11 – Metabolic syndrome, hyperglycemia, and type 2 diabetes

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> *"The goal of many clinicians who manage diabetes is to achieve optimum glucose control alongside weight loss and a minimum number of hypoglycemic episodes."*
>
> *Bergenstal, Lancet, 2010*[1]

This chapter starts with prevention at the level of obesity and the metabolic syndrome, precursors of overt type 2 diabetes. We then cover overall management of diabetes and the standard glycemia-controlling drugs, before emphasizing the incretins which are specifically covered in greater detail. Then follow new sections on new drugs such as bromocriptine and inhibitors of renal sodium-glucose cotransport. The chapter closes with the need for multifactorial intervention.

Obesity has become a common problem in Western society, and it is a strong predictor of type 2 diabetes.[2] In the United States it is estimated that almost one third of the population has a lifetime risk of diabetes. Diabetes, in turn, predisposes to cardiovascular abnormalities, such that persons with diabetes without known coronary heart disease (CHD) have the same prognosis as a patient without diabetes who has CHD.[3] An increased waistline is one of the five criteria of the metabolic syndrome (MetSyn) in addition to fasting hyperglycemia and blood pressure (BP) elevation, increased circulating triglycerides, and decreased circulating high-density lipoprotein (HDL) cholesterol.[4] Three of these are required for the diagnosis of the MetSyn (Fig. 11-1; Table 11-1).[5],[6] The three main factors relating to the metabolic risk of cardiovascular disease are the body mass index (BMI), abdominal girth, and insulin resistance (IR) and response.[7] However, waist circumference rather than obesity reflected by the BMI is the better predictor of the risk of myocardial infarction (MI).[8]

Abdominal adipose tissue is now recognized as a metabolically active organ and regarded as the basic abnormality in the MetSyn by the International Diabetes Federation.[6] There are strong links between excessive abdominal fat leading to excessive circulating free fatty acids (FFAs) and cytokines, which hypothetically lead to the other four features of the MetSyn and could explain IR.[9] Nonetheless, the links between visceral abdominal fat and IR are challenged, the alternate culprit being subcutaneous fat, especially in the upper body.[10] The MetSyn is of clinical importance in that it increases the risk of cardiovascular disease and especially type 2 diabetes.[11] Currently an increasing number of patients with the MetSyn obesity or type 2 diabetes are being treated by cardiologists, often in close collaboration with diabetologists.

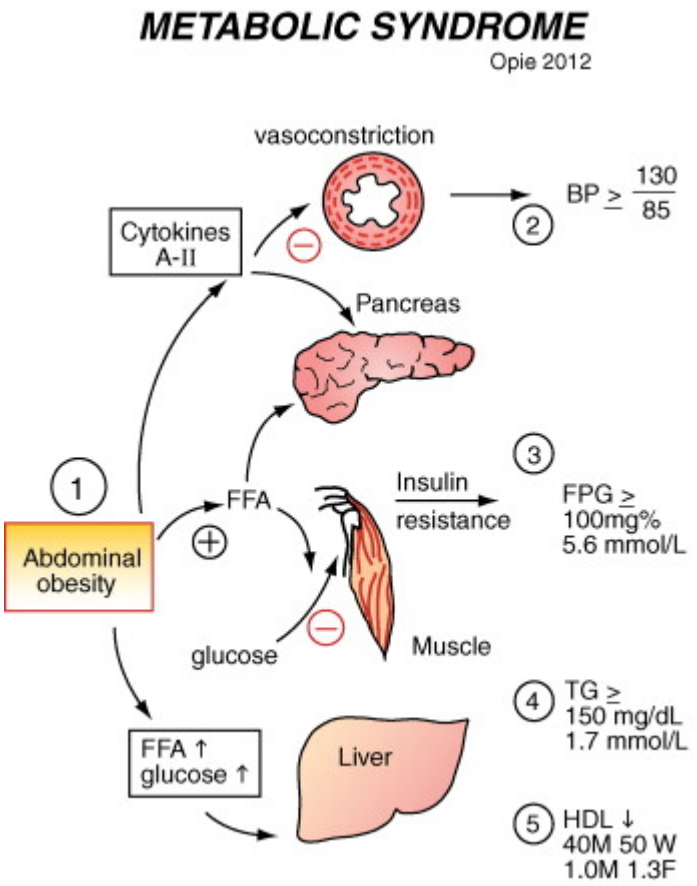

Figure 11-1 Hypothetical sequence of events leading from excess abdominal adiposity to the five features of the metabolic syndrome, of which three are required for diagnosis. The adipose tissue releases increased free fatty acids (FFAs) into the circulation, thereby inhibiting the uptake of glucose by muscle. Plasma glucose rises and elicits an insulin response. However, the pancreas is damaged by the high FFA levels and increased cytokines. The net effect is increased fasting plasma glucose (FPG) despite the increased circulating insulin (insulin resistance). Increased plasma FFA and glucose predispose to increased hepatic synthesis of triglycerides (TGs) and increased blood levels of TG, which in turn decrease levels of high-density lipoprotein (HDL) cholesterol. Increased release of angiotensin II (A-II) from the abdominal fat causes vasoconstriction and increases the blood pressure (BP). For details see Opie LH. Metabolic syndrome, *Circulation* 2007;115:e32.
(Figure © L.H. Opie, 2012.)

Table 11-1 -- Clinical Diagnosis of the Metabolic Syndrome

Risk Factor	Defining Level	Level, Metric Units
Abdominal obesity; waist		
Men	>40 inches	>102 cm
Women	>35 inches	>88 cm
Triglycerides	≥150 mg/dL	≥1.7 mmol/L
HDL cholesterol		
Men	< 40 mg/dL	<1.03 mmol/L
Women	< 50 mg/dL	<1.3 mmol/L
Fasting glucose	≥100 mg/dL	≥5.6 mmol/L
Blood pressure	≥130/85 mm Hg	≥130/85 mm Hg

For those on prior therapy see Table 2 of AHA/NHLBI statement.[5] Note important ethnic variations and lower waistline standards of International Diabetes Federation.[6]

HDL, High-density lipoprotein.

Risks of metabolic syndrome.

MetSyn comprises a group of cardiovascular risk factors, each of which individually may be of only borderline significance, but when taken together indicate enhanced risk of development of overt diabetes or cardiovascular disease. Influential authorities have questioned the predictive value of the MetSyn for the future development of diabetes and stress the role of one of the five components alone (glucose; Fig. 11-2).[12] Others emphasize the predictive value of two components of the MetSyn, modest elevations of glucose and BP, which were mostly responsible for increasing the cardiovascular risk by 71% in one study.[13] For cardiologists, becoming alert to risk-factor clustering, including abdominal obesity, high triglycerides, low HDL cholesterol, prehypertension, and hyperglycemia, is an important widening of vision.[5] The risk of developing future cardiovascular problems is proportional to the number of MetSyn features.[14] With four or five features, the risk of diabetes was 25-fold greater than with no features and still much more than with only one feature.[15] In an analysis of 172,573 persons in 37 studies, MetSyn had a relative risk of 1.78 for future cardiovascular events, and the association remained after adjusting for traditional cardiovascular risk factors (relative risk [RR], 1.54; confidence interval [CI], 1.32-1.79).[16] The International Day for Evaluation of Abdominal Obesity study measured waistlines in 168,000 primary care patients spread worldwide to confirm an association between waist and cardiovascular disease (RR 1.36) and more so with diabetes (RR 1.59 in men and 1.83 in women).[11]

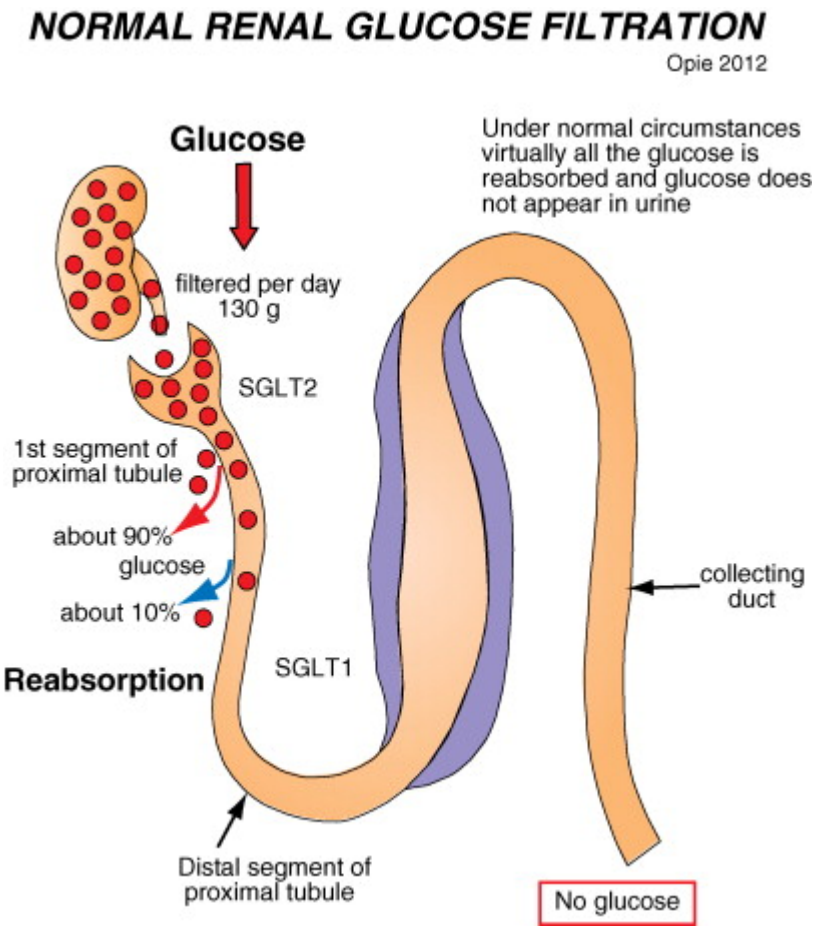

Figure 11-2 Normal renal glucose filtration. Under normal conditions virtually all the glucose that is filtered through the glomeruli is reabsorbed, mostly in the first segment of the proximal tubule by the sodium-glucose transporter (SGLT2)
(Figure © L.H. Opie, 2012.)

Insulin resistance.

