Blood Pressure Control in Diabetic Nephropathy

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Abstract

Epidemiologic studies show a worldwide diabetic epidemic. Diabetes mellitus is associated with a reduced life span due to macrovascular and Microvascular complications. Thus, diabetic nephropathy, which is the major cause of morbidity and mortality for patients with either type 1 diabetes mellitus or type 2 diabetes mellitus, is a public health care problem. Blood pressure control is a proven intervention to prevent progression of diabetic nephropathy and to reduce cardiovascular events in patients with diabetes mellitus. Establishment of optimal blood pressure targets, advantages of one class of drugs over another as well as time of initiation of antihypertensive therapy are those important questions that appear before every doctor. This review addresses these issues.

Abbreviations: ABCD: Appropriate Blood Pressure Control in Diabetes; ACCORD: Action to Control Cardiovascular Risk in Diabetes; ACE: angiotensin-converting-enzyme; ACEI: angiotensin converting enzyme inhibitor; ADA: American Diabetes Association; ADVANCE: Action in Diabetes and Vascular disease: pretarAx and diamicroN modified release Controlled Evaluation; ALLHAT: Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial; ALTITUDE: Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints; ARB: angiotensin receptor blockers; ASCEND: A Study of Cardiovascular Events in Diabetes; AVOID: Aliskiren in the Evaluation of Proteinuria in Diabetes; BP: blood pressure; CALM: CAndesartan and Lisinopril Microalbuminuria; CAPPP: Captopril Prevention Project; CCB: calcium channel blocker; DCCT: Diabetes Control and Complications Trial; DETAIL: Diabetics Exposed to Telmisartan And EnalaprIL; EDIC: Epidemiology of Diabetes Interventions and Complications; ESRD: End Stage Renal Disease; ET-1: endothelin-1; FACET: Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial; GFR: Glomerular Filtration Rate; HOT: Hypertension Optimal Treatment; IDNT: Irbesartan in Diabetic Nephropathy Trial; IRMA2: IRbesartan MicroAlbuminuria type 2; JNC-VII: Joint National Commission VII on Hypertension in the US; MICRO-HOPE - MIcroalbuminuria Cardiovascular and Renal Outcomes and the Heart Outcomes Prevention Evaluation; ONTARGET - Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; RAAS: Renin-Angiotensin-Aldosterone System; RENAAL: Reduction in Endpoints in patients with Non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; TGR: Transgenic (Mren-2)27 Rats; UACR: Urinary Albumin to Creatinine Ratio; UKPDS: United Kingdom Prospective Diabetes Study; VADT: Veterans Affairs Diabetes Trial

Introduction

Diabetes mellitus is becoming pandemic in the US and all over the world. In 2011 the prevalence of diabetes was 366 million people and is predicted to rise to 552 million by 2030 worldwide [1]. Eleven percent of the US population (25.6 million people) aged 20 years or older were diagnosed with diabetes mellitus in 2011 [2]. More than 90% of diabetes in the United States represented is Type 2 Diabetes Mellitus (T2DM) which is associated with a 70–80% chance of premature death from cardiovascular disease. Therefore studies of patients with T2DM are of particular importance [3-7].

Diabetes mellitus is associated with macrovascular disease; affecting the heart; brain and lower extremities; and Microvascular pathology; which leads to blindness; diabetic neuropathy and diabetic nephropathy. A diabetic foot; a consequence of diabetic neuropathy and lower extremity arterial disease; is a main cause of nontraumatic lower-extremity amputations in the US [8]. In turn; diabetic kidney disease remains the major cause of morbidity and mortality for persons with either Type 1 Diabetes Mellitus (T1DM) or T2DM.

Pathophysiology

Mechanisms responsible for diabetic Microvascular complications are also involved in the development and progression of diabetic nephropathy. Hyperglycemia [9] and hypertension [10,11] are the major initiators of metabolic and hemodynamic changes in diabetic renal disease and; in turn; the major determinants of the future treatment strategies. Pathophysiologic changes of diabetic nephropathy include a wide range of molecular mechanisms. Considering the topic of the review; we will focus mostly on early hemodynamic changes; which can be modified by antihypertensive agents. Increased single nephron glomerular filtration rate; intraglomerular hypertension [12] and relative efferent versus afferent arteriolar vasoconstriction [13] observed during micropuncture studies have underscored the main intrarenal hemodynamic abnormalities that lead to renal injury.

Renin-angiotensin-aldosteron system

Brenner's group was one of the first which underlined the role of the Renin-Angiotensin-Aldosteron System (RAAS) in these perturbations. In one animal study short-termed treatment with an Angiotensin Converting Enzyme Inhibitor (ACEI) attenuated these hemodynamic alterations. Moreover; treatment with the ACEI enalapril for a period of 1 year prevented the establishment of diabetic nephropathy despite pronounced hyperglycemia [12]. Experiments in transgenic (mREN-2)27 rats (TGR) with amplified tissue RAAS expression and increased plasma prorenin further proved participation of the RAAS

