The Issue of Drug Therapy

For the Metabolic Syndrome

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The metabolic syndrome is a constellation of cardiovascular risk factors of metabolic origin (1). These "metabolic risk factors" consist of:

- Atherogenic dyslipidemia
- Elevated blood pressure
- Elevated plasma glucose
- Prothrombotic state
- Proinflammatory state

Atherogenic dyslipidemia consists of elevated serum triglycerides, apolipoprotein B (apo B), small low density lipoprotein (LDL) particles, and low levels of high density lipoproteins (HDL). The underlying risk factors of the metabolic syndrome include obesity (especially abdominal obesity), insulin resistance, physical inactivity, advancing age, and genetic and hormonal factors (3,4). Among these, obesity and insulin resistance appear to dominate in causation. The increasing prevalence of metabolic syndrome can be attributed to a growing imbalance between nutrient energy intake and expenditure in the world's population (4).

The risk for atherosclerotic cardiovascular disease is essentially doubled in persons with the metabolic syndrome, compared to those without (5-15). In those without diabetes, the risk for developing type 2 diabetes is increased about five fold (16). The higher risk for diabetes is due to the presence of a chronic insulin resistance, which predisposes to hyperglycemia and is characteristic of most persons with the metabolic syndrome. For ASCVD risk, all of the metabolic risk factors seemingly promote either atherosclerosis or acute cardiovascular syndromes.

First-line clinical intervention for the metabolic syndrome is lifestyle change—weight reduction and increased physical activity (3). If weight can be reduced to desirable levels and if regular exercise is instituted, all of the risk factors of the syndrome will be mitigated. However, because of frequent difficulties in achieving lifestyle change and the higher risk accompanying the syndrome, the possibility of using drug therapy to reduce the metabolic risk factors is attractive.

At present there are no approved drugs that can reliably reduce all of the metabolic risk factors at once, as can lifestyle modification. For this reason, the current strategy is to employ drugs to treat each of the risk factors separately, e.g. lipid-lowering drugs, anti-hypertensive agents, and hypoglycemic agents. The pharmaceutical industry nonetheless has shown great interest in designing drugs that target the metabolic syndrome as a whole. On the other hand, regulatory agencies are reluctant to register drugs for any condition as "nebulous" as the metabolic syndrome. Because of its multifactorial nature, the syndrome is difficult to define in clinical terms that will satisfy regulatory agencies. At present agencies generally take the position that drugs can be registered to treat specific risk factors, but not a non-specific clustering of risk factors. For example, in the United States, consideration will be given to registration of drugs to treat obesity, hypercholesterolemia, hypertension, and diabetes depending on their efficiency on body weight, cholesterol levels, blood pressure, and glucose, respectively. It also may be possible to register a drug on the basis of its ability to reduce ASCVD events, although there will be reluctance to do so if the drug acts outside of established risk factors.

How then will it be possible to encourage the pharmaceutical industry to develop drugs that target the metabolic syndrome? The best approach at present would appear to be to concentrate on designing drugs to treat specific risk factors of the metabolic syndrome, but which also favorably modify other risk factors. This dual-action (or multiple-action) approach will be strengthened if it can be shown that through controlled clinical trials that a new drug of this type will reduce cardiovascular events. Initial registration of the drug can be for the primary risk factor, which likely will be very common in persons with the metabolic syndrome. In the discussion to follow, each of the risk factors of the metabolic syndrome will be considered as possible drug targets.

Obesity

Excess body fat, particularly when present in the upper body, is an underlying risk factor for the metabolic syndrome. In obese individuals with this syndrome, weight reduction will reduce all of the metabolic risk factors (17). Among available modalities, this action on the *metabolic syndrome as a whole* is unique. This accounts for the great interest in the development of drugs to treat obesity. In the USA at least, a drug that effectively reduces body weight and is safe can be registered as a weight-reduction drug for treatment of obesity, especially when it is severe or is accompanied by multiple cardiovascular risk factors. There is no registration allowed for weight-reduction drugs to treat the metabolic syndrome. Nonetheless, if tolerated for long periods, they should be efficacious for this purpose. Regardless, multiple pathways have been identified as potential targets for the development of anti-obesity drugs. These targets and some of the drugs under development or already approved for use include the following:

