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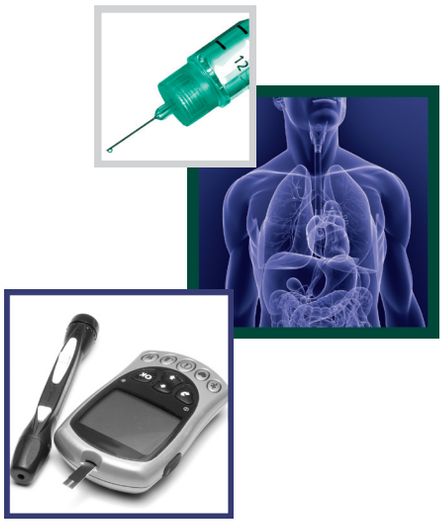

Reducing cardiovascular risk factors in patients with prediabetes

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Practice Points

- The prevalence of prediabetes is high and on the rise. Subjects with impaired fasting glucose and impaired glucose tolerance should be identified because: they are at high risk for diabetes, they are at high risk for cardiovascular disease and they usually have other cardiovascular risk factors.
- Prediabetes is usually associated with the following risk factors that are component of the metabolic syndrome: excess body weight, dyslipidemia and arterial hypertension.
- Treating hyperglycemia in patients with impaired fasting glucose and impaired glucose tolerance with nonpharmacological or pharmacological interventions has been shown to reduce the risk of diabetes. But no studies have addressed the effects of treatment of those risk factors in the prediabetic population on cardiovascular events. However, treating dyslipidemia and hypertension in diabetic and nondiabetic subjects has been shown, in randomized control trials, to reduce cardiovascular disease. Observational studies have shown that weight reduction in diabetic and nondiabetic patients was associated with a decrease in cardiovascular events. If treating obesity, dyslipidemia and hypertension in diabetics and nondiabetic patients has cardiovascular benefit, it should also be beneficial for the prediabetic subjects. Aspirin should be added in subjects with a history of cardiovascular disease.
- To be cost effective, screening for prediabetic subjects should be opportunistic in high risk population. The following procedures can be used: fasting or random plasma glucose, A1C, validated questionnaire and the oral glucose tolerance test. It should also be an opportunity to screen for other risk factors as well as undiagnosed diabetes.
- Treatment targets for cardiovascular risk factors in prediabetes. In general, impaired fasting glucose and impaired glucose tolerance should be treated as aggressively as subjects with diabetes, alhough the treatment has to be individualized, the following targets are usually recommended:
  – Weight reduction: ≥5–7% of body weight
  – Blood pressure: <130/80 mmHg
  – Low-density lipoprotein cholesterol: <2.6 mmol/l (100 mg/dl)

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SUMMARY Type 2 diabetes mellitus is generally preceded by a state that has been termed prediabetes, which is defined as impaired fasting glucose and/or impaired glucose tolerance. The prevalence of prediabetes is as high, if not higher, than that of diabetes in most countries, particularly in developing countries. Prediabetes hyperglycemia is now recognized as an independent risk factor for cardiovascular disease. Furthermore, it is usually associated with other cardiovascular risk factors such as obesity, hypertension and dyslipidemia, all features of the metabolic syndrome. We have very few studies that have evaluated the effects of treatment of those cardiovascular risk factors on cardiovascular events and mortality in the prediabetic population. However, we have a number of prospective randomized intervention trials that have evaluated the effects of treatments of hyperglycemia in the diabetic populations, and the effects of treatments of hypertension and dyslipidemia in diabetic and nondiabetic populations. It has been well demonstrated in those populations that treating hypertension with most antihypertensive drugs and dyslipidemia with statins resulted in a significant reduction in cardiovascular events and mortality. However, it has been more difficult to convincingly show that treating hyperglycemia in patients with diabetes reduced cardiovascular events and mortality. A recent meta-analysis does suggest that intensive glycemic treatment is associated with a reduction in nonfatal myocardial infarction and coronary heart disease but does not seem to affect stroke and all-cause mortality. Observational studies also suggest that treating obesity should be associated with a reduction of cardiovascular disease. Since it is recognized that impaired glucose tolerance has the same cardiovascular risk as newly diagnosed Type 2 diabetes, it is proposed that prediabetes should be screened in high-risk populations and all cardiovascular risk factors should be treated similarly to patients with Type 2 diabetes.

The prevalence of Type 2 diabetes mellitus is increasing worldwide at an epidemic rate, particularly in developing countries. Owing to its high and ever growing prevalence, its associated morbidity and its excess mortality, diabetes is one of the major challenges of the 21st century. It is now generally recognized that diabetes is part of a continuum in the deterioration in carbohydrate metabolism starting years before the disease can be diagnosed. Furthermore, the disease is generally preceded by a state that has been termed 'prediabetes', and includes both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT).

Diagnostic criteria for abnormal glucose tolerance

Table 1 illustrates the criteria for the diagnosis of abnormal glucose tolerance including prediabetes (IFG and IGT), and diabetes [1–5]. In 2003, the American Diabetes Association (ADA) recommended that the threshold for diagnosing IFG be lowered to 5.6 mmol/l or 100 mg/dl [6]. More recently, the ADA, the European Association for the Study of Diabetes (EASD) and the International Diabetes Federation (IDF) appointed a joint International Expert Committee to consider the use of hemoglobin A1C (A1C) for the diagnosis of diabetes in individuals at high risk for diabetes [7]. The Committee recommended that an A1C ≥6.5% be diagnostic of diabetes if confirmed with a repeat A1C test, and that an A1C below 6.5% but ≥6.0% should be considered at a high risk for diabetes and preventive measures should be implemented. However, based on the Data from an Epidemiological Study on the Insulin Resistance syndrome (DESIR) Study Group observations [8], the ADA adopted an even lower threshold for A1C of 5.7% to <6.5% as a category of increase risk for diabetes equivalent to IFG and IGT [9]. The lower threshold for IFG (5.6 mmol/l) as well as the inclusion of A1C for the diagnosis of diabetes (A1C ≥6.5%) were endorsed by the ADA, the American College of Endocrinology (ACE), the American Association of Clinical Endocrinologists (AACE) and the WHO but not by the Canadian Diabetes Association (CDA), the EASD or the IDF [3,4,10–13]. The lower A1C to identify subjects at high risk for diabetes was supported by the ACE and AACE as a screening test to be confirmed by a fasting plasma glucose or an oral glucose tolerance test [4]. Depending on whether only A1C, fasting or fasting and the 2-h plasma glucose are measured, an individual may be placed in a different category.