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in development of diabetic nephropathy [14]. In this study perindopril diminished renal pathology; improved renal function and abrogated proximal tubular renin expression in the diabetic TGR. Andersen et al. investigated components of RAAS in diabetes rats. They showed increased renin and angiotensinogen mRNAs within the kidney in spite of normal plasma renin concentration and serum Angiotensin-Converting-Enzyme (ACE) activity [15]. Moreover; ACE expression in the diabetic kidney appeared to be redistributed: proximal tubule ACE activity was reduced; but ACE immunostaining intensity was enhanced in the glomerulus and renal vasculature. The authors proposed the following interpretations of their findings. First; the redistribution of intrarenal ACE into vasoactive sites in diabetic kidney provides regulation of renal hemodynamics and causes hyperfiltation. The hemodynamic responsiveness to ACE inhibition found in the study is compatible with this explanation. Second; brush border ACE as a dipeptidyl carboxypeptidase might contribute to proximal tubule cleavage of filtered proteins. In contrast; reduced ACE activity within proximal tubules leads to "tubular" proteinuria observed in diabetes. Particular attention should be paid to the interaction of RAAS and nephrin which is one of the slit pore proteins which determine proteinuria in a wide range of nephropathies; including in diabetes. A recent study showed that irbesartan treatment prevented the development of albuminuria and restored the reduced nephrin content in diabetic rats [16].

Besides hemodynamic changes, activation of RAAS leads to a wide range of non-hemodynamic effects. Angiotensin II has been implicated in the development of progressive glomerulosclerosis by stimulating extracellular matrix protein synthesis through induction of TGF-beta and the matrix components biglycan, fibronectin, and collagen type I [17]. Angiotensin II also might contribute to the tubular hypertrophy observed in diabetes [18] which will promote glomerular hyperfiltration, namely protein kinase C [20] and nuclear factor-kappa B [21] with subsequent vasculatur changes. Therefore interruption of the RAAS seems to be an excellent therapeutic approach; not only for Blood Pressure (BP) reduction; but also for nephroprotection and prevention of proteinuria through correction of metabolic; hemodynamic and structural abnormalities.

Other vasoactive hormones

In addition to the RAAS; hemodynamic perturbations in diabetic nephropathy also may be modulated by other vasoactive hormones. The most important mediators of vasomotor tone are endothelin-1; vasopressin; bradykinin; atrial natriuretic factor; certain prostaglandins; nitric oxide and vasodilative factors such as angiotensin (1-7). Among these vasoactive agents studies of endothelin-1 (ET-1) appeared very promising in terms of clinical practice. Plasma and urinary ET-1 levels are elevated in patients with diabetes and correlate with decreased renal function and level of albuminuria [22, 23]. ET-1 may cause vasoconstriction; renal sodium retention; cellular proliferation; inflammation; and fibrosis. Therefore, endothelin receptor antagonists might provide additional renal protection through reduction in proteinuria; hypertension and fibrosis. ET receptor antagonists have been evaluated and progressed to small clinical studies in human subjects. Positive results of treatment by avosentan; an endothelin antagonist; led to a larger long-term study, ASCEND (A Study of Cardiovascular Events in Diabetes) [24]. Avosentan showed impressive reduction in proteinuria in patients with diabetic nephropathy and macro albuminuria. However; severe fluid retention, side effect of avosentan, reduced the current level of enthusiasm for these agents. Additional clinical trials with more long-term outcome analyses are needed to determine their true role and establish safety in the diabetic population.

Nevertheless; novel agents that interrupt different pathological pathways have failed to demonstrate firm evidences of nephroprotection. Only currently available strategies; namely; antihypertensive and hypoglycemic treatment remain the best treatment in routine practice.

Clinical Manifestations of Diabetic Nephropathy

Hypertension; proteinuria (from microalbuminuria to overt proteinuria) and; ultimately; loss of Glomerular Filtration Rate (GFR) represent the clinical spectrum of pathologic diabetic injury of the kidney. Simultaneously microalbuminuria is the earliest clinical and important prognostic feature of diabetic nephropathy. In last decade the overall prevalence of normo-; micro-; and macro albuminuria was 51%; 39% and 10% in T2DM (5); and 95.68%; 3.31% and 1.01% in T1DM respectively [25].

The natural history of diabetic renal disease in patients with T1DM is better understood than in patients with T2DM because the time of clinical onset of T1DM can be more accurately ascertained. Approximately 40% of patients with T1DM progress to clinical diabetic nephropathy after 25 years; the survival is worse in those patients with proteinuria [26]. End Stage Renal Disease (ESRD) appears 10 years after onset of persistent overt proteinuria (>300 mg/24 hours) [27]. In patients with T2DM; like in T1DM; progression to ESRD depends on the severity of nephropathy at a baseline [28].

Forty four percent of new ESRD cases have a primary diagnosis of diabetes mellitus accordingly to the US Renal Data System 2013 Annual Report [29]. The worldwide data is even higher [29]. The US data showed a 35% decline in the incidence rate of ESRD caused by diabetes [8]. However; due to the increase of diabetes mellitus; the likelihood of developing ESRD secondary to diabetes mellitus is rising.

Nevertheless many patients with diabetes renal disease do not develop ESRD; because they die prematurely due to cardiovascular disease [30]. In developing countries patients with diabetes mellitus who progress to ESRD; may not be able to afford renal-replacement therapy. Thus; strategies to prevent the onset of nephropathy and its progression are extremely important. BP and glycemic control represent the major cornerstones of these preventive strategies.

