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Scientific Update™

Optimizing Therapeutic Strategies for Hypertensive Diabetics

Originally presented by: Finlay McAlister, MD; Sheldon Tobe, MD; and Ellen Burgess, MD

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Hypertension in patients with type 2 diabetes mellitus (T2DM) is a prevalent condition, and associated with substantial morbidity and mortality. Hypertension is also a major risk factor for cardiovascular (CV) events, such as myocardial infarction (MI) and stroke, as well as for microvascular complications, including retinopathy and nephropathy. Until recently, little research had been done specifically in patients with diabetes and hypertension. This issue of *Cardiology Scientific Update* reviews the associated pathophysiology and the impact of effective blood pressure (BP) lowering on renal function in diabetics. In addition, the discussion covers the clinical evidence supporting the use of antihypertensive agents in the management of hypertensive diabetes, as well as the ongoing trials examining the use of different antihypertensive drug classes on renal outcomes in diabetic patients with proteinuria.

Antihypertensive therapy in T2DM with or without proteinuria

Hypertension is a common comorbid condition of diabetes that affects 20% - 60% of people with the disease, although different criteria can indicate even higher percentages.[1] CV disease is the most costly complication of diabetes and is the cause of 86% of deaths in patients with T2DM.[2] Numerous studies have demonstrated a relationship between the different stages of renal complications from diabetes and the increased risk of all-cause mortality in T2DM. The Wisconsin Study,[3] a population-based study of diabetic persons from 1984-1986, examined a prospective cohort of 840 subjects with older-onset T2DM who provided urine samples. The presence of microalbuminuria was determined by an agglutination inhibition assay, and gross proteinuria by a reagent strip. The primary outcome was the time to mortality from CV disease, as determined by death certificates. In this cohort with older-onset T2DM, 54.8% had normoalbuminuria, while 24.8% had microalbuminuria and 20.5% had gross proteinuria. During the 12-year follow-up, 364 deaths from CV disease were identified and in comparison with normoalbuminuric patients, those with microalbuminuria and gross proteinuria had significantly higher risks of CV mortality. The relative risk (RR) adjusted for conventional risk factors was 1.84 (95% confidence interval [CI], 1.42-2.40) for those with microalbuminuria, and 2.61 (95% CI, 1.99-3.43) for those with gross proteinuria. These data suggest that both microalbuminuria and gross proteinuria are associated with subsequent mortality from all causes and from CV causes, as well, since they appear independent of known CV risk factors and diabetes-related variables. Plotting a graph of mortality data from the United Kingdom Prospective Diabetes Study (UKPDS),[4] the Reduction of Endpoints in noninsulin dependent diabetes mellitus (NIDDM) with the Angiotensin II Antagonist Losartan (RENAAL) study,[5] and the United States Renal Data System (USRDS)[6] (Figure 1), appears to confirm an increased risk of mortality with increasing renal complications from diabetes.

An observational analysis of the data collected by UKPDS revealed that the microvascular and macrovascular complications associated with T2DM increase with increasing systolic BP. On average, a 10-mm Hg reduction in systolic BP conferred a 12% reduction in the risk of developing a diabetic complication, and a 15% reduced risk of death related to diabetes.[7] Embedded within the UKPDS was a randomized, controlled trial comparing tight BP control using a captopril- or atenolol-based regimen (target BP <150/85 mm Hg) with a less tight BP control (avoiding treatment with angiotensin-converting enzyme [ACE] inhibitors or β-blockers and aiming at a BP <180/105 mm Hg) on the development of complications in hypertensive patients with T2DM. During the median follow-up of 8.4 years, mean BP was significantly lower in the group with tight BP control (144/82 mm Hg) compared with the less tightly controlled group (~154/87 mm Hg). Tight BP control reduced the risk of developing any endpoint related to diabetes by 24% and reduced the risk of diabetes-related mortality (two-thirds of which was due to CV disease) by 32%, compared