The prevalence of prediabetes

Table 2 illustrates the prevalence of IFG based on fasting plasma glucose of 6.1–6.9 mmol/l and IGT in different adult populations of different

Table 1. Criteria for the diagnosis of abnormal glucose tolerance.

Categories	Plasma glucose in mmol/l (mg/dl)		A1C (%)[†]
	Fasting	2-h post 75 g glucose	
Isolated IFG[‡]	5.6–6.9 (100–125)	<7.8 (140)	≥5.7–6.4
Isolated IGT	<5.6 (100)	7.8–11.0 (140–199)	≥5.7–6.4
Diabetes	≥7.0 (126)	≥11.1 (200)	≥6.5

[†]The American Diabetes Association has lowered the fasting plasma glucose to 5.6 mmmo/l for IFG and has included the A1C as a criterion for the diagnosis of abnormal glucose tolerance.
[‡]The American Association of Clinical Endocrinologists/American College of Endocrinology have endorsed the lower threshold for IFG and the A1C for the diagnosis of diabetes but not for prediabetes. The WHO has endorsed the use of A1C for the diagnosis of diabetes but not for IFG/IGT and has not yet accepted the lower threshold for IFG.
A1C: Hemoglobin A1C; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance.

age groups [2]. In most of those populations, IGT is significantly more common than IFG. Interestingly, there is very little overlap between IFG and IGT. Since these categories are metabolically different, the terms isolated IFG and isolated IGT are often used [14]. The prevalence of prediabetes does vary in the different adult populations listed from 8.1 to 37.6%. However, one has to be careful in the interpretation since the age groups studied are different in the various populations. In general, over 50% of the population with prediabetes has isolated IGT, approximately 30% isolated IFG with less than 20% having both IFG and IGT. However, if we use the lower plasma glucose threshold of 5.6 mmol/l for IFG, we increase the prevalence of IFG two- to five-fold across the world [12]. Furthermore, the prevalence of IFG increases markedly (20–25%) such that it exceeds that of IGT [15,16]. It is believed that those two categories have different phenotypes [2,15]. While IGT tends to increase with age in all populations, IFG tends to plateau by the fifth decade. For subjects younger than 55 years, IFG is more common in men, while IGT is more common in women. However, it is not known at the present time whether these different age and sex distributions have different impacts in term of progressing to diabetes or cardiovascular disease (CVD) and mortality. The risk of progressing to diabetes is highest in subjects with combined IFG and IGT varying between 2.5 to 10.5% per year in different populations with a mean of approximately 7% per year. The risk in those with IFG or IGT tends to be similar, with a mean of approximately 4% per year.

Very little data are available on the prevalence of subjects at high risk for diabetes based on an A1C ≥5.7% and <6.5%. In the Atherosclerosis Risk in Communities (ARIC) study, a community-based prospective cohort study, 11,092 middle aged adults from four US communities were followed for a median of 14 years [17]. At baseline, 4714 (43%) had an A1C ≥5.5% to <6.5%. After adjusting for age, sex and other cardiovascular (CV) risk factors, the relative risk (RR) for diabetes was 1.86 (95% CI: 1.67–2.08) and 4.48 (95% CI: 3.92–5.13) for A1C 5.5% to <6.0% and 6.0 to <6.5%, respectively.

It has now been shown that in subjects with prediabetes, particularly in those with IGT, the risk of diabetes can be significantly reduced by lifestyle interventions as well as pharmacological interventions [18].

Prediabetes as a risk factor for CVD & mortality

The diagnostic cut-off for diabetes (a fasting plasma glucose ≥7.0 mmol/l and a 2-h post 75 g glucose ≥11.0 mmol/l or an A1C ≥6.5%) identifies a threshold beyond which the risk of microangiopathy, particularly diabetic retinopathy starts to increase substantially [19,201]. However, macroangiopathy starts years before diabetes develops, even before the stage of prediabetes [20].

Defining the relationship between prediabetic hyperglycemia and CVD has been difficult because of the relatively low incidence rate and the large populations required. It was only made possible mainly by combining data from several studies in meta-analysis **(Table 3)**. In a meta-regression analysis combining 20 studies (n = 95,783), Coutinho *et al.* found a continuous positive relationship between initial fasting and 2-h plasma glucose and CV events, even at values far below the 6.1 mmol/l threshold for IFG and the 7.8 mmol/l for IGT [21]. This unadjusted association was confirmed by the Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe (DECODE) analysis of 13 prospective European observational studies (n = 18,783) between both fasting

Table 2. The prevalence of impaired fasting glucose and impaired glucose tolerance in different adult populations.

