Specific Blood Pressure Targets for Patients With Diabetic Nephropathy?

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Diabetes Care 2016;39(Suppl. 2):S228–S233 | DOI: 10.2337/dcS15-3020

Diabetic nephropathy represents a condition frequently detected in current clinical practice characterized by a very high cardiovascular risk profile. Blood pressure reduction via antihypertension drug treatment represents a therapeutic approach capable of exerting favorable effects on renal and cardiovascular outcomes. The purpose of this article is to review the current literature and results of key clinical trials pertaining to blood pressure goals of antihypertension treatment in these patients. The pros and cons of a less or a more intensive blood pressure goal in diabetic nephropathy will be discussed, with particular emphasis on the cardiovascular and renal effects of each therapeutic strategy.

In patients with diabetes, nephropathy, with or without an increased urinary protein excretion, is accompanied by a much greater risk of progression toward end-stage renal disease (1) as well as of the occurrence of myocardial infarction, heart failure, or stroke (2). A number of randomized controlled trials have documented that in these patients, both progression to renal events and fatal or nonfatal cardiovascular outcomes can be favorably affected by antihypertension drug treatment (3–6). There is no agreement, however, on how low blood pressure should be brought in order to maximize the renal and cardiovascular protective effects of the blood pressure–lowering intervention under this circumstance—namely, whether the target should be similar to the one recommended for the general hypertensive population, i.e., 140/90 mmHg, or lower blood pressure values should be pursued.

This article will examine the evidence in favor or against the less and the more intensive blood pressure–lowering treatment strategy in patients with diabetic nephropathy. The effect of either therapeutic approach on cardiovascular and renal outcomes will be discussed, and data will include patients with nondiabetic nephropathy. This is based on the choice of the recent guidelines jointly issued by the European Society of Hypertension and the European Society of Cardiology to unify the treatment strategies to be adopted in these two clinical conditions (7).

Intensive Blood Pressure Reduction Strategy: "Pro" Arguments

The evidence that in diabetic and nondiabetic nephropathy a more intensive blood pressure reduction below 140/90 mmHg may produce a favorable effect on renal function and survival is multifold. First, epidemiological studies have unequivocally documented that in patients with chronic kidney disease, end-stage renal disease exhibits a linear relationship with blood pressure that extends well below 140/90 mmHg and includes systolic and diastolic values within the high-normal and normal levels (8). Second, more importantly, a similar relationship between blood pressure, renal function, and survival has also been documented for the blood pressure values achieved during antihypertensive drug treatment.

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This publication is based on the presentations at the 5th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this supplement were made possible in part by unrestricted educational grants from AstraZeneca.

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To quote some examples, the MDRD trial randomized 840 patients with a glomerular filtration rate between 23 and 55 mL/min/1.73 m^2 (most of whom did not have diabetes) to achieve a mean arterial pressure of 107 or 92 mmHg over a 2.2-year treatment duration (9). In the subset of patients with pronounced proteinuria (>1 g/day), the more marked blood pressure reduction (126/77 vs. 134/80 mmHg) was accompanied by a less pronounced decline in glomerular filtration rate (primary end point, assessed via iothalamate clearance measurement) (9). This was the case also when patients were tracked for an additional 7-year period, which allowed the outcome measures to extend the evidence of the protective effect to end-stage renal disease and death.

The African American Study of Kidney Disease and Hypertension (AASK) randomized 1,094 African American patients without diabetes with hypertensive nephrosclerosis and a glomerular filtration rate between 20 and 65 mL/min/1.73 m^2 to achieve a mean blood pressure of 102 mmHg (low target group) or 107 mmHg (usual target group) over a 3–6.4 year treatment duration (10). No outcome (50% glomerular filtration rate reduction, end-stage renal disease, and death) difference was detectable between the two groups over the planned follow-up period. Yet, in a subsequent report of the cohort, which was followed for an additional 8.8–12.2 years, patients originally achieving the lower blood pressure target did show a reduced number of renal events compared with the group with the originally higher target, the difference being significant in patients with a greater baseline proteinuria ($P < 0.01$) (11).

The Irbesartan Diabetic Nephropathy Trial (IDNT) randomized 1,590 hypertensive patients with type 2 diabetes with a fairly advanced diabetic nephropathy (serum creatinine ~1.7 mg/dL and urinary protein excretion amounting to 1.9 g/day at baseline) to a treatment based on irbesartan or amlodipine (6,12). The primary result of the study was the demonstration that in this clinical condition a blocker of the renin-angiotensin system is more nephroprotective than a calcium channel blocker. Additionally, however, the study showed that the quartile of patients with an on-treatment systolic blood pressure >149 mmHg had a 2.2-fold risk of developing a renal end point (doubling of serum creatinine or end-stage renal disease) compared with the quartile with systolic blood pressure values <134 mmHg (12). In the same study, a systolic blood pressure reduction ≥20 mmHg conferred a 47% decrease in the risk of a renal end point, regardless of the initial systolic blood pressure values (12).

