Treating Hypertension in Diabetic Nephropathy

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OBJECTIVE — Control of hypertension in patients with diabetic nephropathy improves mortality and slows progression to end-stage renal disease. However, blood pressure is difficult to treat; multiple drug combination therapy is required and treatment algorithms to establish this are lacking. We used a stepped-care algorithm, centered on maximum doses of an ACE inhibitor or angiotensin II receptor blocker, to treat hypertension according to American Diabetes Association recommended blood pressure target goals (<130/80 mmHg) in patients with diabetic nephropathy.

RESEARCH DESIGN AND METHODS — We treated 49 consecutive patients with diabetes (13 with type 1 and 36 with type 2), diabetic nephropathy, and proteinuria ≥500 mg/24 h with a stepped-care blood pressure treatment algorithm. The level of blood pressure control achieved at most recent follow-up was assessed.

RESULTS — Patients were followed for a median of 18 months (range 9–48). Mean blood pressure achieved was 140/75 ± 23/14 mmHg in patients with type 1 diabetes and 146/76 ± 22/14 mmHg in patients with type 2 diabetes. Target blood pressure was reached in 16 (33%) patients, 6 of 13 patients with type 1 diabetes and 10 of 36 patients with type 2 diabetes, whereas systolic blood pressure remained above the target level in the remaining patients. There was no difference in baseline blood pressure, proteinuria, or serum creatinine level between patients who were treated to target and those who were not.

CONCLUSIONS — Levels of blood pressure control similar to those achieved in clinical trials in diabetic nephropathy were obtained with a stepped-care algorithm. However, in most patients, systolic blood pressure was difficult to control to target despite the use of multiple drug combination therapy.

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Hypertension is a major risk factor for cardiovascular morbidity and mortality in patients with diabetes (1,2). Diabetic nephropathy develops in up to 40% of patients with type 1 diabetes (3) and 35% of patients with type 2 diabetes (4), and rigorous treatment of hypertension slows the rate of decrease in renal function and improves mortality (5,6). Few studies have addressed whether recommended targets for blood pressure control (7,8) can be achieved in everyday clinical practice, and although multiple drug combination therapy is needed to treat hypertension in most patients with nephropathy, treatment algorithms for establishing this are lacking and the optimum drug combination remains uncertain. After review of the evidence available in 1998 (7,9–18), we devised a stepped-care algorithm for treating hypertension in diabetic nephropathy and evaluated its ability to treat hypertension to American Diabetes Association recommended blood pressure target goals (8) in consecutive patients with diabetic nephropathy attending a hospital diabetes clinic.

RESEARCH DESIGN AND METHODS — We applied a stepped-care algorithm (Fig. 1) for treating hypertension to 49 consecutive white European patients with overt diabetic nephropathy, defined as persistent proteinuria ≥500 mg/24 h and with no evidence of other kidney disease, renal tract disease, or heart failure, attending a hospital diabetes clinic in the U.K. All community patients with proteinuria are routinely referred from primary care to the hospital clinic for further management (local referral guideline). The stepped-care algorithm involved the sequential addition and titration of antihypertensive drugs to maximum tolerated doses until target blood pressure was achieved and/or maintained. The principle of once-daily dosing of each drug class was used to enhance patient adherence (19). Blockade of the renin-angiotensin system, first demonstrated with ACE inhibition in 1993 (9), confirmed many times since that time (10), and recently extended to include the angiotensin II receptor blocker (ARB) class (11,12) is the accepted cornerstone of treatment in diabetic nephropathy. Therefore, maximum doses of either ACE inhibitor (corresponding to 40 mg enalapril/losartan 150 mg or ramipril 10 mg) or ARB (corresponding to losartan 150 mg or irbesartan 300 mg) in the event of ACE inhibitor–associated cough were used routinely in the stepped-care algorithm. ACE inhibition was induced in steps over a 4-week period before the addition of a diuretic at 6 weeks. Although there is uncertainty regarding the long-term effects of other drug classes (13,17,18), in patients with type 2 diabetes and nephropathy, nondihydropyridine calcium channel blockers (diltiazem and verapamil) seem to possess renoprotective properties broadly equivalent to those of ACE inhibitors and exert a synergistic effect when used in combination with them (18,20).
A drug from this class was therefore used routinely in all patients who were unable to continue treatment with an ACE inhibitor or ARB.