- Drugs affecting the central nervous system
  - Serotonin (5HT) drugs
    - D-fenfluramine
    - Sibutramine
  - Leptin-like drugs
  - Agonists for melanocortin-3 and 4 receptors
  - Gastrointestinal hormone analogues
    - Peptide YY analogues
    - Ghrelin antagonists
    - Cholecystokinin (CCK) agonists
    - Somatostatin receptor agonists (e.g. octreotide)
  - Pancreatic amylin
  - Cannaboid receptor inhibitors
    - Rimonabant
    - SR-147778
  - Antiepilepsy drugs
    - Topiramate
    - Zonisamide
  - Antidepressants
    - Bupropion

- Drugs interfering with food absorption
  - Drugs affecting fat absorption
    Orlistat
- Drugs promoting energy expenditure
  Beta 3-adrenoceptor agonists
  Thyroid Hormone Receptor beta-Subtype Agonist
  PPAR delta agonists

One drug, sibutramine, acting on the CHS, has been approved for weight reduction. Sibutramine acts centrally to inhibit both noradrenergic and serotonergic (SHT) reuptake in the hypothalamus. Weight reduction over a period of testing of about one year is 5-10% of total body weight (18). Favorable changes occur in the metabolic risk factors and appear to be due largely to weight reduction. Unfortunately, the drug has a tendency to raise the blood pressure, which is of concern for patients with the metabolic syndrome.

Another approved drug is orlistat. This drug acts entirely in the intestine to inhibit pancreatic, gastric, and carboxylester lipase (19). This prevents the lipolysis of triglyceride in the intestine and hence reduces fat absorption. Administration of orlistat for periods up to one year result in 5 to 10% loss of body weight. The major side effect of olistat is gastrointestinal distress accompanying fat malabsorption. Simultaneously with weight loss all of the metabolic risk factors are improved. However, it is doubtful that the drug has a direct effect on these risk factors independently of weight loss. The gastrointestinal side effects and the costs of the medication have limited prescription of the drug. Lack of reimbursement by medical insurance undoubtedly also has limited its use.

Another agent acting on the CNS that may be approved in the near future is rimonabant, a selective cannabinoid receptor-1 antagonist. Endocannabioids are lipid mediators that activate G protein-coupled CB_1 receptors in hypothalamus and limbic forebrain. They accentuate hunger and can induce hyperphagia (20.) Their action is antagonized by CB_1 blockage. Rimonabant is a selective CB_1 blocker that suppresses tonic endogenous activation of the endocannabinoid system (21). Recent clinical studies show that rimonabant therapy causes a 5-10% weight loss over a period lasting up to two years (22). One of the more interesting aspects of rimonabant is that it may have systemic as well as central effects that could independently reduce the metabolic syndrome. For example, adipocytes and liver express endocannobinoid-1 receptors (23). In mouse adipose tissue, CB_1 modifies production of adiponectin (24) and lipoprotein lipase(25), whereas in liver, it stimulates fatty acid synthesis (26). These findings raise the possibility that rimanobant will have systemic actions as well as central actions, which could be doubly beneficial in the treatment of the metabolic syndrome.

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Type 2 Diabetes, Pre-Diabetes, and Insulin Resistance

Type 2 diabetes. In the United States, at least 20% of people over aged 40 with the metabolic syndrome have type 2 diabetes (27); and most persons with type 2 diabetes have the

metabolic syndrome. Type 2 diabetes is a high-risk condition, and 75-80% of people with type 2 diabetes ultimately die of cardiovascular disease (28). Drugs that are effective for reducing hyperglycemia can be registered for treatment of patients with diabetes. Lowering hyperglycemia by conventional means per se may favorably modify the metabolic risk factors. For example, insulin therapy and/or sulfonylureas often reduce serum triglyceride levels; however, their effects on other metabolic risk factors are minimal. Glucose lowering with these agents may also reduce risk for ASCVD events in patients with diabetes (29, 30), although this benefit remains to be proven with certainty.