Population	Age (n)	I-IGT1† (%)	I-IFG‡ (%)	IGT/IFG (%)	Total prediabetes (%)	Ref.
Mauritius	25–74 (3713)	13.9	4.2	3.3	21.4	[104]
Pima	≥15 (5023)	10.7	1.9	2.5	15.1	[105]
Sweden	55–77 (1843)	20.3	9.7	7.6	37.6	[31]
NHANES	40–74 (2844)	11.6	4.4	3.9	19.9	[106]
Australia	≥25 (11,247)	8.0	5.7	2.6	16.3	[107]
Hong Kong	18–66 (1486)	6.1	0.9	1.1	8.1	[108]
DECODE	≥30 (25,364)	8.8	6.9	3.1	18.8	[109]

†I-IGT and I-IFG, respectively; the diagnosis of IFG is based on a fasting plasma glucose of ≥6.1 mmol/l and <6.9 mmol/l.
DECODE: Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe; I-IFG: Isolated impaired fasting glucose; I-IGT: Isolated impaired glucose tolerance; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; NHANES: National Health and Nutrition Examination Survey.
Data taken from [2].

and 2-h glucose and mortality. In both analyses, however, it was suggested that the 2-h glucose was more predictive than fasting glucose when adjusted for other risk factors. Furthermore, when adjustment was made for other CV risk factors such as BMI, systolic blood pressure, lipid and smoking, it greatly attenuated the relationships between IFG and death from CVD and all causes, which were only significant at fasting plasma glucose values ≥7.0 mmol/l. On the other hand, such adjustment had little effect on the relationship between 2-h glucose and mortality from CVD and all causes. In a population-based cohort, the Hoorn study found that subjects with IFG using ≥5.6 mmol/l or ≥6.1 mmol/l as the glycemic threshold did not have a higher risk for CV mortality than subjects with normal fasting glucose. It was only those who converted to diabetes who had a high risk of CV mortality [22]. The Australian Diabetes, Obesity, and Lifestyle (AusDiab) study, in a prospective observational evaluation of 10,026 men and women not known to be diabetic, found that IFG (6.1 mmol/l) but not IGT was an independent predictor of CV mortality [23].

A a recent meta-analysis, however, on a larger population obtained from 27 prospective studies (n = 175,152) could not show a different risk for CVD between the hyperglycemia in IFG and IGT [24]. For subjects with IFG defined as a fasting plasma glucose between 6.1 and 6.9 mmol/l inclusively, the RR for CVD was estimated at 1.12 (95% CI: 1.0–1.25) after adjusting for age, smoking, blood pressure and lipids. When the threshold for IFG was lowered to 5.6 mmol/l, the estimated RR was 1.18 (95% CI: 1.09–1.28) after adjusting for other risk factors. The adjusted analysis of studies on IGT provided an estimated RR of 1.20 (95% CI: 1.06–1.35). The few studies providing information on the risk of IFG in men and women could not show any significant differences between genders. There is currently insufficient data regarding IGT and potential sex differences. The DECODE analysis, however, suggested that the risks for CVD in subjects with IGT were very similar between men and women [25].

The relationship between A1C and CVD was demonstrated in the Framingham Heart Study where the relative odds for CVD increased by 1.39% (95% CI: 1.06–1.83) for every 1% increase in A1C above 5% [26]. The Rancho Bernardo Study had shown previously that A1C was related to CV mortality in women but not in men [27]. This relationship was further evaluated in a nondiabetic population within the European prospective investigation of cancer (EPIC)-Norfolk study [28]. In this observational study, 4662 men (3.4% self-reported diabetes) aged 45–79 years were followed for at least 4 years. A1C showed a linear relationship with CV mortality; each 1% increase above 5% was associated with a 30% increase in all-cause mortality and a 40% increase in CV mortality. Even after excluding subjects with known diabetes or those with an A1C ≥7% and those with a history of CVD (n = 522), the RR of all-cause mortality for a 1% increase in A1C was 1.46 (1.00–2.12), p = 0.05, after adjusting for age and other risk factors. In the Hoorn study, there was also a linear relationship between A1C and CV mortality, even within the nondiabetic range (p for linear trend <0.05), but this association disappeared after adjusting for age, sex and other risk factors [29]. More recently, in a 10-year prospective cohort study (n = 553), Cederberg *et al.* found that an A1C 5.7–6.4% was not a predictor of CVD but A1C ≥6.5% was significant in women only, (RR: 2.99

[2.5–3.56]) [30]. However, in the Atherosclerosis Risk in Communities (ARIC) study (n = 11,092), the adjusted RR of coronary heart disease (CHD) was 1.23 (95% CI: 1.07–1.41) and 1.78 (95% CI: 1.48–2.15) for A1C 5.5 to <6.0% and 6.0 to <6.5%, respectively [17]. Except for the ARIC study, all other studies had relatively small numbers of subjects. We therefore need to combine data from all the available studies in a meta-analysis to provide the power to characterize the relationship between the A1C 5.7–6.4% and A1C ≥6.5% with the risk of CVD and CV mortality. Overall, however, it does provide support for the use of A1C for the diagnosis of diabetes and those at high risk of developing diabetes.

Overall, these analyses suggest that hyperglycemia *per se* in prediabetes is associated with an increase risk of CVD [24]. Although many studies suggest that the risk for CVD is greater for IGT than for IFG, more recent analyses do not support this position. Given the high, and still growing prevalence of prediabetes, a moderate increase in risk induced by prediabetic hyperglycemia, assuming a causal relationship to CVD, could translate into substantial numbers of individuals developing or dying from CVD. Furthermore, both IFG and IGT are associated with other CV risk factors. As such, its overall risk has probably been underestimated [31].

The prevalence of other CV risk factors in subjects with prediabetes

Alhough it is recognized that prediabetic hyperglycemia is an independent risk factor for CVD, it is also known that both IFG and IGT are associated with other CV risk factors including hypertension, dyslipidemia, excess body weight and insulin resistance, all features of the metabolic syndrome. Given the different metabolic abnormalities underlying the development of IFG and IGT, different associations with CV risk factors might be expected. However, the few data available suggest that there are few differences, if any, between subjects with isolated IFG and isolated IGT in their association with hypertension and dyslipidemia [32–34].