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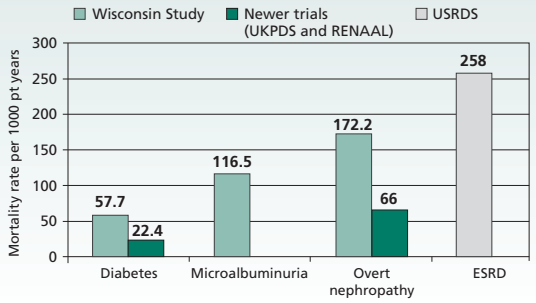
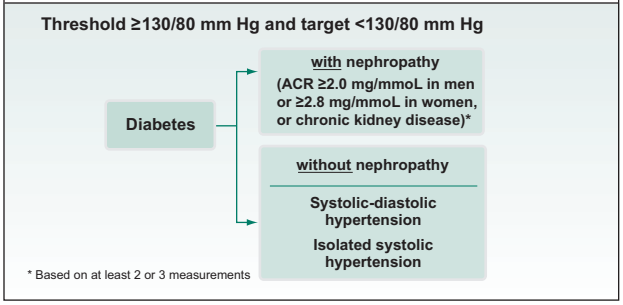
Figure 1: Renal complications from diabetes and mortality[3-6]



UKPDS = UK Prospective Diabetes Study; RENAAL = Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; USRDS = United States Renal Data System; ESRD = end-stage renal disease

Figure 2: Treatment of hypertension in association with diabetes mellitus (CHEP 2009)[12]



CHEP = Canadian Hypertension Education Program; ACR = albumin to creatinine ratio

with less-tight BP control.[4] Captopril- and atenolol-based regimens were equally effective at reducing BP and at reducing the risk of macrovascular and microvascular complications of T2DM in the group with tight BP control.[8] In addition, the 10-year post-trial follow-up data from the UKPDS demonstrate that the risk reductions for relatively tight BP control in the diabetic populations were no longer maintained once the BP differences disappeared.[9] Thus, sustained benefits depend on optimal BP control.

The recently published Action in Diabetes and Vascular Disease: Preterax and Diamicron® Controlled Evaluation (ADVANCE) trial[10] examined the effects of the routine administration of an ACE inhibitor-diuretic combination on serious vascular events in patients with diabetes, irrespective of initial BP levels or the use of other BP-lowering drugs. The study randomized 11 140 patients with T2DM to treatment with a fixed combination of perindopril and indapamide or matching placebo. The primary endpoints were composites of major macrovascular and microvascular events, defined as death from CV disease, nonfatal stroke or nonfatal MI, and new or worsening renal disease or diabetic eye disease. After a mean follow-up of 4.3 years, 73% of those assigned to active treatment and 74% of those assigned to the control group remained on randomized treatment. Compared with patients assigned to placebo, those assigned to active therapy had a mean reduction in systolic BP of 5.6 mm Hg and diastolic BP of 2.2 mm Hg. The relative risk of a major macrovascular or microvascular event was reduced by 9% (861 [15.5%] active vs 938 [16.8%] placebo; hazard ratio [HR] = 0.91; 95% CI, 0.83-1.00, *P*=0.04). The relative risk of death from CV disease was reduced by 18% (211 [3.8%] active vs 257 [4.6%] placebo; HR=0.82, 95% CI, 0.68-0.98, *P*=0.03) and death from any cause was reduced by 14% (408 [7.3%] active vs 471 [8.5%] placebo; HR = 0.86, 95% CI, 0.75-0.98, *P*=0.03). There was no evidence that the effects of the study treatment differed by initial BP level or concomitant use of other treatments at baseline.