One oral hypoglycemic agent that may have a modest effect on other risk factors is metformin. The primary action of this drug appears to be to reduce hepatic glucose output, which reduces insulin resistance and plasma glucose levels (31). This action may be secondary to activation of AMP kinase (32). There are scattered reports that it improves dyslipidemia and lowers the blood pressure; but these are not consistent effects. On the other hand, in one large study in patients with type 2 diabetes, metformin therapy seemingly reduced risk for major coronary events (33). If this is true, the mechanism for the benefit is not known; it is possible that the agent acts in some way to mitigate the metabolic syndrome as a whole (34). Metformin has been available for many years and is relatively inexpensive. It is widely used for treatment of diabetes worldwide. Further clinical trials are needed to determine whether it reduces risk for ASCVD; if so, this could make it a preferred agent for treatment of type 2 diabetes.

Another class of drugs that is potentially efficacious for patients with type 2 diabetes as well as the metabolic syndrome consists of the thiazolidinediones (TZDs). These drugs act by agonizing the peroxisome proliferators-activated receptor gamma (PPARG). This receptor is predominantly expressed in adipose tissue, but also occurs in other tissues (35,36). TZDs almost certainly reduce the secretion of unesterified fatty acids, and adipokines such as tumor necrosis factor alpha, resistin, and PAI-1; they also enhance release of adiponectin (37, 38). The net result of these changes apparently is to reduce insulin resistance in muscle and liver, a prothrombotic state, and a proinflammatory state. Thus, these findings suggest that TZDs are hitting at the heart of the metabolic syndrome. However, it is of interest that in patients with type 2 diabetes, they have only a modest effect on plasma lipoproteins and blood pressure. So while they improve the metabolic syndrome they by no means "cure" it in the presence of type 2 diabetes. Currently available PPARG agonists include pioglitazone and rosiglitazone. More potent TZDs have been developed, but unfortunately they are accompanied by increased side effects.

The major side effects of TZDs are the following:

- Fluid retention (multiple mechanisms proposed)
- Increases in total body fat (possible stimulation of appetite)
- Increased adipogenesis (questionable side effect)
- Carcinogenesis (reported in some animal studies)

TZDs often cause weight gain, which is secondary to both fluid retention and increases in total body fat. The mechanisms underlying fluid retention and peripheral edema associated with TZD therapy may be multifactorial. Proposed mechanisms include an increase in plasma volume

secondary to decreased renal excretion of sodium and an increase in sodium and free water retention, arterial vasodilatation, leading an increase in extracellular volume, increased sympathetic nervous system activity, altered interstitial ion transport, alterations in endothelial permeability, and increased vascular permeability growth factor (39). In addition to fluid retention, the total body fat content often is increased as well (40). Some investigators have speculated that the increase in body fat is secondary to the stimulation of adipogenesis by agonism of PPARG(41, 42). However, it is important to separate adipogenesis from fat accumulation. The effects of the latter resulting from TZDs likely are due to a positive caloric balance, possibly due to stimulation of the appetite. Finally, there has been a concern that TZD may promote carcinogenesis in humans, because PPARG appears to mediate some of the pathways in tumor formation (43). To date however there is no clear evidence for this side effect in humans. Some investigators have speculated that it might be possible to develop PPARG agonists that will have the favorable metabolic actions of current TZDs without the side effects, particularly weight gain. One concept being put forward is that modifications of TZDs, called selective PPAR modulators (SPPARMS), might be developed that would avoid the side effects (44; 45, 46). To date, however, no SPPARMS have been approved for clinical practice.

Another potential benefit of PPARG activation is to suppress inflammatory responses. This may be related to their ability to suppress production of TNF alpha and other inflammatory cytokines (47). Evidence that PPARG agnonists are anti-inflammatory is the reduction of CRP observed during treatment with TZDs (48). Other potentially beneficial responses reported for PPARG activation are increased expression of NO by vascular endothelial cells (49, 50) and potentially favorable changes in vascular smooth muscle cells (51, 52, 53).

A modification of PPARG agonists that may have expanded benefit for the metabolic syndrome are those that agonize PPAR alpha (PPARA) as well as PPARG. These are called dual PPAR agonists (54, 55, 56). PPARA primarily regulates lipid metabolism in the liver, which has a favorable effect on atherogenic dyslipidemia. The role of PPARA agonists in treatment of the latter will be discussed in more detail in the section on atherogenic dyslipidemia. From the point of view of the metabolic syndrome the dual PPARG/PPARA agonists are attractive because they attack two disorders at the same time—the metabolic consequences of obesity and atherogenic dyslipidemia. They may further reduce inflammatory component of atherogenesis.