A number of prospective intervention trials on the prevention of diabetes in subjects with prediabetes, IGT and/or IFG, have documented the prevalence of the classical CV risk factors in those populations **(Table 4)**. In the IGT population of the Diabetes Prevention

Table 3. Impaired fasting glucose and impaired glucose tolerance as risk factors for cardiovascular disease and cardiovascular mortality.

Studies	n	CVD RR (95% CI)	Cardiovascular mortality RR (95% CI)	Ref.
Coutinho†	95,783			[21]
▪ IFG: 6.1‡ mmol/l		1.33 (1.06–1.67)	–	
▪ IGT: 7.8§ mmol/l		1.58 (1.12–2.10)	–	
DECODE	22,514			[25]
▪ IFG: 6.1 mmol/l		–	1.01 (0.84–1.32)	
▪ IGT: 7.8 mmol/l		–	1.32 (1.12–1.56)	
Hoorn	1428			[22]
▪ IFG: 6.1 mmol/l		–	1.50 (0.72–3.15)	
▪ IFG: 5.6¶ mmol/l		–	1.15 (0.69–1.93)	
▪ IGT: 7.8 mmol/l	1812	–	3.00 (1.08–4.10)	[29]
Ford	175,152			[24]
▪ IFG: 6.1 mmol/l		1.12 (1.0–1.25)	–	
▪ IFG: 5.6 mmol/l		1.18 (1.09–1.28)	–	
▪ IGT: 7.8 mmol/l		1.20 (1.06–1.35)	–	
AusDiab	10,428			[23]
▪ IFG: 6.1 mmol/l		–	2.5 (1.2–5.1)	
▪ IGT: 7.8 mmol/l		–	1.2 (0.7–2.2)	

†Unadjusted analysis; when adjusted, IFG was not significant (p = 0.056).
‡IFG with a lower threshold of 6.1 mmol/l.
§IGT with a lower threshold of 7.8 mmol/l.
¶IFG with a lower threshold of 5.6 mmol/l.
AusDiab: Australian Diabetes, Obesity, and Lifestyle Study; CVD: Cardiovascular disease; DECODE: Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; RR: Relative risk.

Table 4. Prevalence of cardiovascular risk factors in subjects with impaired glucose tolerance/impaired fasting glucose from major prevention studies.

Study	n	Obesity[†] (%)	Hypertension[‡] (%)	Dyslipidemia[§] (%)	Ref.
DPP	3234	67.7	28.0	44.5	[35,36]
DPS	522	54.6	61.5	49.4	[37]
STOP-NIDDM	1429	37.0	58.0	46.0	[38]
DREAM	5269	–	43.5	35.5	[39]
Overall	10,454	57.9	41.6	40.3	

[†]Obesity defined as BMI ≥30 kg/m^2.

[‡]Hypertension defined as a blood pressure ≥140/90 mmHg.

[§]Dyslipidemia defined as low-density lipoprotein cholesterol ≥3.4 mmol/l, high-density lipoprotein-cholesterol <1.0 for men and <1.3 mmol/l for women, and triglycerides 2.2 mmol/l.

DPP: Diabetes Prevention Program; DPS: Diabetes Prevention Study; DREAM: Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; STOP-NIDDM: Study to Prevent Noninsulin-Dependent Diabetes Mellitus.

Program (DPP; n = 3234), the prevalence of obesity was 67.7%, that of hypertension, 28%, and that of dyslipidemia, 44.5% [35,36]. In the Finnish Diabetes Prevention Study (DPS) IGT cohort (n = 522), obesity was documented in 54.6%, hypertension in 61.5% and dyslipidemia in 49.4% [37]. In the IGT population of the international Study to Prevent NonInsulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial (n = 1429), 37% had obesity, 58% had hypertension and 46% had dyslipidemia [38]. In the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial (n = 5269), which included both IFG and IGT, 43.5% had a history of hypertension and 35.5% a history of dyslipidemia [39]. These populations could be biased, however, since they were selected on the basis of their high risk to develop diabetes including excess weight, hypertension, dyslipidemia and a family history of diabetes.

A random sample of a Finnish general population (n = 2049) of middle-aged subjects was submitted to an oral glucose tolerance test **(Table 5)** [37]. Overall, 1482 (72%) had normal glucose tolerance, 177 (8.6%) had IFG, 218 (10.6%) had IGT and 172 (8.4%) had Type 2 diabetes mellitus. Using the WHO criteria, the metabolic syndrome was present in 74% of men and 52.4% of women with IFG and in 84.8% of men and 65.4% of women with IGT. All the risk factors were slightly more prevalent in IGT compared with IFG and dyslipidemia and obesity were more frequent in men than women in both categories in this middle-aged population. In a cross-sectional population-based study, which included 902 randomly selected Spanish nondiabetic men and women between 30 and 80 years of age, 132 (15%) had isolated IFG, 59 (6.5%) isolated IGT and 48 (5.3%) had combined IFG and IGT [40]. The prevalence of the metabolic syndrome as defined by the IDF criteria was 57.2 and 64.4% for isolated IFG and isolated IGT, respectively, and 75.6% in those with combined IFG and IGT. Similar observations were made in 3606 subjects from the original Botnia study, with a median follow-up of 6.9 years [41]. In this population, the metabolic syndrome was seen in 10% of women and 15% of men with normal glucose tolerance (n = 1988), in 42% of women and 64% of men with IFG and/or IGT (n = 798), and 78% of women and 84% of men with Type 2 diabetes (n = 1697). In subjects with IFG/IGT associated with the metabolic syndrome, the risk of CHD was increased nearly twofold (hazard ratio [HR]: 1.82 [95% CI: 0.98–3.38]). Although relatively few studies have looked at the prevalence of CV risk factors in prediabetic populations, the available data would suggest that over 50% of patients with both IFG and IGT have the metabolic syndrome and, therefore, are at higher risk for CVD.