The Action in Diabetes and Vascular Disease: PreterAx and Diamicron MR Controlled Evaluation (ADVANCE) trial randomized 11,140 patients with type 2 diabetes to the administration of a combination of perindopril and indapamide or placebo, which led to an on-treatment systolic blood pressure, respectively, <135 mmHg or ~140 mmHg (13). In the patients displaying under treatment the lower blood pressure values, the risk of nephropathy (new-onset microalbuminuria or proteinuria, end-stage renal disease, and renal transplantation) was significantly less (−21%, $P < 0.0001$) than in the group with the higher blood pressure. This was usually the case also for the worsening of nephropathy in patients with nephropathy at baseline as identified by the Kidney Disease Outcomes Quality Initiative graduation (Fig. 1), the detection of an increased urinary protein excretion, or the reduction in the estimated glomerular filtration rate (14).

Finally, more intensive blood pressure reductions by antihypertension drug treatment have also been reported to guarantee greater renal protective effects in meta-analyses of available clinical trials. For example, in a meta-analysis of intervention trials performed in nephropathic patients, the progression of renal dysfunction showed an attenuation as the blood pressure values achieved by antihypertension drug treatment became lower, the slowest progression rate being exhibited by patients with a systolic blood pressure <120 mmHg (15). Furthermore, in studies in patients with diabetic nephropathy a linear relationship has been reported between the magnitude of the treatment-induced blood pressure reduction and the decline of glomerular filtration rate, the minimal decline being observed at an on-treatment mean arterial pressure of 89 mmHg, which corresponds approximately to a systolic and a diastolic blood pressure value amounting to 120 mmHg and 75 mmHg, respectively (16) (Fig. 2).

Further arguments in favor of the protective effects of intensive blood pressure reductions on renal function in nephropathic patients are provided by the well-known relationship between urinary protein excretion and blood pressure. A large number of studies have consistently documented that in both patients with diabetes and patients without diabetes the lower the blood pressure achieved by treatment, the lesser the risk of developing microalbuminuria or proteinuria, with the minimum risk again occurring at systolic

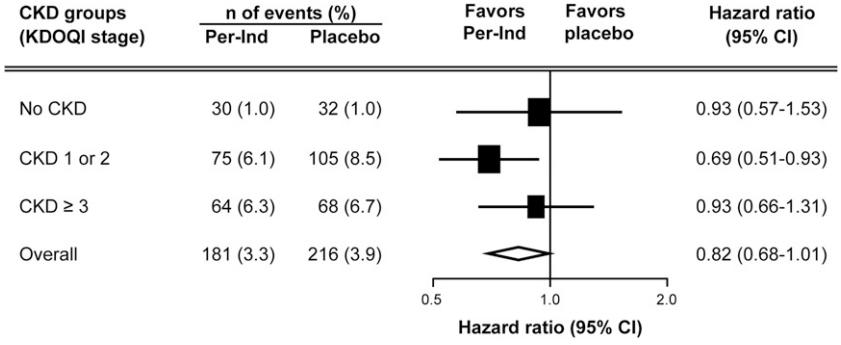

Figure 1—Effect of randomized treatment on the risk of new or worsening nephropathy in patients according to baseline Kidney Disease Outcomes Quality Initiative (KDOQI) chronic kidney disease (CKD) stage. The diamond center represents the overall estimate and the width its 95% CI. Solid boxes represent estimates of treatment effects in subgroups of patients without or with chronic kidney disease. Data from the ADVANCE trial. Per-Ind, perindopril-indapamide. Modified with permission from Heerspink et al. (14).