IR leads to the MetSyn[7] and increased circulating FFA and glycemia (see Fig. 11-1), plus elevated glucose production in the liver, which are the precursors of type 2 diabetes mellitus (T2DM).[17] There is a dose-response effect of elevated plasma FFA on insulin signaling.[9] The dietary routes to IR were studied in more than 7000 young Finns.[18] There were specific circulating metabolic clues, namely increased branched-chain and aromatic amino acids, intermediates of gluconeogenesis, ketone bodies, and fatty acids abnormal in composition and saturation. Taken together, these 20 metabolite measures were strongly associated with the homeostasis model of IR ($P < 0.0005$). Thus early life dietary patterns already predispose to IR.

Where does obesity enter the picture? Obese persons have high blood FFA levels, which even at modest elevations inhibit insulin signaling[9] and stimulate nuclear factor kappa B (NFκB) to promote IR (Fig. 1 in Kim, 2012).[19] NFκB in turn stimulates macrophages to provoke the chronic low-grade inflammatory response (Fig. 2 in Kim, 2012)[19] with increased plasma levels of C-reactive protein, and inflammatory cytokines such as tumor necrosis factor–alpha (TNFα), interleukin (IL) 6, monocyte chemotactic protein (MCP) 1, and IL-8, and the multifunctional proteins leptin and osteopontin.[17] Macrophages in human adipose tissue are the main, but not the only, source of these inflammatory mediators that stimulate IR in multiple organs.[19] Hypothalamic microglia are macrophage-like cells that are also activated by proinflammatory signals causing local production of specific interleukins and cytokines. The “Western” high-fat diet experimentally enhances such cytokine production, whereas exercise diminishes it.[20] The overall sequence is:

$$\text{Obesity} \rightarrow \text{high FFA} \rightarrow \text{NF}\kappa\text{B} \rightarrow \text{macrophages} \rightarrow \text{inflammatory cytokines} \rightarrow \text{insulin resistance}$$

A simple therapeutic attack on the inflammatory response is by high-dose aspirin in impractical doses (approximately 7 g/day).[21]

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From metabolic syndrome to overt diabetes and cardiovascular disease

Lifestyle changes to slow the onset of diabetes.

The transition from MetSyn to full-blown diabetes can be significantly lessened by lifestyle intervention. Thus walking only approximately 19 km per week can be beneficial in treating MetSyn.[22] However, more intense intervention is needed for real change. Tuomilehto et al.[23] studied a group of overweight subjects with impaired glucose tolerance who, on average, also had the features of the MetSyn. Dietary advice and exercise programs were individually tailored. The five aims were weight reduction, decreased fat intake, decreased saturated fat intake, increased fiber intake, and increased endurance exercise (at least 30 min daily). Of these, increased exercise was achieved in 86% of participants, and the other components less frequently. After a mean duration of 3.2 years, the relative risk for new diabetes in the lifestyle intervention group was 0.4 ($p < 0.001$). In the Diabetes Prevention Group[24] similar subjects were given lifestyle modification or metformin for a mean of 2.8 years. Lifestyle intervention was very intense with a 16-lesson curriculum covering diet, exercise, and behavior modification taught by case managers on a one-to-one basis during the first 24 weeks after enrollment. Lifestyle intervention was more effective than metformin in delaying the onset of diabetes, and both were more effective than placebo in preventing new diabetes. The physical exercise in these two preventative studies was intense, and cannot readily be achieved in the average clinic. Please see Update for premature termination of Look-AHEAD study (no change in major cardiovascular outcomes).

Sustainability of lifestyle changes.

Is the protection from diabetes found in the Diabetes Prevention Group study sustained? The 10-year follow-up says no, with an equal incidence of new diabetes in placebo, former lifestyle, and metformin groups. Yet the cumulative incidence of diabetes remained lowest in the lifestyle group. Thus prevention or delay of diabetes with lifestyle intervention or metformin can persist for at least 10 years.

Long-term diet-induced weight loss.

Wadden et al. write, “Physical activity appears to be critical for long-term weight management.”[25] However, weight loss is no easy task. Even in a motivated group receiving in-person support over 2 years, only 41% lost 5% or more of their weight from an initial mean of 103.8 kg.[26] From an excellent review of 21 lifestyle modification studies,[25] only 4 are above average: a 2-year meal replacement program (–10.4 kg); a low-carbohydrate ketogenic diet with nutritional supplements (–12.0 kg) but only over 6 months, when weight loss often peaks; a center-based Jenney Craig diet (–10.1 kg at 12 months); and a Weight Watchers diet plus individual counseling (–9.4 kg at 12 months). However, the standard pattern was weight regain after 12 months, equal to the low-fat and low-carbohydrate diets, and less weight regain in those who are exercising vigorously (300 min or more weekly). Increasingly, “personalized” programs are conducted electronically.

Physical disability in adults with type 2 diabetes.

Could weight loss reduce mobility-related problems in adults with type 2 diabetes who have a high prevalence of disability? The ongoing Action for Health in Diabetes (Look AHEAD) study enrolled more than 5000 overweight or obese persons with type 2 diabetes and mean initial weight was 100.9 kg.[27] At year 4, the lifestyle-intervention group had a relative reduction of 48% in the risk of loss of mobility (odds ratio [OR], 0.52; CL: 0.44-0.63; $P < 0.001$). Both weight loss and improved fitness (assessed on treadmill testing) were significant mediators of this effect ($P < 0.001$ for both variables). Those with the greatest initial disability had correspondingly less benefit. Provisional results of Look-AHEAD, were disappointing. The study had to be stopped because there was no emerging difference in the hard cardiovascular endpoints. See On-line update for details.

Drugs for weight loss.

Few are approved and without danger. Current interest lies in the *naltrexone slow-release (SR)/bupropion SR combination* (Contrave). Bupropion has effects (μ-opioid receptor antagonist and catecholamine inhibitor) that lead to reduced energy intake and increased energy expenditure, whereas naltrexone may potentiate these effects. On June 2, 2011, the Food and Drug Administration (FDA) requested a large safety study of naltrexone before its approval, and the FDA plans an advisory committee for 2012 to discuss the need for cardiovascular safety of all obesity drugs.[28]

The following drugs have been turned down by the FDA:[28] In the *combined phentermine and topiramate* (PHEN/TPM), phentermine induces central norepinephrine release and promotes weight loss by reducing food intake. Topiramate has complex central effects and is approved for treatment of seizures and for migraine prophylaxis. Among the reasons for refusal were depression and cognitive-related complaints. *Lorcaserin* (Lorqess), is a novel serotonergic agent approved by the FDA in 2012, expected to have a reduced cardiac valve risk profile compared with earlier serotonergic agents, such as fenfluramin. However, neuropsychiatric and cognitive-related side effects occurred with approximately double the frequency in patients treated with lorcaserin. *Sibutramine* (Meridia) has sympathomimetic properties, acting centrally to block the neuronal uptake of norepinephrine and serotonin, as well as stimulating peripheral β_3-adrenergic receptors to induce satiety, yet with notable increases in systolic and diastolic BP and heart rate. On October 8, 2010, the FDA asked for the voluntary withdrawal of sibutramine from the US market, a request with which Abbott, the maker of sibutramine, complied.

Orlistat is available over the counter in the USA, European Union, and Australia. The review committee of the European Medicines Agency (February 13-16 2012) evaluated the risk of liver injury with orlistat drugs, such as Xenical and Alli with the conclusion that the weight-loss drug's benefits outweigh the risks in patients with a BMI of more than 28 kg/m[2].[29]

Update: New Content Added *Date Added: 28 February 2013*

Combination of phentermine and extended-release topiramate for weight loss

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Summary

Background. The combination of phentermine and extended-release topiramate (Qsymia, Vivus, Mountain View, CA) was also accompanied by improvements in cardiovascular disease risk factors in patients with dyslipidemia and/or hypertension at baseline (1). The issue of complex cerebral side-effects was not mentioned in the Summary.

FDA approval. Qsymia, previously known as Qnexa, was approved by the US Food and Drug Administration in July 2012 after the Endocrinologic and Metabolic Drugs Advisory Committee voted 20 to 2 in favor of approving the obesity drug early last year. In 2010Qnexa hadnotbeenaoppoaorved (2). This combination tablet of phentermine and topiramate is indicated for adults with a body-mass index (BMI) >30 or adults with a BMI >27 and at least one weight-related comorbidity such as hypertension, type 2 diabetes, or dyslipidemia. During the FDA advisory-panel deliberations, concerns were raised by committee members about possible increases in heart rate with Qsymia, something that physicians should regularly monitor in patients treated with the drug.

On the basis of the FDA analyses of the clinical trial data, it was determined that if after 12 weeks of treatment with lorcaserin a patient has not lost at least 5% of the baseline body weight, use of the drug should be discontinued, since it is unlikely that the patient will achieve meaningful weight loss with continued treatment. Similarly, if after 12 weeks of treatment with phentermine–topiramate at the 7.5 mg/46 mg dose, a patient has not lost at least 3% of the baseline weight, either the drug should be discontinued or the dose increased. If the latter option is chosen and the patient does not lose at least 5% of the baseline weight during an additional 12 weeks of treatment, the drug should be discontinued,

because the patient is unlikely to achieve meaningful weight loss with continued treatment (3)

Trial data. The CONQUER trial was a 56-week phase 3 randomized, double-blind, placebo-controlled study that included patients with a BMI of 27 -45 and weight-related comorbidities (4). Of 2487 patients, 994 were assigned to placebo, 498 to phentermine 7·5 mg plus topiramate 46·0 mg, and 995 to phentermine 15·0 mg plus topiramate 92·0 mg; 979, 488, and 981 patients, respectively, were analysed. At 56 weeks, change in bodyweight was -1·4 kg (least-squares mean -1·2%, 95% CI -1·8 to -0·7), -8·1 kg (-7·8%, -8·5 to -7·1; p<0·0001), and -10·2 kg (-9·8%, -10·4 to -9·3; p<0·0001) in the patients assigned to placebo, phentermine 7·5 mg plus topiramate 46·0 mg, and phentermine 15·0 mg plus topiramate 92·0 mg, respectively. 204 (21%) patients achieved at least 5% weight loss with placebo, 303 (62%; odds ratio 6·3, 95% CI 4·9 to 8·0; p<0·0001) with phentermine 7·5 mg plus topiramate 46·0 mg, and 687 (70%; 9·0, 7·3 to 11·1; p<0·0001) with phentermine 15·0 mg plus topiramate 92·0 mg; for ≥10% weight loss, the corresponding numbers were 72 (7%), 182 (37%; 7·6, 5·6 to 10·2; p<0·0001), and 467 (48%; 11·7, 8·9 to 15·4; p<0·0001).