Although there are similarities between the various definitions of the metabolic syndrome, whether we use the ATP III, the WHO or the IDF criteria, there are also differences. All three definitions perform about the same in identifying people at risk for future myocardial infarction (MI) [42]. However, since these definitions do not consider other risk factors such as age, sex, ethnicity, family history, smoking, exercise, past MI or current treatment, their performances are modest. There are still major controversies on whether or not the diagnosis of the metabolic syndrome is helpful in deciding the therapeutic strategy [43]. Until these are resolved, the clinician should evaluate all known CV risk factors and treat all modifiable risk factors appropriately, regardless of whether or not they fulfill the criteria for the metabolic syndrome.

Intervention studies addressing CV risk factors

Both IFG and IGT should be considered as major risk factors for Type 2 diabetes mellitus, and as important risk markers for CVD of similar prognostic value as other CVD markers. Treating hyperglycemia in patients with diabetes is believed to prevent CVD but has certainly been difficult to prove [44–47]. A meta-analysis of those trials (n = 27,049) showed a 9% reduction in the risk of major CV events (HR: 0.91 [95% CI: 0.84–0.99]) primarily because of a 15% reduced risk of MI (HR: 0.85 [95% CI: 0.76–0.94]) [48]. Aggressively treating dyslipidemia and hypertension in subjects with and without diabetes has been shown to be associated with a significant reduction in CV events and mortality. Epidemiological studies also suggest that treating obesity in subjects with diabetes could reduce CVD. The use of antiplatelet agents for the prevention of CVD has never been tested in subjects with IFG or IGT. Overall, we have very few data on the effects of treatment of those risk factors in prediabetes on CVD and mortality.

■ Treating hyperglycemia

The data from prevention trials in subjects with IGT indicate that a lifestyle modification program including dietary change, weight reduction and exercise had the greatest reduction in the risk of developing diabetes [35,49]. Pharmacological interventions, notably metformin and acarbose, have also been shown to reduce the progression to diabetes, although they were less effective than diet and exercise [35,38]. Only rosiglitazone and pioglitazone were as effective as lifestyle modification in the DREAM and Actos Now for the prevention of diabetes (ACT-NOW) studies [50,51]; because of undesirable side effects, such as heart failure and fracture, these drugs will probably not be used for long-term prevention. While all those interventions were successful in preventing diabetes, it was more difficult to show a beneficial effect of glycemic control on CVD. Not all of those diabetes prevention studies were powered to answer that question. Neither the 20-year follow-up of the Da Qing study and nor the 10-year follow-up of the Finnish Diabetes Prevention Study could show any effect of lifestyle modification on CV morbidity and mortality [52,53]. More recently, nateglinide, a short-acting insulin secretagogue targeting postprandial hyperglycemia, was tested in a larger high-risk population (n = 9306) with IGT for the prevention of diabetes and CVD in the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial [54]. The study was unsuccessful, both for the prevention of diabetes and CV events. In fact, nateglinide resulted in a greater deterioration of the glucose tolerance than placebo suggesting that the drug accelerated the deterioration of the β cells. This would be supported by animal data showing that chronic exposure to glibenclamide, tolbutamide and nateglinide reduced the insulin content and accelerated the apoptotic death of the β cells [55]. Therefore, the NAVIGATOR trial could be interpreted to suggest that the chronic treatment with nateglinide resulted in gradual but accelerated failure of the β cells, thus blunting the effect of the drug on postprandial hyperglycemia and CVD. Of all the drugs tested, only acarbose in the STOP-NIDDM trial was associated with a 49% reduction in overall CV events [56]. Because it was a secondary end point and that the study was not powered to answer the question, the STOP-NIDDM trial suggests but does not provide a definite answer on the efficacy of

Table 5. Prevalence of the metabolic syndrome in subjects with impaired fasting glucose/impaired glucose tolerance.

Studies	n	Men (%)	Women (%)	Ref.
Finnish cohort†	2049			[37]
▪ IFG		74.0	52.4	
▪ IGT		84.8	65.4	
Botnia†	3606			[41]
▪ IFG/IGT		64.0	42.0	
Spanish cohort‡	902			[40]
▪ IFG		57.2		
▪ IGT		64.4		

†WHO criteria
‡IDF criteria; both men and women were included together in the analysis.
IDF: International Diabetes Federation; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance.

acarbose on the prevention of CVD. But we are now testing the hypothesis in a larger population (n = 7500) of subjects with CHD and IGT, the Acarbose Cardiovascular Evaluation (ACE) trial with CV events as the primary outcome. Another ongoing study is the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial where 12,612 subjects with either prediabetes (12%) or newly-diagnosed diabetes (88%) were randomized in a 2 × 2 factorial design to receive insulin glargine and omega 3 or placebo, with major CV events as the primary outcome [57]. Recruitment was started in 2002 and the treatment period is to be 4.5–5 years after the last randomized patient. The results should be available shortly. For the time being, the question as to whether treating prediabetic hyperglycemia could reduce CV events remains unanswered.

Treating dyslipidemia

A prospective meta-analysis of data from 90,046 participants in 14 randomized trials of statins by the Cholesterol Treatment Trialists' collaborators was published in *The Lancet* in 2005 [58]; 18,686 (21%) had a history of diabetes but prediabetes was not recorded. Over a mean follow-up of 5 years, there was a 12% proportional reduction in all-cause mortality per mmol/l in low-density lipoprotein (LDL) cholesterol reduction (RR: 0.88 [95% CI: 0.84–0.91]; p < 0.0001), attributable mainly to the 19% proportional reduction in CHD-related death (RR: 0.81 [95% CI: 0.76–0.85]; p < 0.0001). Overall, there was a highly significant 23% proportional reduction in the incidence of first major coronary events per mmol/l of LDL cholesterol reduction (RR: 0.77 [95% CI: 0.74–0.80]; p < 0.0001), which included a 26% reduction in nonfatal MI (RR: 0.74 [95% CI: 0.70–0.79]; p < 0.0001). These proportional reductions in major coronary events were significant in all prespecified subgroups, including those with and without diabetes.