Pre-diabetes. This condition is defined an either impaired glucose tolerance (IGT) (plasma glucose $\geq$ 140 mg/dL two hours after a 75-mg oral glucose load) and/or impaired fasting glucose (IFG) (fasting plasma glucose $\geq$ 100 mg/dL) (57). At least 50% of patients with pre-diabetes have the metabolic syndrome. Persons with pre-diabetes are at greatly increased risk for development of type 2 diabetes; it is estimated that conversion to diabetes occurs at a rate of 5-10% per year (58). Pre-diabetes further carries increased risk for ASCVD, most likely because of the common association with the metabolic syndrome (59). In the absence of metabolic syndrome, increase in the cardiovascular risk accompanying pre-diabetes appears to be relatively small (60). The question of whether drug therapy to prevent is justified for prevention of type 2 diabetes is a matter of some dispute. One clinical trial, the Diabetes Prevention Program (DPP), along with smaller studies, indicate that both metformin and TZDs can reduced the rate of

conversion of pre-diabetes into categorical type 2 diabetes (58, 61). The rationale for such therapy is that delaying the onset of diabetes will reduce the complications of diabetes—cardiovascular and others. To counter this rationale, issues of aggregate costs, cost effectiveness, and safety of drug therapies are raised. These issues are yet to be resolved to everyone's satisfaction.

Insulin resistance. Since insulin resistance is considered to be one of the underlying risk factors for metabolic syndrome, some investigators have speculated that reducing insulin resistance per se with drugs will reduce the risk for ASCVD. At present, however, the only drugs available to reduce insulin resistance are those used to treat type 2 diabetes, namely, TZDs and metformin. Preliminary studies further suggest that rimonabant reduces insulin resistance beyond weight reduction (22); but if so, this is likely to be a lesser effect on metabolism than that due to loss of weight. Before any drug could be used to treat insulin resistance per se without having direct effects on other metabolic risk factors could be approved for prevention of ASCVD, controlled clinical trials of its efficacy in risk reduction would have to be carried out.

Atherogenic Dyslipidemia.

As noted before, atherogenic dyslipidemia consists of elevated serum triglycerides, apolipoprotein B (apo B), small low density lipoprotein (LDL) particles, and low levels of high density lipoproteins (HDL). Most persons with atherogenic dyslipidemia have the metabolic syndrome. Several drugs are currently available for treatment of patients with atherogenic dyslipidemia. These include the HMG CoA reductase inhibitors (statins), nicotinic acid, fibric acids, and dual PPAR agonists. Several other drugs are under development. The question that can be raised about these drugs is whether they have actions on metabolic risk factors beyond atherogenic dyslipidemia. The effects of each drug can be examined briefly.

Statins. These drugs reduce all of the apolipoprotein B (apo B)-containing lipoproteins (1). They produce a 30-45% percent reduction in apo B levels, depending on the dose employed. This reduction is accompanied by a 30-50% decrease in risk for major coronary events (1). Most of the risk reduction appears to be secondary to a decrease in apo B-containing lipoproteins. However, some investigators speculate that statins are anti-inflammatory beyond their effects on levels of total apo B (62). This speculation is based on the observation that statins significantly reduce C-reactive protein (CRP), which is a marker of an inflammatory process (63). If such were true, then an argument could be made that statins are useful from treatment of the proinflammatory component of the metabolic syndrome. Whether an anti-inflammatory action beyond apo B lowering actually exists however is of little practical importance, because the range of benefit of statin therapy is well established.

Recent studies suggest that marked lowering of apo B-containing lipoproteins ($\geq$ 50%) will give additional benefit in reducing risk for ASCVD beyond that produced by a moderate lowering (e.g. 30-40%) (64, 65). This benefit presumably extends to patients with both metabolic syndrome and type 2 diabetes. There are two way to achieve a marked reduction in levels of serum apo B: (a) high-dose statins (65) and the combination of moderate-dose statin + second LDL-lowering drug. The second drug can be either a bile acid sequestrant (66) or ezetimibe (67).

Nicotinic acid. This agent is a powerful lipid-lowering drug, lowering all apo B-containing lipoprotein and raising HDL cholesterol. In patients with metabolic syndrome and type 2 diabetes, nicotinic acid appears to reduce risk for ASCVD (68). However, it has little effect on other components of the metabolic syndrome. It is particularly promising as a second drug to use in combination with statins (69). On the other hand, nicotinic acid worsens insulin resistance and can exacerbate hyperglycemia in patients with diabetes. Consequently, it is not a candidate as a drug to use to modify non-lipid risk factors of the metabolic syndrome; but this does not rule out its usefulness for reducing risk for ASCVD events in patients with the metabolic syndrome.