Glycemic Control

DCCT (Diabetes Control and Complications Trial) and the follow-up EDIC (Epidemiology of Diabetes Interventions and Complications) study clearly showed the importance of glucose control in prevention and delay of long-termed microvascular complications in patients with T1DM [31]. The United Kingdom Prospective Diabetes Study (UKPDS) provided important results in patients with T2DM [32]. The reduction in HbA1c by mean of 0.9% reduced the risk for albuminuria by 34% after 10 years of follow-up; however; there was no effect on macrovascular complications that account for 75-80% of diabetes-related deaths [33]. The ADVANCE (Action in Diabetes and Vascular disease: pretarAx and diamicroN modified release Controlled Evaluation) trial confirmed benefit of intensive glucose-control strategy in reduction of renal events [34]. In contrast; the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial found that intensive glucose lowering increased cardiovascular events and mortality [35]. VADT study (Veterans Affairs Diabetes Trial) of patients with T2DM again did not show significant effect of tight glucose control on the rates of major cardiovascular events; death or microvascular complications;

with the exception of progression of albuminuria [36]. The associated hypoglycemia and weight gain in the intensive-therapy group may have contributed to the discrepant results in glucose control [35].

Of interest; a follow-up study of DCCT trial found a delayed benefit of intensive glucose control [37]. Strict glycemic control reduced the risk of any cardiovascular disease by 42% and the risk of nonfatal myocardial infarction; stroke or death from any cardiovascular disease by 57 % after 17 years of follow-up. This delayed consequence has been attributed to a "memory" effect of better glucose control. A number of interesting finding were also yielded by recent analysis of ADVANCE trial regarding kidney outcomes [38]. Intensive glucose control significantly reduced the risk of ESRD by 65%; microalbuminuria by 9% and macroalbuminuria by 30%.

As renal function fails; tight glycemic control becomes a challenge because of increased risk of hypoglycemia in both types of diabetes mellitus. What hypoglycemic drugs should be preferred in the treatment of T2DM for preventing and treatment of diabetic nephropathy still remains to be defined. Regarding diabetic nephropathy glycemic control has been established currently as a therapy for prevention of Microvascular complications but not for cardiovascular diseases or death.

Blood Pressure Control

The possible role of blood pressure (BP) reduction in treatment of diabetic kidney disease initially was shown by Scandinavian researchers [39,40]. In 1990s United Kingdom Microalbumin Study exploring the effect of improved glycemic control unexpectedly found that a mean BP (above 93.6 mm Hg) rather than glycated hemoglobin predicts progression from macroalbuminuria to macro albuminuria in patients with T1DM [41]. The UKPDS BP-trial in T2DM revealed that a reduction in BP from 154/87 mm Hg to 144/82 mm Hg over 9 years of follow-up led to decrease in the risk of 24% for any diabetes-related end point; 32% for diabetes-related death and 29% reduction in risk of microalbuminuria [42]. In comparison; intensive blood glucose

control in the United Kingdom prospective diabetes study decreased the risk of any diabetes related end point only by 12% [32] (Figure 1). Thus; sustained management of BP appears to be more important than glycemic control in reducing cardiovascular events; cardiovascular mortality and slowing diabetic renal disease progression.

The prevalence of hypertension in diabetes is approximately twofold that in the nondiabetic population [43]. With the onset of overt diabetic nephropathy; clear-cut hypertension is common in both types of diabetes mellitus; however; about 30% of patients with T2DM are already hypertensive at the time of diagnosis of diabetes [43]. Therefore; it is very important to evaluate the efficacy of antihypertensive therapy in preventing diabetic complications and slowing progression of diabetic kidney disease; as well as; determining optimal BP targets in patients with diabetes. Considering the renoprotective benefits from the ACEIs in treatment of diabetic nephropathy [44,45]; the particular advantages of one class of drugs over another should also be established. The first large interventional trial conducted to address these issues was Appropriate Blood Pressure Control in Diabetes (ABCD) trial.

Appropriate Blood Pressure Control in Diabetes

The primary aim of the prospective; controlled; randomized ABCD trial was to investigate the effect of intensive (diastolic BP 70-79.9 mm Hg) versus moderate BP (diastolic BP 80-89.9 mm Hg) control with respect to preventing or slowing the development of progression of diabetic renal disease; retinopathy; cardiovascular disease and neuropathy in patients with T2DM [46]. Comparison of Calcium Channel Blocker (CCB) (nisoldipine) versus the ACEI (enalapril) in prevention or delaying of diabetic complication was the secondary goal.

