and in the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial, the mortality reduction was at least as good in the diabetic as in the non-diabetic group when comparing high and low doses of lisinopril.<sup>531</sup> Hypoglycaemia has been reported following the institution of ACE-inhibitors in patients with diabetes on glucose-lowering treatment.<sup>534,535</sup> It is therefore recommended to monitor plasma glucose carefully in the early phase of the institution of an ACE-inhibitor in such patients.

### Angiotensin-II receptor blockers

Angiotensin receptor blockers can be used as an alternative to ACE-inhibitors to improve morbidity and mortality in

heart failure patients or even in combination with ACE-inhibitor in symptomatic heart failure patients.<sup>506</sup> The use of angiotensin receptor blockers has not been tested primarily in patients with heart failure and diabetes, but in subgroup analysis of large clinical trials, the beneficial effects were equivalent to that of ACE-inhibitors.<sup>536–538</sup>

### Beta-blockers

Beta-blockade decreases myocardial free fatty acid exposure, thereby changing that metabolic pathway in type 2 diabetes.<sup>539,540</sup> There are no studies that specifically address the use of beta-blockade in patients with diabetes and heart failure. Subgroup analysis of diabetic patients in large heart failure trials has, however, shown that beta-blockers reduce mortality and improve symptoms in moderate-to-severe heart failure to a similar extent in patients with and without diabetes. Since mortality is considerably higher among diabetic patients than non-diabetic heart failure patients, the NNT to save one life is substantially less in the diabetic cohort. The following BBs may, on the basis of the outcome of clinical trials including subgroups of patients with diabetes, be recommended as first-line treatment in patients with heart failure and diabetes: Metoprolol (MERIT-HF), Bisoprolol (CIBIS II), and Carvedilol (COPERNICUS and COMET).<sup>432,541–545</sup>

### Diuretics

Diuretics are mandatory for relief of symptoms that are due to fluid overload. These drugs should, however, not be used in excess since they induce neuro-hormonal activation.<sup>506</sup> Although no studies specifically look into the outcome of the use of diuretics in a heart failure population consisting of diabetic patients, loop diuretics, rather than diuretics which may impair the glucometabolic state, further, are recommended.<sup>546</sup>

### Aldosterone antagonists

The addition of aldosterone antagonists is indicated in severe forms of heart failure and may then improve longevity.<sup>547</sup> No specific information is, however, available from clinical trials on the administration of aldosterone antagonists in patients with diabetes and heart failure. The institution of blockers of the renin-angiotensin-aldosterone system should be made with caution and surveillance of kidney function and potassium, since nephropathy is not infrequent among patients with diabetes and heart failure.

## Glucose-lowering treatment and metabolic modulation

### Insulin

The main effect of insulin is to decrease blood glucose but it may also increase myocardial blood flow, decrease heart rate, and cause a modest increase in cardiac output.<sup>548,549</sup> Insulin treatment in patients with diabetes and heart failure is under debate. It has been shown to have beneficial effects on the myocardial function, but also to be associated with increased mortality.<sup>540,550</sup> Further studies are needed to establish the specific role of insulin treatment beyond the role as an glucose-lowering agent in patients with diabetes and heart failure. In general, it is assumed that meticulous metabolic control would be beneficial in heart failure

patients with diabetes,<sup>524</sup> but this hypothesis has not yet been tested in prospective clinical trials.

### Thiazolidinediones

Thiazolidinediones are insulin sensitizers that are used as glucose-lowering drugs in the treatment of diabetes. Owing to a risk for fluid retention, and thereby worsening of heart failure symptoms, the use of these drugs are considered contraindicated in heart failure patients in New York Heart Association class III–IV.<sup>552</sup> They may, however, if needed, be attempted in patients with milder degrees of heart failure, New York Heart Association class I–II.

### Metabolic modulators

Drugs, such as trimetazidine, etomoxir, and dichloroacetate, which aim to shift myocardial metabolism from oxidation of FFA towards glycolysis, have been tested in patients with myocardial dysfunction and diabetes, but their usefulness has not been demonstrated.<sup>553–556</sup>

## Arrhythmias: atrial fibrillation and sudden cardiac death

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
Aspirin and anticoagulant use as recommended for patients with atrial fibrillation should be rigorously applied in diabetic patients with atrial fibrillation to prevent stroke	I	C
Chronic oral anticoagulant therapy in a dose adjusted to achieve a target international normalized ratio (INR) of 2–3 should be considered in all patients with atrial fibrillation and diabetes, unless contraindicated	Ila	C
Control of glycaemia even in the pre-diabetic stage is important to prevent the development of the alterations that predispose to sudden cardiac death	I	C
Microvascular disease and nephropathy are indicators of increased risk of sudden cardiac death in diabetic patients	Ila	B

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.

## Diabetes, atrial fibrillation, and risk of stroke

### Diabetes and atrial fibrillation

Diabetes is not infrequent in patients with atrial fibrillation. Among patients in the Etude en Activité Liberale sur le Fibrillation Auriculaire (ALFA) study reporting on atrial fibrillation in patients seen in general practice, the proportion of diabetes in patients with chronic atrial fibrillation was 13.1%, making diabetes a common associated condition surpassed only by heart failure and hypertension.<sup>561</sup> Several cardiac and non-cardiac factors have been demonstrated to have an effect on the incidence of atrial fibrillation. The Manitoba Follow-up Study<sup>562</sup> estimated the age-specific incidence of atrial fibrillation in 3983 males. Diabetes was significantly associated with atrial fibrillation with a relative risk of 1.82 in the univariate analysis. However, in the multivariate model, the association with

diabetes was not significant, suggesting that the increased risk of atrial fibrillation in diabetic men may depend of the presence of ischaemic heart disease, hypertension, or heart failure.