Fibric acids. These drugs are agonists of PPARA (38). Fibrates currently in use are gemfibrozil, fenofibrate, and bezafibrate. Their primary use clinical is to treat atherogenic dyslipidemia. They lower triglyceride levels, transform small LDL particles into larger particles, and moderately raise HDL-C concentrations; one of the fibrates, fenofibrate, also causes a moderate reduction in total apo B levels (70). These changes appear to be secondary to multiple changes in lipid metabolism induced by PPARA: increased fatty acid oxidation in the liver, reduced production of apolipoprotein CIII (an inhibitor of lipoprotein lipase), increased activity of lipoprotein lipase, and increased production of apolipoprotein AI (71). Many clinical trials provide support for the ability of fibrates to reduce risk for major coronary events (1). Their efficacy for reducing major coronary events however appears to be less than that of statins. On the other hand, when they are combined with statins, all of the components of atherogenic dyslipidemia are improved (72,73).

PPARA agonists, like those for PPARG, may have additional anti-inflammatory and anti-atherogenic effects that go beyond a lipid-lowering action. They have been reported to repress nuclear factor-kappa B and activator protein-1 signaling (38). Fibrates have been reported in various cellular systems to modify activities or expression of endothelin-1 in arterial endothelium (74), IL-6, cyclooxygenase-2, nitric oxide (NO) synthase (38), tissue factor (76), and fibrinogen. Other activities that could be anti-inflammatory or anti-atherogenic are being explored (38). Whether these activities account in part for the reduction in CHD risk reported for fibrates in clinical trials is uncertain. Nonetheless a review of clinical trial data show that the benefit of fibrate therapy is limited largely to patients who exhibit the metabolic syndrome or type 2 diabetes (78-81). Moreover, it is difficult to account for the degree of risk reduction observed in patients of the latter types by changes in lipoprotein patterns alone. An important question currently under study is whether fibrates produce additional risk reduction in individuals with the metabolic syndrome beyond what can be achieved with statin therapy.

Dual PPARs. As mentioned before, an attractive new class of drugs for treatment of metabolic syndrome with or without diabetes are the dual PPARG/PPARA drugs (54, 55, 56). In the United States, the Food and Drug Administration is proceeding cautiously in the approval of these drugs. By simulating two nuclear receptors at the same time, they have a multiplicity of actions. These actions not only may increase efficacy of therapy, but they also could compound the side effects. Even so, several pharmaceutical companies are proceeding with their development. If they are approved, this likely will be first exclusively for patients with type 2 diabetes; but later, if both efficacy for ASCVD risk reduction and safety can be demonstrated in such patients, expansion of their use in other forms of the metabolic syndrome is a possibility.

Other than weight-reduction drugs, the PPARA/PPARG drugs the most-immediate and promising agents for treatment of the metabolic syndrome beyond the established risk factors.

PPAR delta (PPARD) agonists. PPARD is widely expressed and regulates fatty acid oxidation (82, 83). Recently a few PPARD agonists have been developed. In obese monkeys one such drug lowers serum triglycerides and raises HDL-C (84). Evens et al. (85) speculate that whereas PPARG promote fat storage in adipose tissue PPARD stimulates fat burning in muscle. Indeed, PPARD-deficient mice are prone to obesity, presumably because of sluggish fat oxidation (86). Moreover, in animal studies, PPARD is more potent for oxidation of fatty acids than in PPARA (84, 87-90). Although PPARD agonists are in an early stage of development, they have many of the properties of an "ideal" drug for treatment of the metabolic syndrome and type 2 diabetes.