At enrollment nephropathy; retinopathy; cardiovascular disease and neuropathy were significantly more prevalent in hypertensive patients than normotensive among 950 patients recruited into the study. The results of the 5-year follow-up ABCD trial; therefore; were analyzed separately for the hypertensive and normotensive cohorts (Figure 2) [47]. A significant relationship was found between
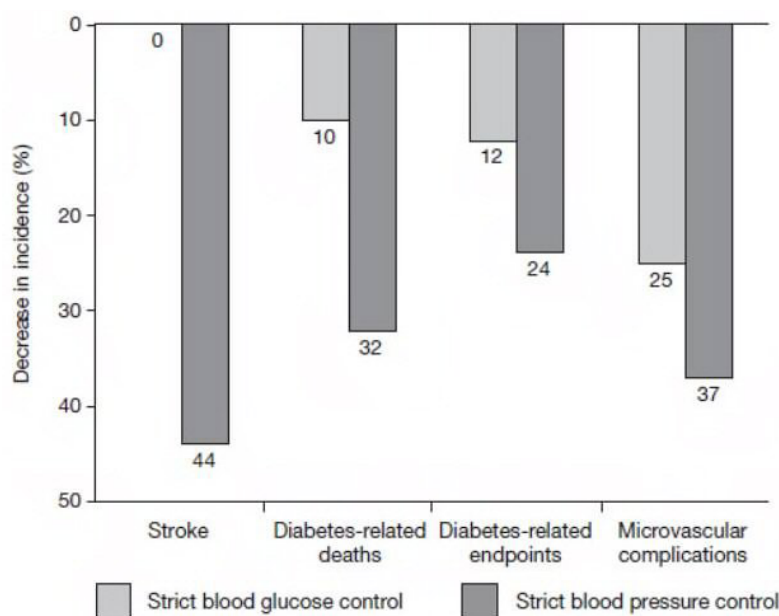

Figure 1: Results of the randomized UKPDS trial show that strict control of blood pressure is more effective than strict control of blood glucose level in decreasing the incidence of both microvascular and macrovascular complications in patients with type 2 diabetes [74].

albuminuria and high BP; both systolic (>140 mm Hg) and diastolic (>90 mm Hg) [47]. Moreover; hypertension produced an 86% increase in the risk for diabetic kidney disease. The study also revealed a strong association of urinary albuminuria with retinopathy; neuropathy and cardiovascular disease [48].

Benefits of Antihypertensive Treatment in Patients with Type 2 Diabetes Mellitus and Hypertension

Angiotensin-converting-enzyme inhibitors and cardiovascular disease

The baseline characteristics of patients in the hypertensive cohort of five year follow-up ABCD study were comparable. Randomization protocol is shown in Figure 3. Data and Safety Monitoring Committee halted the comparison between the ACEI and the CCB in the hypertensive cohort after 4 years of follow-up because of the lower incidence of myocardial infarction in the enalapril group than in the nisoldipine group (Figure 4) [49]. Result did not change after adjustment for BP level; blood glucose level and cholesterol level. Importantly; the lower incidence of myocardial infarction in the enalapril group was strongly associated with a decrease in left ventricular mass [50].

Later Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) showed similar results in patients with T2DM [51]. Despite a greater systolic BP reduction in patients treated with the CCB; patients randomized to the ACEI were about 50% less likely to experience major cardiovascular events. The Captopril Prevention Project (CAPPP) also revealed a 66% lower rate of fatal and non-fatal miocardial infarction in both type 1 and 2 diabetic patients treated with the captopril than diuretics or beta-blockers [52]. Moreover; the frequency of all cardiac events and total mortality was significantly lower. The MICRO-HOPE study (the MIcroalbuminuria; Cardiovascular; and Renal Outcomes and the Heart Outcomes Prevention Evaluation); placebo controlled trial; confirmed these intriguing findings [53]. The study was stopped 6 months earlier (after

4.5 years of follow-up) because ramipril lowered the risk of major cardiovascular outcomes by 25–30% irrespectively of type 1 or 2 diabetes and the type of hyperglycemic treatment. As in ABCD trial; adjustment for BP differences in comparison groups did not change the result. This shows the advantage of antihypertensive regimen based on the ACEIs over other drugs in prevention of cardiovascular disease in patients with diabetes mellitus.

However; Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT) did not find this advantage [54]. There were no significant differences in incidence of the fatal coronary heart disease and nonfatal myocardial infarction for those assigned to chlorthalidone compared with lisinopril; as well as; in the incidence of combined coronary heart disease; total mortality and ESRD in diabetic population. A large proportion of African-American; a third of the study population; and significantly lower systolic BP in those people assigned to chlorthalidone; which was even lower in black population; explain this result.

Early antihypertensive therapy for preservation of renal function

After the comparison between enalapril and nisoldipine was stopped in the hypertensive ABCD cohort; in the remaining follow-up all patients were treated with enalapril. The average BP achieved for the intensive and the moderate antihypertensive arms was 132/78 mm Hg and 138/86 mm Hg respectively [55].

The mean renal function of patients starting with normoalbuminuria (<30 mg/24 h) or microalbuminuria (30-300 mg/24h) remained stable in both antihypertensive arms independent of initial therapy. In contrast; patients with overt nephropathy at a baseline had a significant and continuous decline of the renal function at a rate approximately 5 ml/min/year (Table 1). Neither initial therapy; nor level of achieved BP influenced this decline.

