Learning Objectives

- Define what we expect from therapy of Metabolic Syndrome;
- Review the different drugs used in the Metabolic Syndrome;
- Understand the timing of drug intervention in the Metabolic Syndrome;
- Compare cost effectiveness of lifestyle intervention, drug therapy and bariatric surgery.

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Key messages

- Therapy of metabolic syndrome should address each of its components to prevent diabetes and cardiovascular disease and to reduce overall mortality;
- There is a need to consider all the metabolic effects and the safety profile of each drug;
- Cost effectiveness of drug therapy may vary from country to country and during the lifespan as Metabolic Syndrome progresses;
- Bariatric surgery is a therapeutic option both for obesity and for metabolic diseases.
1. What is the Ideal Drug for the Metabolic Syndrome (MS)?

1.1 Addressing the Existence of Metabolic Syndrome as a Separate Entity

MS has different definitions and we will use the WHO criteria which underline both the different features of the MS and the patho-physiology of the MS (Table 1). The main underlying factors for the development of metabolic syndrome (MS) are obesity with intra-abdominal fat distribution and insulin resistance leading to endothelial inflammation. There is debate about the predictive value of MS compared to that of each of its components (1) but agreement on the need to address each component of MS since there is no drug which treats all the metabolic defects (2). Although the environmental factors leading to MS are well known: increased caloric intake, increased body weight, increased saturated fat intake, decreased physical activity, and are the basis for lifestyle intervention to treat MS, the genetic factors are uncertain and may preclude the development of specific drugs. The other limiting factor in the development of drugs for MS is the fact that many patients with the MS are already treated by drugs which are confounders in clinical trials with new agents for the MS (3).

**Table 1**

WHO criteria for the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Insulin resistance identified as one of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Type 2 diabetes mellitus</td>
</tr>
<tr>
<td>• Impaired fasting glucose</td>
</tr>
<tr>
<td>• Impaired glucose tolerance</td>
</tr>
<tr>
<td>• If FG &lt; 110 mg/dl (6.1 mmol/l), hyperinsulinaemic, euglycaemic clamp-uptake in lowest 25%</td>
</tr>
<tr>
<td>Plus 2 of the following:</td>
</tr>
<tr>
<td>• BMI &gt; 30 kg/m² or waist-to-hip ratio &gt; 0.9 (male) or 0.85 (female)</td>
</tr>
<tr>
<td>• Triglycerides ≥ 150 mg/dl (1.7 mmol/l)</td>
</tr>
<tr>
<td>• HDL-cholesterol &lt; 35 mg/dl (0.9 mmol/l) (male) or &lt; 39 mg/dl (1 mmol/l) (female)</td>
</tr>
<tr>
<td>• Blood pressure &gt; 140/90 mmHg or medication</td>
</tr>
<tr>
<td>• Urinary albumin excretion ≥ 20 µg/min or albumin/creatinine ratio ≥ 30 mg/g (3.5 mg/mmol)</td>
</tr>
</tbody>
</table>

Knowing the exact pathophysiology of the MS could be useful to target treatment in MS as an entity. Many mechanisms from insulin resistance, low grade inflammation, endothelial dysfunction, gut microbiome, perivascular tissue as well as the angiotensin system or corticosteroids receptors have been implicated in the pathophysiology linking the different features of the MS (4, 5, 6). Up to know there is no uniform view of the MS’s pathophysiology making difficult to treat MS as an entity and not each of its components.

1.2 Addressing the Pathophysiology of Metabolic Syndrome as a Therapeutic Target

Obesity is a common pathway to many features of MS. Environmental factors leading to obesity and MS are well known: increased caloric intake, increased body weight, increased saturated fat intake, decreased physical activity. Lifestyle intervention, which
are the basis to treatment in MS can reverse part of the negative effects of the westernized way of life. Treatment of obesity, medically or surgically, can improve features of MS but has a relatively low rate of success in the long term. Obesity and particularly abdominal obesity are targets for drug development but in recent years. Polygenicity of obesity makes difficult to target one physiologic pathway. Some of the anti-obesity drugs have been removed from the market due to serious adverse events. Recently, liraglutide was introduced in the market and showed a positive effect on weight reduction as well on components of the MS (7). Prevention through education to healthy way of life could be more suitable, although involving many partners, aside the medical one.