To estimate the incremental cost-effectiveness of intensified hypertension control, intensive glycemic control, and a reduction in serum cholesterol levels for patients with T2DM, a cost-effectiveness analysis was carried out on a hypothetical cohort of individuals living in the United States (US), aged ≥25 years and newly diagnosed with T2DM.[11] Costs were based on those in community practices in the US. The incremental cost-effectiveness ratio for intensive glycemic control is $41 384 (1997 US dollars) per quality-adjusted life-year (QALY); this ratio increased with age at diagnosis from $9 614 per QALY for patients aged 25 to 34 years to $2.1 million for patients aged 85 to 94 years. The cost-effectiveness ratio for reduction in serum cholesterol level is $51 889 per QALY; this ratio varied by age at diagnosis and is lowest for patients diagnosed between the ages of 45 and 84 years. For intensified hypertension control the cost-effectiveness ratio is $1 959 per QALY. These findings suggest that intensified hypertension control reduces costs and improves health outcomes, whereas intensive glycemic control and reduction in serum cholesterol levels increase costs and improve health outcomes.

The 2009 Canadian Hypertension Education Program (CHEP) recommendations for the management of hypertension,[12] harmonized with those from the Canadian Diabetes Association (CDA)[13] and Canadian Society of Nephrology (CSN), have provided detailed guidelines for the management of hypertension in T2DM patients (Figure 2). Patients with T2DM should be treated to attain a diastolic BP <80 mm Hg (Grade A) and systolic BP <130 mm Hg (Grade C). For persons with T2DM and normal urinary albumin excretion (urinary albumin to creatinine ratio [UACR] <2.0 mg/mmol for men; <2.8 mg/mmol for women) and BP ≥130/80 mm Hg despite lifestyle interventions, the Guidelines recommend any of the following: an ACE inhibitor; an angiotensin II receptor blocker (ARB); a dihydropyridine (DHP) calcium channel blocker (CCB); or a thiazide or thiazide-like diuretic. The level of evidence for these therapeutic options depends on age (Grade A for ≥55 years; Grade B for <55 years), with the exception of ARBs (Grade A for ≥55 years and presence of left-ventricular hypertrophy [LVH]; Grade B for absence of LVH irrespective of age).

If these drugs are contraindicated or cannot be tolerated, a cardioselective β-adrenergic blocker (Grade B) or a non-DHP-CCB (Grade B) can be substituted. If BP targets cannot be reached despite monotherapy at standard doses, then additional antihypertensive drugs should be considered (Grade B); however, patients with diabetes and normal urinary albumin levels should not receive combination therapy with an ACE inhibitor and ARB (Grade B).

Diabetic nephropathy

Diabetic nephropathy is associated with a high rate of CV morbidity and mortality and is the primary cause of end-stage renal failure in Canada and the western world. In both T1DM and T2DM, elevated microalbuminuria is the earliest sign of a progressive decline in renal function. Normally, albumin excretion

rate (AER) ranges from 10-30 mg/day. As microalbuminuria develops, AER increases to 300 mg/day. This is associated with progressive proteinuria, where total urinary protein increases from 7-20 µg/min (the normal range) to approximately 500 mg/day (200 µg/min). Macroalbuminuria (>300 mg/day) subsequently develops, followed by nephrotic syndrome. Screening for microalbuminuria (with laboratory tests such as radioimmunoassay) is important to detect nephropathy at the earliest stage. Glomerular hypertension and hyperfiltration play an important role in the development of diabetic nephropathy. Therefore, antihypertensive therapy (in combination with glycemic control) may also help prevent the progression of diabetic nephropathy.[14-16]

The RENAAL[5] and the Irbesartan Diabetic Nephropathy Trial (IDNT)[17,18] studies have demonstrated that ARB use improves the composite renal outcome (doubling of the baseline serum creatinine concentration, end-stage renal disease [ESRD], or death) in patients with diabetic nephropathy.[5,18] The IRbesartan MicroAlbuminuria Type 2 Diabetes (IRMA 2) study evaluated the renoprotective effect of the ARB, irbesartan, in hypertensive patients with T2DM and microalbuminuria.[19] The primary endpoint was the time to the onset of diabetic nephropathy, defined by persistent albuminuria in overnight specimens (urinary albumin excretion rate >200 µg/min and ≥30% higher than baseline). The event rates for the primary endpoint were 15%, 10%, and 5% in the control (placebo in addition to other nonexcluded antihypertensive therapies), irbesartan (150 mg), and irbesartan (300 mg) groups, respectively. This corresponded to relative risk reductions of 39% for irbesartan (150 mg) vs the control group (P=0.08) and 70% for irbesartan (300 mg) vs the control group (P<0.001). Two important secondary endpoints in IRMA 2 included change in overnight urinary AER and change in creatinine clearance (CrCl). AER was reduced in the 2 irbesartan groups throughout the study (-24% and -38% at 24 months, compared with baseline, in the irbesartan 150 mg and 300 mg groups, respectively). AER remained unchanged in the control group (-2% at 24 months compared with baseline): P<0.001 for the comparison between the control group and the 2 irbesartan groups combined. CrCl remained in the normal range in all 3 groups throughout the study. Regression to normoalbuminuria (<20 µg/min, or <30 mg/day) at the last visit was more frequent in patients treated with irbesartan (300 mg) than in the control group (34% vs 21%, respectively, P=0.006).