In the Framingham Heart Study,<sup>563</sup> diabetes was significantly associated with atrial fibrillation in both genders even after adjustment for age and other risk factors (OR 1.4 for men and 1.6 for women). Although the mechanisms underlying this association remain to be elucidated, diabetes seems to favour the occurrence of atrial fibrillation.

#### Diabetes and risk of stroke in atrial fibrillation

The atrial fibrillation investigators group<sup>565</sup> analysed the data from the pooled control groups of five primary prevention trials with warfarin or aspirin in patients with atrial fibrillation. The purpose of the analysis was to identify clinical features indicative of a high vs. low risk of stroke. At the time of randomization, 14% of patients had diabetes. Risk factors that predicted stroke in multivariate analyses of control patients were increasing age, history of hypertension, previous transient ischaemic attack (TIA) or stroke, and diabetes. Specifically, a diagnosis of DM was an independent risk factor for stroke with a relative risk of 1.7.

The rate of embolic events originating from the atrium in patients with atrial fibrillation increases with the reduction of left atrial appendix flow velocity and the presence of echo contrast at transoesophageal ultrasound examination.<sup>575</sup> A relation between the number of additional risk factors in patients with atrial fibrillation, including diabetes, and the presence of echo contrast or reduced flow velocity in left atrial appendix has been demonstrated,<sup>576</sup> suggesting that factors like hypertension and diabetes may influence the complex thromboembolic mechanisms.

#### Antithrombotic therapy in atrial fibrillation

A meta-analysis of 16 randomized clinical trials on 9874 patients was performed to characterize the efficacy of anticoagulant and antiplatelet agents for the prevention of stroke in atrial fibrillation.<sup>577</sup> Oral anticoagulation was effective for primary and secondary prevention of stroke in studies comprising 2900 patients, with an overall 62% reduction of relative risk (95% CI 48–72). The absolute risk reduction was 2.7% per year for primary prevention and 8.4% for secondary prevention. Major extracranial bleedings were increased by anticoagulant therapy by 0.3% per year. Aspirin reduced stroke by 22% (95% CI 2–38), with an absolute risk reduction of 1.5% per year for primary prevention and 2.5% per year for secondary prevention. In five trials, comparing anticoagulant therapy with antiplatelet agents in 2837 patients, warfarin was more efficacious than aspirin, with a relative risk reduction of 36% (95% CI 14–52). These effects were observed in both permanent and paroxysmal atrial fibrillation.

Oral anticoagulation is most beneficial for patients at higher risk for stroke, whereas the risks outweigh the benefit in patients at low risk. Thus, quantifying the risk of stroke is crucial for determining which atrial fibrillation patients would benefit most from anticoagulant therapy.

#### Diabetes and stroke risk stratification schemes

Different stroke risk stratification schemes have been proposed for patients with atrial fibrillation, and in most of them, diabetes is taken into consideration as an important risk factor for stroke. Patients are considered at low, moderate, and high risk of stroke in relation to age, previous stroke or TIA, and the presence of additional risk factors, such as hypertension, diabetes, CAD, and heart failure. However, the importance of diabetes as a risk factor for stroke differs among the stratification schemes. In the atrial fibrillation investigators scheme,<sup>565</sup> diabetic patients are considered at high risk, independent of age. In the American College of Chest Physicians (ACCP) scheme, they are classified at moderate risk, and high risk only if another risk factor is present,<sup>578</sup> whereas diabetes is not included as a risk factor in the Stroke Prevention in Atrial fibrillation III Study (SPATRIAL) scheme.<sup>579</sup> Two recently developed schemes are based on scores: the CHADS2 (acronym derived from the individual stroke risk factors: Congestive heart failure, Hypertension, Age > 75 years, Diabetes, prior Stroke or TIA) and the Framingham scheme.<sup>580,581</sup> In CHADS2, two points were given for prior stroke or TIA (hence, the 2) and one point was assigned for each of the other factors. In the Framingham scheme, a point system based on age (0–10 points), gender (6 points for female; 0 for male), blood pressure (0–4 points), DM (4 points), and prior stroke or TIA (6 points) was developed. A prospective cohort study tested the predictive accuracy of these five stroke risk stratification schemes by pooling individual data from 2580 participants with non-valvular atrial fibrillation, who were prescribed aspirin in five multicentre trials on antithrombotic therapy.<sup>582</sup> All schemes predicted stroke, but the number of patients categorized as low and high risk varied substantially. Atrial fibrillation patients with prior cerebral ischaemia were classified as high risk by all five schemes, and low-risk patients were also identified by all schemes. However, only CHADS2 successfully identified primary prevention patients who were at high risk of stroke. Of note is that the presence of diabetes is an important contributor in the risk stratification of this scheme. In the 2006 guidelines on atrial fibrillation from the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) task force,<sup>583</sup> diabetes is classified as a moderate risk factor together with age >75 years, hypertension, heart failure, and a left ventricular ejection fraction <35%.

#### Antithrombotic therapy in diabetic patients

Both the 2006 AHA/ACC/ESC guidelines for atrial fibrillation<sup>583</sup> and the American College of Chest Physicians<sup>584</sup> recommend antithrombotic therapy for all patients with atrial fibrillation, apart from those with contraindications. The choice of antithrombotic agent should be based on the relative risk and benefit for the individual patient, considering the absolute risk for stroke and bleeding with various treatment modalities. In patients with permanent or paroxysmal atrial fibrillation who already had a stroke or a TIA, anticoagulant therapy with an INR between 2.0 and 3.0 is indicated, independently of age or the presence of additional risk factors. Also, patients with more than one moderate risk factor for thromboembolism, out of which

diabetes is one, should receive anticoagulant therapy. In patients considered to be at increased risk for bleeding (e.g. >75 years of age) but without clear contraindications to oral anticoagulation, a lower INR target of 2.0 (1.6–2.5) may be considered.