Low grade inflammation, endothelial dysfunction and insulin resistance as a consequence of environmental factors or obesity could, as well, be a target in treat or prevent of MS. Metformin which reduces insulin resistance and is the core treatment of impaired glucose metabolism (diabetes and to a lesser extent pre-diabetes) (8, 9) still has some non-elucidated cellular mechanisms. Its action on reducing superoxide production from the mitochondria could be a common pathway to explain its beneficial aspects on reducing both complications of diabetes and mortality in diabetic patients. In contrast with the long term results of the UKPDS study, a recent large meta-analysis collecting data from 13 randomized controlled trials (which included a total of more than 13,000 patients) the authors found that compared to other drugs, metformin had no effect on the risk of death from all causes or on the risk of death from cardiovascular disease and had no significant effect on the risk of developing cardiovascular conditions such as heart attacks, strokes, and heart failure (10). This study stresses the fact that even very well accepted therapy doesn't always meet the criteria for the "ideal drug" and that we need a critical eye on the effectiveness of a drug used in preventive medicine.

Insulin resistance is a consequence of unhealthy way of life but has some genetic components that may preclude the development of specific drugs. The other limiting factor in the development of drugs for MS is the fact that many patients with the MS are already treated by drugs which are confounders in clinical trials with new agents for the MS (3).

1.3 Addressing the Known Clinical Consequences of Metabolic Syndrome

People with MS are twice as likely to die from and three times likely to have an heart attack or stroke compared with people without the syndrome as well as they are at an increased risk to develop type 2 diabetes mellitus. The main morbidity due to diabetes mellitus is cardiovascular diseases. The interrelationship of all the components of MS, makes essential an holistic view of intervention/drugs and in 2008, the Federal Drug Administration asked to check the cardiovascular effect of all anti diabetic drugs coming to the market. Recently empagliflozin, a sodium-glucose receptor-2 inhibitor, beside its hypoglycaemic effect, showed a cardiovascular benefit in a population of people with type 2 diabetes and high cardio-vascular risk compared to placebo (11).

Cognitive function as well as mental health, have been related to the MS. Low grade inflammation could be a common pathway leading to disruptions of neuroregulatory systems, including the serotonergic, dopaminergic, and neuropeptide Y systems, as well as dysregulation of the hypothalamic-pituitary-adrenal axis. Metabolic syndrome in
pregnant women also exposes the developing fetal brain to inflammatory factors that predispose the offspring to metabolic syndrome and mental health disorders. Due to the shared nature of these conditions, treatment should address aspects of both mental health and metabolic disorders. As for diabetes drugs should be choose according to their cardiovascular safety, anti schizophrenic drugs should be choose according to their metabolic consequences and not only for their effect on mental health (12).

1.4 Addressing the Peitrophic Actions of Each Drug

The ideal drug to treat MS should improve each of its components, should reduce the risk of cardiovascular disease and diabetes more than the individual drugs known to treat each of its components, and should have a good safety profile. Since we are dealing with preventive medicine the safety profile should be very high and "Do no harm" criteria must be taken into account. Considering the components and pathogenetic mechanisms of the MS, we understand that treatment of the MS would involve: a) Treatment of abdominal obesity; b) Treatment for the insulin resistance; c) Treatment for each one of the risk factors involved in the syndrome. Candidate drugs for treatment of the MS as a whole are weight-loss drugs, peroxisome proliferator-activated receptor (PPAR)-alpha agonists (fibrates), PPAR-gamma agonists (thiazolidinediones), dual PPAR agonists, incretin based drugs. When using a drug for a specific component of the MS (ie obesity, hypertension, hypercoaguability, hyperlipidaemia, diabetes) it should benefit this specific component without leading to deterioration of the other components of MS. Lately most candidate drugs for obesity have been withdrawn from the market due to major adverse events. In the thiazolidinedione family the only drug now on the market is pioglitazone but even then with some alerts (the need to monitor excessive weight gain, consider risk of development or aggravation of congestive heart failure, risk of hepatic failure, bladder cancer, fractures). Hard endpoint trials do not support the use of peroxisome proliferator-activated receptor (PPAR)-alpha agonists (fibrates) beyond the use of statins in preventing cardiovascular disease. The new monoclonal antibody that inhibits proprotein convertase subtilisin kexin type 9 (PCSK9), Evolocumab, in an extension study showed a decrease in LDL-Cholesterol as well a reduction in cardiovascular events (13). No dual PPAR agonists are yet on the market and former compounds didn’t get through drug development because of adverse events. The relatively new incretin based drugs have a good safety profile regarding weight, lipid profile, hypertension and cardiovascular risk besides their hypo glycaemic actions. In this drug category not all drugs are equal regarding their metabolic effects and will be reviewed later in this chapter.

1.5 Addressing Adherence to Treatment

The need to treat many metabolic disorders implies the use of polypharmacy. Polypharmacy increases the risk of drug interactions, and long-term adherence to a complicated therapeutic plan is difficult. Adherence to treatment for hypertension improves when using single daily doses when compared to daily multiple doses (14). Fixed dose simple tablet antidiabetic and antihypertensive combinations exist and improve adherence to treatment. In the diabetes and hypertension field the different mode of actions of drugs can have a synergistic glucose or blood pressure lowering
effect. These synergistic actions form the basis for development of polypills (15, 16). (Table 2).

