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Managing Hypertension in Patients with Diabetes

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1. Introduction

Cardiovascular disease remains the leading cause of death in industrialized nations. Type 2 diabetes confers cardiovascular risk comparable to a previous myocardial infarction, and is the most common cause of chronic kidney disease. Diabetes and hypertension account for 2/3 of cardiovascular risk [1]. Over 75% of adults with diabetes are hypertensive, or being treated with hypertensive medications [2] In patients with type 1 diabetes, the presence of hypertension signals significant kidney damage whereas in patients with type 2 diabetes, hypertension is usually present at the time of diagnosis [2]. On the other hand, many hypertensive treatments, specifically diuretics, worsen glucose control; the overall implications of this are as yet unclear [2]. Because of the singular risk resulting from the combination of diabetes and hypertension, significant effort has been expended to improve patient outcome. While several recent excellent reviews address different aspects of this issue [1-3], we will evaluate the management of hypertension in diabetes, particularly from the perspective of managing hypertension in metabolic syndrome. We will evaluate the metabolic effects of different agents used for blood pressure control, consider specific patient-related issues, discuss shortcomings of recent trials, and consider possible future directions in genetic analyses.

There are over 65 million hypertensives in the United States [4]. Unfortunately, the pharmacological treatment of these individuals has had less than the predicted benefit on coronary heart disease (CHD) mortality [5-7]. For many years, It has been postulated that treatment with some antihypertensives might have metabolic and other untoward effects that negate some of the benefits of blood-pressure lowering [5, 8]. This may be particularly true for individuals with the metabolic syndrome, a constellation of anthropometric and metabolic abnormalities that includes central obesity, hypertension, elevated levels of fasting glucose and triglycerides, low concentrations of high-density lipoprotein cholesterol (HDL-C), and insulin resistance which is associated with increased cardiovascular disease morbidity and mortality [9-11]. Of the five diagnostic criteria for metabolic syndrome, hypertension and central obesity are most frequently present [12, 13].

Why is this increasingly important in the US? The prevalence of obesity has doubled in the US in the past 20 years [14]; the number of extremely obese individuals with a BMI >35

kg/m^2 is almost 5% of the population. Obese compared with normal weight individuals have a 3.5 fold increased risk of developing hypertension while up to 60% of obese individuals have hypertension [15, 16]. The association between obesity and hypertension may be related to greater insulin resistance, leptin-mediated enhancement of sympathetic activity, sodium and fluid retention, and adipocyte-mediated effects on angiotensin II and atrial natriuretic peptide levels [17]. Patients with hypertension have an increased prevalence of type 2 diabetes mellitus and impaired glucose tolerance [18, 19]. Patients with mild hypertension also have lower HDL-cholesterol concentrations and higher HDL catabolic rates; these findings appear to correlate with insulin resistance [20]. With hypertension, obesity and diabetes mellitus increasing in frequency, it is not surprising that the age-adjusted prevalence of metabolic syndrome in the general US population is 24.0% for men and 24.3% for women [21].

Lifestyle therapies for patients with metabolic syndrome, including weight reduction, increased physical activity, decreased sodium and alcohol reduction, reduced consumption of saturated and trans fats and cholesterol, and increased consumption of fresh fruits and vegetables are extremely important. Studies have shown that dietary changes can lower blood pressure and improve other metabolic syndrome components [22, 23]. Increased exercise can also lower blood pressure [24].

Despite the benefits of lifestyle changes, pharmacological treatment of hypertension is frequently needed. However, the choice of an antihypertensive is controversial. Studies suggest that treatment with different antihypertensive drug classes may have varied effects on glucose and lipid metabolism [25]. Changes in insulin sensitivity are associated with adverse effects on glucose control [26, 27]. Increases in blood glucose during antihypertensive treatment have been found to be a predictor of myocardial infarction [28]. Insulin resistance is also associated with endothelial dysfunction, which is also predictive of future cardiovascular events [29]. Lind et al. have reported that these metabolic effects persist with long-term (> 2-3 years) antihypertensive treatment [30]. In this context, it would be important to choose antihypertensives that have the least adverse metabolic effects, particularly in patients with the metabolic syndrome.

In addition, to the choice of antihypertensive agent, the degree of blood pressure lowering is important. The lower the goal, the greater the number of antihypertensive agents needed, the cost of these agents and the potential for side effects. Patient adherence declines with the number of medications required. It is important to balance these drawbacks with improvement in clinical outcomes.

2. Evidence for blood pressure goals

By some standards, the Action to Control Cardiovascular Risks in Diabetes Study (ACCORD) was a disappointment. ACCORD was a large well-designed trial that attempted to study the effects of tight control of blood sugar, hypertension, and lipids in patients with type 2 diabetes mellitus [31]. In the original report, published in the *New England Journal of Medicine* in 2008, 10,251 patients (mean age, 62.2 years and median glycated hemoglobin level of 8.1%) were assigned to receive intensive therapy targeting a glycated hemoglobin level below 6 % or standard therapy targeting a level from 7.0 to 7.9% [31]. Of these patients, 38% were women and 35% had had a previous cardiac event. The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes. Details of the glycemic and lipid control arms have been presented [31, 32], and analyzed [33] elsewhere. The results of the blood pressure arm will be focused on below.