Office blood pressure was measured and recorded by one of three observers at each clinic visit according to the recommendations of the British Hypertension Society (21). Treatment targets were systolic blood pressure <130 mmHg and diastolic blood pressure <80 mmHg (8). The interval between clinic visits was determined on an individual case basis, according to current blood pressure level and response, but was at least every 3 months and usually every 6 weeks during dose-titration phases. At each clinic visit, patients were also provided with clear written instructions, where necessary, for the titration/addition of drug therapies between clinic visits by their primary care teams to optimize therapy. Details of antihypertensive drugs used and withdrawn because of adverse effects were routinely recorded at each visit. ACE inhibitor/ARB therapy was withdrawn if hyperkalemia developed, defined as a sustained serum potassium level ≥6.0 mmol/l, despite concurrent thiazide or loop diuretic therapy and avoidance of other drugs impairing potassium excretion (nonsteroidal anti-inflammatory drugs, potassium-sparing diuretics) or dietary potassium supplementation (Losalt, a salt substitute), or if worsening renal impairment developed, defined as a sustained increase in serum creatinine level ≥30% over 3 months (22). All patients were also treated with aspirin and a statin if total cholesterol level exceeded 5.0 mmol/l. Patient case notes and computerized hospital pathology records were scrutinized in a retrospective analysis and data were extracted at initial presentation of nephropathy (baseline) and at the most recent clinic attendance (follow-up).

Comparisons of demographic and blood pressure data that followed a normal distribution were examined by Student’s t test. For all other comparisons, Mann-Whitney U test was used. Differences in proportions were examined by Fisher’s exact test.

RESULTS — In all 49 patients, blood pressure was above target at baseline (Table 1) and mean ± SD blood pressure in the entire cohort was 168/88 ± 28/16 mmHg. Patients were followed for a median of 18 months (range 9–48). Blood pressure at most recent follow-up was similar in patients with type 1 diabetes (140/75 ± 23/14 mmHg) and type 2 diabetes (146/76 ± 22/14 mmHg). Target blood pressure was achieved in 16 patients (33%): 6 of 13 patients with type 1 diabetes and 10 of 36 patients with type 2 diabetes. Target diastolic blood pressure, with systolic blood pressure remaining above target, was reached in an additional 24 patients (29%), but in the remaining 9 patients (18%), adequate control of either antihypertensive drugs used and withdrawn because of adverse effects were routinely recorded at each visit. ACE inhibitor/ARB therapy was withdrawn if hyperkalemia developed, defined as a sustained serum potassium level >6.0 mmol/l, despite concurrent thiazide or loop diuretic therapy and avoidance of other drugs impairing potassium excretion (nonsteroidal anti-inflammatory drugs, potassium-sparing diuretics) or dietary potassium supplementation (Losalt, a salt substitute), or if worsening renal impairment developed, defined as a sustained increase in serum creatinine level ≥30% over 3 months (22). All patients were also treated with aspirin and a statin if total cholesterol level exceeded 5.0 mmol/l. Patient case notes and computerized hospital pathology records were scrutinized in a retrospective analysis and data were extracted at initial presentation of nephropathy (baseline) and at the most recent clinic attendance (follow-up).

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Figure 1—Stepped-care algorithm for treatment of hypertension in diabetic nephropathy.

Table 1—Baseline clinical characteristics of the patients

<table>
<thead>
<tr>
<th></th>
<th>Type 1 diabetes</th>
<th>Type 2 diabetes</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (male:female)</td>
<td>13 (+9)</td>
<td>36 (28:8)</td>
<td>—</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42.0 ± 12.9</td>
<td>61.3 ± 10.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.8 ± 4.7</td>
<td>31.1 ± 6.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>132 (52–395)</td>
<td>112 (62–341)</td>
<td>0.73*</td>
</tr>
<tr>
<td>Proteinuria (mg/24 h)</td>
<td>1000 (620–5,940)</td>
<td>1,670 (500–6,110)</td>
<td>0.80*</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>9.4 ± 1.5</td>
<td>7.1 ± 1.2</td>
<td>0.005</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.3 ± 1.5</td>
<td>4.9 ± 0.9</td>
<td>0.30</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>154 ± 20</td>
<td>174 ± 30</td>
<td>0.023</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>77 ± 14</td>
<td>92 ± 16</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data are means ± SD or median (range). *Mann-Whitney U test. BP, blood pressure.
systolic or diastolic blood pressure was impossible despite multiple drug combination therapy. There were no differences between patients treated to target and those who were not in baseline systolic blood pressure (172 ± 31 vs. 168 ± 28 mmHg; P = 0.69), diastolic blood pressure (92 ± 17 vs. 87 ± 17 mmHg; P = 0.31), or proteinuria (1,820 vs. 2,080 mg/24 h; P = 0.27). During follow-up, end-stage renal disease developed in two patients, in whom renal replacement therapy was initiated, and eight patients died. Of the patients who died, blood pressure only was controlled in two patients, diastolic blood pressure only was controlled in one patient, and neither systolic nor diastolic blood pressure was controlled in three patients. More patients with type 1 diabetes (10 of 36) were treated to the target pressure goal; however, this difference was not statistically significant.

One patient with severe widespread atherosclerotic vascular disease, bilateral renal bruits, and renal impairment was not treated initially with an ACE inhibitor or ARB. These drugs had to be discontinued in an additional 12 patients: 5 with sustained hyperkalemia, 3 with worsening renal impairment, and 1 with intracutaneous allergy. All patients with treatment resistance (blood pressure > 160/90 mmHg) despite three synergistic agents at full dosage were evaluated for secondary hypertension. The three patients with worsening renal impairment on ACE inhibitor/ARB therapy were all evaluated for underlying renovascular disease, although no lesions amenable to angioplasty or stent insertion were identified.