Table 2
Fixed-dose single tablet/injection combinations for treatment of components of MS

<table>
<thead>
<tr>
<th>Tablet/injection pen</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucovance(Metformin+Glibenclamide)</td>
<td>Metformin+ Sulfonylurea</td>
</tr>
<tr>
<td>Metaglip(Metformin+Glipizide)</td>
<td>Metformin+Thiazolidione</td>
</tr>
<tr>
<td>Copetact Actoplusmet (Metformin+Pioglitazone)</td>
<td>Metformin+ DPP4 inhibitor</td>
</tr>
<tr>
<td>Janumet(Metformin+Sitagliptin)</td>
<td></td>
</tr>
<tr>
<td>Eucreas(Metformin+Vildagliptin)</td>
<td></td>
</tr>
<tr>
<td>Trajenta Duo(Metformin+Linagliptin)</td>
<td></td>
</tr>
<tr>
<td>Prandimet (Metformin+Repaglinide)</td>
<td>Metformin +Glinide</td>
</tr>
<tr>
<td>Vascace Plus ( Cilazapril+Hydrochlorothiazide)</td>
<td>Converting enzyme inhibitor+Thiazide</td>
</tr>
<tr>
<td>Exforge( Amlodipine+Valsartan)</td>
<td>Calcium channels blockers+ Angiotensin receptor blockers</td>
</tr>
<tr>
<td>Xultophy(Liraglutide+Degludec)-Lixilan (Lixisenatide+Glargine)</td>
<td>Long acting insulin+ GLP1 analogues</td>
</tr>
<tr>
<td>Xigduo XR (Dapagliflozin+Metformin)</td>
<td>SGLT-2 inhibitor+Metformin</td>
</tr>
<tr>
<td>Glyxambi (Empagliflozin+Linagliptin)</td>
<td>SGLT-2 inhibitor+ DPP4 inhibitor</td>
</tr>
</tbody>
</table>

† Brand names may vary in different countries

The "metabolic wonder pill" acting on many pathological mechanisms and yet with a good safety profile is a subject of research and debate and will hopefully emerge as we better understand the pathophysiology of MS. The cost effectiveness of such a pill has not been proven (16).

Many challenges still exist in developing the ideal drug for MS and we will review the existing possibilities of drug therapy.

2. Drugs Used in Treatment of the Metabolic Syndrome

We will review drug therapy of each component of the MS and describe effects on the other components and on the long-term risks that the MS conveys.

2.1 Drugs and Obesity

Orlistat has been till recently the only anti-obesity drug on the market for long-term use. Treatment with orlistat has shown to be effective as an adjuvant to dietary treatment and lifestyle changes in reducing weight and cardiovascular factors related to being overweight. The "Xenical in the prevention of diabetes in obese subjects" study (XENDOS) studied obese patients with normal or impaired glucose tolerance (NGT, IGT) at baseline and was able to demonstrate a decrease in the incidence of type 2 diabetes
mellitus by 37% vs placebo (Fig.1) in patients with IGT. Orlistat, beyond weight reduction, has beneficial effects on other components of MS, with reduction of total cholesterol, LDL cholesterol, blood pressure and an improvement in coronary heart disease risk in clinical studies (18). The improvement of insulin sensitivity (IS) with Orlistat was not superior to the IS improvement with lifestyle induced weight loss. In the ORLlstat and CARdiovascular risk profile in patients with metabolic syndrome and type 2 DIAbetes (ORLCARDIA) study (19), the combination of orlistat with a hypocaloric diet for 6 months reduced the proportion of patients meeting the diagnostic criteria of the MS by 35% while hypocaloric diet alone only reduced it by 9% in patients with both diabetes and the MS (Fig. 2). Although Orlistat could be a good drug for MS, its prolonged use is limited by gastrointestinal effects leading to a high discontinuation rate.

![Image of bar chart](image)

**Fig. 1** Impact of Orlistat compared to placebo, on metabolic parameters and metabolic syndrome

The Food and Drug Administration (FDA) approved three anti-obesity drugs: Qsymia, a combination of phentermine and topiramate - Belvik, Lorcan, a serotonin modulator - Liraglutide at a 3mg dose, a Glucagonlike peptide 1 analogue. The two former drugs are not available in Europe (20).