4,733 participants in ACCORD were randomly assigned to intensive blood pressure therapy, targeting a systolic pressure of <120 mm Hg or standard therapy targeting a systolic pressure of <140 mm Hg [34]. Again, the primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years. The annual rate of the primary outcome was 1.87% in the intensive therapy group and 2.09% in the standard therapy group (P=0.20). The annual death rates from any cause were 1.28% and 1.19% in the two groups, respectively (P=0.55). The annual stroke rate, a pre specified secondary outcome, were 0.32% and 0.53% in the two groups, respectively (P=0.01). Serious adverse events attributed to antihypertensive treatment occurred in 77 of the 2,362 participants in the intensive therapy group (3.3%) and 30 of the 2,371 participants in the standard therapy group (1.3%) (P <0.01). There were more subjects with a decrease of their estimated glomerular filtration rate to less than 30 ml per minute per 1.73 m^2 of body surface area in the intensive therapy group than in the standard therapy group (99 versus 52 events, P <0.01).

The interpretation of the ACCORD blood pressure results is complicated by a number of factors. The event rate observed in the standard therapy group was almost 50% lower than expected. This result may have been a consequence of the frequent use of statins and inclusion criteria that directed participants with dyslipidemia into the ACCORD lipid trial, leaving participants who were at lower risk in the blood pressure trial. Additionally, ACCORD may have been under powered and of too short of duration to discern a benefit [35]. In ACCORD the confidence intervals were wide and do not exclude a 27% benefit for the intensively treated group for the primary end point at 5 years. It is also possible that the effects of intensive blood pressure control in the setting of good lipid and glucuose control may differ for cerebrovascular and coronary events. That is, intensive blood pressure control is more likely to prevent strokes than myocardial infarctions. In a classic meta analysis, Collins and colleagues found that the decrease in stroke from antihypertensive therapy in clinical trials was what would be predicted based on epidemiologic studies [5]. However the decrease in coronary artery disease (CAD) was about one-half of what would be predicted.

The ACCORD blood pressure study population was relatively healthy and thus unlikely to have a high proportion of events. The 5,000 patients pre study mean systolic blood pressure was 140 mm Hg of mercury. Their mean age was 62 years and nearly one-half were women. The mean serum creatinine of this group was 0.9 mg per deciliter and 87% were receiving antihypertensive medication at the time of enrollment. The average glycated hemoglobin level was 8.3% and the mean body mass index was 32 kg/m^2. The mean urinary albumin/creatinine ratio was 14.3. Although these middle-aged patients were overweight and had type 2 diabetes, they had no substantial evidence of kidney disease and appeared to have good blood pressure control. At the 12 month visit, nearly 90% of patients were receiving a drug that blocks the renin angiotensin system, while more than 50% received β-blockers, about 40% received a calcium channel blocker, and nearly 60% received statins and platelet inhibitors. One might conclude that at 5 years, people with type 2 diabetes who have good quality cardiovascular care and no evidence of kidney disease do not have a major therapeutic advantage from lowering systolic blood pressure to <120 mm Hg. A longer follow-up time might be necessary to see a benefit of lowering blood pressure to this degree.

The negative outcome in ACCORD in the intensely treated blood pressure arm might also be attributed to the lack of effect on ischemic heart disease events that are included in the

composite end point. In the intensive treatment arm, investigators were advised to begin a regimen of an ACE inhibitor or angiotensin receptor blocker (ARB) plus a thiazide-like diuretic, chlorthalidone [36]. The same requirements were not given to the less intensively treated group. This resulted in the intensively treated group receiving roughly twice as much chlorthalidone as the less intensively treated group. That is, diuretics were used 83% and 89% of the time at 12 months and at the last visit, respectively, in the intensively treated group while in the standard care group, the usage was 52% and 56%. This amount of diuretic usage could account for the greater prevalence of hypokalemia seen in the intensive treatment group (P=.01) [8]. Data from the Systolic Hypertension in the Elderly Program (SHEP Trial), suggest that this degree of hypokalemia would essentially eliminate the projected benefit on ischemic heart disease events from the blood pressure reduction achieved in ACCORD [37].

The United Kingdom Prospective Diabetes Study (UKPDS) was a randomized, prospective, multicenter trial that, in addition to its attention to glycemic control, randomized patients to a "tight" blood pressure control regimen including ACE inhibition (captopril) or β-blocker therapy (atenolol), or "less-tight" blood pressure control that excluded these agents [38]. For tight compared to less-tight control of blood pressure, there were dramatic and significant improvements in risk reduction in any diabetes-related end point (24%), diabetes-related death (32%), stroke (44%), and microvascular disease (37%) [39]. In UKPDS, the goal blood pressure for the tight group was <150/85, and for the less-tight, <180/105. The mean achieved blood pressures were 144/82 and 154/87 mm Hg for the tight and less-tight groups, respectively. Of note, the mean blood pressure, at entry, was 160/94.

The Steno-2 Study reported a post interventional benefit for micro- and macrovascular complications of diabetes that persisted after risk factor intervention, although within-trial differences in risk factors for these complications (e.g., blood pressure) diminished, suggesting a persistent effect of earlier improvement in risk factors—a so-called legacy effect [40]. The diminishment in the difference of risk factors resulted from different phenomena: In the intensively-treated group, systolic blood pressure rose slightly in follow-up, while it remained stable in the conventionally-treated group. On the other hand, diastolic blood pressure remained low in the intensively-treated group, while it continued to fall in the conventional group. Recently, the survivor cohort of UKPDS was evaluated after a 10-year post-interventional follow-up that examined whether a continued benefit of improved blood pressure control could be demonstrated [41]. In contrast to the Steno-2 Study, the benefits of previously-attained improved blood pressure control were not sustained when between-group differences were lost. There were no differences in blood pressure control in patients treated with captopril or atenolol. Again, in contrast to the Steno-2 findings, in both "tight" and "less-tight" groups, blood pressures actually improved in follow-up and were indistinguishable, in the mid-140's/high 70's range. Thus, it may be that it was the improved blood pressure control in the "less-tight" group, as opposed to treatment failure in the "tight" group that decreased treatment differences.

