VA PRACTICE Matters

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DIABETES CARE PRIORITIES: PREVENTING CARDIOVASCULAR COMPLICATIONS

- *About 1 in 8 patients seen in the VHA system has diabetes.*[1]
- *In 1997, US health care costs for people with diabetes exceeded $77 billion dollars (8% of all health care spending).*[2]
- *Veterans with diabetes account for more than 75,000 VHA hospital admissions and 3.8 million outpatient clinic visits annually and for more than 25% of pharmacy expenditures.*
- *Cardiovascular disease (e.g., heart attacks, strokes, and congestive heart failure) is the leading cause of complications and death in people with diabetes, and middle-aged diabetic patients have 2-4 times higher risk of cardiovascular events and death than age-sex matched controls.*[3-4]
- *Optimal risk factor management can substantially reduce cardiovascular events and death in people with diabetes.*
- *Strict attention to blood pressure control is the single most important medical intervention to prevent complications and premature death in the typical patient with type 2 diabetes.*

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BACKGROUND:

Providing optimal care to patients with diabetes can be a challenge. In addition to the long list of recommended health maintenance interventions and the ongoing task of managing blood glucose levels, patients with diabetes often have many symptomatic problems that must be addressed during office visits. Although the average veteran with diabetes has more than 10 office visits a year, fewer than half of these are with their primary care physician, allowing just 3-5 brief office visits to manage this complex, multi-system disease. Perhaps due to the complexities of blood sugar control, interventions to prevent cardiovascular complications are sometimes overlooked, although these complications pose the greatest single threat to the health of people with diabetes.[3-4] As we strive to meet all of the diabetes related guidelines and performance measures,[5] we should remain aware that control of hypertension and hyperlipidemia are those interventions which are most likely to impact morbidity and mortality in the typical patient with type 2 diabetes.

TREATMENT GOALS AND THERAPIES:

Treatment goals are chiefly directed at preventing strokes and heart attacks, but some treatments are also directed at decreasing risk of peripheral vascular disease (and therefore amputations), congestive heart failure, end-stage renal disease, and visual impairment.

Blood Pressure Control

Most veterans with diabetes also have hyper–tension and for most of these patients, controlling their blood pressure is the single most important medical intervention in improving their health and prolonging their lives. Blood pressure control has 1) twice the absolute benefit in diabetic patients than it does in non-diabetic patients[6] and 2) dramatically improves both cardiovascular and microvascular (eye and kidney) outcomes.[7-8] How tightly must blood pressure be controlled? No one knows for sure, but for diabetic patients 140/90 is not a sufficient goal. The ADA recommends 130/85 as the best target. Using a strictly evidence-based approach, updated VA guidelines recommend 140/85 as a minimum goal, but acknowledge that there may be benefits to achieving even tighter blood pressure control.[6-8]

Patients with hypertension often receive suboptimal treatment for their blood pressure. Even in a randomized controlled trial, it may be extremely difficult to achieve tight blood pressure control. Although the Hypertension Optimal Treatment (HOT) trial strove to get the diastolic blood pressure in patients with hypertension decreased to <80 mmHg, the mean blood pressure was still 82-83 mmHg in the intensive treatment group.[7] Studies suggest that it is even more difficult to achieve intensive control of systolic blood pressure. No large randomized controlled trial of patients with diabetes and hypertension has achieved a mean blood pressure below 135 systolic, even with the use of 3-4 anti-hypertensive agents. In contrast, using 3-4 anti-hypertensive medications is generally successful in achieving blood pressures of 140/90 or better.[7] Therefore, common recommendations for tight control (such as blood pressure <130/85) may best be used as ideal goals that clinicians should try to achieve, within reason. Considering achievement of these strict goals as a quality or performance standard, without allowing for the number of blood pressure medications that the patient has been prescribed, is probably not appropriate.

Anti-Hypertensive Agents

- *Angiotensin converting enzyme (ACE) inhibitors*: ACE inhibitors have generally been considered the preferred first choice agent in most patients with diabetes because of possible advantages over other anti-hypertensive medications in preventing renal insufficiency.[3] However . . .

- *Beta-Blockers:* The recently completed United Kingdom Prospective Diabetes Study (UKPDS), a large randomized trial, found no overall benefit of using an ACE inhibitor versus a beta-blocker as a first choice agent in treatment of hypertension. Indeed, there was a non-statistically significant trend for patients treated with beta-blockers having better overall outcomes.[10]

- *Calcium channel blockers:* In contrast, two studies found that calcium channel blockers may not be ideal as a first line choice for treatment of hypertension for those with diabetes. These two studies suggest that when used as a first choice agent, calcium channel blockers are less effective than other agents in preventing important cardiovascular outcomes.[11-12] This has led some to recommend that calcium channel blockers, given their greater expense and possible lower efficacy, be reserved as a third or fourth choice agent.