Adverse effects: The most common adverse events (4) were dry mouth (24 [2%], 67 [13%], and 207 [21%] in the groups assigned to placebo, phentermine 7·5 mg plus topiramate 46·0 mg, and phentermine 15·0 mg plus topiramate 92·0 mg, respectively), paraesthesia (20 [2%], 68 [14%], and 204 [21%], respectively), constipation (59 [6%], 75 [15%], and 173 [17%], respectively), insomnia (47 [5%], 29 [6%], and 102 [10%], respectively), dizziness (31 [3%], 36 [7%], 99 [10%], respectively), and dysgeusia (11 [1%], 37 [7%], and 103 [10%], respectively). 38 (4%) patients assigned to placebo, 19 (4%) to phentermine 7·5 mg plus topiramate 46·0 mg, and 73 (7%) to phentermine 15·0 mg plus topiramate 92·0 mg had depression-related adverse events; and 28 (3%), 24 (5%), and 77 (8%), respectively, had anxiety-related adverse events.

Topiramate and the CNS: Complex CNS effect of topiramate are noted In reference (2), and that this drug is approved for the therapy of seizures and migraine.

Comments: In an Interview with Heartwire, Davidson (1) stated that “facilitating weight loss by augmenting lifestyle changes with pharmacotherapies may decrease the risk for cardiovascular disease in obese and overweight patients with comorbidities.” Note the interpretation in The Lancet (4): The combination of phentermine and topiramate, with office-based lifestyle interventions, might be a valuable treatment for obesity that can be provided by family doctors.

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Gastric surgery for weight loss.

Although lacking long-term outcome studies, the impressive and often sustained weight loss after gastric bypass surgery seems to be one way to counter recalcitrant obesity for those who have failed in weight loss programs.[30] Further data are awaited.

Blood pressure and lifestyle.

Modest BP elevation, a component of the MetSyn, is often associated with overweight and obesity. Loss of weight and exercise in the setting of intensive behavioral intervention in the MetSyn can reduce systolic BP in the range of 8 mm Hg with small additional reductions if the Dietary Approaches to Stop Hypertension diet is added.[31] However, in a parallel study, similar reductions in BP were not observed at 18 months.[32] When added drugs are required, β-blockers and diuretics should be considered second-line agents and avoided except when there are compelling indications. There is now growing but controversial evidence that new diabetes may develop during the therapy of hypertension, more so with β-blockers and diuretics than with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) (Fig. 11-3).[33-36] There is a "weight of evidence against β-blockers" as first choice for obese patients with hypertension.[37] A network metaanalysis linked diuretic and β-blocker therapy separately to new diabetes in hypertension (Fig. 11-3).[38] Thus current European Hypertension Guidelines counsel against initial use of a β-blocker in MetSyn.[39] Nebivolol may be an exception,[40] but lacks outcome studies. In view of the potential increased risk of new diabetes with β-blockers and diuretics in the therapy of hypertension, and as new diabetes is the major risk of the MetSyn, it seems prudent to give preference to antihypertensive therapy initially based on ACE inhibitors or ARBs, with low-dose diuretics (hydrochlorothiazide 12.5 to 25 mg) as needed (unless there are compelling indications for β-blocker–diuretic therapy).

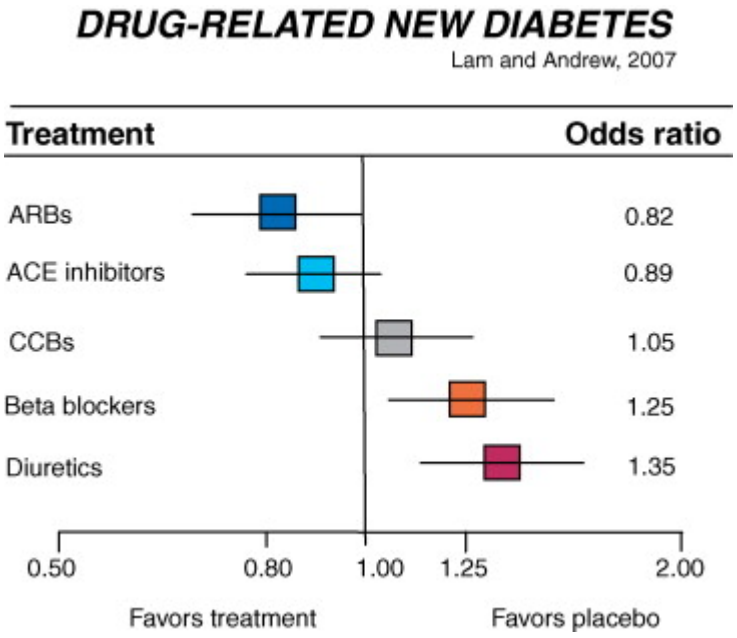

Figure 11-3 Drug-related new diabetes. Note protective effect of angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors, and deleterious effects of β-blockers and diuretics. Network metaanalysis of 22 trials with 143,153 patients, using placebo as referent agent, and including earlier higher-dose diuretic trials. *CCB,* Calcium channel blocker. *From Lam SKH, et al. Incident diabetes in clinical trials of antihypertensive drugs. Lancet 2007;369:1513.*

Which drugs halt the slide to diabetes?

Metformin 850 mg twice daily when given in the Diabetes Prevention Study[24] reduced future diabetes, albeit less than vigorous lifestyle changes. *Glitazones* increase hepatic and peripheral insulin sensitivity by activation of peroxisome proliferator–activated receptor–γ (PPAR-γ) receptors. Rosiglitazone helps limit the evolution of prediabetic state into overt diabetes.[41] However, rosiglitazone has the risk of precipitating heart failure or MI (see later). In the ACT NOW trial, pioglitazone, as compared with placebo, reduced the risk of conversion of impaired glucose tolerance to T2DM by 72%, but was associated with significant weight gain and edema.[42]

Acarbose inhibits the gastric absorption of glucose. Although often poorly tolerated because of gastrointestinal symptoms, it has well-documented reduction in MI and it reduces the incidence of new hypertension (RR reduction 34%).[43] *Rimonabant* is a selective central cannabinoid-1 receptor blocker, initially highly promising because it reduced body weight, triglyceride levels, glycemia, and increased HDL cholesterol.[44] However, psychiatric side effects have led to rejection by the FDA and other bodies.

Comparative choices.

Because there have been no comparative studies between metformin, acarbose, and glitazones, it is difficult to say with certainty which would be most effective in preventing progression to new diabetes should lifestyle modifications prove inadequate. However, metformin and pioglitazone have convincing data.

What can be achieved?

For lifestyle by itself to be effective in preventing transition to diabetes as well as reducing BP, major changes have to be effected, requiring intense input from professional personnel such as nutritionists and exercise physiologists. Although this intensive counseling may not be a cost-effective approach when applied to the general population, it is undeniable that the ideal strategy for the whole population is a broad behavior modification that avoids obesity. Drug therapy to prevent the transition to type 2 diabetes is both feasible and effective in selected patients, yet not widely applied.

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Cardiovascular control in established type 2 diabetes

In general, control of BP and of blood lipids improves macrovascular disease and clinical outcome, whereas the control of glycemia limits microvascular disease (retina, kidneys, nerves). Both are important endpoints of effective therapy. Macrovascular disease predominates in type 2 diabetes.[45] However, with the increasing life expectancy of patients with type 2 diabetes, microvascular complications may well become increasingly prevalent. Of note, agents with equivalent glucose-lowering properties may be very different in their ability to improve cardiovascular outcomes.

Weight loss

Intense lifestyle intervention aimed at a less calorie intake and more exercise over 1 year gave improved diabetic control and decreased cardiovascular risk factors such as BP and lipid profiles; mean hemoglobin A1c (HbA1c) dropped from 7.3% to 6.6%.[46]

Blood pressure control

In the prospective observational UKPDS 36 Study over a mean of 8.4 years, reduction of systolic pressure toward or even less than 120 mmHg, was associated with a decreased incidence of both macrovascular and microvascular events.[47] However, prospective data are required to validate outcomes at such low levels. In the ADVANCE study[48] the mean BP in high-risk diabetic patients in the placebo group (on existing treatment) was 140/77 mm Hg, and was further reduced to a mean of 137/75 mm Hg by the addition of an ACE inhibitor, perindopril, together with a diuretic, indapamide. Over the study period, the mean reduction of systolic pressure was 5.6 mm Hg systolic, whereas the diastolic fell by 2.2 mm Hg. Risk of death from cardiovascular disease fell by 18% (p = 0.03) and all-cause mortality by 14% (RR 0.86; CI 0.75-0.98, p = 0.03), in addition to strong trends toward reductions in macrovascular- and microvascular disease. Future trials will hopefully prospectively test the hypothesis that additional reduction of BP toward a target systolic BP of 120 mm Hg will yield greater reduction of microvascular and macrovascular events. In the meantime ADVANCE teaches us that greater reduction of BP can give mortality benefits.

Control of intraglomerular pressure.

Third-generation dihydropyridine calcium channel blockers such as manidipine inhibit T-type calcium channels on vascular muscular cells such as those localized on postglomerular arterioles.[49] In the DEMAND study on 380 subjects for a mean of 3.8 years, combined manidipine and ACE-inhibitor therapy reduced both macrovascular events and albuminuria in hypertensive patients with T2DM, whereas the ACE inhibitor did not. Worsening of IR was almost fully prevented in those on combination therapy.

Statin therapy: Impressive overall benefits

The benefits of adding atorvastatin 10 mg to diabetic therapy were shown in the CARDS study (see Chapter 10, p. 406). Entry criteria were type 2 diabetes and at least one other cardiovascular risk factor such as hypertension, smoking, or diabetic complications. Atorvastatin 10 mg daily taken by patients with type 2 diabetes reduced the low-density lipoprotein (LDL) cholesterol from a mean of approximately 118 mg/dL to approximately 72 mg/dL, as well as decreasing major cardiovascular events including, surprisingly, a reduction in stroke of 48%.[50] Although LDL levels remain the major indication for statins, there can be normal LDL cholesterol levels but small LDL particles. However, in practice the standard indices for statin therapy remain valid.[51]

Statin-induced diabetes.