Recommendations for antithrombotic therapy in atrial fibrillation in the presence of only one moderate risk factor is, according to the 2006 AHA/ACC/ESC guidelines, aspirin 81–325 mg daily or anticoagulant therapy. Aspirin is indicated in a dose of 325 mg daily as an alternative in patients with contraindications to oral anticoagulation. In all patients with atrial fibrillation in whom anticoagulant therapy is indicated, INR should be determined at least weekly at the beginning of therapy and monthly when the patient is stable.

Overall and although data from multicentre randomized studies investigating the role of anticoagulants or aspirin in the prevention of stroke in patients with diabetes and atrial fibrillation are not available, it seems appropriate to conclude that diabetes is a risk factor for stroke and that this should be taken into account in the decision on appropriate therapy.

## Sudden cardiac death

### Epidemiology of sudden cardiac death in diabetes

Although there are no doubts on the excess of total mortality of patients with diabetes after MI, more debate surrounds the issue of whether diabetes increases sudden cardiac death, and conflicting results are present in the literature. Sudden death is a difficult endpoint to be assessed in clinical trials because of several methodological reasons. First of all, the definition of sudden cardiac death may vary substantially from one study to another; additionally, the modality of death (sudden or not sudden) may be 'arbitrary' especially when death is unwitnessed; finally, the methodology used to define the cause of death (autopsy vs. death certificate vs. whatever information is available) may also determine important differences in the percentage of death labelled as sudden cardiac.<sup>585</sup> When investigating the link between diabetes and sudden cardiac death, the methodological difficulties double, as also the definition of glucose intolerance/diabetes may vary among different studies, thereby affecting the proportion of 'diabetic' patients present in various studies. Having made these considerations, the presence of discrepancies between results in the different studies that have investigated the role of diabetes as a risk factor for sudden cardiac death will appear less surprising. Interestingly, however, it appears that studies with large series of patients with very long follow-up (>20 years) support the existence of a positive association between diabetes and sudden cardiac death.

In the Framingham study, diabetes was associated with an increased risk of sudden cardiac death in all ages (almost four-fold), and the sudden death risk ratios associated with diabetes were consistently greater in women than men.<sup>586</sup> The importance of diabetes as a risk factor for sudden cardiac death in women was recently investigated using data from the Nurses' Health Study,<sup>587</sup> which included 121 701 women aged 30–55 followed for 22 years. It was reported that sudden cardiac death occurred as the first sign of heart disease in 69% of cases, even if almost all the

women who died suddenly had at least one cardiac risk factor. Diabetes was a very strong risk factor, as it was associated with almost a three-fold increased risk of sudden death compared with hypertension, which was associated with a 2.5-fold increased risk, and obesity, with a 1.6-fold increased risk. Interestingly, data are also available to demonstrate that diabetes increases the relative risk for sudden cardiac death in different ethnic groups. The Honolulu Heart Programme<sup>588</sup> investigated the role of diabetes as a predisposing factor in middle-aged Japanese-American men followed for 23 years. This study showed an increased relative risk for sudden cardiac death in subjects with diabetes and glucose intolerance compared with the non-diabetic individuals. More recently, the investigators of the Paris Prospective study<sup>589</sup> demonstrated that the risk of sudden cardiac death, but not that of fatal MI, was increased in patients with diabetes compared with those without. Similarly, the Group Health Cooperative<sup>590</sup> presented a large study including 5840 individuals and reinforced the view that diabetes is a strong risk factor for sudden cardiac death in a French population. It seems logical to conclude that most of the evidence concurs to support the concept that diabetes is a risk factor for sudden cardiac death.

### Pathophysiology of sudden cardiac death in diabetes

Diabetic patients have a higher incidence of cardiac arrhythmias, including ventricular fibrillation and sudden death. The causes underlying the increased vulnerability of the electrical substrate in these patients are unclear and it is likely to be the consequence of the interplay of several concomitant factors: (i) atherosclerosis and (ii) microvascular disease are increased in patients with diabetes and they concur to the development of ischaemia that predisposes to cardiac arrhythmias; (iii) diabetic autonomic neuropathy<sup>592,593</sup> leads to abnormal reflexes and innervation of the diabetic heart influencing electrical instability; and (iv) the electrocardiogram of diabetic patients presents repolarization abnormalities manifesting as prolonged QT interval and altered T-waves<sup>593</sup> that may reflect abnormal potassium currents.<sup>595</sup> It seems therefore likely that factors like CAD, direct metabolic alterations, ion channel abnormalities, and autonomic dysfunction may all contribute to create the substrate for sudden cardiac death in the diabetic heart.