In the past there were some concerns about using beta-blockers and thiazide diuretics for treatment of hypertension in diabetic patients. However, recent evidence suggests that these medications are effective, safe and relatively inexpensive treatments for controlling blood pressure and preventing adverse cardiovascular events, especially when used in low or moderate doses.[6, 10, 13] Often other conditions, such as angina or benign prostatic hypertrophy, will guide the choice of anti-hypertensive agent so that two conditions can be treated with a single medication. In general, the medication used is less important than the commitment to use up to 3-4 anti-hypertensive agents, as necessary, in an attempt to achieve strict blood pressure control.[6-8]

Treatment of High Cholesterol

Hyperlipidemia is common in patients with type 2 diabetes. While any pattern of hyperlipidemia can be seen in diabetes, common findings include elevations in serum levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides, often associated with low levels of high-density lipoprotein (HDL) cholesterol.[4] Each of these has been found to be an independent predictor of coronary artery disease in observational studies, but only treatment of elevated LDL cholesterol with HMG-CoA reductase inhibitors ("statins") has been shown to reduce mortality in randomized controlled trials. Treating patients who have high LDL cholesterol levels with statins reduces cardiovascular risk.[3-4] Given the high risk of cardiovascular complications in type 2 diabetes there is general agreement that LDL cholesterol should be treated aggressively.[3-5, 9] Yet, because there are no studies of primary prevention specifically in patients with diabetes, the optimal treatment goal for diabetic patients is not known and is therefore somewhat controversial.

The National Cholesterol Education Program advocates that LDL cholesterol should be treated to <100 mg/dl in all diabetic patients, since their risk of cardiovascular complications are similar to those with known coronary artery disease. However, except for patients with post coronary-artery bypass surgery, there are no studies indicating that there is a reduction in cardiovascular events by decreasing LDL cholesterol from 130 mg/dl to 100 mg/dl, although several trials are in progress.[9] The VA guidelines suggest that lipids should be measured annually for veterans with diabetes, with an LDL cholesterol target level of less than 130 and a triglyceride target level of 400 mg/dl; individual clinicians and patients may wish to try for even tighter control.[5]

A recent VA study demonstrated that treatment with gemfibrozil in patients with low HDL cholesterol levels (< 45 mg/dl) but normal LDL cholesterol levels is effective in reducing cardiovascular events, but not total mortality.[14] The absolute benefit of treating these patients is smaller than treating elevated LDL cholesterol, and because the evidence is recent, there are no current recommendations from any major guideline group suggesting that patients with isolated low HDL cholesterol levels should receive drug therapy.

Daily Aspirin

Daily aspirin use is a simple, effective and inexpensive medical intervention. Unfortunately, it is often forgotten among the complexities of diabetes care. Subgroup analyses of randomized controlled trials suggests that a low daily dose of aspirin may lower cardiovascular risk twice as much in patients with diabetes as it does in those without diabetes.[15-16] Given the high risk of cardiovascular disease in diabetes, unless aspirin therapy is contraindicated due to drug intolerance or bleeding risk, this simple inexpensive intervention is an absolute must.

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EXPERT OPINION

There has been an explosion of information on the value of lowering blood pressure in diabetic individuals with hypertension. ACE-inhibitor therapy is beneficial in diabetic subjects with high cardiovascular risk. Lowering of LDL cholesterol by statin therapy is clearly beneficial in diabetes. The VA-HIT study provides strong support for therapy with gemfibrozil for diabetic dyslipidemia.

Aspirin reduced cardiovascular risk by 15% over that provided by antihypertensive therapy in the HOPE Trial. C-reactive protein (CRP) is a new cardiovascular risk factor, and aspirin therapy reduced cardiovascular risk in CRP positive men in the U.S. Physicians' Health Study.

There are other new cardiovascular risk markers. Fibrinolysis is activated by tissue plasminogen activator (tPA) and is inhibited by plasminogen activator inhibitor-1 (PAI-1). Studies have shown elevated PAI-1 levels in type 2 diabetes, and PAI-1 is a predictor of future cardiovascular events. PAI-1 levels in diabetes are lowered by metformin and troglitazone. Large scale trials are needed.