This suggests that prevention of diabetic nephropathy requires early intervention at the normoalbuminuric or microalbuminuric
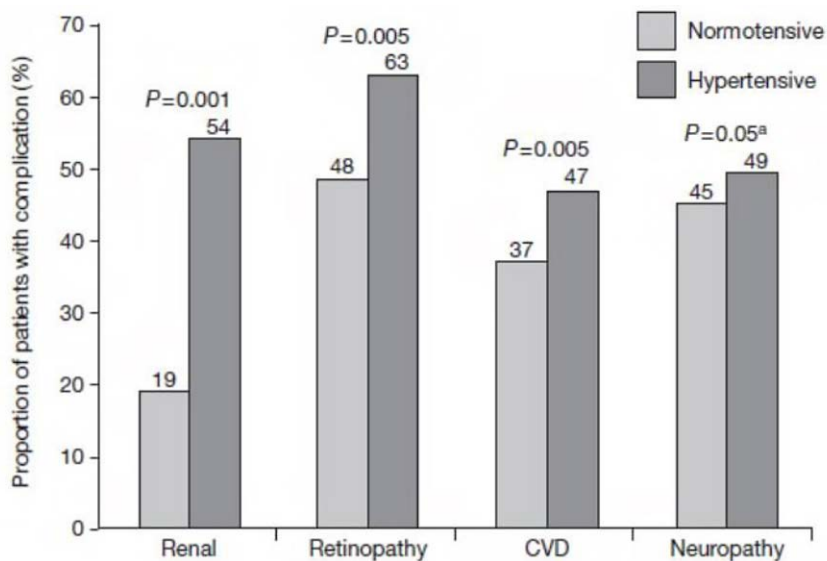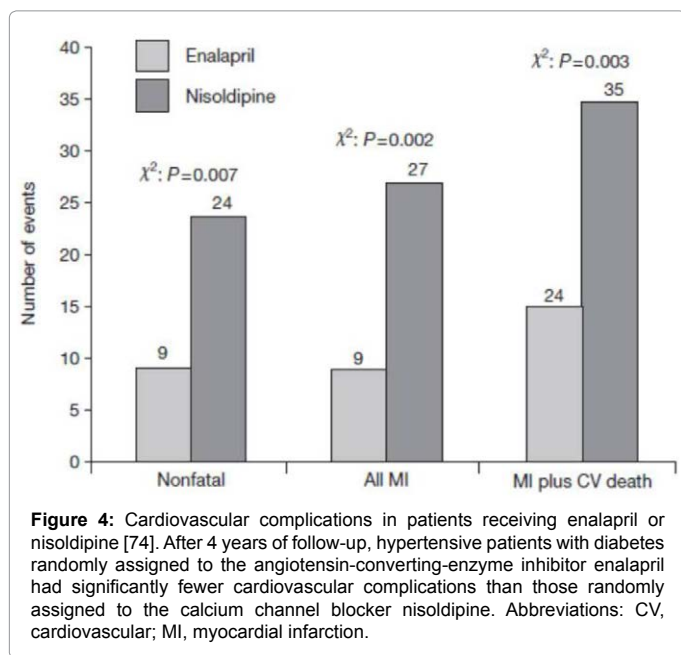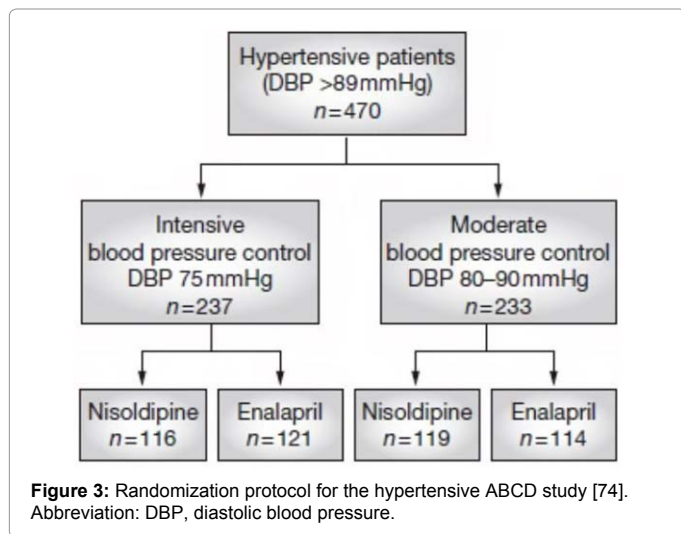

Figure 2: Complications at baseline in patients enrolled in the ABCD randomized clinical trial (47). There were significantly more complications in hypertensive than in normotensive patients with type 2 diabetes.
aFor systolic hypertension only.
Abbreviation: CVD, cardiovascular disease.
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Figure 3: Randomization protocol for the hypertensive ABCD study [74]. Abbreviation: DBP, diastolic blood pressure.

Figure 4: Cardiovascular complications in patients receiving enalapril or nisoldipine [74]. After 4 years of follow-up, hypertensive patients with diabetes randomly assigned to the angiotensin-converting-enzyme inhibitor enalapril had significantly fewer cardiovascular complications than those randomly assigned to the calcium channel blocker nisoldipine. Abbreviations: CV, cardiovascular; MI, myocardial infarction.

Degree of blood pressure control	Mean creatinine clearance (ml/min/1.73^2 ± SE)		P value
	Baseline	**5 years**	
Hypertensive patients			
Intensive	75.0 ± 4.4	56.9 ± 5.8	0.035
Moderate	77.5 ± 5.5	52.6 ± 5.8	0.006
Normotensive patients			
Intensive	84.5 ± 7.2	57.7 ± 9.2	0.032
Moderate	76.0 ± 6.3	52.9 ± 9.7	0.042

Table 1: Effect of intensive versus moderate blood pressure control on the renal function of hypertensive and normotensive patients with overt diabetic nephropathy in the ABCD trial (57).

stage. Recently scientists described renal impairment in both types of diabetes mellitus which can occur without albuminuria or without progression from microalbuminuria to proteinuria [56]. Considering this nonalbumiuric pathway of diabetic kidney disease; the ability of antihypertensive therapy to preserve renal function is even more important.