INVEST (INternational VErapamil-SR/Trandolapril STudy) studied patients with multiple risk factors [42]. Of the 22576 participants (who were recruited because they had both coronary disease and hypertension), 6400 (28%) had diabetes. These patients were evaluated for the effects of achieved systolic blood pressure on the risk of cardiovascular events. Patients were categorized into three groups on this basis: tight (<130), usual (130-<140), and

uncontrolled (≥140) mm Hg achieved systolic blood pressure. Tight control was not associated with improved cardiovascular outcome compared to usual control. Uncontrolled patients did worse. A similar post hoc analysis of INVEST compared participants with and without peripheral arterial disease (PAD) [43]. 41.4% of PAD patients and 26.6% of those without PAD had diabetes (P<0.001). A J-shaped relationship was observed for patients with PAD: the hazard ratio for the primary outcome (all-cause death, nonfatal myocardial infarction, or nonfatal stroke), when plotted against achieved blood pressure, showed fewest events at blood pressures of 135-145/60-90); this was more pronounced for systolic blood pressure. Patients without PAD did not manifest this J-shaped association with systolic blood pressure. Patients with or without diabetes were not analyzed separately.

What lessons can be drawn about goal blood pressure for patients with metabolic syndrome from the studies cited above? It does not appear that the notion "the lower the better" applies to blood pressure in patients with type 2 diabetes, especially in those who are nonsmokers, have reasonable glycemic control and are taking statins and anti-platelet therapy. In ACCORD, lowering systolic blood pressure from the mid-130s to 120 mm Hg did not further reduce cardiovascular events, with the possible exception of stroke, which should be a pre-specified primary endpoint in future blood pressure clinical trials that aim for such low blood pressures. The price of lowering blood pressure to this degree in ACCORD was generally one additional antihypertensive and it was accompanied by a significantly higher rate of serious adverse events. Thus, it appears that lowering systolic blood pressure to 120 mm Hg is not warranted and recommendations to aim for a systolic blood pressure of <140 mm Hg and a diastolic blood pressure, based on the HOT and UKPDS results presented above, of <80 mm Hg are best supported by current evidence. However, it must be remembered that longer term follow-up of ACCORD may lead to different conclusions.

3. Effect of different classes of antihypertensive on components of the metabolic syndrome

Thiazide diuretics

Several studies have suggested an association between thiazide use and the development of glucose intolerance and diabetes. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the group randomized to chlorthalidone had a higher proportion of patients who developed diabetes than those randomized to either amlodipine or lisinopril [44]. In the Systolic Hypertension in the Elderly Program (SHEP), there was not a statistically significant increased rate of diabetes comparing chlorthalidone with placebo after 3 years, but in a later 14.3 year follow-up, 13% of patients given chlorthalidone versus 8.7% of those given placebo (P < 0.0001) developed diabetes [45, 46]. In a large study of hypertensive men and women, after adjustment for BMI, those taking compared with those not taking thiazide diuretics had an increased risk of developing diabetes [47]. We studied 2624 patients who were initiated on thiazide diuretics [48]. Increasing values of fasting blood glucose (FBG) were associated with increasing baseline BMI and there was a positive association between a new diagnosis of diabetes after thiazide initiation and increasing BMI that ranged from 2.7% in the first quartile of BMI to 6.5 % in the heaviest quartile. Studies have also found an association between blood glucose and thiazide dose [49, 50]. A review of nine studies using a relatively low dose (12.5 mg) of

hydrochlorothiazide as monotherapy found that increases in glucose levels were nether clinically nor statistically different from baseline levels [51]. Interestingly, in most of these studies, there was little relationship between blood pressure effects and diuretic dose. An association between hypokalemia and glucose intolerance, even in euglycemic subjects, has been described [48, 52, 53]. In patients on thiazides, hypokalemia has been associated with higher FBG that improved after replacement of potassium [54].

Thiazide diuretics may impair glucose metabolism by decreasing peripheral insulin sensitivity, resulting in increasing insulin secretion [55-57]. Our results suggest that the probability of developing new diabetes after thiazide initiation is associated with increasing BMI [48]. This association is supported by our previous work (DS). In 139 patients randomized to 50 mg of hydrochlorothiazide for 2 months, there was an increasing change from baseline serum insulin levels as a consequence of increasing body mass index [18].

Diuretics may also affect lipid metabolism. In general, high dose diuretics have been reported to increase serum total cholesterol by about 4% and serum LDL-cholesterol by 10% [51]. In ALLHAT, the group randomized to chlorthalidone had a higher total cholesterol levels at 2 years by about 3 mg/dL (~1.5%) than those randomized to either amlodipine or lisinopril (P<.001 for both); this difference diminished at 4 years for amlodipine, although not for lisinopril [44]. In SHEP, there was a small but significant increase of total cholesterol (P<.01) and decrease of HDL-cholesterol (P<.01) comparing chlorthalidone to placebo after 3 years. In another study, there was a 10% increase (P<.05) in fasting triglycerides from baseline after 16 weeks of treatment with hydrochlorothiazide compared with those treated with valsartan [58]. In a cross-sectional study from Brazil, hypertensive patients treated with diuretic monotherapy had a more atherogenic lipid profile (increased total- and LDL-cholesterol and apolipoprotein B) than patients on combined diuretic-based medication regimes, suggesting that the nondiuretic therapy had a mitigating effect on the lipid profile [59]. The mechanism of diuretic induced dyslipidemia may be related to increased hepatic production, in part mediated by a reduction in insulin sensitivity [51].