Goldfine states, “Statins may simply be unmasking disease in people who were likely to develop diabetes anyway”—those in older age, with high baseline fasting glucose levels, and other features of the MetSyn.[52]

Although a large metaanalysis found a 9% increased risk for incident diabetes over a 4-year period, the risk with rosuvastatin was 18%, based on the results of JUPITER and two other clinical trials. Logically, the more powerful the statin, the greater the risk of diabetes.[53] The other metaanalysis compared intensive- with moderate-dose statin therapy in five studies on 32,752 persons without diabetes at baseline. The number needed to treat (NNT) annually to harm was 498 for new-onset diabetes versus a NNT of 155 for reduced cardiovascular events. Thus the approximate ratio of benefit to harm for high versus medium doses was approximately 3:1.[54]

Glycemic control: How tight?

Selection of drugs from a large number of oral agents to obtain glycemic control or when to use insulin are decisions optimally made by close collaboration between diabetologists and cardiologists. As the blood glucose increases, so does cardiovascular risk and total mortality, as shown in the large DECODE Study in 29,714 persons over 11 years,[55] so that reduction of glycemia should be equally beneficial. In general, guidelines recommend an HbA1c level of less than 7,[56] largely on the basis of the UK series of studies.[57] German guidelines advise less than 6.5%. However, “the cardiovascular safety and efficacy of available glucose-lowering strategies remain to a large degree uncertain.”[58] Thus there is an increasing need for trials with cardiovascular outcomes and mortality, reaching beyond glycemic control. One large study, ADVANCE, which aimed at intense glucose lowering by a regimen based on gliclazide, succeeded in reducing both cardiovascular events and glycated hemoglobin (HbA1c) from 7.5 to 6.53.[59] In patients with diabetes at high cardiovascular risk, perhaps similar to those that a cardiologist might see, the National Institutes of Health–supported Action to Control Cardiovascular Risk in Diabetes (ACCORD) study compared intense versus standard glycemic control. Mean HbA1c levels were 6.4% in the intense and 7.5% in the standard arms. Unexpectedly, mortality increased after 3.7 years yet without reducing major cardiovascular events as compared with standard therapy.[60] After termination of the intensive therapy, the target HbA1c level was eased to 7 to 7.9. Although reduced 5-year nonfatal MIs decreased, 5-year mortality increased. The ACCORD study researchers write, “Such a strategy cannot be recommended for high-risk patients with advanced type 2 diabetes.”[61] Also, another prospective-randomized trial in patients with advanced type 2 diabetes (VADT) failed to demonstrate a significant benefit in terms of overall or cardiovascular mortality from lowering HbA1c to 6.9% in the intensive-therapy group versus 8.4% in the standard-therapy group.[62]

A high-quality metaanalysis assessed the effects of intensive glycemic versus conventional glycemic control on all-cause and cardiovascular mortality, microvascular complications, and severe hypoglycemia in patients with type 2 diabetes.[63] All-cause mortality was unchanged, nonfatal MI was reduced (RR 0.85; P = 0.004; 28,111 participants, eight trials), as was the composite microvascular outcome (RR 0.88, P = 0.01; 25,600 participants, three trials) and retinopathy (RR 0.80, P = 0.009; 10,793 participants, seven trials). However, strict statistical testing by trial sequential analyses showed insufficient evidence for any beneficial conclusions except that hypoglycemia increased by 30%.

The updated 2012 recommendation of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) is to individualize treatment targets.[64] In older adults, often with comorbidities and vascular complications, less stringent control is advocated (e.g., 7.5%-8% HbA1c [59-64 mmol/mol]); nonetheless, the ideal goal remains less than 7 (<53 mmol/mol) to reduce microvascular disease.

The *bottom line* is that an HbA1c of 7% to 7.9% is often appropriate for cardiovascular patients, but consider less than 7% for younger, newly diagnosed patients.

Insulin.

After failed oral therapy, insulin clearly is the remaining requirement, as in the current guidelines.[64] The major problem with insulin is that control hyperglycemia may be bought at the cost of hypoglycemia. The long-acting flat profile of new *degludec insulin* forms a deposit of soluble subcutaneous multihexamers from which insulin is slowly and continuously absorbed into the circulation, thus being “not a revolution but an evolution” of insulin therapy for type 1 and type 2 diabetes.[65] The often presumed increased risk of heart failure caused by fluid retention with insulin treatment has not been translated into a consistent increase in the rate of mortality or hospitalization for heart failure.[66] Overall, the paucity of well-controlled studies in this area do not allow any final conclusion about the potential effects of insulin therapy on patients with diabetes and heart failure.

Metformin.

Singly or in combination, metformin is standard to promote glycemic control. Metformin reduces glucose production by the liver and increases glucose uptake by muscle by increasing glucose transporter–4 mediated glucose uptake (Fig. 11-4). Importantly, it also suppresses appetite and appears to be devoid of cardiovascular harm and may benefit when given to patients with diabetes and heart failure.[66] In the prolonged UKPDS study, metformin was the only drug to reduce diabetes-related and all-cause mortality.[45] Since then, it has been the first-line treatment in overweight patients with type 2 diabetes.

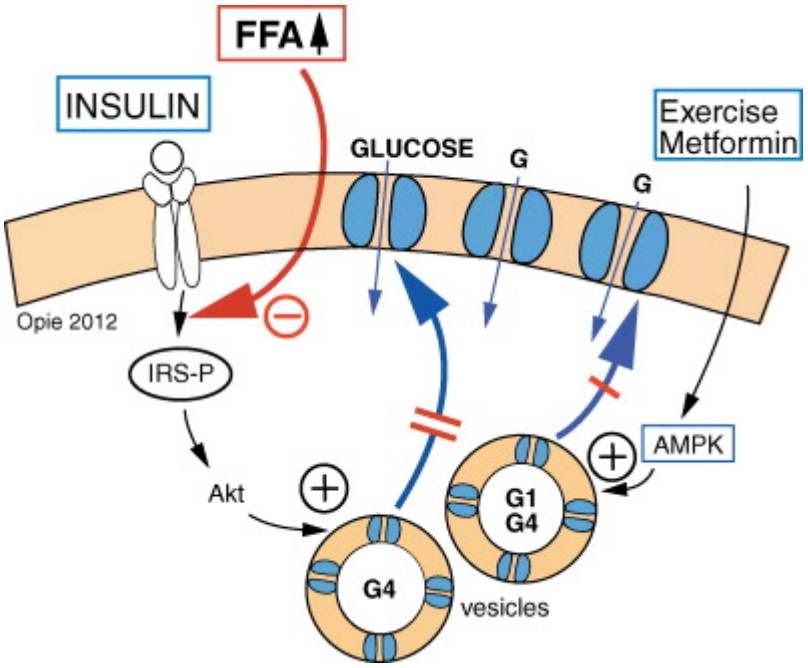

Figure 11-4 Site of action of metformin. Molecular steps leading from increased free fatty acid (FFA) to insulin resistance. Excess FFA entering the muscle cell is activated to long-chain acyl coenzyme A, which inhibits the insulin signaling pathway so that there is less translocation of glucose transporter vesicles (GLUT-4 and GLUT-1glucose) to the cell surface. Glucose uptake is decreased and hyperglycemia promoted. The increased uptake of FFA promotes lipid metabolites accumulation in various organs, including the heart and pancreas. Metformin and exercise, by stimulating adenosine monophosphate protein kinase (AMPK), promote the translocation of transport vesicles to the cell surface to promote glucose entry and to oppose insulin resistance. Protein kinase B, also called *Akt,* plays a key role. *G,* Glucose; *IRS-P,* insulin receptor substrate–phosphatidyl.
(Modified from Opie LH. Heart Physiology, from Cell to Circulation. 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2004. p. 313.)

Metformin versus secretogogues.

In a large UK general practice research database on 91,521 people with a mean follow up of 7.1 years, metformin had a favorable risk of mortality as compared with sulphonylureas.[67] In a German primary care study, sulfonylureas doubled the risk of hypoglycemia.[68]

First stop, metformin? Of 11 quality guidelines, 7 favor metformin as the first-line agent.[69] Yet the guidelines, normally taking months or years to finalize, could not have taken into account the 2012 metaanalysis on 13 controlled trials that showed no evidence that metformin has any clear beneficial or harmful effect on all-cause mortality, nor on cardiovascular mortality or morbidity among patients with type 2 diabetes.[70] In yet another metaanalysis, when combined with insulin, metformin reduced HbA1c by 0.5% and weight gain by 1 kg, whereas the insulin dose fell by 5 U/day.[71] Of note, metformin remains the first agent recommended by the influential 2012 ADA-EASD guidelines[64] and remains the usual first choice in clinical practice.

Metformin and kidney disease.

Metformin is renally excreted. Bearing in mind that moderate to severe renal disease with estimated glomerular filtration rate (eGFR) less than 60 mL/min occurs in 20%-30% of patients with T2DM, the dose of metformin must be reduced. Suggested cut-off eGFR values are the following: if more than 60, no problems; if 45-60, use but monitor renal function; if 30-45, don't start, and if already giving metformin, use with care, decrease dose, and repeat eGFR every 3 months; and if less than 30 don't use.[72] In the UK, the policy is less tight, allowing use of metformin with monitoring down to 30 mL/min (see reference 14 in Inzuchi et al., 2012[64]).

The *bottom line* is that ideal evidence-based first-line therapy is not yet established. In practice, metformin stays the standard for comparators.

Two or three drug combinations: 2012 guidelines.

Starting with metformin, what comes next? *To achieve glycemic control,* 2012 guidelines recommend that after initiation of therapy with metformin, there are five choices: added sulfonylureas, added thiazolidinedione (TZD; glitazones), added dipeptidyl peptidase (DPP)–4 inhibitor (oral), added glucagon-like peptide (GLP)–1 receptor agonist (injectable), or insulin (Table 11-2).[73] There are few long-term comparative trials available; thus the best agent to combine with metformin is not an easy choice. Sulfonylureas are less chosen than before. Rather, the ADA-EASD 2012 guidelines recommend a GLP-1 agonist as under test in large outcome trials, or even basal insulin; the higher the HbA1c, the greater the need for insulin. Note the benefits of a strict low-carbohydrate diet with liraglutide and metformin.[74] However, DPP-4 inhibitors also are under test in the large outcome trials and are orally available, meaning that, apart from cost, they are also used as second agents although inferior to GLP-1 receptor agonists in a metaanalysis.[75] The *importance of cardiovascular risk assessment* is reinforced by Gore et al.[76] The patient is monitored for HbA1c, hypoglycemia, weight, and major side effects, and costs are considered. Then, if needed, advancing to a three-drug combination after about 3 months, the guidelines give the choice between sulfonylureas or glitazones or an incretin stimulator (if not yet used), with insulin the choice if the HbA1c is high.