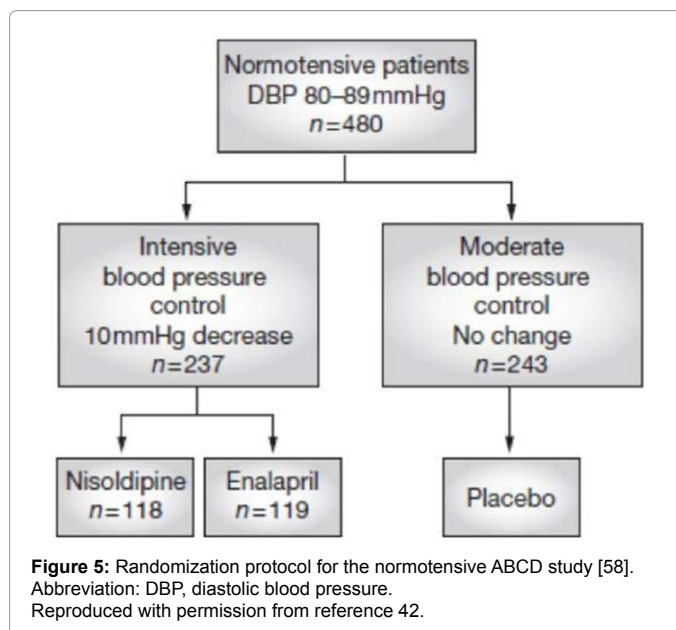## Angiotensin-converting-enzyme inhibitors and albuminuria

There was no difference in the level of BP with regard to individuals progressing from normoalbuminuria to microalbuminuria (25% intensive therapy vs. 18% moderate therapy; P = 0.20) or microalbuminuria to overt albuminuria (16% intensive therapy vs. 23% moderate therapy; P = 0.28). This might be attributed to poor glycemic control in ABCD study or necessity of longer follow-up and/or larger group of patients. An initial decrease of urinary albuminuria was observed in the ABCD study with enalapril treatment; but after 3.5 years it disappeared. The same was demonstrated in the UKPDS - tight BP control resulted in a lower urinary albumin concentration; but this difference was not apparent after 6 years [42]. FACET also did not find any change in urinary protein excretion with the ACEIs [51]. In contrast; Ravid et al showed that the ACEIs did reduce the new onset of albuminuria in the normotensive patient with T2DM over 6 year period in a placebo-controlled study [57]. The MICRO-HOPE study presented clear benefit of RAAS blockade [53]. Ramipril compared with placebo lowered the risk of overt nephropathy by 24% in the large diabetic population. Thus; the ACEIs have renoprotective actions in diabetic renal disease beyond their antihypertensive effects.

Intensive antihypertensive therapy

In ABCD study intensive BP control over the 5 years of follow-up significantly decreased the incidence of all-cause mortality (5.5% versus 10.7%; P <0.037) in patients with hypertension. Moreover; this level of BP control (132/78 mm Hg) appeared to be quite safe.

Benefits of Antihypertensive Treatment in Normotensive Patients with Type 2 Diabetes Mellitus

The baseline characteristics of patients in the five year normotensive cohort of ABCD study were comparable. The randomization protocol for normotensive cohort of five year follow-up ABCD study is shown in Figure 5. As in the hypertensive cohort of ABCD study; in the normotensive cohort (normal BP < 140/90 mm Hg) both intensive (mean BP 128/75 mmHg) and moderate (mean BP 137/81 mmHg) control of BP stabilized renal function over 5 years in patients starting

Figure 5: Randomization protocol for the normotensive ABCD study [58]. Abbreviation: DBP, diastolic blood pressure. Reproduced with permission from reference 42.

with normoalbuminuria and microalbuminuria [58]; but not in those patients starting with overt proteinuria.

By contrast with hypertensive cohort; in normotensive cohort intensive BP control stabilized urinary albumin excretion and slowed the progression of proteinuria in patients starting with normoalbuminuria and microalbuminuria. Moreover; 23 patients from both antihypertensive regimes reverted from microalbuminuria to normoalbuminuria. However; albuminuria progressed in patients starting with overt proteinuria.

In addition to the decreased reduction of all-cause mortality in hypertensive cohort; in normothensive cohort the intensive BP control significantly lowered incidence of stroke and decreased a progression of diabetic retinopathy when compared to the group with moderate BP control (Table 2). These beneficial effects were observed in the absence of any differences between study groups in blood glucose concentration; lipid levels; smoking prevalence or antihypertensive medications.

Results from normotensive cohort further indicate that primary prevention of diabetic kidney disease demands early administration of antihypertensive therapy at the normoalbuminuric or microalbuminuric stage even in normotensive patients.