Liraglutide, a glucagonlike peptide-1 analogue, at a once-daily dose of 3.0 mg, injected subcutaneously has been studied in a study involving 3731 patients who did not have type 2 diabetes and who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of at least 30 or a BMI of at least 27 if they had treated or untreated dyslipidemia or hypertension. At baseline, the mean (±SD) age of the patients was 45.1±12.0 years, the mean weight was 106.2±21.4 kg, and the mean BMI was 38.3±6.4; a total of 78.5% of the patients were women and 61.2% had prediabetes. In this study, 3.0 mg of liraglutide, as an adjunct to diet and exercise, was associated with reduced body weight and improved metabolic control compared to the placebo group. The liraglutide group lost a mean of 8.4±7.3 kg of body weight, and those in the placebo group had lost a mean of 2.8±6.5 kg (7).

2. Drugs and Glucose Metabolism

The path from normal glucose tolerance to impaired glucose metabolism is a continuum. Prediabetes, defined as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) which fails to reach the level required for a diagnosis of diabetes, is a strong predictor for subsequent diabetes. Moreover the risk of cardiovascular morbidity and mortality starts before the diagnosis of diabetes. The prediabetes state offers an opportunity for early intervention to prevent diabetes.

In the last decades many new hypoglycemic drugs entered the market. Since 2008 the new requirements of the FDA to evaluate cardiovascular safety of these drugs gave us some insight in the pleiomorphic actions of different drugs.

Besides lifestyle intervention, metformin, alpha-glucosidase inhibitors and thiazolidinediones have been used to prevent progression of prediabetes to diabetes (21,
Two large multicentre studies lasting 3 years, the Finnish Diabetes Prevention Study and the Diabetes Prevention Program (DPP) (23, 24), reported that a decrease of 5-7% of body weight brought a 58% decrease in the conversion rate to type 2 diabetes of people with previous IGT, while the decrease was 31% on treatment with metformin (Fig. 4). In the DPP study, 53% of the participants had the MS at baseline, but the incidence during the study in the remainder was reduced by 41% in the lifestyle group and by 17% in the metformin group (Fig. 3) (25).

![Graph showing weight loss and diabetes incidence reduction in the lifestyle and metformin arms compared to the control group. Lower panel: reduction in the risk of developing MS in the two intervention arms (metformin and lifestyle).](image)

**Fig. 3** US Diabetes Prevention Study. Upper panel: weight and diabetes incidence reduction in the lifestyle and metformin arms compared to the control group. Lower panel: reduction in the risk of developing MS in the two intervention arms (metformin and lifestyle) (24).
There is currently no universally recognized treatment for type 2 diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) compared the efficacy of different treatment regimens (diet, sulfonylurea, metformin, and insulin) on glycaemic control and the complications of diabetes in about 4000 newly diagnosed patients with type 2 diabetes. Over 10 years, the average HbA1C value was 7.0% in the intensive therapy group compared with 7.9% in the conventional therapy group. The risk for any diabetes-related endpoint was 12% lower in the intensive therapy group and 10% lower for any diabetes-related death (26). Most of the risk reduction in the intensive therapy group was due to a 25% risk reduction in microvascular disease; there was a borderline statistically significant reduction in macrovascular disease, and the benefits of intensive therapy appeared to be independent of the type of treatment administered. The post-trial monitoring of the UKPDS patients showed benefit from early intensive glucose lowering intervention in reducing cardiovascular risk and 8.5% respectively), baseline differences were lost by one mortality in the long run, and brought out once again the concept of the ‘glucose memory” as a predictor of future events (with no evidence for "hypertensive memory"). Although the mean HbA1C was better in the intensive versus conventional therapy group at the beginning of the post-trial monitoring period (7.9% and year. After five years of post-trial observation, there were no significant differences in HbA1C (approximately 7.8%) body weight, lipid levels, or blood pressure in patients previously assigned to intensive or conventional groups (27). This study with others, help to change the algorithm for treatment of type 2 diabetes (28). The main recommendations are the need for early, often combined, therapy in the course of glucose perturbations, and the need for early and persistent intensification of treatment with a “treat to target” strategy. These goals should be attained with safety, taking into account drug actions on weight, hypoglycaemia, and their cardiovascular risk profile – there is a need to individualize treatment.

In diabetes, metformin is the drug of choice in patients without a contraindication. Metformin reduces hepatic glucose production with an improvement in insulin resistance, while weight neutral or even yielding modest improvement in weight, and it has no atherogenic effects. A recent meta-analysis puts a question mark however on the benefits of metformin on cardiovascular morbidity and mortality (10).

Many other drugs are on the market but the most promising, regarding their actions on metabolic defects of diabetes, are the incretin-based drugs as well as the newly introduced sodium-glucose cotransporter-2 inhibitors.