Table 11-2 -- Choices in the Further Management of Hyperglycemia in Type 2 Obese Diabetic Already on Metformin

	Pioglitazone	Exenatide/Liraglutide	DPP-4 Agonists	Insulin
Mechanism	PPAR-γ ↑Glucose metabolism ↑ Liver fat ↓	Incretin: insulin release ↑; glucagon ↓Gastric emptying ↓	Prevent the rapid breakdown of endogenous GLP-1	Glucose metabolism ↑
Daily dose	15-45 mg	Weekly or daily injections	Oral	One or more daily injections
Advantages	**Versus Insulin:**Oral; Hypoglycemia ↓ Weight gain same HDL-C ↑	**Versus Insulin:**Weight loss; Glucose better; Less hypoglycemia CV protection under study in large trials	**Oral**Controls glycemia CV protection under study in large trials	**Versus Glitazones:**Lower cost Versus Exenatide: More injections No GI side effects
Disadvantages	Cost ↑ versus insulinBone density ↓ Weight gain versus exenatide	ExpensiveInjections Side effects: Nausea; ?pancreatitis	**Oral Expensive**No weight loss	**Injections**Hypoglycemia Weight gain

Modified from Goldberg et al.[73]

CV, Cardiovascular; *DPP,* dipeptidyl peptidase; *GI,* gastrointestinal; *GLP,* glucagon-like peptide; *HDL-C,* high-density-lipoprotein cholesterol; *PPAR*-γ, peroxisome proliferator–activated receptor-γ.

Tailoring drugs to patients.

Not all patients are the same. More stringent HbA1c control is proposed for highly motivated, adherent patients who are capable of self-care, often newly diagnosed, with long life expectancy and without established vascular complications (Fig. 1 in Inzucchi et al., 2012[64]). Self-management of type 2 diabetes, including avoidance of hypoglycemia, is complex, but the effect of cognition on safe self-management is not well understood. Poor *cognitive function* increases the risk of severe hypoglycemia in patients with type 2 diabetes.[77] Prospective cohort analysis of data from the ACCORD trial included 2956 adults aged 55 years and older with type 2 diabetes and additional cardiovascular risk factors.[78] After a median 3.25-year follow-up, a 5-point-poorer baseline score on the cognitive tests was predictive of a first episode of hypoglycemia requiring medical assistance. Cognitive decline over 20 months increased the risk of subsequent hypoglycemia to a greater extent in those with lower baseline cognitive function (P for interaction: 0.037).

Sulfonylureas.

These are insulin secretagogues that stimulate insulin secretion act by inhibiting adenosine triphosphate (ATP)–sensitive potassium channels of β-cells. Because the sulphonylurea receptor SUR2a is also expressed on cardiomyocytes, it has long been held that these drugs might also interfere with cardiac function. Indeed, several smaller-scale clinical trials and experimental studies have suggested an impairment of ischemic preconditioning with sulphonylurea drugs.[79]

Besides these potential direct effects of sulphonylureas on cardiac and vascular functions, hypoglycemia, as commonly seen during sulphonylurea therapy, is associated with cardiac arrhythmias, thereby providing an additional potential mechanism linking these drugs to increased cardiovascular events.[80]

There are few prospective studies on the long-term major clinical effect of these agents on outcomes in type 2 diabetes. The UGDP study from the 1960s has initially suggested a high incidence of cardiovascular mortality in patients treated with the sulfonylurea agent tolbutamide.[81]

In contrast, the UKPD study revealed no significant effect of glibenclamide on either mortality or the incidence of cardiovascular events.[57]

There are few prospective studies on the long-term major clinical effect of these agents on outcomes in type 2 diabetes. Monotherapy with the most used agents, including glimepiride, glibenclamide, glipizide, and tolbutamide, was associated with increased mortality and cardiovascular risk compared with metformin in a large prospective registry trial.[82] Gliclazide and repaglinide were not statistically different from metformin in patients both without and with previous MI. A gliclazide modified release (MR)–based regimen together with BP lowering by perindopril-indapamide in 11,140 persons with type 2 diabetes reduced the risk of new or worsening nephropathy by 33%, new onset of macroalbuminuria by 54%, and of microalbuminuria by 26%, together with an 18% reduction in the risk of all-cause death.[83]

Thiazolidinediones.

TZDs, also called the *glitazones,* are drugs that activate the PPAR-γ (gamma) transcriptional system, thereby promoting the metabolism of glucose. The main drugs are rosiglitazone, the first, but now suspended in Europe, and the safer pioglitazone.[84] The FDA restricted access to rosiglitazone in September 2010. Glitazones favorably increase HDL by 19%, potentially offsetting an LDL increase of 8%, while reducing triglycerides and glycemia (Fig. 11-5).[85] More specifically, pioglitazone reduced LDL-particle concentration, whereas rosiglitazone increased it.[86] Both drugs increased LDL-particle size with pioglitazone having the greater effect. Pioglitazone increased HDL particle size, decreased by rosiglitazone. Total LDL cholesterol rose more with rosiglitazone, whereas pioglitazone increased HDL levels much more than rosiglitazone.[87] Pioglitazone decreased fasting triglyceride, which was increased by rosiglitazone.[87] These changes help to explain why rosiglitazone but not pioglitazone monotherapy was associated with increased MI[88],[89] and mortality.[84] Pioglitazone has also improved clinical outcomes in type 2 diabetes in the PROactive study.[90] In the ACT NOW trial, pioglitazone, reduced the risk of conversion of impaired glucose tolerance to T2DM by 72%, but, and thereby lies the snag, was associated with significant weight gain and edema.[42] Overall, based on a General Practice Research Database (206,940 patients), higher risks for death (overall and caused by cardiovascular disease) and heart failure were found for rosiglitazone compared with pioglitazone. These excess risks were twofold for ages 65-74, threefold for 75-84, and

sevenfold for older ages. The European regulatory decision to suspend rosiglitazone is supported by this study.[84]

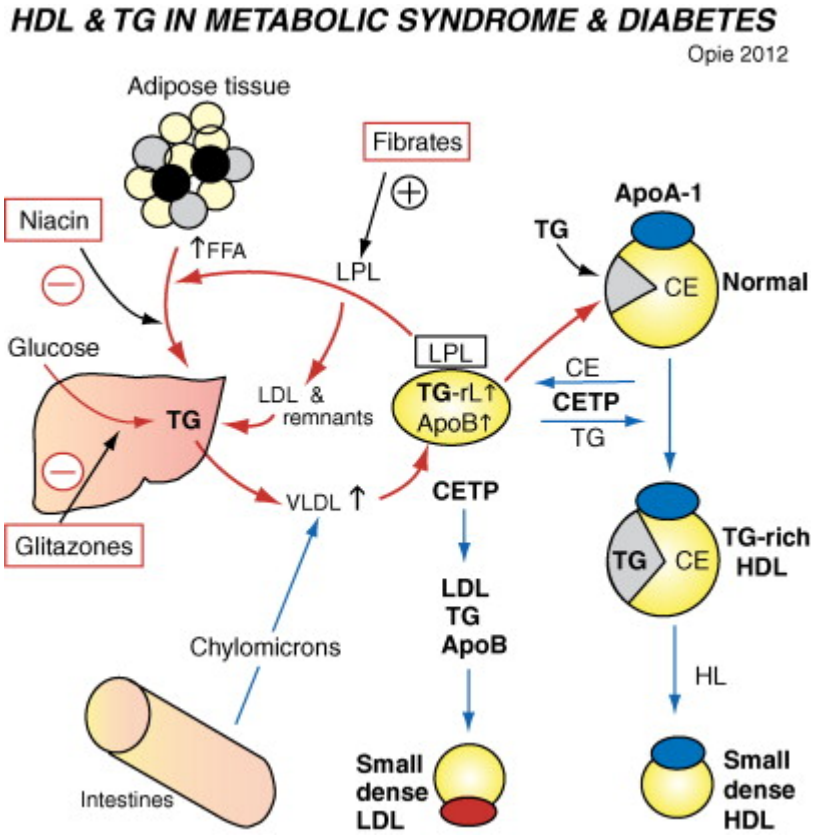

Figure 11-5 Proposed patterns of dyslipidemia in metabolic syndrome and type 2 diabetes. Consistent features (see *right side* of the figure) are the increased circulating levels of triglycerides (TGs) and decreased high-density lipoprotein (HDL) cholesterol. The basic problem lies in increased levels of the atherogenic particles: very-low density lipoproteins (VLDLs), triglyceride-rich lipoprotein (TG-rL) and apoliprotein (Apo) B. (Apos have detergent-like properties that solubilize the hydrophobic lipoproteins.) Levels of TG-rL and Apo B are increased by (1) excess hepatic synthesis of VLDL, (2) high postprandial TG concentrations after a fatty meal, and (3) low levels of lipoprotein lipase activity. Adipose tissue releases excess free fatty acids (FFAs), which with hyperglycemia leads to increased hepatic production of VLDL. Cholesterol-ester transfer protein (CETP) increases the transfer of TG to HDL particles to form TG-rich HDL, with a simultaneous transfer of cholesteryl esters (CE) from the HDL particles to TG-rL. TG-rich HDL is broken down by hepatic lipase (HL) to form small, dense HDL particles. A similar process leads to increased formation of small dense low-density lipoprotein (LDL) particles. For further details see Syvanne and Taskinen, 1997. *LPL,* lipoprotein lipase.
(Figure © L.H. Opie, 2012.)

The incretin system.