What about intensive blood glucose management? The Department of Veterans Affairs, the National Heart, Lung, and Blood Institute, and NIH, are sponsoring long-term trials to address this important issue. Presently, it is prudent to take a multifactorial approach to prevention of cardiovascular disease in diabetes which includes aggressive antihypertensive and lipid-treatment strategies as well as low dose aspirin as top priorities. Glycemic regulation will slow progression of microvascular disease, and may eventually be shown to be beneficial in preventing progression of macrovascular disease.

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For VA Diabetes Practice Guidelines visit the web at http://www.va.gov/health/diabetes/default.htm

RECOMMENDATIONS

- Up to 3-4 anti-hypertensive agents should be used, as needed, in an attempt to achieve strict blood pressure control in patients with diabetes (<140/85 mmHg at minimum and even lower blood pressures may be desirable).
- Choice of specific anti-hypertensive agent is less important than level of blood pressure achieved. However, due to higher costs, and possibly lower effectiveness in preventing cardiovascular complications, calcium channel blockers should usually be reserved as a third or fourth choice agent.
- LDL-cholesterol should be treated with statins as the first choice agent, to achieve levels of at least <130 mg/dl, and lower levels may be beneficial.
- Unless aspirin use is contraindicated, patients with type 2 diabetes should take a low dose of aspirin each day.
- Smoking cessation counseling is a high priority for all patients who smoke, and this is particularly true for those with diabetes.

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TREATMENT GOALS AND THERAPIES

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Smoking cessation counseling

As a cost-effective behavioral intervention, counseling and support for smoking cessation is a priority for all patients who smoke. Given the high overall cardiovascular risk associated with type 2 diabetes,[3, 17] this is especially crucial for diabetes care.

Diabetes care can be complex and difficult. Attempts to improve glycemic control, foot care and early identification and treatment of microvascular complications are other very important interventions, especially for those with early onset diabetes and those with poor glycemic control.[18] However, we must not allow these other aspects of care to distract us from the major killer of people with diabetes — cardiovascular disease. The above treatment goals, directed at prevention of cardiovascular complications, may garner more benefit than all other aspects of diabetes care combined.

Evidence Chart for Diabetes Interventions

Major Blood Pressure Trials

Study	*Participants*	*Intervention*	*Outcome*
SHEP (JAMA 1996; 276:1886-92)	N=583 pts with T2DM and isolated systolic HTN	Chlorthalidone plus atenolol or reserpine as needed	34% (95% CI, 6%-54%) risk reduction (RR) in major cardiovascular events
HOT (Lancet 1998; 351:1755-62)	N=1501 pts with T2DM and HTN	Randomized to target DBP of ≤90, ≤85, or ≤80 using stepped protocol	For DBP target of ≤90 vs ≤80; RR major CVD events = 2.1 (1.2 – 3.4) RR CV mortality = 3.0 (1.3 – 7.1) RR total mortality = 1.8 (0.98– 3.2)
UKPDS (BMJ 1998; 317:703-13)	N=1148 pts with T2DM and HTN	Randomized to "tight" (target BP <150/85) vs "less tight" (target BP <180/105) control using stepped protocol	For tight control vs. less tight control: RR any DM end pt = 0.76 (0.62-0.92) RR total mortality = 0.82 (0.63-1.08) RR microvascular disease = 0.63 (0.44-0.89)
ABCD (N Engl J Med 1998; 338:645-52)	N=470 pts with T2DM and HTN	Comparison of enalapril and nisoldipine for treatment of HTN for 5 years	RR of MI in nisoldipine group = 9.5 (2.3-21.4)
FACET (Diabetes Care 1998; 21:597-603)	N=300 pts with T2DM and HTN	Comparison of fosinopril and amlodipine for treatment of HTN for 2.5-3.5 years.	For fosinopril vs. amlodipine: RR major cardiovascular events = 0.49 (0.26-0.95)

Major Asprin Trials

Study	*Participants*	*Intervention*	*Outcome*
Antiplatelets Collaboration (BMJ 1994; 308:81-106)	Meta-analysis of RCTs: N=1300 pts with T2DM	ASA vs. placebo	Odds reduction of major CVD events = 25% (non-significant trend)
ETDRS (JAMA 1992; 268: 1292-9)	N=3711 pts with type 1 and 2 DM	ASA vs. placebo	RR MI = 0.83 (99% CI = 0.66-1.04) No harmful effects; note use of 99% rather than 95% CI.

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