The incretin-based drug family has glucose lowering effects, mainly on post-prandial glucose levels when glucose is ingested orally and induces, in a glucose dependent way, both an increase in insulin secretion and inhibition of glucagon secretion. Nowadays many GLP1 receptor agonists (Exenatide, Liraglutide, Dulaglutide) which need parenteral (sub cutaneous) administration, and dipeptyl dipeptidase IV (DPP-IV) inhibitors (sitagliptin, vildagliptin, linagliptine, saxagliptin) which can be administered orally (Fig. 6). Dipeptidyl peptidase IV is an ubiquitous enzyme expressed on the surface of most cell types, that deactivates a variety of other bioactive peptides, including GIP and GLP-1. The main therapeutic effects are through the action of GIP (glucose dependent insulinogetic polypeptide) and GLP1 (glucagon like peptide 1) which are secreted by the intestinal L cells. Incretin-based therapy has positive effects on other component of the MS and reduces total cholesterol, triglyceride and LDL cholesterol levels, with an increase
of HDL cholesterol, and reduces systolic and diastolic blood pressure. Incretin-based therapy improves cardiovascular risk factors, inflammatory cytokines, post-prandial oxidative stress and anthropomorphic parameters in patients with MS without type 2 diabetes (29). Hard data on cardiovascular outcomes are studied and some of them yet are available. Sitagliptine has been proved to have a neutral effect on cardiovascular disease in the TECOS study (30). Saxagliptine in the SAVOR-TIMI study was as well neutral on cardiovascular disease but an increased number of hospitalization for congestive heart failure was observed (31). GLP1 receptor agonists can induce weight loss and the DPP-IV inhibitors are weight neutral. Neither drug type - when used alone - induces hypoglycaemia. Nausea, abdominal pain, nasopharyngitis, urinary tract infection and headache a side effects of incretin-based therapy. Pancreatitis risk was not increased in the TECOS study (Fig. 4).

**Fig. 4** Actions of GIP and GLP1 on key tissues in glucose homeostasis. Both GIP and GLP1 promote insulin biosynthesis and secretion. GLP1 inhibits glucagon secretion, gastric emptying and food intake. CCK and gastrin do not regulate plasma glucose levels (32). CCK: cholecystokinin; GIP: glucose dependent insulintropic polypeptide; GLP-1: glucagon-like peptide 1

The sodium glucose cotransporter 2 inhibitor have a positive outcome on cardiovascular disease and mortality. In the EMPA-REG study, that included a total of 7020 patients empagliflozin treated patients at a dose of 10 mg or 25 mg in a population of Patients
with type 2 diabetes at high risk for cardiovascular events had a lower rate of cardiovascular disease and of death from any cause when the study drug was added to standard care as compared with the placebo treated group (11). Among patients receiving empagliflozin, there was an increased rate of genital infection but no increase in other adverse events.

The American College of Clinical Endocrinologists as well as the American Diabetes Association, in conjunction with the European Association for the Study of Diabetes agreed on the following principles in the treatment of type 2 diabetes, but there is no uniform recommendation for glucose-lowering drugs. The main principles include personalized medicine according to the patient’s characteristics (lean or obese, low or high risk for cardiovascular disease or hypoglycaemia, chronological and physiological age, diabetes duration, family history, co-morbidities, out-patient or in hospital setting, ethnic origin, country’s medical system, etc.) with a tailored made treatment with the tools that exist, keeping in mind the pathophysiological actions of drugs as described by De Fronzo and Inzucchi (Fig. 5).

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Fig. 5 Upper panel: known mechanisms leading to hyperglycemia: Lower panel: Matching patient's and drugs' characteristics according to site action of drugs (33, 49)

AGIs: Alpha glucosidase inhibitors-TZD: Thiazolidinedione-SGLT2I: Sodium-glucose co-transporter-2 inhibitor- SU: Sulfonylurea

2.3 Drugs and Lipid Metabolism

In MS both high triglycerides and low HDL cholesterol constitute targets for treatment, bearing in mind that prevention of cardiovascular events and death is the main goal. High triglycerides level may preclude perturbations in glucose metabolism as a result of early perturbation in post prandial insulin secretion.

Dietary interventions as well as peroxisome proliferator-activated receptor (PPAR)-alpha agonists (fibrates) are very effective in improving high triglyceride levels, but since
prevention of cardiovascular disease and death is the main goal, the third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) guidelines (34) recommend LDL-C as the primary target of lipid-lowering therapy when a patient's triglyceride level is below 500 mg/dl (5.5 mmol/L) (Table 3), to reduce cardiovascular morbidity and mortality. Level of triglycerides above 500 mg/dl impairs the ability to use calculated LDL Cholesterol as a target and non-HDL cholesterol should be used. High triglyceride levels should be addressed to decrease pancreatitis risk.