In a study by Jouven *et al.*,<sup>590</sup> the investigators moved away from the evaluation of the risk of sudden cardiac death in diabetic vs. non-diabetic patients, instead focusing on the relative risk of sudden cardiac death in groups of patients with different values of glycaemia. The study showed that the higher the values of glycaemia, the higher the risk of SCD. Following adjustment for age, smoking habits, systolic blood pressure, heart disease, and glucose-lowering treatment, even patients with borderline diabetes defined as non-fasting glycaemia between 7.7 and 11.1 mmol/L (140 and 200 mg/dL) had an increased risk of sudden cardiac death [odds ratio (OR) 1.24 compared with patients with normoglycaemia]. The presence of microvascular disease, defined as retinopathy or proteinuria, and female gender increased the risk of sudden cardiac death in all groups. This study importantly emphasizes that glucose intolerance seems to be a continuous variable directly related to the risk of sudden cardiac

death, rather than supporting the previous view of risk being related to a specific threshold of glucose intolerance as suggested by the 'dichotomous' approach of comparison between diabetic vs. non-diabetic patients. This fits with the present concept that cardiovascular risk increases well below present thresholds for diabetes and at glucose levels that usually have been considered fairly normal.<sup>64</sup>

The Framingham investigators<sup>600</sup> studied the influence of glucose levels on heart rate variability in a large community-based population. They demonstrated that, after adjusting for covariates, indexes of reduced heart rate variability were influenced by plasma glucose. High glycaemic levels were followed by a lower heart rate variability. Similar findings were reported by the Atherosclerotic Risk in Community (ARIC) study,<sup>601</sup> which showed that even the pre-diabetic patients already have abnormalities of autonomic cardiac function and altered heart rate variability. These two studies confirmed that glucose levels should be considered as a continuous variable influencing the autonomic control of the heart. Unfortunately, these studies were not designed to answer the question whether reduced heart rate variability in diabetic patients is an independent predictor of sudden cardiac death. At present, this pressing question remains unanswered.

The Rochester diabetic neuropathy study<sup>602</sup> was designed to define the risk factors for sudden cardiac death and the role of diabetic autonomic neuropathy in a population of 462 diabetic patients followed for 15 years. In a univariate analysis, many covariates were statistically associated with sudden cardiac death, including older age, HDL cholesterol, nephropathy stage, creatinine, microalbuminuria and proteinuria, previous MI, prolonged corrected QT (QTc), bundle branch block, and a composite autonomic severity score, among several others. Interestingly, necropsy findings demonstrated that all victims of sudden cardiac death had signs of coronary artery or myocardial disease, and a bivariate analysis showed that autonomic dysfunction QTc and HDL lost their significant association with sudden cardiac death after adjusting for nephropathy. Overall, the data from this study suggest that kidney dysfunction and atherosclerotic heart disease are the most important determinants of the risk of sudden cardiac death, whereas neither autonomic neuropathy nor QTc are independent predictors of the risk for sudden cardiac death. Unfortunately, this study did not include heart rate variability among the parameters introduced in multivariate analysis. Thus, robust data assessing the value of heart rate variability as an independent predictor of sudden cardiac death in diabetic patients are still lacking.

On the basis of available evidence, it seems that glucose intolerance, even at a pre-diabetic stage, is associated with progressive development of a variety of abnormalities that adversely affect survival and predispose to sudden cardiac death.

The identification of independent predictors of sudden cardiac death in diabetic patients has not yet progressed to a stage where it is possible to devise a risk stratification scheme for the prevention of such deaths in diabetic patients.

In a single study, microvascular disease and nephropathy have been identified as indicators of increased risk of sudden cardiac death in diabetic patients.

## Peripheral and cerebrovascular disease

### Peripheral vascular disease

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
All patients with type 2 diabetes and CVD are recommended treatment with low-dose aspirin	Ia	B
In diabetic patients with peripheral vascular disease, treatment with clopidogrel or low molecular weight heparin may be considered in certain cases	Iib	B
Patients with critical limb ischaemia should, if possible, undergo revascularization procedures	I	B
An alternative treatment for patients with critical limb ischaemia, not suited for revascularization, is prostacyclin infusion	I	A

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.

### Background

Subjects with diabetes have a two- to four-fold increase in the incidence of peripheral vascular disease, and an abnormal ankle-brachial blood pressure index is present in ~15% of such patients.<sup>603-605</sup> The symptomatic manifestations of peripheral vascular disease are intermittent claudication and critical limb ischaemia. Impairment of the circulation in the foot owing to diabetic macro- and microvascular diseases is the most common non-traumatic reason for limb amputation. The prevalence of peripheral vascular disease increases with advancing age, duration of diabetes, and peripheral neuropathy. The latter condition may mask the symptoms of limb ischaemia and thus disease progression may be advanced before patients and healthcare providers realize that peripheral vascular disease is present.

Early diagnosis of peripheral vascular disease in diabetic patients is important for the prevention of progression of peripheral vascular disease as well as for the prediction of overall cardiovascular risk. The vascular obstructions in subjects with diabetes are often located more distally than in non-diabetic subjects. Thus, the typical diabetic peripheral vascular disease is located in the popliteal artery or in the vessels of the lower leg.<sup>606,607</sup> The calcification of the media layer of the vessels is also a typical hallmark of diabetic peripheral vascular disease.<sup>607,608</sup>

### Diagnosis

Symptoms of leg ischaemia in diabetic patients with peripheral neuropathy are often atypical and vague. Rather than experience pain in the legs, the patient may suffer from leg fatigue or only inability to walk at a normal pace. Physical examination is of critical importance for the diagnosis. Palpation of pulses in the leg and visual inspection of the feet are essential. Dependent rubor, pallor when the foot is elevated, absence of hair growth, and dystrophic toenails are signs of peripheral ischaemia.

An objective measure of peripheral vascular disease is the ankle-brachial blood pressure index, defined as the ratio between the arterial pressure at the ankle level and in the brachial artery with the highest pressure. The ankle-brachial blood pressure index should normally be  $>0.9$ . This measurement is valuable for early detection of peripheral artery disease and also for a better stratification of overall cardiovascular risk. An ankle-brachial blood pressure index  $<0.5$  or an ankle pressure  $<50$  mm Hg is indicative of severely impaired circulation to the foot. An ankle-brachial blood pressure index above 1.3 indicates poorly compressible vessels as a result of stiff arterial walls, which usually in diabetic patients are due to atherosclerosis in the media layer of the arterial wall.