In patients who continued treatment with an ACE inhibitor or ARB, follow-up systolic blood pressure (145 ± 22 vs. 145 ± 22 mmHg, P = 0.01) and diastolic blood pressure (78 ± 13 vs. 71 ± 14 mmHg, P = 0.15) was not different from patients in whom the drug was withdrawn. The median number of drug classes used in both type 1 and type 2 diabetes was 3 (range 1–5).

A total of 16 patients (24%) experienced an AE sufficient to necessitate withdrawal of one or more (range 1–3) antihypertensive drugs. A total of 23 individual drug withdrawals occurred; two resulted from a severe interaction between a β-blocker and diltiazem (bradycardia necessitating hospital admission), two resulted from diuretic intolerance (one thiazide, one loop), and one each resulted from intolerance to β-blocker (fatigue), dihydropyridine CCB (amlodipine; edema), nondihydropyridine CCB (verapamil), moxonidine (dizziness, edema), hydralazine, and minoxidil (edema).

Patients with type 2 diabetes were older (61 ± 11 vs. 42 ± 13 years; P < 0.001) and more obese (BMI 31 vs. 27 kg/m²; P = 0.04) than those with type 1 diabetes and were also significantly more hypertensive, with both higher systolic blood pressure (174 vs. 154 mmHg; P = 0.02) and diastolic pressure (92 vs. 77 mmHg; P = 0.003) at baseline (Table 1). Glycemic control was significantly better in patients with type 2 diabetes than those with type 1 diabetes (HbA1c, 7.1 vs. 9.4%; P = 0.005), but there were no significant differences in baseline proteinuria (P = 0.80), serum creatinine level (P = 0.73), or serum cholesterol level (P = 0.35) (Table 1).

**CONCLUSIONS**—Achieved levels of blood pressure reported in the large-scale clinical trials in diabetic nephropathy have ranged between 128–134/77–82 (9) and 140–144/77 mmHg (11,12). Although similar levels were obtained in patients with both type 1 and type 2 diabetes with the stepped-care algorithm, differences in ethnic background between the patients in this study, an exclusively white European population, and the more heterogeneous populations in the clinical trials may influence direct comparison, particularly if blood pressure is more difficult to control in nonwhite patients. However, the target blood pressure goals remained difficult to reach in many patients, particularly those with type 2 diabetes, and blood pressure was controlled to target in only one third of patients. Systolic blood pressure was more difficult to control. The stepped-care algorithm achieved blood pressure control similar to that reported in clinical practice from another diabetes clinic in the U.K. (mean ± SD blood pressure 146/72 ± 23/14 mmHg) (23) and better than that reported (mean blood pressure 159/85 mmHg) at referral to a U.K. specialist renal clinic (24). Greater difficulty in treating patients to target may be a feature of patients with diabetes (25), and achieved blood pressure levels in clinical trials of diabetic nephropathy were consistently higher than those reported in similar trials of nondiabetic renal disease (5,14,15). It has been suggested that tight control of hypertension may exert a greater impact on the progression of chronic nephropathies than the renoprotective properties of individual antihypertensive drug classes (7,13–16); however, when blood pressure exceeds 125/75 mmHg, renoprotection seems to exert clinical influence.

The association between hypertension and obesity is well recognized (26). This may contribute to the greater difficulty experienced in treating hypertension in type 2 diabetes and suggests that more aggressive treatment strategies will be needed (27). A surprisingly high rate of hyperkalemia was seen in this study, which is unexplained, although higher doses of ACE inhibitor/ARB were used than in some earlier studies. Pooled data from clinical trials suggest a hyperkalemia rate < 2% with ACE inhibitor/ARB treatment (9,12,14), similar to that seen with regimens not using that strategy (28). Although dual blockade of the renin-angiotensin system may further lower blood pressure in treatment-resistant hypertension in type 2 diabetes (29), lower doses (underdosing) of ACE inhibitor were used than in this study and the benefits of the addition of ARB to maximum doses of ACE inhibitor remain unknown.

The use of once-daily dosing schedules should have optimized compliance. Although not assessed in this study, compliance may, in fact, not be a significant contributor to treatment resistance (30). There were a number of treatment failures due to adverse effects with the various antihypertensive drug classes used in the algorithm, which may contribute toward treatment resistance by restricting treatment options.

In everyday clinical practice, blood pressure is often difficult to control in diabetic nephropathy, but a stepped-care approach can achieve a similar degree of control to that reported in the clinical trials. A treatment target < 130/80 mmHg (8) is difficult to reach in many patients, and more stringent targets (7,31) may be even less achievable in the majority of patients.

**References**

1. Hypertension in Diabetes Study (HDS): increased risk of cardiovascular complica-