Table 3
Stratification of targets of therapy for hyperlipidaemia according to the ATP III panel (34)

<table>
<thead>
<tr>
<th>ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL Cholesterol – Primary Target of Therapy</td>
</tr>
<tr>
<td>&lt;100</td>
</tr>
<tr>
<td>100-129</td>
</tr>
<tr>
<td>130-159</td>
</tr>
<tr>
<td>160-189</td>
</tr>
<tr>
<td>≥ 190</td>
</tr>
<tr>
<td>Total Cholesterol</td>
</tr>
<tr>
<td>&lt;200</td>
</tr>
<tr>
<td>200-239</td>
</tr>
<tr>
<td>≥ 240</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
</tr>
<tr>
<td>&lt; 40</td>
</tr>
<tr>
<td>≥ 60</td>
</tr>
</tbody>
</table>

Statins, drugs acting on the HMG-CoA reductase, have shown to reduce risk for major cardiovascular events in patients with the MS (Fig. 3) and decrease risk of stroke but not of fatal stroke (35). Statin therapy for primary prevention is effective over a wide range of baseline LDL-C levels and lipid profiles and carries a similar relative risk reduction to statin therapy in secondary prevention. The absolute magnitude of benefit, however, is typically lower than in secondary prevention, but greater than the benefit of treating mild hypertension. A meta-analysis that reanalyzed existing trials of statins, but carefully limited the inclusion of patients to involve only those with no prior cardiovascular disease, found a reduction in mortality that was not statistically significant (36), thus stressing the uncertainty of effectiveness in the population with the MS. Statin therapy has side effects that should be considered particularly in this population. Besides myopathy and increased liver enzymes, after the publication of two recent meta-analyses, the Food and Drug Administration added a warning about an increased incidence of diabetes in statin users. The increased diabetes incidence was shown mainly in intensive statin therapy compared to moderate statin therapy (37, 38). Statin induced proteinuria is believed however to be a benign finding.
Fig. 6 Reduction of cardiovascular events by simvastatin in non-diabetic coronary heart disease patients with (●) or without (○) the metabolic syndrome: subgroup analyses of the 4S Study (39).

Their overall efficacy associated with a fair safety profile sets statins as the main pharmaceutical intervention for atherogenic dyslipidaemia in the MS. Questions exist about the additive value of other agents. In the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes trial (AIM-HIGH) (40), niacin was compared with placebo, with a primary outcome of a composite of cardiovascular events. Among patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of less than 70 mg/dl (1.81 mmol/l), there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up period, despite significant improvements in HDL cholesterol and triglyceride levels. Fibrates have favourable effects on lipids, but there is evidence that fibrates as a group may have less favourable effects on overall clinical outcomes. A meta-analysis of 10 randomized trials (36,489 patients; both primary and secondary prevention trials) found that treatment with fibrates showed a trend toward increased all-cause mortality, an increase in non-cardiac mortality, and no effect on cardiovascular mortality (41). A subsequent meta-analysis of 18 trials (45,058 patients) found no effect on all-cause mortality or cardiovascular mortality, and a trend toward increased non-cardiovascular mortality (42). Currently there is no evidence of additive value from fibrates in statin treated patients in reducing the risk of major cardiovascular events.

When triglycerides are >500 mg/dL (5.5mmol/l), they are the primary target of treatment because of the risk of acute pancreatitis. A very low fat diet, weight management and physical activity as well as the use of fibrates and nicotinic acid are recommended. The ATP III recommends turning to LDL-lowering therapy when triglycerides are < 500 mg/dl (34).

When combination therapy with a statin is needed, fenofibrate combined with a statin seems to be less likely to cause myopathy than is gemfibrozil (43), and higher doses of...
the statin should be used. Patients with impaired glucose metabolism who are treated with nicotinic acid should be carefully monitored for possible worsening of hyperglycaemia. Resins are not recommended in MS patients because of their triglyceride-raising effect. When LDL goals are not met on statin therapy, the addition of ezetimibe, a new selective inhibitor of intestinal cholesterol absorption, could provide a further 15–20% LDL-C lowering in patients with either DM or MS (44). In patients with high triglycerides, omega-3 fatty acids could be useful as they have been shown to decrease triglyceride levels and improve insulin resistance, although their possible effects on total mortality, combined cardiovascular events, and cancer have not been confirmed in a recent systematic review (44). In Table 4, efficacy patterns as well as side effects of current lipid-lowering agents are shown (46). It should be noted that myopathy is a common side effect of statins: important as it may, unhelpfully, compromise physical activity.