A patient with critical limb ischaemia is defined as a patient with chronic ischaemic rest pain, ulcers, and gangrene attributable to objectively proved arterial disease.<sup>609</sup> It is important to consider that ulcers may often exist in the diabetic foot despite a normal macrocirculation. These ulcers are then due to disturbances in the microcirculation and most often also to neuropathy. Nevertheless, such ulcers must be dealt with in a meticulous fashion, since gangrene and amputation may result also from this condition.<sup>610</sup>

A thorough investigation, aiming at a detailed description of the anatomy of the vascular obstructions, should only be performed in patients in whom an invasive procedure to restore blood flow is indicated. The method of choice is duplex ultrasound. An arterial angiography should only be performed when it is likely that an invasive intervention to restore arterial circulation may be possible. *Table 16* depicts the different methods for evaluating the peripheral circulation.

**Table 16** Investigations of the peripheral circulation in diabetic patients

At the physicians' office in every patient

Inspection	Dependent rubor Pallor with elevation Absence of hair growth Dystrophic toenails Ulcers or gangrenes
Palpation	Pulses Dry and cool skin Sensibility
Pressure measurement	Ankle and arm blood pressure

At the vascular laboratory (when appropriate)

Distal and/or segmental pressure measurements  
Oscillography  
Treadmill testing (with or without distal pressure after exercise)  
Duplex sonography

*For evaluation of the microcirculation*

Transcutaneous oxygen pressure  
Vital capillaroscopy

At the radiology department

Magnetic resonance imaging  
Angiography

## Treatment

### General measures and platelet inhibition

For diabetic patients with peripheral vascular disease, general measures to reduce overall cardiovascular risk should be intensive, as it has been described in detail in another section of this summary. Treatment of hypertension should be vigorous, but in patients with critical limb ischaemia and very low distal perfusion pressures, it may be dangerous for the foot to lower blood pressure too much. The survival of tissues in the distal extremities must be prioritized until the critical situation resolves. In such cases, blood pressure should be kept at a level permitting adequate arterial inflow to the distal extremity.

Platelet inhibition with low-dose aspirin, in the magnitude of 75–250 mg per day, is indicated in all patients with type 2 diabetes and CVD who do not have a contraindication and for patients with severe peripheral vascular disease; further inhibition of platelet aggregation by clopidogrel or dipyridamole may be indicated in certain cases, along with anticoagulation with low molecular weight heparin as the first agent of choice.<sup>611–614</sup>

In patients with non-ischaemic neuropathic ulcers, it is of utmost importance to remove any external pressure from the ulcer area, sometimes necessitating immobilization of the patient in a wheel-chair. These ulcers will then most often heal without any intervention directed towards improving the macrocirculation. Careful wound dressing and orthopedic shoes or appropriate bandaging should be handled by a specialized clinic.<sup>610</sup> Unfortunately, many amputations have been performed in cases where careful conservative treatment would have saved the extremity.

### Revascularization

If anatomically possible, a revascularization procedure should be attempted in all patients with critical limb ischaemia.<sup>609</sup> This can be performed by means of a percutaneous transluminal angioplasty or as a surgical procedure, preferably a bypass with the saphenous vein as the conduit. Percutaneous transluminal angioplasty is the method of choice if short-segment stenoses occur in proximal segments above the knee. Proximal percutaneous transluminal angioplasty can be combined with a more distal bypass operation. Patients with intermittent claudication should be revascularized if they have disabling symptoms and proximal vessel disease.<sup>609</sup> For patients with claudication, who need a bypass to the lower leg vessels, a more conservative approach is indicated.

### Medical treatment of critical limb ischaemia

The only pharmacological agent so far convincingly shown to have a positive influence on the prognosis of patients with critical limb ischaemia is a synthetic prostacyclin (Iloprost), which is given intravenously daily for a period of 2–4 weeks. In a meta-analysis, rest pain and ulcer size improved in comparison with placebo. More importantly, the probability of being alive with both legs still intact after 6 months was 65% in the Iloprost treated group, compared with 45% in the placebo-treated patients.<sup>615</sup>

## Stroke

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
For stroke prevention, blood pressure lowering is more important than the choice of drug. Inhibition of the renin-angiotensin-aldosterone system may have additional benefits beyond blood pressure lowering <i>per se</i>	Ila	B
Patients with acute stroke and diabetes should be treated according to the same principles as stroke patients without diabetes	Ila	C

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.

### Background

The relative risk for stroke is increased in subjects with diabetes by a factor of 2.5–4.1 for men and 3.6–5.8 for women. After correction for other risk factors for stroke, the risk is still more than two-fold, meaning that DM is a strong independent risk factor for stroke.<sup>83,618</sup> The relationship between hyperglycaemia *per se* and stroke is much less clear than the relationship between hyperglycaemia and MI. Diabetic complications such as proteinuria, retinopathy, and autonomic neuropathy increase the risk for stroke.<sup>619,620</sup> The type is usually ischaemic. TIA has been shown to predict the occurrence of a stroke within 90 days, thus underlining the severity of TIA especially in diabetic patients.<sup>623</sup>

### Prevention of stroke

Measures to prevent stroke should be based on a multifactorial strategy aimed at the treatment of hypertension, hyperlipidaemia, microalbuminuria, and hyperglycaemia and the use of antiplatelet medication, as outlined elsewhere in this summary.