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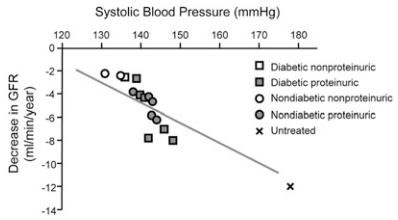

Figure 2—Data from prospective clinical trials on nephropathy progression with a follow-up duration ≥2 years showing the relationships between the systolic blood pressure values achieved during antihypertensive drug treatment and the decrease in glomerular filtration rate (GFR). Modified with permission from Yamout et al. (16).

values of <120 mmHg (17). In addition, much evidence is available that treatment-induced blood pressure reductions and absolute values bear a linear relationship with the degree of reduction of an existing microalbuminuria or proteinuria, namely, that the same relationship applies to individuals with chronic nephropathy. To cite recent examples, in the very large number of patients of the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET), a reduction of systolic blood pressure from 154 mmHg to 125 mmHg was accompanied by a progressive reduction in the incidence of new-onset microalbuminuria and macroalbuminuria as well as by a progressively greater return to normoalbuminuria in patients who exhibited an abnormal urinary albumin excretion at baseline (18) (Fig. 3). Likewise, in the few normotensive patients with diabetes with an increased urinary protein excretion recruited in the Appropriate Blood Pressure Control in Diabetes–Part 2 with Valsartan (ABCD-2V) trial, a blood pressure reduction to 118/75 mmHg (intensive therapy) was associated with a pronounced antiproteinuric effect (from 54.2 to 5.5 μg/min), whereas proteinuria increased from 70.4 to 121.7 μg/min when treatment reduced blood pressure only to 124/80 mmHg (moderate therapy) (19). In this context, it is important to emphasize that several studies have shown that in both patients with diabetes and patients without diabetes, treatment-induced changes of urinary protein excretion predicted the risk of progression to end-stage renal disease (17). A recent example is again provided by observations made in the pooled patients from ONTARGET and from the Telmisartan Randomized AssessmenNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) trials (20,21). Compared with patients who during treatment exhibited no change or a reduction of urinary protein excretion, an on-treatment increase or a persistent proteinuria was associated with a greater risk of renal function worsening. This finding was detected both in the general population of the two trials and in the subjects of the trials with diabetes. In the patients with diabetes, the predictive importance of an unfavorable effect of antihypertension treatment on urinary protein excretion exceeded that of failure to achieve blood pressure control by the pharmacological intervention (20,21).

A renal protection should imply cardiovascular protection as well because renal function displays a close direct relationship with the risk of myocardial infarction, congestive heart failure, and stroke (22,23). However, evidence that in diabetic and nondiabetic nephropathy intensive blood pressure reductions do lead to a greater cardiovascular protection is more scanty. One reason is that the clinical trials that have explored the relationship between antihypertension drug treatment targets and renal function in nephropathic patients were all of a limited size, with, therefore, an overall incidence of events insufficient to provide the results with enough statistical power, despite the higher cardiovascular risk associated with nephropathy (16,24). Nevertheless, in the above-mentioned ADVANCE trial, patients with chronic kidney disease and an on-treatment systolic blood pressure of ≤135 mmHg showed a trend toward a reduced incidence of fatal and nonfatal cardiovascular events compared with patients displaying an on-treatment systolic blood pressure value of ~140 mmHg (13). Furthermore, in the Appropriate Blood Pressure Control in Diabetes (ABCD) trial in normotensive patients with diabetes without or with nonproteinuric nephropathy, achieving blood pressure values of 128/75 mmHg or 137/81 mmHg over a 5.3-year treatment duration did not translate into a difference in the end-of-treatment creatinine clearance (the primary end point) or in the overall number of cardiovascular events (25). However, the lower blood pressure values were associated with a slight reduction in the incidence of new-onset microalbuminuria as well as with a marked and significant reduction in the incidence of stroke (1.7 vs. 5.4%, $P < 0.03$) (26). Similar observations have been reported in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial in 10,251 patients with type 2 diabetes at high risk for cardiovascular events, in whom a systolic blood pressure reduction to 119 mmHg did not lead to a significant reduction in the risk of overall cardiovascular outcome (−12%, P = NS) but reduced stroke by 41% compared with a systolic blood pressure reduction to only 133 mmHg (27,28).

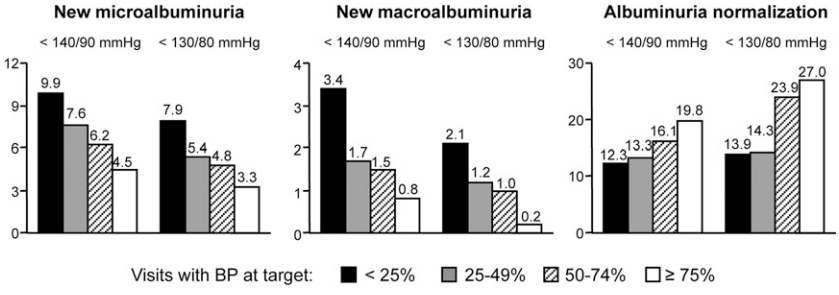

Figure 3—Incidence of new microalbuminuria, new macroalbuminuria, and normalization of albuminuria in relation to the percentage of clinical visits in which blood pressure (BP) values were reduced to <140/90 mmHg or to <130/80 mmHg. Data from the ONTARGET trial. Modified with permission from Mancia et al. (18).