**Table 4**

**Characteristics of the main classes of hypolipemic drugs**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Lipid/lipoprotein effects</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG CoA reductase inhibitors</td>
<td>LDL ↓18-55%</td>
<td>Myopathy</td>
<td>Absolute:</td>
</tr>
<tr>
<td>(statins)</td>
<td>HDL ↑5-15%</td>
<td></td>
<td>- Active or chronic liver disease</td>
</tr>
<tr>
<td></td>
<td>TG ↓7-30%</td>
<td>Increases liver enzymes</td>
<td>Relative:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Concomitant use of certain drugs*</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>LDL ↓15-30%</td>
<td>Gastrointestinal distress</td>
<td>Absolute:</td>
</tr>
<tr>
<td></td>
<td>HDL ↑3-5%</td>
<td>Constipation</td>
<td>Dysbetalipoproteinaemia</td>
</tr>
<tr>
<td></td>
<td>TG ↔</td>
<td>Decreased absorption of other drugs</td>
<td>TG &gt; 400 mg/dl (4.4mmol/l)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Relative:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TG &gt; 200 mg/dl (2.2mmol/l)</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>LDL ↓5-25%</td>
<td>Flushing</td>
<td>Absolute:</td>
</tr>
<tr>
<td></td>
<td>HDL ↑15-35%</td>
<td>Hyperglycaemia</td>
<td>Chronic liver disease</td>
</tr>
<tr>
<td></td>
<td>TG ↓20-50%</td>
<td>Hyperuricaemia or gout</td>
<td>Severe gout</td>
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<td></td>
<td></td>
<td>Gastrointestinal distress</td>
<td>Relative:</td>
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<tr>
<td></td>
<td></td>
<td>Hyperuricaemia or gout</td>
<td>Diabetes</td>
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<td></td>
<td></td>
<td>Gallstones</td>
<td>Hyperuricaemia</td>
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<td></td>
<td></td>
<td>Myopathy</td>
<td>Peptic ulcer disease</td>
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<tr>
<td>Fibric acids</td>
<td>LDL ↓5-20% may increase in patients with high TG</td>
<td>Dyspepsia</td>
<td>Absolute:</td>
</tr>
<tr>
<td></td>
<td>HDL ↑10-20%</td>
<td>Gallstones</td>
<td>Severe renal disease</td>
</tr>
<tr>
<td></td>
<td>TG ↓20-50%</td>
<td>Myopathy</td>
<td>Severe hepatic disease</td>
</tr>
<tr>
<td>PCSK9 inhibitors</td>
<td>LDL Chol reduction 50-60%</td>
<td>Local injection site reactions</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Mild neurocognitive changes</td>
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<td></td>
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<td>Allergic reactions</td>
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2.4 Drugs and Hypertension

Few prospective trials have been conducted in the search of the ideal antihypertensive regimen in patients with obesity and the metabolic syndrome. Though caution exists regarding the use of thiazide diuretics due to potential metabolic derangements, there is insufficient data to show worsened cardiovascular or renal outcomes in patients treated with these drugs. In regard to beta blockers, the risk of accelerating conversion to diabetes and worsening of inflammatory mediators described in patients treated with traditional beta blockers appears much less pronounced or absent when using the vasodilating beta blockers. Renin-angiotensin-aldosterone system (RAAS) inhibition with an ACE or an ARB and treatment with calcium channel blockers appears safe and well tolerated in obesity-related hypertension and in patients with metabolic syndrome (14).

3. Timing of Intervention

We review different properties of drugs on the MS. Beside the particularity of different drugs, the timing of intervention has an influence on clinical outcomes.

3.1 Early Versus Late in Disease

In the diabetes field timing of intervention has been studied on different clinical outcomes. With longer duration of diabetes the value of intensive glucose therapy is more controversial. Several large trials trying to demonstrate a positive effect of intensive glucose control on cardiovascular morbidity and mortality have been conducted in long-standing diabetes populations with or without prior cardiovascular disease. The intensive glucose lowering arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, a multicentre study of type 2 diabetes, was halted in 2008 due to a higher number of total and cardiovascular deaths (257 versus 203) in subjects assigned to intensive therapy (HR 1.22 95% CI 1.01-1.46) (47, 48). This increased mortality was not explained and has not been seen in other trials (ADVANCE, VADT) (49, 50). To date, no randomized clinical trial has convincingly demonstrated a beneficial effect of intensive therapy on macrovascular outcomes in individuals with long-standing type 2 diabetes (51). On the other hand as mentioned earlier in this chapter, the post-trial monitoring of the UKPDS patients showed benefit from early intensive glucose lowering intervention in reducing cardiovascular risk and brought out once again the concept of the "glucose memory" as a predictor of future events. In this same trial no evidence for "hypertensive memory" was shown (52). When considering drug therapy for abnormal glucose metabolism the timing of intervention may preclude the anticipated benefit, and at present the clinical evidence supports initiating intensive therapy with the goal of lowering HbA1C levels to <7.0% as early as possible in the course of diabetes or impaired glucose metabolism (27).