The Heart Outcomes Prevention Evaluation (HOPE) study and Perindopril Protection Against Recurrent Stroke Study (PROGRESS) suggested that the reduction of stroke incidence in diabetic subjects during treatment based on ACE-inhibitors was greater than would be anticipated from the blood pressure-lowering effect alone and evident also in normotensive individuals.<sup>373,624</sup> In the LIFE trial, a similar trend was found with an angiotensin receptor blocker.<sup>378</sup> However, in several other trials, including ALLHAT, there was no apparent benefit of one class of anti-hypertensive drug over another in this respect.<sup>380,384</sup>

In the HPS, a sizeable subgroup of 5963 diabetic patients were randomized to placebo or 40 mg of simvastatin daily. Simvastatin reduced the incidence of stroke by 24%.<sup>344</sup>

Antiplatelet therapy reduces the incidence of stroke in diabetic patients and is indicated for both primary and secondary prevention.<sup>625</sup> Aspirin in a low dose (75–250 mg daily) should be the initial choice, but in case of intolerance, clopidogrel 75 mg once daily should be given.<sup>438,613</sup> In patients with recurrent stroke, a combination of aspirin and dipyridamol should be considered.<sup>626,627</sup> The combination of aspirin and clopidogrel was associated with an increased risk of bleeding without any benefit in terms of cardiovascular outcome in the MATCH-trial, performed in 7599 patients of whom 68% had diabetes.<sup>628</sup> Further, in the CHARISMA-study, no benefit was evident from long-term dual antiplatelet therapy with aspirin and clopidogrel.<sup>629</sup>

The high frequency of early stroke following TIA motivates investigation within 7 days of the index event to reduce the risk of a subsequent, and potentially more serious, neurological event. Evaluation with echocardiography and carotid ultrasound is indicated. An increase in cerebral microemboli is detectable by transcranial doppler, and high microembolic loads appear to be surrogate markers for future neurological events.<sup>631</sup> After a TIA or stroke caused by carotid-artery disease, medical treatments can be optimized, avoiding the need for emergency carotid surgery, allowing patients to undergo safer elective surgery.<sup>632</sup> Carotid endarterectomy for the prevention of stroke in patients with high-grade stenosis of the carotid artery is effective but it has not been specifically investigated in diabetic patients.<sup>632</sup> Since complications during and after this procedure are more frequent in diabetic subjects compared with non-diabetic subjects, special consideration should be paid to the overall risk for peri- and post-operative morbidity and mortality when deciding on surgical interventions in the patient with diabetes.<sup>633</sup> An alternative to endarterectomy is carotid artery angioplasty and stenting, which has been found to be at least not inferior to endarterectomy and may prove to be a preferable method in high-risk patients.<sup>634</sup>

### Treatment of acute stroke

The treatment in the acute phase of stroke in diabetic patients should follow the same principles that govern the treatment of stroke in the general population. Thrombolysis is an effective treatment for ischaemic stroke if instituted within 3–4 h.<sup>635</sup> It reduces mortality and disability from stroke, but is associated with a risk of haemorrhage and its use and effects in diabetes require further evaluation by registration in an existing quality registry (SITS-MOST, [www.acutestroke.org](http://www.acutestroke.org)).

Conservative treatment of stroke includes close surveillance of vital functions and optimization of circulation and metabolic conditions, including glycaemic control, in a stroke ward.<sup>636</sup> Patients should receive early neurological rehabilitation and correction of abnormalities, as outlined in the section 'Prevention of stroke' in this chapter. Recent studies suggest that early intervention against hypertension during the acute phase of stroke may be beneficial but currently it is recommended to acutely reduce only very high blood pressures, above 220 mm Hg systolic and/or 120 mm Hg diastolic, and then with great caution not to lower blood pressure to levels which may enhance ischaemia and not by more than 25% during the first day of treatment.<sup>637</sup>

### Intensive care

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
Strict blood glucose control with intensive insulin therapy improves mortality and morbidity of adult cardiac surgery patients	I	B
Strict blood glucose control with intensive insulin therapy improves mortality and morbidity of adult critically ill patients	I	A

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence

## Hyperglycaemia and outcome of critical illness

The stress imposed by critical illness leads to the development of metabolic and endocrine abnormalities. The patients usually become hyperglycaemic, owing to insulin resistance and accelerated glucose production, known as 'stress diabetes' or 'diabetes of injury'.<sup>638,639</sup> In the acute phase of critical illness, hepatic glucose production is enhanced by upregulation of both gluconeogenesis and glycogenolysis, although serum levels of insulin, which normally suppresses these pathways, are high. Increased levels of glucagon, cortisol, growth hormone, catecholamines, and cytokines all play a role.<sup>640-645</sup> Apart from stimulated glucose production, impaired peripheral insulin-mediated glucose uptake contributes to the hyperglycaemic state.

Several recent studies clearly identify hyperglycaemia as an important risk factor in terms of mortality and morbidity of these patients. A meta-analysis on patients with MI revealed a strong and consistent association between the development of stress hyperglycaemia and increased risk of in-hospital mortality and congestive heart failure or cardiogenic shock.<sup>646</sup> Even mild elevations of fasting glucose levels in patients with CAD undergoing PCI have been associated with a substantial mortality risk.<sup>647</sup> Furthermore, the glucose level of patients undergoing CABG appeared to be an important predictor of delayed extubation.<sup>648</sup> A retrospective analysis of a heterogeneous population of critically ill patients also revealed that even a modest degree of hyperglycaemia was associated with substantially increased hospital mortality.<sup>649</sup> Approximately 30% of these patients were admitted to the ICU for cardiac indications. Similarly, hyperglycaemia predicted increased morbidity and mortality after stroke,<sup>651</sup> severe brain injury,<sup>652,653</sup> trauma,<sup>654,655</sup> and severe burn injury.<sup>656</sup>