Angiotensin Receptor Blockers in Diabetic Nephropathy

Interruption of the RAAS by the ACEIs was proven to slow the progression of diabetic renal disease; but angiotensin receptor blockers (ARBs) have also been studied in this population. RENAAL (Reduction in Endpoints in patients with Non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan) compared different doses of losartan with placebo in hypertensive patients with renal insufficiency and T2DM [59]. The ARB treatment was associated with reduction in ESRD; a 35% decrease in proteinuria and a major reduction in hospitalization for heart failure. In the IRMA2 (IRbesartan MicroAlbuminuria type 2) trial irbesartan dose-dependently reduced the onset of proteinuria in patients with preserved renal function [60]. IDNT (Irbesartan in Diabetic Nephropathy Trial) examined patients with proteinuria and reduced GFR [61]. Although there was no change in the rates of death or cardiovascular end-points; the antihypertensive therapy of irbesartan decreased the occurrence of ESRD and slowed the progression of nephropathy comparing with calcium channels blocker amlodipine in T2DM. Importantly; adjustment for BP did not change results. As a result; American Diabetes Association (ADA) recommended both the ARBs and the ACEIs as a first line therapy for hypertension in diabetic patients with microalbuminuria or clinical nephropathy [62].

Since the ARBs may offer more complete blockade of the RAAS and appeared to be more effective in delaying the progression of renal injury in some animal models of diabetes; researchers undertook the DETAIL (Diabetics Exposed to Telmisartan and EnalaprIL) trial to compare the ARB versus the ACEI in diabetic kidney disease [63]. No difference was found in renoprotective effects between these two classes of drugs in patients with preserved renal function after 5 years of follow-up [63].

Dual Inhibition of Raas In Diabetes Mellitus

In an attempt to achieve better nephroprotection; combining agents targeting RAAS were suggested. However; ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) conducted in a high risk general population demonstrated that dual inhibition of RAAS did not appear to be more effective and may be even harmful [64]. Specifically; combination therapy with the ACEIs and the ARB at full dose reduced proteinuria to a greater extent but increased major renal outcomes, namely, acute renal failure, hyperkalemia and symptomatic hypotension. Substudy of diabetic population from ONTARGET trial showed that dual therapy at full dose does not increase strokes or alter other major cardiovascular or renal events in patients with diabetes, however, the same adverse events tended to be more frequent with dual therapy [65]. Thus; this substudy did not demonstrate a clinical advantage of dual therapy and had a greater incidence of adverse renal events.

In contrast; the CALM (CAndesartan and Lisinopril Microalbuminuria) study showed in T2DM that dual blockade of the RAAS with submaximal doses of drugs was more effective in the reduction of Urinary Albumin To Creatinine Ratio (UACR) than monotherapy in patients with microalbuminuria and preserved renal function [66]. However; researchers did not exclude the possibility that reduction of UACR might be caused by more effective reduction of BP. Moreover; this study has several limitations. First; the follow-up of one year was too short. Secondly; 24-hour urinary albumin excretion was not reported.

AVOID (Aliskiren in the Evaluation of Proteinuria in Diabetes) study proposed an alternative dual the RAAS blockade with direct renin inhibitor and the ARB in patients with T2DM and overt proteinuria [67]. In this combination the ARB, while blocking the RAAS, indirectly increases renin; which is blocked then by aliskiren. The patients who received maximal dose of losartan were randomized to receive a maximal dose of aliskiren or placebo for 6 months. After adjustment for the difference in systolic BP the combined treatment strategy reduced the mean UACR by 18% compared with placebo without increasing adverse events.

After these promising results premature termination of the ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints) study was disappointing [68]. Patients with chronic kidney disease; T2DM and cardiovascular disease were administered maximal dose of aliskiren or placebo in addition to the ACEIs or the ARBs. The reduction of UACR in aliskiren group did not offset higher level of adverse events, namely, hyperkalemia, renal impairment and increased incidence of strokes; this led to halting of the ALTITUDE trial after 33 months of follow-up.

Therefore; combinations providing dual blockade of the RAAS is not recommended in the diabetic population; especially since

Disease Status	Blood pressure control (% of patients who progressed)		*P* value
	Intensive	Moderate	
Normoalbuminuria to microalbuminuria	17	28	0.02
Incipient to overt diabetic nephropathy	18	37	0.02
Retinopathy	35	46.5	0.02
Stroke	1.75	5.5	0.03