The impact of the ALLHAT findings on clinical recommendations is controversial [44]. On the one hand, are the metabolic abnormalities associated with chlorthalidone noted above. On the other hand, is the fact that those patients randomized to chlorthalidone had virtually identical clinical outcomes compared with lisinopril and amlodipine in terms of the primary outcome: the occurrence of coronary heart disease and nonfatal myocardial infarction. For secondary outcomes, chlorthalidone was superior to amlodipine in preventing heart failure, and compared with lisinopril, chlorthalidone was superior as a means to lower blood pressure and prevent stroke, as well as to prevent combined cardiovascular disease and perhaps heart failure. At present, we believe that thiazide diuretics (especially chlorthalidone) are alternative first choice agents in nondiabetic patients with metabolic syndrome but should be used carefully in patients with elevated BMI. In those instances where patients become diabetic after initiation of thiazides, we recommend that an alternative antihypertensive class be used rather than treat the metabolic consequences of thiazides with diabetic medications. In diabetics, thiazides diuretics may also be used. However, in those instances where initiation of these agents results in a worsening of glucose control, again, we would recommend the use of alternative agents.

β-Blockers

The place of β-blockers in the treatment of hypertension is controversial. This is partly based on the finding that these agents are less effective in reducing the incidence of stroke [60, 61], myocardial infarction and death than are other antihypertensives [61, 62]. These findings are

complicated by the diversity of β-blockers that have varying pharmacological properties. The mechanisms of action and pathophysiological effects vary widely among the nonselective, selective, and vasodilating β-blockers. Added to this variation are the effects of agents such as carvedilol that have both non-selective β-blocker and α_1-blocking properties.

In several studies of non-selective [63] or β_1 selective [64-66] β-blockers, there was a significant decrease in insulin sensitivity in hypertensive patients. This decrease in insulin sensitivity may have a deleterious effect on glycemic control in patients with hypertension or in those with type 2 diabetes mellitus. In patients with the metabolic syndrome, decreases in insulin sensitivity may be initially compensated for by increases in insulin secretion by pancreatic β-cells. However, after a period of time, the β-cells are no longer able to keep up with the increasing insulin demands and increase in blood glucose, and potentially overt diabetes, may result.

In the Atherosclerosis Risk in Communities Study (ARIC), hypertensives treated with β-blockers had a 28% increased risk of developing type 2 diabetes compared with patients taking no medication [67]. In INVEST, hypertensives randomized to verapamil-based therapy had a 15% lower incidence of new onset diabetes than subjects in the atenolol group [68]. Other studies have found similar results comparing β-blockers to either the angiotensin-converting enzyme (ACE) inhibitors [69] or angiotensin receptor blockers (ARBs) [70] .

Several actions of β-blockers may affect insulin sensitivity and glycemic control. β-blockers block pancreatic β_2 receptors resulting in an inhibition of insulin secretion that results in an impairment of glucose metabolism leading to hyperglycemia [55]. This effect is more pronounced with nonselective β-blockers, but can also be seen with higher doses of selective β-blockers [71]. β-blockers have been associated with weight gain leading to the metabolic syndrome due to the weight gain itself as well as through obesity mediated impairment of insulin sensitivity [72, 73]. Insulin promotes vasodilatation resulting in increased blood flow in skeletal muscles [74]. During treatment with nonselective β-blockers, unopposed α_1-activity causes vasoconstriction leading to decreased blood flow to muscles [75]. This may result in decreased insulin-stimulated glucose uptake and insulin resistance. In insulin-resistant states such as type 2 diabetes and obesity, endothelium-dependent insulin-mediated vasodilatation is impaired which may also lead to insulin resistance [74, 76]. In the metabolic syndrome, the interaction of obesity and hyperglycemia with β-blockers may lead to more severe skeletal vasoconstriction resulting in worsening insulin resistance.

Newer β-blockers that cause vasodilatation appear to not have the deleterious effects on insulin sensitivity and glucose metabolism described above. Carvedilol, as noted above, a non-selective β-blocker with α_1-blocking properties has been found to improve insulin sensitivity. In 72 hypertensive patients without diabetes, carvedilol compared with metoprolol resulted in a 14% increase in insulin sensitivity while metoprolol led to a decrease [77]. A study comparing carvedilol with atenolol had similar results [78]. In two trials comparing carvedilol with metoprolol, the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial and the Carvedilol or Metoprolol European Trial (COMET), the carvedilol group had decreases in both insulin resistance and HbA_{1c} while the metoprolol group had an increase in HbA_{1c} and no change from baseline in insulin resistance (GEMINI) [79], and improved rates of survival and cardiovascular hospitalizations (COMET). In GEMINI, although blood pressure was similar between groups, progression to microalbuminuria was less frequent with carvedilol than

with metoprolol. This may reflect an antioxidant effect specific to carvedilol [80]. Findings from GEMINI also suggest that the use of vasodilating β-blockers may not result in weight gain [81]. In addition to carvedilol, vasodilating β-blockers available in the US are labetalol and nebivolol.

The effects of β-blockers on lipid metabolism are modest, but also vary according to β-blocker type. Nonselective β-blockers increase serum triglycerides and tend to lower HDL-cholesterol, while cardioselective β_1-blockers and β-blockers without intrinsic sympathomimetic activity have qualitatively similar but less pronounced effects. These effects may be, at least in part, mediated by weight gain. In the Losartan Intervention for Endpoint (LIFE) reduction study, HDL- cholesterol decreased more and remained lower during the first 2 years of the study in those treated with the β_1-selective blocker atenolol compared with those randomized to losartan [82]. In a study comparing atenolol with metoprolol, treatment increased serum triglycerides by 21% and 29%, respectively, compared with placebo, and decreased HDL-cholesterol by about 7% [65]. In a recent study comparing the effects of carvedilol and metoprolol on serum lipids in diabetic hypertensive patients, both drugs decreased HDL-cholesterol and increased triglycerides [83]. Comparing the two drugs, there was no difference in HDL-cholesterol levels but carvedilol resulted in statistically significant lower levels of total cholesterol, triglycerides and non-HDL cholesterol.