## Blood glucose control with intensive insulin therapy in critical illness

A landmark prospective, randomized, controlled study on a large group of patients admitted to the ICU predominantly after extensive surgery or for complications developing after extensive surgery revealed major clinical benefits of intensive insulin therapy during critical illness.<sup>445</sup> In the conventional insulin therapy group, only excessive hyperglycaemia >11.9 mmol/L (215 mg/dL) was treated with insulin, aiming to keep concentrations between 10.0 and 11.1 mmol/L (180–200 mg/dL). This protocol resulted in mean blood glucose levels of ~8–9 mmol/L (150–160 mg/dL), i.e. hyperglycaemia. Insulin was administered to the patients in the intensive insulin therapy group to maintain blood glucose levels between 4.4 and 6.1 mmol/L (80–110 mg/dL) and resulted in mean blood glucose levels of ~5–6 mmol/L (90–100 mg/dL), i.e. normoglycaemia, without detectable risk of hypoglycaemia-induced adverse events. Tight blood glucose control with insulin strikingly lowered the mortality during the period in the ICU from 8.0 to 4.6% (43% reduction). This benefit was most pronounced among patients who required intensive care for more than 5 days, with an ICU mortality reduction from 20.2 to 10.6% and an in-hospital mortality reduction from 26.3 to 16.8%. More than 60% of the total patient population was included after cardiac surgery. In this subgroup, intensive insulin therapy reduced ICU mortality from 5.1 to 2.1%.

Besides saving lives, intensive insulin therapy largely prevented several critical illness-associated complications, including critical illness polyneuropathy, blood stream infections, anaemia, and acute renal failure.<sup>445</sup> Patients were also less dependent on prolonged mechanical ventilation and intensive care. The clinical benefits of this therapy were equally present in most diagnostic subgroups, including the cardiac patients. For the latter subgroup, a follow-up study showed that intensive insulin therapy also improved long-term outcome when given for at least a third day in ICU, with maintenance of the survival benefit up to 4 years after randomization.<sup>657</sup> Particularly in the patients with isolated brain injury, intensive insulin therapy protected the central and peripheral nervous system from secondary insults and improved long-term rehabilitation.<sup>657</sup> Importantly, the Leuven protocol of glycaemic control in a predominantly surgical patient population<sup>445</sup> was recently proved, in a large randomized, controlled trial, to be similarly effective in a strictly medical ICU patient population.<sup>659</sup> In the intention-to-treat group of 1200 patients, morbidity was significantly reduced, with lower occurrence of newly developed kidney injury, earlier weaning from mechanical ventilation, and earlier discharge from the intensive care and from the hospital. In the intention-to-treat group, insulin therapy did not significantly alter mortality (in-hospital mortality from 40.0 to 37.3%,  $P = 0.3$ ). This was not surprising, as the study was not powered for this mortality endpoint. In the target group of long-stay patients (at least a third day in ICU), for which the study was powered, intensive insulin therapy reduced in-hospital mortality from 52.5% in the conventional to 43.0% in the intensive insulin therapy group ( $P = 0.009$ ) and reduced morbidity even more strikingly. A summary of different trials on intensive insulin therapy in critical illness is given in *Table 17*.

## Mechanisms behind improved outcome with intensive insulin

Multivariate logistic regression analysis indicated that hyperglycaemia and a high dose of insulin were associated with a high risk of death.<sup>665</sup> Hence, it was the blood glucose control and/or other metabolic effects of insulin that accompany tight blood glucose control, but not the insulin dose administered *per se* that contributed to the improved survival with intensive insulin therapy. The association between high insulin dose and mortality is likely explained by more severe insulin resistance in the sicker patients, who have a high risk of death. The risk of death indeed appeared to linearly correlate with the degree of hyperglycaemia, with no clear cut-off below which there was no further benefit.<sup>665</sup> Patients who received conventional insulin therapy and who developed only moderate hyperglycaemia (6.1–8.3 mmol/L or 110–150 mg/dL) had a lower risk of death than those with severe hyperglycaemia (8.3–11.1 mmol/L or 150–200 mg/dL), whereas they were at higher risk of death than patients whose blood glucose levels were controlled <6.1 mmol/L (110 mg/dL) with intensive insulin therapy. Other data also suggest that the mortality benefits can be attributed to glycaemic/metabolic control, rather than the absolute insulin doses administered.<sup>649,666</sup> For the prevention of critical illness polyneuropathy, bacteraemia, anaemia, and acute renal failure, tight



**Table 17** Published trials on intensive insulin therapy in critical illness

Study reference	Van den Berghe <i>et al.</i> <sup>445</sup>	Van den Berghe <i>et al.</i> <sup>659</sup>	Krinsley <sup>660</sup>	Grey and Perdrizet <sup>661</sup>	Furnary <i>et al.</i> <sup>662</sup>
Patient population	Surgical	Medical	Surgical/medical	Surgical	Cardiac surgery in diabetes patients
Number of patients	1548	1200/767 <sup>a</sup>	1600	61	4864
Randomized study	Yes	Yes	No	Yes	No
Target glucose	<6.1	<6.1	<7.8	<6.7	<8.3
Mortality	↓	↓	↓		↓
Critical illness polyneuropathy	↓				
Bacteraemia/severe infections	↓	—	—	↓	
Acute renal failure	↓	↓	↓		
Red blood cell transfusions	↓		↓		
Duration of mechanical ventilation	↓	↓			
Length of stay	↓	↓	↓		↓
Deep sternal wound infections					↓

<sup>a</sup>Morbidity effect in all intention-to-treat patients ( $n = 1200$ ); morbidity and mortality effect in the patients who required at least a third day in ICU ( $n = 767$ ).