Table 2: Effect of intensive versus moderate blood pressure control on the progression of complications in patients with type 2 diabetes in the normotensive ABCD study (57).
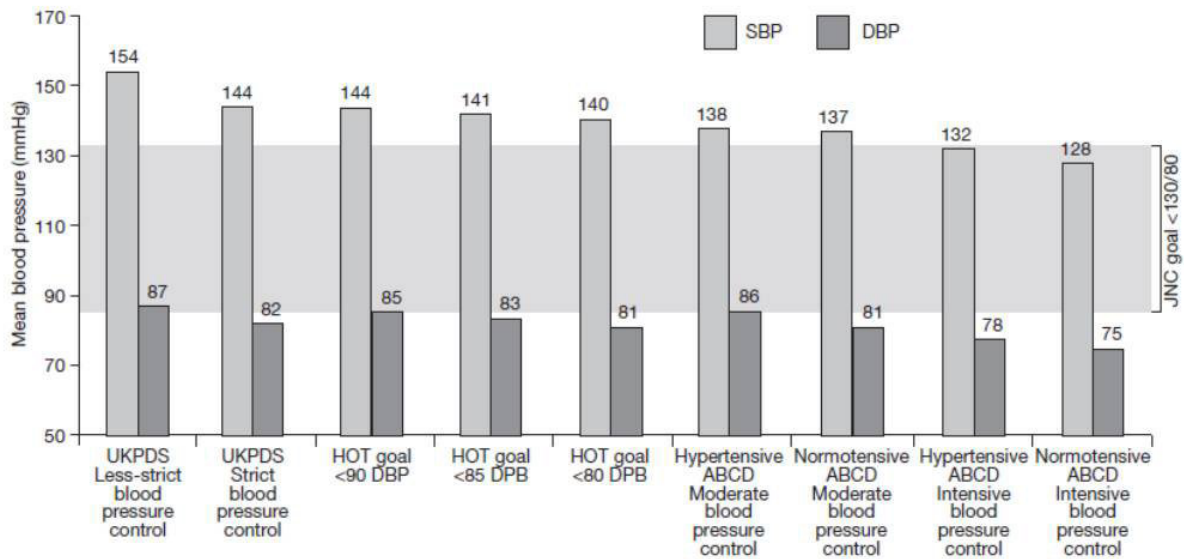
Figure 6: Mean blood pressure achieved in diabetic patients in the UKPDS, HOT and ABCD trials [74]. Only the intensive blood pressure control groups in the hypertensive and normotensive ABCD studies reached the consensus JNC goal of <130/80 mmHg.
Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure

hyperkalemia; hypotension or acute renal failure may occur. However; combination of submaximal doses may be taken into consideration; providing careful monitoring of GFR; BP and level of potassium.

Blood Pressure Goals in Diabetes Mellitus

Hypertension is a modifiable risk factor of cardiovascular events and progression of diabetic kidney disease. However; the optimal BP target for diabetes mellitus has not been established. In the general population an advantage of strict BP control was shown in HOT (Hypertension Optimal Treatment) randomized trial. The lowest risk of cardiovascular mortality occurred at a diastolic BP of 86.5 mm Hg. The subgroup analysis of patients with diabetes mellitus in HOT trial revealed that major cardiovascular events decreased twice as much in patients who achieved BP goals of less than 80 mm Hg compared with a diastolic BP goals of 90 mm Hg [69]. The reduction of the stroke risk in the CAPPP study was also attributed to lower levels of BP. However; the study investigated the general; but not the diabetic; population [52]. The ABCD study also proved that intensive BP is beneficial in diabetic population. Tight antihypertensive therapy led to decrease of all-cause mortality in patients with pre-existing hypertension; while in patients with normal BP strict BP control (reduction of diastolic BP by 10 mm Hg) stabilized renal function decline and lowered incidence of stroke. American Diabetes Association and Joint National Commission on Hypertension in the US (JNC-VII) have recommended a lower BP to levels 130/80 or less in diabetic patients. Only the intensive BP control groups in the hypertensive and normotensive ABCD studies reached the consensus JNC VII (Figure 6) [70]. Data from ABCD-2 Valsartan trail provided some support for BP targets of 120/80 mm Hg in patients with T2DM [71]. Intensive BP control reduced the progression of albuminuria and in some cases even caused regression of albuminuria started in patients with normo- and mocroalbuminuria; albeit these patients were normotensive. Nevertheless; the ACCORD BP-trial revealed somewhat disappointing findings [72]. The study investigated patients with T2DM; normal GFR and normoalbuminuria. Unexpectedly there was no difference in the incidence of nonfatal myocardial infarction or death from cardiovascular causes between the

group of intensive (average systolic BP was 119.3 mm Hg) and standard BP control (average systolic BP 133.5 mm Hg). However; some study limitations might explain these results; namely; open-labeled design and reduced statistical power of study; as well as; selective recruitment of patients. Thus; the most beneficial BP targets for diabetic population are not clearly established. Further studies are necessary.

Conclusions

Diabetes mellitus is increasing all over the world because of population growth, aging, urbanization, high prevalence of obesity and physical inactivity. Moreover; the number of patients with diabetic nephropathy and ESRD will increase significantly. The main therapies for primary and secondary prevention of diabetic kidney disease are management of BP and blood glucose. Many questions about diabetic treatment are not yet answered. However; results of conducted trials presented in this article can draw some conclusions.

To summarize:

1) Glycemic control is a therapy for prevention and delay of Microvascular diabetic complications.

The American Diabetes Association's "Standards of Medical Care in Diabetes" recommend lowering HbA1c to < 7.0% in most patients to reduce the incidence of diabetic chronic kidney disease [73,74].

BP control is a proven benefit in reducing cardiovascular events; cardiovascular mortality and slowing diabetic renal disease progression.

The primary prevention of diabetic nephropathy requires early administration of antihypertensive drugs; namely in normoalbuminuric or microalbuminuric stages. This approach allows preserving renal function; stabilizing proteinuria and slowing its progression.

Lowering BP in "normotensive" diabetic patients (BP < 140/90 mm Hg) is probably indicated.

BP goal of < 130/80 mm Hg is recommended in diabetic patients.

ACEIs are drugs of choice in prevention of CVD and lowering

the risk of overt proteinuria in patients with diabetes mellitus. ARBs therapy provides similar results.

Dual RAAS blockade is not recommended.

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