Based on the above, it appears logical in patients with the metabolic syndrome, who require a β-blocker, to treat them with one of the newer vasodilating agents that have neutral or beneficial metabolic effects. That said, at present, there are few studies that directly compare the different types of β-blockers on hard clinical outcomes, especially total mortality. Adding to this uncertainty is the fact that newer β-blockers are far more expensive than older agents such as atenolol and metoprolol.

ACE inhibitors and angiotensin receptor blockers

Over20 years ago, the ACE inhibitor captopril was shown to benefit glucose metabolism and insulin resistance, particularly in comparison to thiazides [55]. ACE inhibitors and ARBs may exert beneficial effects on glycemic control through a variety of mechanisms related to the inhibition of angiotensin II. Angiotensin II activates the sympathetic nervous system resulting in impairment of insulin secretion and peripheral glucose uptake [84]. Angiotensin II also impairs pancreatic blood flow and enhances insulin resistance, while ACE inhibitors directly improve insulin sensitivity primarily in skeletal muscle [85].

The magnitude of the beneficial effect of ACE inhibitors on glucose metabolism is demonstrated by clinical trials such as the HOPE (Heart Outcomes Prevention Evaluation) Study, which demonstrated a reduced rate of new onset diabetes mellitus in patients taking the ACE inhibitor ramipril [86]. Angiotensin II has a central role in glucose metabolism, in addition to its effect on the sympathetic nervous system and aldosterone release, that includes activation of insulin-stimulated mitogenic pathways that promote vascular smooth muscle proliferation (MAPK), but suppression of pathways involved in glucose transport (PI-3K) [87-91]. Nitric oxide synthase may play a key role in mediating angiotensin effects [92], as might oxidative stress [93, 94]. In an animal model of atherosclerosis, (the Watanabe Heritable Hyperlipidemic Rabbit), the combination of the aldosterone antagonist eplerenone with the ACE inhibitor enalapril led to additive protective effects on endothelial function and atherosclerotic changes [95]. In patients with documented atherosclerosis, ramipril lowered highly sensitive C-reactive protein [96]. This “crosstalk” between vascular growth

and metabolic pathways may explain many of the defects in the metabolic syndrome. In patients with cardiac allograft vasculopathy, ACE inhibitors appear to be associated with plaque reduction [97].

While many of the studies reviewed above have grouped ACE inhibitors and ARBs together as generally having similar mechanisms of action, there are differences both among ACE inhibitors and between ACE inhibitors and ARBs. The ACE inhibitors enalapril and perindopril were compared in normotensive patients with coronary artery disease; neither agent lowered blood pressure, but perindopril was superior in terms of anti-oxidant, antithrombotic, and profibrinolytic activities [98]. In mild hypertensive patients, zofenopril (a sulfhydryl-containing ACE inhibitor) lowered LDL-cholesterol, oxidized LDL, peroxide, and increased flow-mediated dilation (a marker of endothelial function) compared to ramipril (a carboxylic-containing ACE inhibitor), and atenolol. Blood pressure was comparable in all three groups [99].

ARBs do not appear to be active on these pathways. Furthermore, there may be differences among ARBs. Telmisartan, for example, seems to activate insulin-sensitizing PPAR-γ pathways [100], with benefit in preclinical and clinical studies [101, 102]. Studies in nondiabetic hypertensive patients shown improvement in insulin sensitivity, measured by the homeostasis model assessment (HOMA) technique, when telmisartan was used alone; this effect was blunted when the drug was used in combination with the dihydropyridine calcium channel blocker nisoldipine [103]. This benefit occurred without changes in serum values of the adipose tissue-derived cytokine, adiponectin. Similar results on insulin sensitivity, also assessed by HOMA, were reported in a study of hypertensive type 2 diabetic patients [104]. Other investigators have found that telmisartan is associated with decreased vascular inflammation, reduced visceral fat, and increased adiponectin [105], while others have reported that telmisartan, compared to candesartan lowered fasting plasma glucose and body weight, and increased adiponectin. Diastolic blood pressure was comparably reduced in both treatment groups compared to control [106]. Losartan, another ARB, has an uricosuric effect that may be of benefit in cardiovascular risk [107].

A recent development in this treatment approach includes renin inhibitors, that improve blood pressure but have not been studied for their metabolic effects [108, 109], although recent data suggests an improvement (reduction) in atherosclerosis progression with aliskerin [109].

Calcium Channel Blockers

Calcium channel blockers (CCBs) may impair insulin release, but this effect on glucose metabolism appears to be balanced by their action to increase peripheral glucose uptake [110, 111]. CCBs have been shown to have no significant adverse metabolic effect [112, 113], or a slight negative effect [114]. Some short-term studies have even suggested a slight positive effect on glucose and insulin metabolism [66]. In one study, long-acting CCBs have been reported to have no significant metabolic effect [115], while an early study comparing short-acting nifedipine to atenolol showed improvement in postprandial glucose (suggesting improved insulin action since concurrent insulin concentrations were unaffected) and triglyceride values, as well increased HDL values, with the former agent [66].