Few data are available on the benefit of fibrates on CV events and mortality. The Helsinki Heart Study, in a primary prevention study of 4081 middle-aged men with primary dyslipidemia, showed that gemfibrozil treatment reduced fatal and nonfatal coronary events by 34% without affecting mortality rate [59]. The Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) demonstrated, in 2531 middle-aged men with CHD and low HDL cholesterol, that gemfibrozil treatment over 5.1 years was also associated with a reduction of 22% in the rate of death from CHD or nonfatal MI (95% CI 7–35; p = 0.006) [60]. However, this was mainly owing to the reduction in nonfatal MI, mortality from CHD by itself was not significant. The studies on the effects of fibrates in subjects with Type 2 diabetes are even more controversial. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study randomized 9795 subjects with Type 2 diabetes (2131 with previous CVD) to fenofibrate or placebo, looking at the effect of the drug on nonfatal MI and CV death [61]. The effects on the primary end points, whether analyzed separately or together, were not significant. More recently, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study could not show any effect of fibrate on CV events and mortality in high-risk diabetic patients when added to a statin [62]. Again, no studies looked at fibrate treatment in the prediabetic population.

In all the trials conducted in subjects with prediabetes for the prevention of diabetes, dyslipidemia was aggressively treated. The nonpharmacological and the pharmacological interventions, however, did impact the CV risk factors. Both the Diabetes prevention Program and the Finnish Diabetes Prevention Study showed that intensive lifestyle modification in subjects with IGT resulted in significant reduction in triglycerides, but not metformin [63,64]. Neither lifestyle modification nor metformin had any effect on CV events, very likely owing to the small number of events. Only acarbose treatment in the STOP-NIDDM trial was associated with a significant reduction in triglycerides and a significant reduction in CV events (49%; p = 0.03) [56].

Treating hypertension

Hypertension is also commonly associated with prediabetes and diabetes. In the prediabetic population of the DREAM trial, treatment with the angiotensin-converting enzyme inhibitor ramipril did not alter the CV outcome [65]. However, the DREAM population excluded patients who had CVD and, as such, was a low-risk population for CVD. Furthermore, because of the low event rate expected, it was recognized that it would not provide sufficient power to detect even a modest effect on CV outcome. In the high-risk population of the Heart Outcomes Prevention Evaluation (HOPE) study, with 47% having a history of hypertension and

38.5% a history of diabetes, ramipril reduced the risk of CV death by 26% ($p < 0.001$), the risk of MI by 20% ($p < 0.001$), the risk of stroke by 32% ($p < 0.001$) and the risk of death from any cause by 16% ($p < 0.005$) [66]. In the diabetic population of the HOPE study, ramipril treatment was also associated with a significant (25%) reduction in the risk for the composite end point of MI, stroke and CV death [67]. In the newly diagnosed Type 2 diabetic population of the UK Prospective Diabetes Study, tight blood pressure control with captopril or atenolol was associated with a 32% risk reduction in CV mortality ($p = 0.019$) [68]; there was no difference between captopril and atenolol on their effects on CV events. In the Hypertension Optimal Treatment (HOT) study, 19,193 patients with hypertension were randomized to one of three diastolic blood pressure target groups: ≤90, ≤85 or ≤80 mmHg [69]. The lowest incidence of major CV events occurred at a mean achieved diastolic blood pressure of 82.6 mmHg. In a subgroup of patients with Type 2 diabetes mellitus, there was a 51% reduction in major CV events in the target group ≤80 mmHg compared with target group ≤90 mmHg (p for trend = 0.005). The Blood Pressure Lowering Treatment Trialists' Collaboration published a meta-analysis of 27 randomized trials (n = 158,709 patients with hypertension, 33,395 with diabetes and 125,314 without diabetes) that included treatment regimens based on angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, β-blockers and calcium channel blockers [70]. The main finding was that treatment with any of the blood pressure lowering regimens was effective in reducing the risk of major CV events, and, the extent of the risk reduction was directly proportional to the degree of blood pressure-lowering, whether they had diabetes or not. In the ACCORD blood pressure trial, 4733 patients with Type 2 diabetes mellitus and hypertension were randomly assigned to intensive therapy targeting a systolic blood pressure of less than 120 mmHg or less than 140 mmHg [71]. The difference in the effects of those two different target treatments on the primary composite outcome (nonfatal MI, nonfatal stroke and CV mortality) was not significantly different. Their effects on the incidence of stroke, however, a prespecified secondary end point, was significantly lower in the less than 120 mmHg systolic blood pressure group (HR: 0.59 [95% CI: 0.39–0.89]; $p = 0.01$).

Blood pressure was also treated aggressively in subjects with prediabetes participating in the diabetes prevention trials. Both the Diabetes Prevention Program and the Finnish Diabetes Prevention Study showed that intensive lifestyle modification in subjects with IGT resulted in significant reduction in blood pressure, while metformin had little effect [63,64]. Again, only acarbose in the STOP-NIDDM trial was associated with a significant reduction in systolic and diastolic blood pressure and new cases of hypertension as well as a significant reduction in CV events [56].