This is the focus of major current attention. Major trials on 73,500 patients are underway. Incretins are gastrointestinal peptide hormones released during absorption of nutrients to augment insulin secretion. GLP-1 is a hormone secreted into the circulation by the intestinal L-cells in response to ingested food (Fig. 11-6). Besides acting on blood glucose, “targeting the incretin axis might address the elusive goal of an antidiabetic agent that improves cardiovascular disease.”[91] The incretin response system is disturbed in T2DM. The incretin axis also includes the enzyme DPP-4, a serine protease that rapidly degrades GLP-1 and other proteins. Ultimately, this “arc of discovery” has led to new approved antidiabetic therapies: GLP-1 analogs (exenatide, liraglutide, and others) and DPP-4 inhibitors (saxagliptin, sitagliptin, and others).[91] More than 73,000 patients are in various trials (Table 11-3).

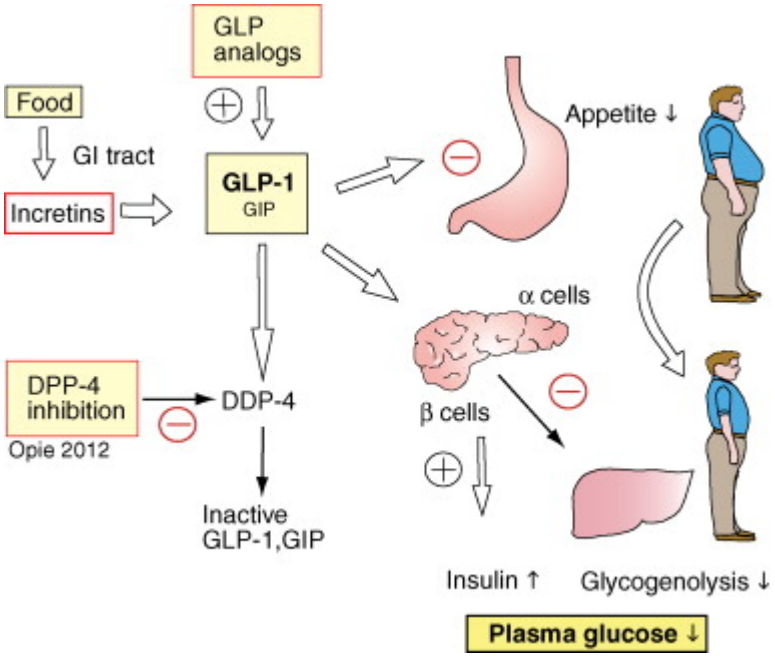

Figure 11-6 Site of action of incretins. *DPP,* Dipeptidyl peptidase; *GI,* gastrointestinal; *GIP,* glucose-dependent insulinotropic polypeptide; *GLP,* glucagon-like peptide.
(Figure © L.H. Opie, 2012.)

Table 11-3 -- GLP-1 Enhancers for Type 2 Diabetes: Major Trials in 73,500 Patients

Drug	Trial	Duration	Patients (n)
GLP-1 analogues			
Dulaglutide	REWIND	8 years (2019)	9,600
Exenatide LAR	EXSCEL	5.5 years (2017)	9,500
Liraglutide	LEADER	5 years (2016)	9,000
Lixisenatide	GetGoal-Mono	4 years (2013)	6,000
Taspoglutide	T emerge 8	2 years	2,000
Dipeptidyl peptidase-4 inhibitors			
Alogliptin	Examine	4 years (2014)	5,400
Linagliptin	CAROLINA	8 years (2018)	6,000
Saxagliptin	SAVOR-TIMI 53	5 years (2015)	12,000
Sitagliptin	Tecos	5 years (2014)	14,000

For all trials, see: http://clinicaltrials.gov/.For liraglutide clinical trials, see Nauck MA. The design of the liraglutide clinical trial programme. Diabetes Obes Metab 2012 Apr;14 Suppl 2:4-12.For lixisenatide in monotherapy, see Fonseca VA, et al. on behalf of the EFC6018 GetGoal-Mono Study Investigators. Efficacy and safety of the once-daily GLP-1 receptor agonist lixisenatide in monotherapy: a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes. Diabetes Care 2012 Mar 19.For alogliptin versus pioglitazone, see Defronzo RA, et al. Efficacy and tolerability of the DPP-4 inhibitor alogliptin combined with pioglitazone, in metformin-treated patients with Type 2 Diabetes. J Clin Endocrinol Metab 2012 Mar 14.For linagliptin, see Toth PP. Linagliptin: a new DPP-4 inhibitor for the treatment of type 2 diabetes mellitus. Postgrad Med 2011;123:46–53.For saxagliptin, see Scirica BM, et al. The design and rationale of the saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus-thrombolysis in myocardial infarction (SAVOR-TIMI) 53 study. Am Heart J 2011;162:818–25.

GLP, Glucagon-like peptide.

The generous help of Troels Munk Jensen, NovNordisk, Denmark, is acknowledged.

GLP-1–based therapies could potentially target both diabetes and cardiovascular disease.[92] They regulate glucose metabolism through multiple mechanisms and have beneficial cardiovascular effects, possibly independent of the glucose-lowering activity, which include changes in BP, endothelial function, body weight, cardiac metabolism, lipid metabolism, left ventricular function, atherosclerosis, and the response to ischemia-reperfusion injury.

Incretin mimetics.

Incretin mimetics are GLP-1 receptor agonists. GLP-1 regulates glucose levels by stimulating glucose-dependent insulin secretion and biosynthesis, and by suppressing glucagon secretion, delayed gastric emptying and promoting satiety. In view of the somewhat disappointing results of adding sulfonylureas (exception: gliclazide) to metformin and the risk for heart failure with the glitazones, attention is now shifting to combining metformin with incretin-based therapy.[93] This combination efficiently improves glycemia patients with type 2 diabetes, and within 16-30 weeks there is a more pronounced reduction in HbA1c with long-acting GLP-1 receptor agonists (liraglutide and exenatide long-acting release) than with DPP-4 inhibitors, both with a very low risk of adverse events, including hypoglycemia.

The Cochrane analysis reported that GLP-1 agonists in use or in the licensing process include exenatide and liraglutide as the most extensively studied, the others being albiglutide, dulaglutide, lixisenatide, and taspoglutide.[94] In comparison with placebo, all GLP-1 agonists reduced glycosylated HbA1c levels by approximately 1%. Both exenatide and liraglutide led to greater weight loss than most active comparators. Vagal-induced nausea, which can be regarded as an exaggerated form of appetite suppression, is a relatively common side effect of the GLP-1 agonists. These adverse events were strongest at the beginning and then subsided. β-cell function was improved with GLP-1 agonists, but the effect did not persist after treatment stopped. Exenatide 2 mg once weekly and liraglutide 1.8 mg reduced HbA1c by 0.20% and 0.24% respectively more than insulin glargine. Major outcome trials are still in the offing (see Table 11-3).

Assessment of incretin-based drugs.

Incretin-based drugs seem to offer several benefits in terms of improving cardiovascular risk factors. Thus in addition to reducing hyperglycaemia, the GLP-1 receptor agonists and DPP-4 inhibitors are associated with moderate reductions in BP and some reduction in triglyceride levels.[95]

Furthermore, body weight is typically lowered during GLP-1 receptor agonist treatment. On the other hand, a consistent trend toward a higher pulse rate (approximatley 4-6 beats per minute) has been seen with liraglutide[96] and exenatide-LAR.[97] Increased heart rate might require readjustment of antianginal drugs, but there are no clinical studies on this issue.

This increase in heart rate is less obvious with the DPP-4 inhibitors. Several smaller-scale studies have also suggested improvements in endothelial function in patients with type 2 diabetes and coronary disease,[98] and in those with class III/IV heart failure.[99]

Exenatide.

Exenatide *(Bydureon)* is a degradation-resistant GLP-1 peptide analog (incretin mimetic) that reduces HbA1c as well as producing moderate weight loss and is given by injection. The FDA has approved a once-weekly extended-release formulation as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. There is a boxed warning on the possible risk of medullary thyroid carcinoma (MTC) as found in animal studies, and the FDA required a 15-year registry on this and other risks such as acute pancreatitis. The boxed warning also states that the drug is contraindicated in patients with a personal or family history of MTC and in patients with multiple endocrine neoplasia syndrome type 2.

Exenatide 2 mg once weekly reduced HbA1c more than exenatide 10 mcg twice daily, sitagliptin, and pioglitazone.[94] In the DURATION-2 trial, 514 patients receiving metformin were randomized to receive 2 mg exenatide injected once weekly; 100 mg oral sitagliptin once daily; or 45 mg oral pioglitazone once daily.[100] After 26 weeks, addition of exenatide once weekly to metformin achieved the goal of optimum glucose control plus weight loss and with minimal hypoglycemic episodes more often than did addition of maximum daily doses of either sitagliptin or pioglitazone. Hypoglycemia is uncommon except when

combined with sulfonylureas (but not with metformin). Exanitide is also cardioprotective by decreasing reperfusion-induced cell death.[101] It decreased final infarct size by 30% only in patients within a short delay of 132 minutes or less from symptom onset to reperfusion. However, this finding must be confirmed in larger studies.

Liraglutide.

Liraglutide (Victoza) is another incretin mimetic given once a day that also reduces HbA1c with weight loss. Liraglutide is an effective GLP-1 agent to add to metformin, superior to sitagliptin for reduction of HbA1c, and well tolerated with minimum risk of hypoglycemia.[96] It is approved by the FDA in combination with metformin for adults with type 2 diabetes who require more than one medication to lower blood glucose. There are similar FDA warnings and postmarketing cancer registry requirements to those on exenatide regarding the possible risk of MTC and its implications. Pancreatitis also occurred more often, although still rarely in patients given liraglutide than with other antidiabetic medications, so that it should be stopped if there is severe abdominal pain. The most common side effects observed with liraglutide have been headache, nausea, and diarrhea.

A small but important proof-of-concept study tested the effect of dietary carbohydrate restriction in conjunction with liraglutide and metformin on metabolic control in patients with type 2 diabetes.[74] Insulin or oral antidiabetic drugs (excluding metformin) were stopped. After 6 months of liraglutide and metformin, body weight fell by 10% and HbA1c fell from 9% to 6.7%. Longer-term and larger outcome studies would cement this approach.

Dipeptidyl peptidase–4 inhibitors.