Dihydropyridine CCBs (i.e., nifedipine) have no antiproteinuric effect, unlike the benzothiazepine diltiazem and the phenylalkylamine verapamil, and do not slow the progression of diabetic nephropathy [116]. This may have particular relevance in these high-risk patients. In a study of 12 550 nondiabetic hypertensives, subjects taking β -blockers, but

not those taking thiazides, ACE inhibitors or calcium channel blockers, were at increased risk of developing diabetes [67]. In a study of 16176 coronary patients with hypertension, CCB-based therapy (verapamil SR) was less likely to result in the development of newly diagnosed diabetes mellitus than β-blocker (atenolol) based treatment [68]. In this study, addition of the ACE inhibitor trandolapril to verapamil SR decreased diabetes mellitus risk and the addition of hydrochlorothiazide to atenolol increased risk. In hypertensive patients with chronic kidney disease (stage not defined, but baseline creatinine ~1.6), treated with either telmisartan or amlodipine, creatinine, proteinuria, IL-6, MMP-9, and total cholesterol all declined, while 24 hour urinary creatinine clearance improved with telmisartan but not with amlodipine, despite comparable blood pressure reduction [117]. In another trial, treatment with the ARB valsartan was associated with a greater reduction in new onset diabetes compared with amlodipine [118].

CCBs appear to have systemic antiinflammatory effects that may be additive with other antihypertensive agents [119-121]; there may also be improvement (reduction) in oxidized LDL-cholesterol levels [122].

α-Antagonists

Prazosin, using fasting and postprandial glucose and insulin data, has been found to improve insulin sensitivity in patients with essential hypertension [123]. Pollare, et al. similarly reported that prazosin directly improved insulin sensitivity [124]. Prazosin has also been reported to improve HDL kinetics [125]. Terazosin appears to have no effect on glucose tolerance or insulin sensitivity [126], although men with benign prostatic hypertrophy treated with terazosin have improved lipid values [127]. No data is available for tamsulosin.

Doxazosin improved glucose and lipid metabolism in diabetic patients and in patients with impaired glucose tolerance [128, 129]. It has also been reported to improve insulin resistance, and increase LDL particle size [130, 131]. Doxazosin has also been described as acting synergistically with acarbose in patients with impaired glucose tolerance [132]. When doxazosin was added to existing therapies in patients with inadequately treated hypertension and impaired glucose metabolism, blood pressure control was improved in over 1/3 of cases, with concomitant improvement in glucose and lipid parameters and a reduction in atherosclerotic cardiovascular disease risk [133]. Similar metabolic benefit occurred when doxazosin was compared to bendrofluazide in hypertensive patients [134], and when doxazosin was compared to atenolol [135]. Doxazosin also reduced serum concentrations of oxidized LDL-cholesterol (a more atherogenic lipid fraction) in hypertensives [136]. Urapidil has no major effect on glucose metabolism, but favorably affects another cardiovascular risk marker, fibrinogen [137].

Central-acting α-agonists

Clonidine, which acts by binding to central α-2-adrenergic and imidazoline receptors, appears to be metabolically neutral in terms of glucose and insulin effects [138]; more recently developed imidazoline agonists have not been widely studied from this perspective [139]. However, rilmenidine has recently been reported to have similar blood pressure, lipid, and glucose effects to lisinopril in hypertensive women with metabolic syndrome [140].

The metabolic effects of antihypertensives are summarized in the Table.

Class of agent	Glucose and insulin effects		Lipid effects			
	Glucose	IR	Total Chol	HDL-C	LDL-C	TG
Thiazide (inc. chlorthalidone)[1]	↑	↑	↑	↓	↑	↑
β-blockers (nonselective)	↑	↑		↓		↑
Cardioselective β-blockers (β1)	↑	↑		↓		↑
Vasodilating β-blockers	↓	↓	↓	↓	↓	↓
ACEI/ARBs	↓	↓			↓	
Renin inhibitors	Unk.	Unk.	Unk.	Unk.	Unk.	Unk.
Calcium channel blockers	↓	↓	↓	↑	↓	↓
α-antagonists	↓	↓	↓	↑	↓	↓
Central α-agonists (e.g., clonidine)	neutral	neutral	neutral	neutral	neutral	neutral

Where IR=insulin resistance, and Total Chol, HDL-C, LDL-C, and TG are total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides, respectively. Unk=unknown. ACEI refers to angiotensin converting enzyme inhibitors, and ARBs refer to angiotensin receptor blockers.

[1] Thiazide diuretics (especially chlorthalidone) are alternative first choice agents in nondiabetic patients but should be used carefully in patients with elevated BMI. In those instances where patients become diabetic after initiation of thiazides, an alternative antihypertensive class should be used. For details, see text.

Table 1. Metabolic effects of antihypertensive agents.

Current treatment recommendations for blood pressure control in patients with diabetes are based on these considerations of balancing metabolic, blood pressure, renal, neurologic (dizziness) and electrolyte effects. Initial treatment should include RAS blockers (either ACE inhibitors or ARBs), followed with a calcium channel blocker or thiazide-like diuretic as 2nd line. Current data suggests that the deleterious metabolic effects that may result do not override the benefit of blood pressure reduction [3], although the recent ACCOMPLISH study (Avoiding Cardiovascular Events Through COMbination Therapy in Patients Living With Systolic Hypertension) pointed out that combining the ACE inhibitor benazepril with amlodipine, compared to benazepril with hydrochlorothiazide, resulted in benefit in terms of reduction in cardiovascular events such as acute clinical events and revascularizations; blood pressure was comparable between the two groups [141].