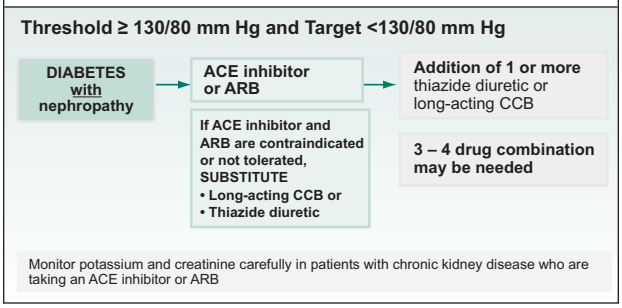
In the CHEP 2009 recommendations, for the treatment of patients with diabetes and albuminuria (urinary AER >30 mg/day), an ACE inhibitor or an ARB is recommended as initial therapy (Grade A; Figure 3).[12] If BP remains >130/80 mm Hg despite lifestyle interventions and the use of an ACE inhibitor or an ARB, then the addition of 1 or more of a thiazide diuretic, a long-acting CCB, or an ACE inhibitor and an ARB in combination can be considered (Grade D). If an ACE inhibitor and an ARB cannot be tolerated, a cardioselective β-adrenergic blocker (Grade B), long-acting CCB (Grade C), or a thiazide diuretic can be substituted (Grade B).

Trials in diabetic hypertension: proteinuria and BP-lowering

The aforementioned data indicate that ACE inhibitors and ARBs lower BP and improve renal outcomes, while reducing proteinuria in patients with diabetes. Lowering BP reduces proteinuria; specifically, reducing intraglomerular pressure can reduce proteinuria (and glomular filtration rate [GFR]) further. Adjusting the integrity of the glomerular barrier may affect the extent of proteinuria. Reducing the endothelial stress in glomerular capillaries may also reduce proteinuria. Indeed, improving the function of the proximal tubule may reduce proteinuria and reduce tubulointerstitial drivers of fibrosis. ACE inhibitors and ARBs inhibit constriction of the efferent artery through blockade of the renin-angiotensin system. Their preferential dilation of the efferent artery is due to its high concentration of angiotensin II (AT_1) receptors (vs the afferent artery).[20] By contrast, CCBs (both DHP and non-DHP) have been shown to preferentially dilate the afferent artery.[21,22] This may be due to a higher concentration of voltage-gated calcium channels present on the afferent artery. The question clinicians may ask is whether reducing proteinuria matters, ie, is proteinuria a marker of disease, or is it also a driver to ESRD?