3.2 Age at the Time of Intervention

Maternal obesity is associated with an increased risk of developing gestational diabetes mellitus and it also results in an increased risk of giving birth to a large baby with increased fat mass. Furthermore, it is also contributes to an increased risk of obesity and insulin resistance in the offspring in childhood, adolescence and adult life. Prenatal glucose control in women with diabetes has an influence on the foetus and on the
offspring (53). The ADA/EASD guidelines recommend a less stringent glucose control in the elderly or frail adult (32) and there is controversy about the role of lipid control or use of aspirin in the aging population. A lot of uncertainty still exists about when how early in the lifespan to start statin in patients with diabetes.

Data is still missing to practice an evidence based tailored made treatment in the different age groups.

4. Cost Effectiveness of Lifestyle Intervention, Drug Therapy and Bariatric Surgery

Interventions aimed at increasing exercise combined with diet are able to decrease the incidence of type 2 diabetes mellitus in high risk groups (people with impaired glucose tolerance or the metabolic syndrome) (54). These findings were reproducible in many different settings as for example in China, India, northern and southern Europe, and the USA. The Finnish Diabetes Prevention Study (DPS) randomly assigned 522 middle-aged patients with impaired glucose tolerance to a weight-reduction and exercise programme or a control group with a four-year intervention programme and a non-interventional seven-year follow-up. At the end of the follow-up period comparing intervention and control groups, the hazard ratio for diabetes was 0.57 (95% CI 0.43-0.76), with a cumulative incidence of diabetes of 23% versus 38% at the end of year 6 (43% reduction over the entire period) (24). This benefit was not uniform, and patients who were homozygous for a polymorphism of the hepatic lipase gene (56% of subjects) were less likely to benefit from the lifestyle intervention, and therefore were more likely to develop diabetes (13% versus 1% in subjects who had at least one normal allele). In the Diabetes Prevention Program (DPP) lifestyle changes were superior to metformin in preventing diabetes in the trial as a whole, while lifestyle and metformin were similarly effective in reducing the incidence of diabetes in women with a history of gestational diabetes (GDM) (24). These findings strengthen the need for individualized interventions.

Obesity has a high cost, in the PROCEED study, mean healthcare cost was significantly higher in the higher BMI classes [control ($456±937) versus overweight ($1084±3531) and obese ($1186±2808)] (56).

A model using the DPS data indicated that the programme would be cost-saving from the healthcare payers' perspective and associated with an increase in estimated survival of 0.18 years. Taking into consideration increased consumption by patients due to their longer survival, the predicted cost-effectiveness ratio was 2,363 Euros per quality-adjusted life-year gained (57). The cost effectiveness of different diabetes prevention studies will not however be uniform but will depend on the country’s healthcare system as well as the type of intervention. In Israel, for example, the main Health Care Organization adopted a prediabetes intervention programme in 2012, while a national programme promoting healthy lifestyle started at the end of 2011 in accordance to the European evidence-based guideline for the prevention of type 2 diabetes (58). Lifestyle intervention directed toward high-risk subjects tends now to be considered cost-saving for the healthcare payer and highly cost-effective for society as a whole (59).

Evidence about the comparative efficacy of intensive medical therapy and bariatric surgery may change the approach to the treatment of MS and its metabolic components.
The International Diabetes Federation (IDF), in a position statement, recognized bariatric surgery as an appropriate treatment for obese patients with type 2 diabetes in whom recommended glycaemic targets are not reached with the available medical therapies. The IDF recommends the inclusion of bariatric surgery in future algorithms for the treatment of type 2 diabetes (60). In recent years bariatric surgery has proved to be superior to medical therapy to induce remission of type 2 diabetes and to improve metabolic control (61, 62, 63). Some evidence exists in favour of a reduction in future cardiovascular risk with bariatric surgery (64, 65). Bariatric surgery may be a tool in earlier stages of diabetes in obese patients.

Fig. 7 Resolution of the metabolic syndrome according to treatment. The numbers within or above the columns represent the percentage resolution after treatment; the numbers below the columns in parentheses indicate the number of studies (50).

5. Summary

Beside healthy lifestyle, polypharmacy is a cornerstone of the treatment of the Metabolic Syndrome. In the late years many new drugs entered the market in the field of metabolic diseases giving an opportunity to better tailor treatment, according to the patient profile and the availability of the different treatment options. Metabolic surgery is an option in the therapy of MS, keeping in mind that behavioural changes and healthy lifestyle are needed to keep the benefit of this intervention in the long run. Therapeutic patient education (TPE) is essential in the treatment of chronic disease as the MS to increase the adherence to healthy lifestyle and drug therapy. TPE is the link to translate the progress of medical research to the level of each patient and close the gap between medical recommendations and clinical practice. Timing and age of intervention is crucial to metabolic diseases, stressing the value of early detection to enable early intervention and postpone the consequences of the MS and assure a good quality of life.
6. References


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