■ Treating obesity

Although there are no randomized trials that have looked specifically at the effects of diet and exercise on CV events, a number of epidemiological and observational studies in nondiabetic and diabetic populations do suggest that such an intervention should be associated with reduction in CV events [72–75]. Both the Diabetes Prevention Program and the Finnish Diabetes Prevention Study showed that intensive lifestyle modification in subjects with IGT resulted in significant weight loss [63,64]. Despite significant weight loss, neither lifestyle modification nor metformin had any effect on CV events, very likely owing to the small number of events [52,53]. In the STOP-NIDDM trial, acarbose treatment was associated with a significant reduction in body weight, waist circumference and BMI, and a significant reduction in CV events [56].

■ Antiplatelet therapy

It is well established that CVD including MI, ischemic stroke and peripheral vascular disease are the leading cause of morbidity and mortality in patients with diabetes. Based on the evidence for the use of aspirin for the secondary prevention of CVD in diabetes [76–78,202], many diabetes organizations have recommended its use for primary prevention in this population despite major controversies [79]. The RR of vascular complications in subjects with IFG and IGT are doubled compared with those with normal glucose tolerance. However, the use of antiplatelet therapy for the primary or secondary prevention of CVD has never been evaluated in subjects with prediabetes.

Recently, De Berardis *et al.* published a meta-analysis on the use of aspirin for primary prevention of CV events in patients with diabetes [80]. The analysis included six randomized controlled

trials totaling 10,117 individuals with diabetes followed for 3.6–10.1 years. The authors found no significant reduction in the risk of major CV events (HR: 0.90 [95% CI: 0.81–1.00; p = 0.06]), in MI (HR: 0.86 [95% CI: 0.61–1.21; p = 0.37]), in stroke (HR: 0.83 [95% CI: 0.60–1.14; p = 0.25]), and in CV mortality (HR: 0.94 [95% CI: 0.72–1.23]). However, aspirin significantly reduced the risk of MI in men but not in women. Aspirin treatment was associated with bleeding (RR: 2.50 [95% CI: 0.76–8.21]), but the increase risk was not statistically significant. The authors concluded that "a clear benefit of aspirin in primary prevention of major CV events in people with diabetes remains unproved". In the prevention of progression of arterial disease and diabetes (POPADAD) trial, 1276 adults with diabetes and asymptomatic peripheral arterial disease were randomized in a 2 × 2 factorial design to aspirin and antioxidant therapy or placebo and followed for a median of 6.7 years documenting major CV events as the primary outcome [81]. There was no significant reduction in primary outcome (HR: 0.98 [95% CI: 0.76 – 1.26]) nor in CHD or stroke (HR: 1.23 [95% CI: 0.79–1.93]).

■ Conclusion

It can be concluded that the bulk of the evidence do support that aggressive treatment of dyslipidemia (LDL-C), hypertension and probably obesity should result in significant reduction in major CV events. However, the use of aspirin is more controversial, certainly for primary prevention. Although there are few intervention studies in the prediabetic population, it can be assumed that if treating those CV risk factors in the non-diabetic and diabetic populations reduces the risk of major CV events, it should also be beneficial for the inbetween prediabetic population. It should, therefore, be recommended to treat all CV risk factors in both IFG and IGT. The question is when should we treat and how aggressive should we be?

Proposed recommendations for the treatment of CV risk factors in prediabetes

Screening strategies have to be developed and implemented if we consider treating prediabetes. Many strategies have been proposed for the screening of prediabetes, but none have been validated **(Table 6)** [82–89]. It is clear that screening the general population would not be cost effective. However,

Table 6. Description of some screening strategies.

Study	Population	n	Procedures/criteria	Sensitivity/specificity (% prevalence)		Ref.
				IGT	Diabetes	
Bortheiry *et al.*	Random	21,847	FCG ≥5.6 mmol/l → OGTT†	59.0/77.4	87.2/59.2	[84]
Welborn *et al.*	Opportunistic	50,859	Questionnaire ≥2 risk factors + random glucose >5.5 mmol/l → OGTT†	(2.0)‡	(3.4)	[89]
DPP	High risk	79,190	Age ≥40 years BMI ≥30 kg/m^2 FCG ≥5.5 mmol/l → OGTT†	(27)	(13)	[82]
Anand *et al.*	High risk	936	FPG ≥5.7 + A1C ≥5.9% → OGTT†	–	71.0/95.0	[83]
IGLOO study	High risk	1377	Risk score questionnaire ≥9 → OGTT†	77.0/45.0†	86.0/41.0	[86]
Colagiuri *et al.*	High risk	11,247	≥1 risk factors → FPG ≥5.5 mmol/l → OGTT†	51.9/86.7	79.9/79.9	[85]
Smith *et al.*	Opportunistic	3821	Questionnaire ≥2 risk factors random plasma glucose ≥5.5 mmol/l → OGTT†	(3.9)	(0.8)	[88]

†Performance of screening strategy was based on an OGTT.
‡FCG.
A1C: Hemoglobin A1C; DPP: Diabetes Prevention Program; FCG: Fasting capillary glucose; FPG: Fasting plasma glucose measured by the laboratory; IFG: Impaired fasting glucose; IGLOO: Impaired Glucose Tolerance and Long-Term Outcomes Observational; IGT: Impaired glucose tolerance; OGTT: Oral glucose tolerance test.

several studies have shown that a screening strategy targeting a high-risk population as part of a diabetes screening program could be cost effective [87,90,91]. This is what has been proposed by the ADA and the CDA guidelines [92,93]. Therefore, to be cost effective, screening for IGT and IFG should be carried out in opportunistic and high-risk populations (**Box 1**) [86,87]. At the same time, screening for other CV risk factors should be conducted and then treated appropriately.