glycaemic control  $<6.1$  mmol/L (110 mg/dL) similarly appeared of crucial importance.<sup>665</sup> If indeed avoiding hyperglycaemia is crucial, it appears striking that by doing so only for the relatively short period, during the patient's need for intensive care, this strategy prevented the most feared complications of critical illness. Normal cells protect themselves from moderate hyperglycaemia by downregulation of glucose transporters.<sup>667</sup> On the other hand, chronic hyperglycaemia causes complications in diabetic patients in a time frame which is several orders of magnitude longer than the time it took to prevent life-threatening complications during intensive care. Thus, hyperglycaemia appears more acutely toxic in critically ill patients than in healthy individuals or diabetic patients. Upregulation of insulin-independent glucose uptake, mediated by the glucose transporters GLUT-1, GLUT-2, or GLUT-3 and resulting in cellular glucose overload, may play a role.<sup>668</sup> Part of the improvement with intensive insulin therapy is therefore likely explained by preventing glucose toxicity.<sup>658,668–671</sup> However, also other effects of insulin may contribute to improved outcome.<sup>668,669,671–673</sup>

## Health economics and diabetes

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
Lipid-lowering provides a cost-effective way of preventing complications	I	A
Tight control of hypertension is cost-effective	I	A

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## Cost-of-illness studies

The most widely used method to assess the burden of diabetes is through cost-of-illness studies, which strives to assess the total cost caused by a disease or condition.<sup>679,680</sup> The CODE 2 study<sup>706</sup> was designed to measure the total healthcare costs for patients with type 2 diabetes in eight European countries, using the same methodological approach. Patients from Belgium, France, Germany, Italy,

The Netherlands, Spain, Sweden, and the UK were included. The study used a bottom-up, prevalence based design, which means that all healthcare costs for diabetes patients were collected. Because of the strong impact of co-morbidity in type 2 diabetes patients, it is not possible to separate which resource use is due to diabetes and which is due to other diseases. This can only be done with epidemiological methods, comparing patients with and without diabetes. Efforts were made to ensure consistency in terms of data collection, analysis, and reporting of results, which means that this study gives an opportunity for international comparisons. *Table 18* shows the total cost per country, the cost per patient, and the share of healthcare costs accounted for by patients with diabetes.

The total healthcare cost for patients with diabetes in the eight countries amounted to €29 billion. Per capita cost varied from €1305 per patient in Spain to €3576 in Germany. In addition, the estimated share of total healthcare costs varied significantly between countries, indicating that despite striving for the same method of data collection, there may have been differences between how the study was conducted in different countries.

The very low figure for The Netherlands may reflect lower costs, but more probably a selection bias in the patients studied and/or a too low estimate of the prevalence of type 2 diabetes. Differences in the definition of healthcare expenditures between countries may also be a factor to consider when analysing the differences between countries.

## The cost of complications

The results from the CODE-2 study show that the main cost-driver in diabetes is not the disease as such or the treatment of diabetes, but rather the complications caused by diabetes. In the study, patients were divided into complication free, having microvascular complications only, having macrovascular complications only, or having both macro- and microvascular complications. In these three groups, the relative costs were 1.7, 2.0, and 3.5 times higher than the costs among patients without complications.<sup>707</sup> The key driver of this increase in costs was a higher cost for

**Table 18** Direct medical costs for patients with type 2 diabetes in eight European countries and percentage of healthcare expenditure in the respective countries (1998)<sup>706</sup>.

Country	Total costs (million €)	Cost per patient (€)	Cost of healthcare expenditure (%)
Belgium	1 094	3295	6.7
France	3 983	3064	3.2
Germany	12 438	3576	6.3
Italy	5 783	3346	7.4
The Netherlands	444	1889	1.6
Spain	1 958	1305	4.4
Sweden	736	2630	4.5
UK	2 608	2214	3.4
All countries	29 000	2895	5.0

hospitalization among patients with complications. This is natural, since patients are not frequently hospitalized for their diabetes, whereas macrovascular complications, such as MI, lead to immediate hospitalization. Hospitalizations are the largest cost component in the sample as a whole as well, once again indicating the importance of complications. It is interesting to note that cardiovascular drugs are the single most important category of drugs, accounting for about one-third of drug costs. This is more than the costs of insulin and oral diabetic drugs together.

It is important to realize that the CODE-2 study only captures part of the cost of the diabetes, as only direct healthcare costs are included. Lost production, caused by sick absence, early retirement, and early mortality, also carries high costs. In studies that have included this component, it sums up to >50% of the total costs.<sup>696,697</sup>

### Cost-effectiveness of intervention

Lipid-lowering using statins in diabetics have been studied in several studies. In a subgroup of the 4S trial, cost-effectiveness ratios of treating diabetic patients with 20–40 mg simvastatin were found to be well below the levels that are usually considered cost-effective.<sup>708</sup> Diabetic patients were also enrolled in the HPS, which indicated acceptable cost-effectiveness ratios for patients with this risk level.<sup>709</sup> One important thing to consider about these studies is that they used a cost of simvastatin prior to the expiry date of the patent. Thereafter, the price dropped substantially, which would mean that statin use in diabetics is likely to be cost-saving in secondary prevention and associated with very low cost-effectiveness ratios in primary prevention.

Another approach to prevention of macrovascular complication is through blood-pressure control. This has been studied as part of the UKPDS, where tight blood-pressure control using BBs and ACE-inhibitors was investigated. A recent cost-effectiveness analysis of this intervention indicated that this treatment strategy was associated with a very high cost-effectiveness.<sup>711</sup>

It can be concluded that the costs associated with diabetes make up a considerable share of the resources spent on healthcare throughout Europe. As the most important cost drivers are complications caused by the disease, proper management in the prevention of complications is essential.

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