Elevated Blood Pressure

The majority of individuals with the metabolic syndrome have some elevation of blood pressure; and by the time the syndrome progresses into type 2 diabetes, hypertension usually is present. Treatment of hypertension in patients with type 2 diabetes will reduce risk for cardiovascular events (91). Most likely the same is true in patients with the metabolic syndrome. There is almost universal agreement that treatment of categorical hypertension in anyone, regardless of the associated conditions, is indicated to reduce risk of stroke, ASCVD events, and other cardiovascular complications. But the question of which of the anti-hypertensive agents, and if necessary, in what combination of drugs, is preferred for patients with various associated conditions is not fully resolved. One school of thought holds that almost all of the benefit of anti-hypertensive drugs is mediated through blood pressure lowering (92); according to this view, it is immaterial which agents are employed to achieve the goals of therapy. Another school however holds that different drugs or different combinations are preferable in different types of patients. This issue is somewhat confounded by the pharmaceutical industry which has so much to gain financially through the choice of their own agents. Nonetheless, it is well known that different agents lower blood pressure through different biological mechanisms; and for this reason, it is possible that some mechanisms are more beneficial than others in some condition, for example, the metabolic syndrome and type 2 diabetes.

Diuretics and beta-blockers, two of the older drugs for treatment of hypertension, are still widely used. Both have been reported to worsen insulin resistance and dyslipidemia (93, 94). In the ALLHAT study (95), a thiazide diuretic, chlorthalidone, tended to raise the plasma glucose, and in some patients, seemingly induced category hyperglycemia (type 2 diabetes). Mechanisms whereby thiazides and beta-blockers worsen insulin resistance are not fully understood. In spite of these side effects, JNC7 (96) was loath to recommend against use thiazides and beta-blockers for treatment of hypertension because of the impression that the benefits outweigh the side effects. Recent studies show that one beta-blocker, carvedilol, does not have an adverse metabolic effect and theoretically might be preference to standard drugs in this category (97). In spite of the reported effects of beta blockers and diuretics on insulin resistance and the metabolic risk factors, clinical trials demonstrate their efficacy for prevention of multiple cardiovascular events (96). Moreover, they are often required as a component of

multidrug regimens for treatment of hypertension to achieve the recommended goals for blood pressure lowering.

Another class of anti-hypertensives,the calcium channel blockers appear between neutral with respect to both lipids and insulin resistance. Conversely, alpha1-blockers and imidazoline I1-imidazoline receptor agonists (e.g. moxonidine) have been reported to increase insulin sensitivity (98). Moxonidine and a related drug, rilmenidine, inhibit sympathetic outflow, causing vasodilatation; it is possible that vasodilatation in itself by enhance peripheral insulin action, reducing insulin resistance. Drugs of this type may hold promise for treatment of the metabolic syndrome.

A final group of agents that lower blood pressure are those that interfere with the renin-angiotensin-aldosterone system (RAAS). There are two types of agents affecting RAAS: angiotensin converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB). Beyond blood pressure lowering, these drugs may have beneficial actions on metabolism, inflammation, and vascular biology. If so, they could be particularly beneficial for patients with the metabolic syndrome and type 2 diabetes. Clinical trails document their efficacy for reducing major cardiovascular events. Some investigators report that ACE-Is and ARBs reduce insulin resistance, although this response has not been consistent for all studies (99). Even so, several clinical suggest that ACE-Is and ARBs reduce the risk for developing type 2 diabetes in patients with pre-diabetes (100). In addition, a variety mechanisms have been postulated whereby ACE-Is or ARBs will reduce progression of atherosclerosis. Some of these mechanisms include improvement of endothelial function, favorable changes in fibrinolytic balance, enhanced nitric oxide release and vascular inflammation (101).

One unique ARB, telmisartan, seemingly manifests selective PPARG modulating activity. This dual-action, ARB/PPARG drug is reminiscent of PPARG/PPARA drugs, and could be a prototype for future agents to treat the metabolic syndrome (102).

To date, there is no strong evidence that one class of anti-hypertensive agent has unique properties for reducing risk for cardiovascular events beyond blood-pressure lowering (103, 104). Nonetheless, the possibility still exists that some anti-hypertensive drugs may be preferable to other in specific subgroups of patients, such as those with metabolic syndrome or type 2 diabetes.