DPP-4 inhibitors are chemically –derived, selective, competitive inhibitors of DPP-4 and can be administered orally. Of note, not only GLP-1, but also other potentially important peptides, such as glucose-dependent insulinotropic polypeptide (GIP), B-type natriuretic peptide, neuropeptide Y, peptide YY, and so on, are subject to DPP-4 cleavage, thereby suggesting that the metabolic and cardiovascular effects of the DPP-4 inhibitors might not be exclusively mediated via GLP-1. As a second-line treatment, DPP-4 inhibitors were inferior to GLP-1 agonists and similar to pioglitazone in reducing HbA1c, and had no advantage over sulfonylureas in a metaanalysis.[75] As a group, they are well tolerated as found in a review of 45 clinical trials, and rates of weight gain, gastrointestinal adverse effects, and hypoglycemia were minimal.[102] They counteract the degradation of plasma GLP-1 and GIP after eating. Like GLP-I agonists, these agents have antidiabetic activity by stimulating the release of insulin from the pancreas and by inhibiting that of glucagon. However, they differ from the GLP-I agonists in that there are few gastrointestinal side effects such as nausea and no marked inhibition of gastric emptying. Also in contrast to GLP-1 agonists they are weight neutral rather than promoting weight loss.[75],[103],[104] Furthermore, insulin secretion decreases if the plasma concentration falls to less than 70 mg/dL, thus lessening the risk of hypoglycemia.

Trial data.

Typically, in randomized clinical trials, DPP-4 inhibitors achieved HbA1c reduction from 0.6% to 0.9% and, so far, have shown an optimal safety profile, not being associated with serious adverse effects. Importantly, the incidence of hypoglycemia in DPP-4 inhibitor–treated patients in clinical trials was similar to placebo and thus significantly lower than with other insulin-secretagogues, such as sulphonylureas and meglitinides. For these reasons, and for ease of oral administration, DPP-4 inhibitors are increasingly used in the treatment of type 2 diabetes.[105] Nasopharyngitis was more prevalent with the DPP-4 inhibitors than with placebo, but rates of pancreatitis were lower than with other oral antihyperglycemic agents.[102] Besides the control of glycemia, in experimental models of ischemia and reperfusion injury, GLP-1 is cardioprotective and reduces myocyte death.[106]

Currently, most DPP-4 inhibitors have been approved for the combination with insulin as well as for monotherapy in Europe.

Alogliptin given to type 2 diabetic patients inadequately controlled by metformin, in doses of 12.5 and 25 mg daily combined with pioglitazone, gave additive reduction in HbA1c and improved measures of β-cell function.[107] Thus far it is not FDA approved.

Linagliptin has a unique xanthine-based structure that experientially promotes wound healing and thus

should benefit diabetic ulceration.[108] It was FDA approved in May 2011. A new treatment option, also FDA approved, combines linagliptin and metformin in a single tablet taken twice daily in adults with type 2 diabetes who require more than one medication to lower blood glucose. Phase 3 clinical trials on more than 4000 patients have demonstrated the efficacy of linagliptin as monotherapy or in combination with other antidiabetic agents.[109]

Saxagliptin is approved by the FDA and by the European Union for use as monotherapy or in combination regimens for the treatment of T2DM. It is the drug chosen (5 mg daily, 2.5 mg in moderate or severe renal impairment) by the TIMI Harvard-based group for the SAVOR-TIMI 53 outcome study that aims to examine cardiovascular complications.[106] The trial will continue until approximately 1040 primary endpoints accrue, providing 85% power to identify a 17% relative reduction of the primary cardiovascular endpoints.

Sitagliptin is licensed in the United States for use with diet and exercise to control glycemia alone or with metformin, glitazones, or sulfonylureas. It also exerts direct, DPP-4–independent effects on intestinal L-cells, activating cyclic adenosine monophosphate (AMP) and extracellular signal-regulating kinase 1 and 2 (ERK1/2) signaling and stimulating total GLP-1 secretion.[110]

Vildagliptin is available in combination with metformin. It is registered for use in the European Union but not in the United States. Vildagliptin add-on (50 mg twice daily) had similar efficacy to glimepiride (up to 6 mg/day) in reducing HbA1c levels after 2 years' treatment, with markedly reduced hypoglycemia risk and no weight gain.[111]

Meglitinide analogs.

Meglitinide analogs such as *repaglinide* and *nateglinide* act on the pancreatic β-cells where, similarly to the sulfonylureas, they regulate ATP-dependent potassium channels to induce insulin secretion.[112] These agents affect chiefly early insulin release, reducing postprandial hyperglycemia, whereas the sulfonylureas improve late insulin release to act more on the fasting glucose level. Repaglinide has an FDA license rather similar to that of sitagliptin. The ability of these short-acting insulin secretagogues to reduce the risk of diabetes or cardiovascular events in people with impaired glucose tolerance remains unknown. There are few outcome studies. Nateglinide up to 60 mg thrice daily for 5 years did not reduce the incidence of diabetes or the co-primary composite cardiovascular outcomes in those with impaired glucose tolerance.[113]

Bromocriptine.

Bromocriptine acts on the hypothalamus of the brain as a dopamine D2 receptor agonist. It is the first of its class of agents approved by the FDA that acts at the level of the brain. Bromocriptine-QR provides a short-duration dopamine pulse to brain centers that regulate peripheral fuel metabolism. It is administered in the morning, within 2 hours of waking, to increase central dopaminergic tone at that time of day when that tone normally peaks in healthy but not in diabetic persons, thereby improving glycemic control and lessening postprandial hyperglycemia that is thought to be an independent risk factor for macrovascular and microvascular complications.[114]

Sodium-glucose cotransporter-2 inhibition

(Fig. 11-7). In patients with type 2 diabetes inadequately controlled with metformin monotherapy, dapagliflozin was compared with glipizide.[115] Despite similar 52-week glycemic efficacy, dapagliflozin reduced weight and produced less hypoglycemia. In patients with type 2 diabetes inadequately controlled on pioglitazone, the addition of dapagliflozin further reduced HbA1c levels and mitigated the pioglitazone-related weight gain without increasing the risk of hypoglycemia.[116] A side effect in both studies was that genital infection increased.

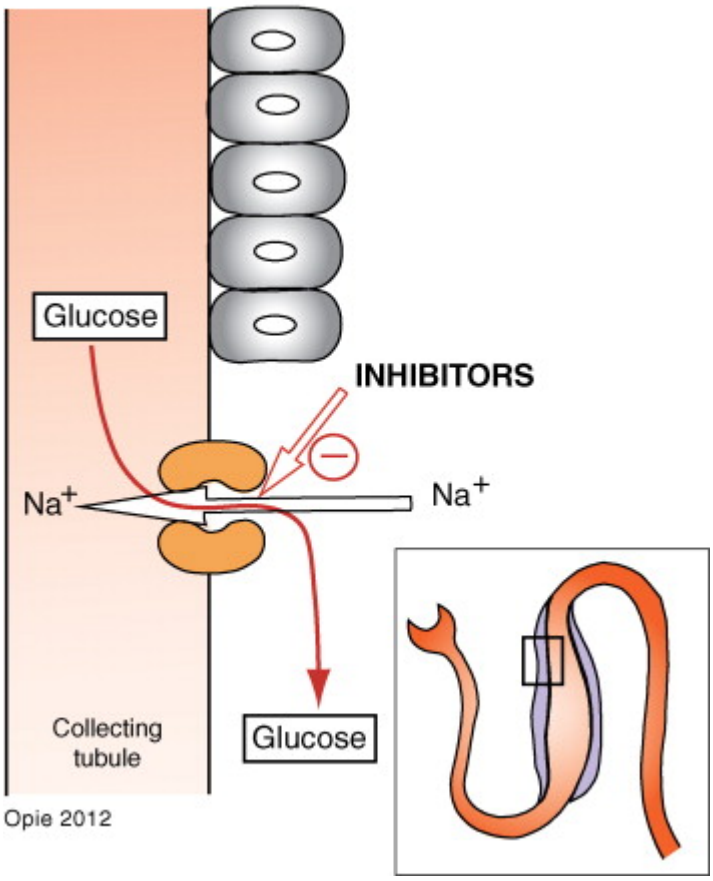

Figure 11-7 Site of action of inhibitors of glucose reuptake. These agents, not yet widely available for clinical use, inhibit the reuptake of glucose by sodium-glucose exchange in the collecting tubule.
(Figure © L.H. Opie, 2012.)

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DRUGS FOR THE HEART
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Ideal control of glycemia, blood pressure, and lipids: Multifactorial intervention

The accord studies.

The ACCORD trials examined whether ultraintense cardiovascular risk-factor reduction could improve clinical outcomes. To improve on the impressive baseline control of risk factors in the patients assigned to standard therapy in ACCORD was a formidable task, illustrating the synergistic effects of the multifactorial risk-reduction regimen. The respective intense arms achieved a more than 1% absolute difference in HbA1c, a 14.2-mm Hg lower systolic pressure, and plasma triglycerides of approximately 145 mg/dL. For each of the three separate questions, further reduction of BP or glycemia or triglycerides, despite the more intense therapies, the primary clinical composite was not significantly reduced, as assessed in a *Circulation* editorial.[117]

Hypoglycemia.

Avoiding hypoglycemia and its possible cerebral effects is a major aim in vigorous glycemic control. Less often appreciated is that preexisting cognitive impairment can predispose to hypoglycemia, because poor cognitive function increases the risk of severe hypoglycemia in patients with type 2 diabetes. Clinicians should consider the cognitive function of their patients in assessing whether safe diabetes self-management is realistically possible.[118],[119]

As control of BP and of blood lipids independently reduce major events and mortality in those with type 2 diabetes, a logical aim would be multifactorial intense intervention by drugs to control glycemia, BP, and lipids, with lifestyle modification, as in the Steno-2 study that stretched over 13.3 years.[120] In addition, ACE inhibitors or ARBs were given to prevent progression of microalbuminuria, plus low-dose aspirin for primary prevention. Intense versus conventional therapy reduced the absolute risks of death, the primary endpoint, by 20%, cardiovascular events by 29%, and renal dialysis by 6.3%. Probably the major benefits were achieved by statins (LDL cholesterol 83 mg/dL) and antihypertensive agents (BP 131/73 mm Hg), followed by hypoglycemic agents (HbA1c 7.9%) and aspirin. Although observational data argue that for each 1% reduction in HbA1c, there is a 14% reduction in MI, a 37% reduction in microvascular events, and 21% fall in deaths related to diabetes,[121] the ACCORD and Steno-2 trials both provide evidence against overvigorous control of glycemia. In type 2 diabetes, a HbA1c of 7%-7.9% seems reasonable,[122] although in one large study slow reduction to 6.9% was associated with outcome benefit especially when combined with BP control (see next paragraph). The benefits of tight LDL control have been settled by Steno-2 and CARDS[123] and metaanalyses.[124] ACCORD will tell us whether the BP should be driven down below the levels reached in ADVANCE and Steno-2. It remains reasonable to hypothesize that multifactorial control of glycemia, BP, and lipids is the ideal.