There are no specific recommendations for the treatment of CV risk factors in the prediabetic population and, therefore, the proposed recommendations are the authors' personal opinions based on intervention trials in diabetic and nondiabetic populations. This is also the position of the ACE/AACE for dyslipidemia and hypertension [3]. The recommendations for the nondiabetic and the diabetic populations are based on the evaluated risk of CV events over the next 10 years. Although CV risk assessment remains imperfect, use of the Framingham Risk Score (FRS) is recommended to estimate the 10-year risk [94]. The FRS is based on age, total and HDL cholesterol, systolic blood pressure, smoking and the presence or not of diabetes, with age as the strongest predictor. It is also adjusted for gender; a score of 11 for men and 13 for women provides a 10% risk of CVD over the next 10 years, which is considered a moderate risk. The same evaluation should be made in the prediabetic subjects and the same recommendations should apply according to the estimated risk of CV events.

Excess body weight, which is usually associated with IGT and IFG should be treated with a lifestyle modification program including a well-balanced/weight-reducing diet and moderate exercise. Both the DPP and the DPS have shown that an intensive lifestyle modification targeting a weight reduction of 5–7% of body weight was very effective in reducing the risk (58%) of developing diabetes [35,49,95]. Although there are no randomized trials that have looked specifically at the effects of diet and exercise on CV events, the epidemiological and observational studies available in nondiabetic and diabetic populations do suggest that such an intervention should be associated with reduction in CV events [72–75].

Dyslipidemia should be treated according to CV risk. Subjects with prediabetes should be considered as diabetics and treated according to their Framingham Risk Score. Subjects with a 10-year FRS ≥20% or with evidence of atherosclerosis (coronary artery disease, stroke and peripheral artery disease) should be considered at high risk, those with a 10-year FRS ≥10% but <20% at moderate risk and those <10% at low risk. Based on their FRS, they should be treated aggressively as diabetics according to local guidelines [3,9,96].

Similarly, there are no specific recommendations for the treatment of hypertension in subjects with prediabetes. The guidelines usually address the problem in subjects with and without diabetes. In subjects with diabetes, most guidelines recommend that elevated blood pressure should be aggressively treated to achieve a target of <130/80 mmHg to reduce the risk of both micro- and macro-vascular complications [93,97]. It is now recognized that prediabetes has the same risk for macrovascular complications as newly-diagnosed diabetes [31]. Furthermore, microvascular complications have been documented in subjects with IGT: retinopathy 7.9% [98], microalbuminuria 16.1% [99] and neuropathy 11.2% [100]. All these observations suggest that prediabetes should be considered with the same vascular risk as individuals with newly-diagnosed Type 2 diabetes mellitus. As such, subjects with prediabetes should probably be treated as aggressively as subjects with Type 2 diabetes mellitus aiming for a target of <130/80 mmHg [101–103]. The systolic target of 130 mmHg was recently challenged

Box 1. Risk factors for prediabetes and diabetes.

- Age ≥40 years
- First-degree relative with Type 2 diabetes
- Member of high-risk population (e.g., people of Aboriginal, Hispanic, South Asian, Asian or African descent)
- History of IGT or IFG†
- Presence of complications associated with diabetes
- Vascular disease (coronary, cerebrovascular or peripheral)†
- History of gestational diabetes mellitus
- History of delivery of a macrosomic infant
- Hypertension†
- Dyslipidemia†
- Overweight†
- Abdominal obesity†
- Polycystic ovary syndrome†
- Acanthosis nigricans†
- Schizophrenia‡

†Associated with insulin resistance.

‡The incidence of Type 2 diabetes is at least three-times higher in people with schizophrenia than in the general population.
IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance.
Data taken from [9,93].

by the ACCORD blood pressure trial in patients with Type 2 diabetes mellitus. The study did not find any difference in CV outcome between the group targeting <120 versus the one targeting <140 mmHg [71]. However, since we do not have the data on the impact of these systolic blood pressure targets on the microvascular complications, it is probably wise to maintain the recommendations of the current guidelines aiming for a blood pressure target of <130/80 mmHg for the individuals with prediabetes as well as with diabetes [9].

Conclusion & future perspective

The progression of normal glucose tolerance to diabetes is a continuum, whether we look at the deterioration of plasma glucose, insulin sensitivity or insulin secretion. These three different components involved in the development of diabetes evolve at different rates over time. That is why we can have normal plasma glucose with decreased insulin sensitivity or elevated plasma glucose with normal insulin sensitivity and decreased insulin secretion. It is still difficult to dissect the role of plasma glucose versus insulin resistance versus insulin deficiency in the development of diabetes and CV complications. That is the reason why it is difficult to identify specific thresholds for the fasting plasma glucose and the 2-h glucose post 75 g glucose load for the diagnosis of prediabetes. Furthermore, it is complicated by the fact that the threshold for the development for diabetes and that for CVD are different.

In view of the enormity of the problem of diabetes worldwide and with the understanding that the disease can be prevented or delayed, much research is being done in what has been termed 'prediabetes'. Lifestyle interventions as well as drug interventions in subjects with isolated IFG at the lower threshold are needed to evaluate their efficacy in the prevention of diabetes and CVD. Future intervention trials should, therefore, include both IFG at the lower threshold and IGT, and should be powered to assess the CV events as well as the progression to diabetes. The importance of taking plasma glucose values into account as part of the overall CV risk assessment need to be further evaluated. Intervention randomized trials in patients with CHD and in those with dyslipidemia and hypertension should consider glucose tolerance testing at baseline so that intervention in the subgroup with prediabetes can be determined. We need to identify clinical determinants as well as biological and genetic markers that will help us to evaluate the different levels of risk of conversion to diabetes and the development of CVD. We need to better characterize the role of insulin resistance in the development of diabetes and CVD. We also need to develop better methods of measuring the β-cell mass and the β-cell function so that we can better define their role in the development of diabetes and better evaluate the beneficial effect of our intervention on those processes. With the acquisition of this new information, we will be in better position to identify those subjects at increased risk and have a more targeted approach to the prevention of diabetes and its CV complications.

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