Lifestyle changes (weight loss, exercise, reduction of alcohol intake, smoking cessation,) should not be ignored. Glucose control, while laudable conceptually, may be problematic (see elsewhere). Potassium monitoring should continue, and potassium-containing foods and use of nonsteroidal antiinflammatories may need to be limited [3]. Combination agents, where available, might improve adherence [3]. α–blockers, while powerful in terms of blood pressure and prostate effects, may contribute to orthostatic dizziness and may need to be limited or avoided [3]. We should not forget that microalbuminuria is a marker of early diabetic nephropathy as well as a risk factor for microvascular and macrovascular

cardiovascular disease [142] and should be monitored, with efforts expended to mitigate it. These overall recommendations are summarized in current American Diabetes Association (ADA) guidelines [143]. The Figure represents a treatment strategy derived from ADA (143) and other (2) guidelines.

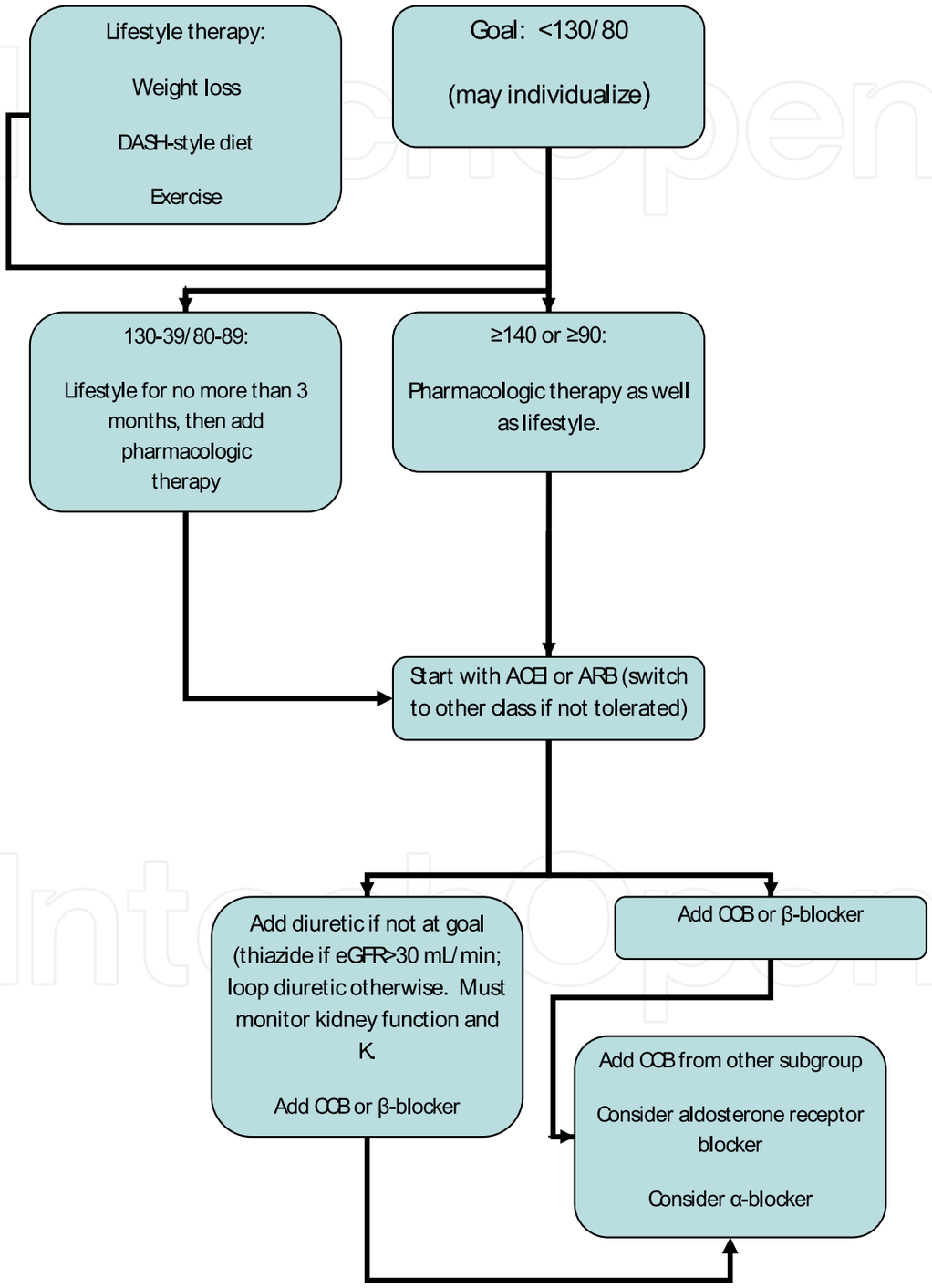

Fig. 1. Recommendations for blood pressure control in patients with diabetes (2, 143)

4. Genetic markers and treatment of hypertension in patients with the metabolic syndrome

As noted above, treatment of hypertension in the metabolic syndrome can exacerbate other of its components (e.g., glucose and lipid control). Further, hypertensive treatment in diabetics, may have less than the expected benefit in terms of preventing coronary disease and mortality. Is it possible that evolving genetic markers can help guide therapy more precisely?

The INVEST study observed that patients with more severe vascular disease, particularly those of Hispanic ethnicity, were at greater risk for developing diabetes, especially with hydrochlorothiazide treatment. This risk was attenuated by more aggressive BP control and use of a verapamil-trandolapril combination [144]. There is developing data that suggests that the CYP3A5 genotype, which does not appear to contribute importantly to the risk of hypertension, may influence response to calcium channel blockers [145]. Similarly, the KCNMB1 genotype (which contributes to polymorphisms in the large-conductance calcium and voltage-dependent potassium channel β1 subunit) may influence response to verapamil and potentially adverse outcomes [146].