Microvascular control.

To lessen microvascular events, the aim is tight control of hyperglycemia that promotes the debilitating microvascular complications in the eyes, nerves, and kidneys. In the ACCORD study, intensive therapy did not reduce the risk of advanced measures of microvascular outcomes, but delayed the onset of albuminuria and some measures of eye complications and neuropathy.[125] Also in ACCORD, at 4 years, the rates of progression of diabetic retinopathy was slowed from 10.4% with standard therapy to 7.3% with intensive glycemia treatment (OR, 0.67; P = 0.003) with a similar decrease with fenofibrate for intensive dyslipidemia therapy.[126]

Macro- and microvascular control.

Both macro- and microevents were the targets in BP lowering and intensive glucose control in patients with long-standing type 2 diabetes.[127] Therapy was perindopril-indapamide and a gliclazide MR–based regimen (with target HbA1c < or = 6.5%) in 11,140 participants with type 2 diabetes. Combination treatment by

routine BP lowering and intensive glucose control on macrovascular and microvascular outcomes in patients with type 2 diabetes reduced the risk of new or worsening nephropathy by 33% (CI 12-50%, P = 0.005), new onset of macroalbuminuria by 54% (35%-68%, P < 0.0001), and new onset of microalbuminuria by 26% (17%-34%). Combination treatment was associated with an 18% reduction in the risk of all-cause death (P = 0.04). Of note, this degree of control was achieved over 4.3 years of follow up, whereas the disastrous sudden drop of HbA1c in ACCORD was over weeks and months.

Diabetes and coronary disease requiring intervention

Regarding prevention, as already discussed, the emphasis must be on tight control of BP and blood lipids. Although generally recommended, one study suggests that low-dose aspirin may be less effective than expected.[128] Regarding percutaneous coronary interventions (PCI), observational and cohort studies suggest that diabetes is a risk factor for stent thrombosis, especially among patients with multivessel disease and complex lesions.[129] In patients with diabetes and multivessel coronary disease, PCI with drug-eluting stents was less effective than coronary artery bypass graft (CABG),[130] and among randomized patients, balloon angioplasty was inferior to CABG when an arterial conduit was used.[131]

Acute MI poses special problems for the diabetic patient. Tight glycemic control has been recommended either by insulin low-dose glucose[132] or by oral agents.[133] The IMMEDIATE trial, which started glucose-insulin-potassium (GIK) in the ambulance with positive outcome data, suggests that the GIK regimen gives specific protection to patients without diabetes by decreasing infarct size.[134]

Diabetes and heart failure

Revival of the fatty heart concept.

Atherogenic lifestyle may eventually evoke a fatty heart as follows.[135] Excessive adipose tissue, associated with less exercise and excess calories, leads to increased blood levels of FFAs, which waste myocardial oxygen[136] and may also be deposited in the heart of overweight subjects as triglyceride.[137] Cardiomyocyte fat, now measured by magnetic resonance spectroscopy, correlates well with BMI and is increased even in uncomplicated obesity. It is associated with impaired diastolic filling in apparently asymptomatic obese subjects and is more severe in the presence of glucose intolerance or diabetes.[135] Supporting the lipid-heart link, a marked increase in plasma FFA and in myocardial triglyceride after only 3 days of a very-low-calorie diet was associated with decreased diastolic function.[138]

Myocardial steatosis.

Metabolically, in humans with heart failure there is increased myocardial triglyceride.[139] Thus overall data support the existence of a diabetic cardiomyopathy with diastolic heart failure in type 2 diabetes. The origin is multifactorial, with contributions from hypertension and coronary disease. Whenever heart failure is established, then the adrenergic–fatty acid load is likely to worsen the situation, therefore arguing for therapy by β-blockade added to BP control.[140] In contrast, in type 1 diabetes the influence of hypertension and coronary disease is very much less, so that there is a “pure” metabolic cardiomyopathy resulting from the increased blood fatty acids in poorly controlled diabetes,[141] leading to increased myocardial uptake of toxic FFAs, mitochondrial oxygen wastage, and increasing risk of systolic heart failure. Here tight diabetes control should be protective.[139]

Prevention of heart failure?

Can tight glycemic control prevent later heart failure in type 2 diabetes? No, says a 37,229 patient analysis.[142] Furthermore, intensive glycemic control with TZDs increased the risk of heart failure. More surprisingly, and inexplicably, in a small cohort with very advanced heart failure and diabetes, a higher HbA1c seemed to be associated with better outcomes protective.[143]

Glitazones and heart failure.

A series of metaanalyses,[66],[89],[144-147] have confirmed a higher incidence of congestive heart failure (CHF), a previously known major side effect of glitazones.[90] In ADOPT rosiglitazone was associated with more cardiovascular events, specifically heart failure, and bone fractures than glyburide, the sulfonylurea,[148] and with more heart failure than pioglitazone.[84] A proposed mechanism of the CHF is that PPAR-γ acts on the distal nephron to promote sodium and fluid retention,[149] which in the presence of lipid-induced incipient diastolic heart failure,[137] precipitates CHF.[144] This issue has caused widespread concern, which led the FDA to insert a black box warning about heart failure for the glitazones.

Glitazones and myocardial infarction.

The Nissen and Singh metaanalyses,[89],[147] focusing on rosiglitazone, also found significantly increased MI. By contrast, pioglitazone (Actos) although found to increase CHF, was associated with decreased mortality, MI, and stroke.[85],[145] A large Canadian case-control retrospective cohort study on an entire population of older adults with diabetes, confirmed that rosiglitazone but not pioglitazone monotherapy increased heart failure and MI.[88] Similarly, in a large UK general practice research database on 91,521 people with a mean follow up of 7.1 years, pioglitazone was associated with reduced all-cause mortality compared with metformin and with rosiglitazone.[67] The increased MI with rosiglitazone in these studies may be related to the changes in the lipid profile previously reviewed.[73],[86] Of 11 quality guidelines, 10 agreed that TZDs as a group are associated with higher rates of edema and CHF compared with other oral

medications to treat type 2 diabetes.[69] In a trial on 224 type 2 diabetic patients with class I or II heart failure, rosiglitazone improved glycemic control without adversely affecting left ventricular function despite more fluid-related events (dyspnea, edema).[150]

Summary

1. ***MetSyn.*** The MetSyn is rapidly increasing in incidence worldwide. It conveys increased risk for type 2 diabetes and for cardiovascular disease. To prevent the transition to these two entities, the ideal therapy is intensive lifestyle modification. Failing that, metformin and, when indicated, other medications to control hypertension and dyslipidemia should be considered. In view of the known increased risk of new diabetes with β-blockers and diuretics in the therapy of hypertension, and because new diabetes is the major risk of the MetSyn, it seems prudent to give preference to antihypertensive therapy initially based on ACE inhibitors or ARBs, either with low-dose diuretics as needed (unless there are compelling indications for β-blocker–diuretic therapy).
2. ***Cardiovascular disease.*** In established type 2 diabetes there is increased risk of vascular disease with coronary and cerebral complications. The key to prevention lies in tight BP and lipid control. The role of very tight glycemic control is not as well established and argued against by the cessation of this arm of ACCORD. Furthermore, the cardiovascular advantages of weight loss and the antidiabetic drugs that promote weight loss must be emphasized.
3. ***Multivessel coronary artery disease.*** Multivessel coronary artery disease in type 2 diabetics often needs assessment for intervention. Among patients with multivessel disease and complex lesions, PCI is less successful than in nondiabetics and there is a stronger case for CABG using an arterial conduit.
4. ***Glycemic control.*** To achieve glycemic control, 2012 guidelines suggest starting off with metformin, followed by one of five add-on choices: sulfonylureas, TZDs (glitazones), DPP-4 inhibitors, GLP-1 receptor agonists, or insulin. Sulfonylureas are less favored than previously. However, there are few long-term comparative trials; thus the best agent to combine with metformin is not an easy choice. Of the add-ons, the 2012 guidelines recommend a GLP-1 agonist or insulin; the higher the HbA1c, the greater the need for insulin. Advancing to the third agent, any one of the five not yet used could follow, but insulin is often preferred.
5. ***TZDs (glitazones).*** TZDs improve insulin sensitivity at the cost of side effects: weight gain, edema, bone fractures, and heart failure. Nonetheless, they are among the five guideline choices to follow metformin. Whereas pioglitazone is associated with improved lipid profiles, rosiglitazone has the reverse effects so that its use is now being restricted. The proposed mechanism for heart failure is fluid retention added to diabetic diastolic heart failure caused by lipid overload. The current proposal that excess adiposity tissue can lead to clinical heart failure requires further study, including validation of effective treatment strategies.
6. ***Agents acting on the incretin system.*** This is an extremely active area of investigation, with approximately 73,500 patients currently in nine mega trials. *GLP-1* is a natural incretin postprandial hormone that is secreted by the gut in response to a meal. It stimulates insulin release from the pancreas. These therapeutic effects can be magnified by inhibiting its breakdown by DPP-4 inhibitors or by agonists acting on the pancreatic receptor (exenatide, liraglutide, and others). In patients with difficult to control type 2 diabetes who are already on metformin or other oral hypoglycemics, these agents when added have advantages over insulin. In view of better weight and lipid control than with sulfonylureas, and less risk of heart failure than with the glitazones, a current trend is to use exenatide or liraglutide after lifestyle and metformin. A once-weekly formulation of exenatide has FDA approval.
7. ***How tight to control?*** Observational studies have suggested reductions of diabetic complications, both microvascular and macrovascular, by tight control of glycemia and of BP, with outcome studies arguing for tight LDL cholesterol lowering. ACCORD argues against very tight HbA1c control, at least in established patients with diabetes at high cardiovascular risk. Decreased BP less than 140/90 mm Hg is argued for by two outcome trials (ADVANCE, Steno-2) but ultratight BP control gave no outcome benefit in ACCORD. Guidelines strongly suggest tight control for younger patients at the onset of their disease, to prevent microvascular complications. Overall, multifactorial intervention

remains the ideal.

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