Intensive Blood Pressure Reduction Strategy: "Against" Arguments

Several important arguments can be raised against lowering blood pressure too intensively in patients with chronic kidney disease of diabetic or

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nondiabetic origin. The following considerations should be taken into account. First, the evidence in favor of the advantages of intensive blood pressure reductions in patients with chronic kidney disease has been obtained in studies that in many cases did not have, as a major goal, the comparison of the benefits associated with the lower and the higher blood press targets. Furthermore, and not less importantly, all favorable evidence originates from "post hoc" analysis of trial results, i.e., by comparing nonrandomized groups of patients often displaying marked differences in the clinical variables and sometimes even in the demographic characteristics. This represents a serious limitation because baseline differences can majorly affect the results despite the attempt to limit their impact by statistical adjustment procedures. It is thus widely agreed that post hoc evidence should be regarded as hypothesis generating rather than conclusive evidence, which can only be derived from the results of clinical trials following a randomized design.

Second, in the available randomized trials in patients with chronic kidney disease in which the goal was to compare different blood pressure targets, no difference in the risk of renal outcomes between groups with less or more intensive blood pressure reductions induced by antihypertensive drug treatment has been reported. In the MDRD trial, for example, the results obtained in all of the patients until the end of the randomized trial phase did not show any reduction in the progression of renal disease, assessed as decline in glomerular filtration rate, when on-treatment blood pressure values were reduced to 126/77 mmHg rather than to 134/80 mmHg (9). Furthermore, in the randomized data of the AASK trial no renal outcome difference between the groups at the lower and higher on-treatment blood pressure (128/78 and 141/85 mmHg) was detected (10). Finally, in the Ramipril efficacy In Nephropathy (REIN)-2 trial, which was carried out in 338 patients with nondiabetic nephropathy (glomerular filtration rate ~35 mL/min/1.73 m^2 and proteinuria close to 3 g/day), end-stage renal disease also did not differ in patients achieving blood pressure values of 130/80 mmHg (intensively treated group) versus those remaining at values amounting to 134/82 mmHg (conventionally treated group) (29).

Third, the post hoc evidence in favor of the renal or cardiovascular advantages of more intensive blood pressure reductions is by no means consistent or easily defensible on numerical grounds. For example, in the patients with diabetes with normal or diseased kidney recruited for the ACCORD trial the incidence of end-stage renal disease as well as of cardiovascular outcomes was similar at an on-treatment systolic blood pressure >130 mmHg or <120 mmHg (27). In the ABCD trial, the patients with diabetes in whom blood pressure was more markedly reduced showed evidence of a reduced incidence of new-onset microalbuminuria and strokes compared with that detected in the patients under so-called moderate therapy (25). However, the number of these events was so small (53 vs. 58 cases for new microalbuminuria and 4 vs. 13 cases for the occurrence of stroke) as to make the data little more than descriptive (25). The number of strokes was also small (32 in the intensively treated vs. 62 in the standard treatment groups) in the patients with diabetes largely without nephropathy of the ACCORD trial (27), making the reported cerebrovascular benefit of the more intense blood pressure reduction also underpowered. In ONTARGET, again in patients mostly with normal renal function, more intensive blood pressure reductions (approximately −4 mmHg systolic blood pressure) achieved by the combination of an ACE inhibitor and an angiotensin II receptor blocker worsened rather than improving renal function compared with what was seen in patients in whom the ACE inhibitor and the angiotensin II receptor blocker were used in monotherapy (30). Finally, the results of the ADVANCE trial are also not without limitations because of the inconsistent statistical significance of the greater beneficial effect on cardiovascular and renal outcomes exhibited by the chronic kidney disease patients with a greater blood pressure reduction (13).

There is, on the other hand, also no question that intensive blood pressure reductions have a greater ability to prevent microalbuminuria or proteinuria as well as to achieve normoalbuminuria in patients with an increased urinary protein excretion and thus with renal disease. This has been seen in so many studies as to make intensive blood pressure lowering the accepted treatment strategy pursued for obtaining a marked antiproteinuric effect in addition to the use of blockers of the renin-angiotensin system. However, whether a treatment-induced reduction in urinary protein excretion predicts a reduced risk of renal and cardiovascular outcomes has not yet been conclusively demonstrated. This is because while some studies have shown that this is the case, other studies have not. In ACCORD, for example, reducing systolic blood pressure values to <120 mmHg did reduce proteinuria without affecting the risk of renal and cardiovascular events (27). This was the case also in other studies, such as the Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) and the Randomized Olmesartan And Diabetes MicroAlbuminuria Prevention (ROADMAP) trials (31,32), which leaves the question of the clinical conditions on which an antiproteinuric effect can be safely considered as a proxy for patient's protection still largely unanswered.