Data from the RENAAL study have demonstrated that the amount of proteinuria at baseline and the change in proteinuria over time predict CV outcomes.[23] In clinical practice, ARBs and ACE inhibitors are currently used in the maximum approved doses and, until recently, the effects of higher doses of these agents on proteinuria had not been studied. The Diovan Reduction Of Proteinuria (DROP) study[24] examined dose-related effects of the ARB valsartan on urinary protein excretion. This multicentre, double-blind study included 391 participants with T2DM, high BP, and high levels of urinary (U) protein (ie, UAER 20-700 µg/min). All participants received valsartan (160 mg) for the first 4 weeks, and were then randomized to continue that dose or receive 320 mg or 640 mg, twice the highest approved dose, for 26 additional weeks.[24] Comparable UAER reductions from baseline were seen in all groups at Week 4 (P<0.001). Subsequently, a significant incremental UAER reduction occurred with the valsartan 320- and 640-mg doses, vs a modest additional change with 160 mg. Greater UAER reductions also occurred with valsartan 640 mg vs 160 mg during weeks 0 to 30, but only in patients achieving BP <130/80 mm Hg. The Supra-Maximal Atacand Renal Trial (SMART)[25] is a Canadian study designed to assess the effect of high doses of candesartan (64 and 128 mg) on proteinuria compared with a 16-mg active control in subjects with at least a 6-month history of proteinuria >1 g/day, due to primary glomerular disease,

Figure 3: Treatment of hypertension in association with diabetic nephropathy (CHEP 2009)[12]



ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CCB = calcium-channel blocker

diabetic nephropathy, or hypertensive nephrosclerosis. The preliminary results demonstrated that by intent-to-treat analysis, the mean reduction in urinary protein for patients receiving 128 mg of candesartan compared with 16 mg was 33.05% (P<0.0001; 95% CI, -45.70 to -17.44). The mean difference between the candesartan 16- and 64-mg groups was -16.91% (P=0.0492; not significant after adjusting for 2 comparisons). Changes in BP were very small in all groups and all doses were well tolerated with no observed dose-related increases in serum potassium, creatinine, or adverse events. No deaths were reported.

Clinically, what further can be done to prevent proteinuria and progressive renal disease in patients with diabetes? The 2009 CDA recommendations include DHP-CCBs (Grade B, Level 2) and thiazide-like diuretics (Grade A, Level 1A) as alternatives to ACE inhibitors and ARBs in persons with diabetes, normal UAER, without chronic kidney disease, and with BP >130/80 mm Hg. These recommendations are based, in part, on the results from the clinical outcomes in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) substudy in people with diabetes.[26] However, until recently, it remained unclear whether DHP-CCBs are as efficacious as non-DHP-CCBs, since the data supporting non-DHP-CCBs were not generalizable to current practice because the studies were conducted without first-line therapy with an ACE inhibitor or an ARB.

To assess whether adding a non-DHP- rather than a DHP-CCB to ACE inhibition may more effectively lower proteinuria, Toto et al[27] carried out a multicentre, active-control, prospective, randomized, open-label, blinded endpoint (PROBE) trial in 304 patients with T2DM that was designed to determine whether a fixed-dose combination (FDC) of an ACE inhibitor (trandolapril) and a nondihydropyridine CCB (verapamil) was superior to an FDC of an ACE inhibitor (benazepril) with a dihydropyridine CCB (amlodipine) in reducing albuminuria in patients with hypertension and diabetic nephropathy. The primary outcome was percentage change in UACR from baseline to endpoint (Week 36 or final visit). Prespecified secondary outcomes included absolute changes in systolic and diastolic BP, logarithm of UACR, estimated GFR, and within group paired t-test analyses of absolute change in UACR and urinary protein/creatinine ratio (UPCR). Both groups experienced a nonsignificant increase in the adjusted mean percentage change in the UACR (29.3% for trandolapril/verapamil [T/V] group and 8.5% for benazepril/amlodipine [B/A] group; P=0.34). There was likewise no significant difference in the reductions in absolute UACR between the 2 groups (T/V -0.11, B/A -0.08; P=0.78). As well, neither group reached the target BP of 130/80 mm Hg; endpoint BPs for the T/V and B/A groups, respectively, were 142.4/75.1 mm Hg (+1.2/-2.1 mm Hg from baseline) and 136.7/71.4 mm Hg (-5.9/-4.9 mm Hg from baseline). No significant association was found between a change in BP and change in UACR. As a result, this multicentre trial in T2DM patients with hypertension and nephropathy suggests that administering an FDC of an ACE inhibitor with either a non-DHP- or a DHP-CCB can effectively reduce albuminuria in this population.

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