Prothrombotic State

The metabolic syndrome is characterized by an increase in circulating factors that shift the homeostatic balance from an antithrombotic to a prothrombotic state (105). Coagulation changes that have been reported to be associated with the metabolic syndrome are increases in circulating fibrinogen, Factor VII, and PAI-1. These factors have been implicated both in atherogenesis itself and in the thrombosis that can complicate atherosclerotic lesions. Both undoubtedly predispose to major cardiovascular events. The prothrombotic state associated with the metabolic syndrome appears to be analogous to that induced by COX-2 inhibitors, which also

predispose to major cardiovascular events. At the present time, no practical drugs are available for treatment of the prothrombotic state other than low-dose aspirin, and under special circumstances, clopidogrel. Current indications for aspirin therapy in patients with metabolic syndrome are similar to those for other patients at risk. They depend on the absolute risk of the patient. Most persons with established ASCVD are candidates for anti-platelet therapy (106). Although clinical data in patients with type 2 diabetes are sparse, most authorities recommend use of low-dose in these patients even when do not have established ASCVD (106). Moreover, some authorities recommend aspirin prophylaxis in individuals with multiple risk factors when the their 10-year risk for major coronary events is $\geq$ 10% (107, 108). Other investigators are more conservative and restrict usage to high-risk patients because of the danger of bleeding. If new anti-inflammatory drugs could be developed that are proven to reduce risk for major cardiovascular events, it is possible that these also would a thromobotic tendency. In the pharmaceutical industry, the research fields for anti-atherogenic and anti-thrombotic agents is active, but so far, progress has been relatively slow.

Proinflammatory State

The metabolic syndrome is associated with an increase in inflammatory cytokines and inflammatory markers (110). The former appear to be produced in adipose tissue. This excess of cytokines seemingly elicit elevations of serum CRP, plasma fibrinogen, and other acute phase reactants. An elevation of CRP is further associated with increased risk for major cardiovascular events. The mechanisms underlying this association are not well understood. Some investigators speculate that this "proinflammatory state" accompanying the metabolic syndrome tends to produce plaque instability in atherosclerotic lesions and hence predisposes to acute vascular events. If so, a dampening of inflammation might reduce the risk for such events. At present the only accepted clinical marker for a proinflammatory state is an elevation of CRP. If this is a reliable marker, any agent that reduces CRP might be considered to be anti-inflammatory. Of interest, several lipid-lowering drugs do in fact reduce CRP levels (63). Among these, the most consistent are the statins. Hence some investigators believe that statins are anti-inflammatory as well as being cholesterol-lowering drugs. This hypothesis however has not been rigorously confirmed; and some investigators are doubtful. On the basis of results from other lipid-lowering diets and drugs, statins reduce major cardiovascular events to the extent that would be expected from the degree of serum cholesterol lowering.

Other drugs currently available and commonly used for prevention of ASCVD have been reported to be potentially anti-atherogenic (Table 1). These agents theoretically act in one way or another to reduce inflammation in the arterial wall. If so, this is another example a secondary action beyond modifying a specific risk factor that could be beneficial for individuals with the metabolic syndrome. In addition, a variety of other agents are being studied as being potentially anti-inflammatory and anti-atherogenic (Table 1). If any of these drugs prove to be efficacious, they could be added to standard regimens for prevention of ASCVD.

Future of Drugs for Treatment of the Metabolic Syndrome

The success of drugs used to treat established cardiovascular risk factors has been so great that it sets a high bar for new drugs to demonstrate added efficacy. The combination of

LDL-lowering drugs, low-dose aspirin, and anti-hypertensive drugs appears to reduce risk for major cardiovascular events by 50 to 60%. In patients with diabetes, hypoglycemic therapy may provide some additional risk reduction. Certainly in patients with established ASCVD and/or diabetes, risk for future vascular events remains unacceptably high. Therefore, additional approaches are needed. But unless new therapies are able to achieve a sizable risk reduction, it may be difficult to demonstrate added efficacy through clinical trials such as those carried out in the past. In other words, more efficacious means of demonstrating efficacy are needed as well as new agents to further reduce risk.

Table 1.

Candidates for Anti-Atherogenic Drugs

Currently Available Drugs

Statins
PPAR Gamma agonists
PPAR Alpha agonists
ACE inhibitors and angiotensin receptor blockers (ARBs)
Calcium channel blockers
Probucol
Vitamin E and vitamin E analogs
Aspirin and clopidogrel
Estrogens and tamoxifen

Drugs Under Study

Phospholipase A2 inhibitors
Inhibitors of acyl coenzyme A:cholesterol acyltransferase
Apolipoprotein A-1 Milano, apo A-1 mimetics,
and apolipoprotein/phospholipid complexes
Anti-atherosclerosis vaccines

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