A discussion on the advantages and disadvantages of more versus less intensive blood pressure reductions in patients with diabetic and nondiabetic nephropathy should also consider real-life aspects of treatment. One of these is the increased incidence of orthostatic hypotension that characterizes chronic kidney disease (33), particularly in the presence of diabetes or in elderly people, because of the accompanying dysautonomia that affects both the parasympathetic and the sympathetic modulation of the cardiovascular system (33–35). This can add a practical element of risk to the more intensive blood pressure–lowering strategies that, albeit not supported by trial evidence, treatment guidelines should not forget.

Blood Pressure Target in Diabetic and Nondiabetic Nephropathy and Guidelines

The above arguments have been given different weight by different guidelines whose recommendations thus differ considerably. Guidelines such as those

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of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommend that blood pressure values should be reduced to 130/80 mmHg in patients with diabetic or nondiabetic nephropathy (36), this also being the recommendation of the American Diabetes Association (37) and the European Association for the Study of Diabetes (38). The new American hypertension guidelines (no longer supported by the Joint National Committee), on the other hand, do not consider the target blood pressure to be pursued in these patients to be <140/90 mmHg, i.e., similar to the one recommended for all hypertensive patients up to 60 years of age (39). The same target has been adopted by the hypertension guidelines of the European Society of Hypertension and the European Society of Cardiology (7), which, however, also issue an intermediate recommendation for patients with a pronounced proteinuria in whom the possibility of lowering blood pressure <130/80 mmHg is not excluded, provided that patient follow-up is close and renal function frequently monitored. The authors' opinion is that this recommendation is in line with available evidence that does not conclusively prove, but does also not disprove, the additional benefit of a more pronounced antiproteinuric effect. In contrast to the differences in the blood pressure target, guidelines appear consistent on the type of drug treatment to be adopted in the presence of diabetic or nondiabetic nephropathy. Given the need for combination of several drugs in most cases, one should be a blocker of the renin-angiotensin-aldosterone system because at any blood pressure level renin-angiotensin system blockade enhances the effect and adds, compared with non–renin-angiotensin–blocking drugs, to the renal protective effect. No difference between ACE inhibitors and angiotensin receptor blockers is mentioned, whereas concomitant administration of the two drugs is discouraged because of the evidence of their adverse effects in subjects with diabetes and subjects without diabetes recruited in trials (39).

Conclusions

The data reviewed here allow the following conclusions to be drawn. First, the three randomized prospective studies performed in advanced proteinuric nondiabetic nephropathy fail to support achievement during treatment of blood pressure values <130/80 mmHg to further slow nephropathy progression (9,10,29). Second, the only randomized clinical trial carried out in early diabetic nonproteinuric nephropathy, the ABCD-2V study, failed to show a benefit of achieving lower blood pressure values, although it should be recognized that it was underpowered for testing this outcome (19). Third, for cardiovascular events the ACCORD trial failed to show a benefit of lower blood pressure on cardiovascular outcomes in diabetes, although it documented a benefit of more intensive blood pressure reduction on stroke event incidence (27,28). Finally, results obtained in this context in the ONTARGET and TRANSCEND trials are based on post hoc analysis and thus should be regarded as hypothesis generating rather than conclusive evidence (20,21).

Summarizing Points

1) Patients with diabetic nephropathy and macroalbuminuria are at very high cardiovascular risk, and an optimal risk factor control in general should be the ambition, controlling not only hypertension but also hyperglycemia and hyperlipidemia, as well as avoidance of tobacco smoking.
2) The blood pressure goal in these patients with macroalbuminuria could be <130/80 mmHg but at the same time taking into account that many patients may have overt or subclinical ischemic heart disease and thus risk coronary hypoperfusion if the systolic blood pressure level is lowered too far.
3) It is currently debated whether the same blood pressure goal should be applied in patients with microalbuminuria. The lack of evidence has been taken as a reason to keep a more conservative blood pressure goal (<140/85–90 mmHg), but some proponents would like to see an ambitious blood pressure goal (<130/80 mmHg) also in these patients.
4) Further evidence is needed based on randomized controlled clinical trials before this clinical dilemma can be settled.
5) A blocker of the renin-angiotensin system is recommended to be one part of a multiple drug combination approach to control hypertension in patients with macroalbuminuria or microalbuminuria.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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