Other data from Beitelshees and colleagues suggests that polymorphisms in the CACNA1C gene may help identify groups that benefit most from calcium channel blocker therapy, a group that benefits from β-blocker therapy, and a third group in which calcium channel blocker and β-blocker therapy are equivalent [147]. Similar analyses leading to possible future predictions are available for β-blocker treatment outcomes based on β-adrenergic receptor gene polymorphisms [148], and promoter polymorphisms in angiotensin-converting enzyme [149]. This last group of analyses may explain the variation between populations in cardiovascular risk and treatment outcomes, since certain alleles are more frequent in African-Americans than in either Hispanics or Caucasians [149]. Adducin is a ubiquitously expressed cytoskeleton protein that is coded by ADD1. Polymorphisms in this gene may lead to increased renal tubular sodium reabsorption and hypertension; certain alleles have been shown to manifest an excess risk for a cardiovascular event or death, particularly in African-Americans [150].

5. Conclusions

The prevalence of obesity, hypertension and type 2 diabetes mellitus, and, as a consequence, the metabolic syndrome, is increasing in the US. In this setting, it is important to individualize antihypertensive therapy and to monitor its metabolic consequences so that potential adverse effects that would negate some of the benefits of blood-pressure lowering are minimized. Strategies to improve blood pressure control in patients with metabolic syndrome, including decisions concerning the best pharmacological treatment for these patients, will have major morbidity and mortality consequences. The predominance of evidence favors a strategy to lower blood pressure to a level approaching the criteria for this syndrome (<130/80) [151, 152]. However, a goal blood pressure of <130/80 is not supported by current evidence. In hypertensives whose blood pressure is more than 20/10 above target, this frequently will require the initiation of a combination of antihypertensives [153].

Treatment with different antihypertensive drug classes has varied effects on glucose and lipid metabolism. Thiazide use in hypertensives has been associated with the development of glucose intolerance and diabetes. Studies suggest that the probability of worsening

glucose metabolism and the development of new diabetes after thiazide initiation is associated with increasing body mass index. Thiazide use also results in small increases in total and LDL-cholesterol and triglycerides and decreases in HDL-cholesterol. These changes are more pronounced with high dose thiazides.

Non-selective or β_1 selective β-blockers may also lead to decreased insulin sensitivity in hypertensive patients. On the other hand, β-blockers, such as carvedilol, that cause vasodilatation may not have these deleterious effects on insulin sensitivity and glucose metabolism. The effects of β-blockers on lipid metabolism may also vary according to β-blocker type. Nonselective β-blockers modestly increase serum triglycerides and tend to lower HDL-cholesterol, while cardioselective β_1-blockers and those without intrinsic sympathomimetic activity have qualitatively similar but less pronounced effects. Vasodilating β-blockers appear to have even smaller deleterious effects on lipids.

ACE inhibitors and ARBs may exert beneficial effects on glycemic control through a variety of mechanisms related to the inhibition of angiotensin II. These agents may be particularly useful in patients with microalbuminuria to slow the progression of renal disease. While there may be some small differences among different classes of CCBs, there is little net effect of these agents on glucose or lipid metabolism. The α-antagonists generally appear to improve glucose and lipid metabolism in diabetic and non-diabetic patients but the increase in cardiovascular endpoints in the ALLHAT study with doxazosin suggests that until there is evidence to the contrary, this class of antihypertensive should not be used as first line agents.

The choice of an antihypertensive also has important implications for the cost of medical care. Thiazide diuretics and β-blockers are considerably less expensive than most other antihypertensive medications and have been shown to be effective antihypertensive treatment in several major studies [6, 7, 44]. However, some of the medication cost savings would be negated if thiazide and β-blocker use is complicated by an increased probability of developing glucose intolerance and even diabetes with its attendant medication and other costs associated with its treatment and manifestations. Most of the studies we have reviewed have focused on one agent in comparison to another; there is scant data on net metabolic effects of combining drug classes. Furthermore, individual patient responses may vary from the expected.

The coexistence of hypertension, dyslipidemia and glucose intolerance increases the risk of coronary artery disease, stroke, peripheral vascular disease, nephropathy, neuropathy and retinopathy [154-156]. The metabolic syndrome is associated with cardiovascular disease and the development of diabetes [157-159]. In treated hypertensive patients, occurrence of new diabetes portends a risk for subsequent cardiovascular disease that is similar to that of other diabetics [160]. The use of an antihypertensive that results in improvements in dyslipidemia, insulin sensitivity and glucose metabolism would be a logical choice in patients with metabolic syndrome, but this recommendation needs to be supported with clinical trials with hard clinical outcomes, especially total mortality.

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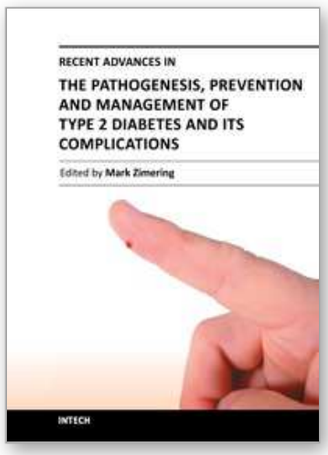

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Type 2 diabetes â€œmellitusâ€ affects nearly 120 million persons worldwide- and according to the World Health Organization this number is expected to double by the year 2030. Owing to a rapidly increasing disease prevalence, the medical, social and economic burdens associated with the microvascular and macrovascular complications of type 2 diabetes are likely to increase dramatically in the coming decades. In this volume, leading contributors to the field review the pathogenesis, treatment and management of type 2 diabetes and its complications. They provide invaluable insight and share their discoveries about potentially important new techniques for the diagnosis, treatment and prevention of diabetic complications.

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