REVIEW ARTICLE doi: 10.1111/j.1463-1326.2009.01052.x

Management of hypertension in patients with diabetes: the place of angiotensin-II receptor blockers

Rigas Kalaitzidis and George Bakris

Hypertensive Diseases Unit, Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, Pritzker School of Medicine, University of Chicago, Chicago, IL, USA

Hypertension is an important cardiovascular (CV) risk factor in patients with diabetes mellitus. In this setting, tight control of blood pressure (BP) significantly reduces CV morbidity and mortality. In the UK Prospective Diabetes Study, a 10 mmHg reduction in systolic blood pressure (SBP) was superior to a 0.7% decrease in glycosylated haemoglobin A1c (HbA1c) as far as reducing morbidity and mortality was concerned. In the Hypertension Optimal Treatment study, the risk of CV events decreased by 51% among patients with type 2 diabetes randomized to the lower BP level. Based on these findings, contemporary treatment guidelines recommend a target SBP/diastolic blood pressure of <130/80 mmHg for patients with diabetes.

Keywords: ACE inhibitors, angiotensin-II receptor blockers, diabetic nephropathy, hypertension, type 2 diabetes mellitus
Received 24 November 2008; returned for revision 16 January 2009; revised version accepted 9 February 2009

Patients with diabetes and hypertension should be aggressively treated to achieve target blood pressure (BP). Antihypertensive agents suitable for patients with diabetes should delay the onset and slow the progression of diabetic nephropathy. Angiotensin receptor blockers (ARBs) produce reductions in BP comparable to angiotensin-converting enzyme inhibitors (ACEIs), do not interfere with glycaemic control and are well tolerated. Like ACEIs, ARBs have renoprotective effects in patients with diabetes. Agents in this class improve the glomerular filtration rate and urinary albumin : creatinine ratio (ACR) and retard progression from 'microalbuminuria' to nephropathy. Moreover, treatment with an ARB significantly reduces the incidence of doubling of serum creatinine, onset of end-stage renal disease (ESRD) and death in patients with type 2 diabetes and hypertension and overt nephropathy. The antihypertensive effects of ARBs, combined with their nephroprotective effects and better tolerability compared with other antihypertensive agents, support recommendations for their use in patients with type 2 diabetes and hypertension.

Overview of the Epidemiology of Hypertension in Patients with Diabetes

There has been a general trend towards a reduction in cardiovascular (CV) morbidity and mortality in the USA since 1980 in large part because of changes in risk factors [1]. Diabetes mellitus is an exception to this trend. An analysis of data from the Framingham study has shown that the proportion of CV risk attributable to diabetes has increased significantly over the past five decades [2]. These data suggest that further reductions in CV-related morbidity and mortality must involve aggressive treatment of risk factors in patients with diabetes [2].

Correspondence:
George L. Bakris, MD, Director, Hypertensive Diseases Unit, Pritzker School of Medicine, University of Chicago, 5841 S. Maryland Avenue, MC 1027, Chicago, IL 60637, USA.
E-mail:
gbakris@gmail.com
Conflict of interest:
Neither R. K. nor G. B. has any conflicts with this manuscript. No payments were received from any company.

Hypertension is a common and important CV risk factor in patients with diabetes. Patients with type 2 diabetes are at particular risk for CV events because of the presence of multiple risk factors in addition to systolic hypertension, which typically include smoking, obesity, hyperglycaemia, hyperlipidaemia and microalbuminuria [3].

Numerous large epidemiological studies have demonstrated the high prevalence of hypertension in patients with type 2 diabetes. After adjusting for the influence of age and obesity, BP tended to be higher in patients with type 2 diabetes than in those with type 1 diabetes in a cohort of 5842 patients with diabetes. The highest incidence of systolic blood pressure (SBP)/diastolic blood pressure (DBP) >160/90 mmHg was in patients with type 2 diabetes who were older than 55 years of age (43% in men and 52% in women) [3].

Among 3648 newly diagnosed patients with type 2 diabetes (mean age 52 years, 59% male) recruited for the UK Prospective Diabetes Study (UKPDS), the prevalence of hypertension, defined as an SBP/DBP of >160/90 mmHg, was 39% [4]. In addition to establishing the high prevalence of hypertension in this population, the Hypertension in Diabetes Study, as this phase of the UKPDS is known, reported that patients with hypertension had a significantly higher mean body mass index (BMI) and significantly higher mean fasting plasma triglyceride and insulin levels than those without hypertension. Moreover, patients with hypertension and newly diagnosed diabetes were significantly more likely to have experienced a previous CV event or to have microalbuminuria, evidence of ischaemia on ECG or left ventricular hypertrophy than those without hypertension.

On the basis of a more conservative definition of hypertension (SBP/DBP >130/85 mmHg) recommended in the previous Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) [5], the prevalence of hypertension was determined to be 86.6% in a retrospective cohort study of 371 221 US veterans, of whom 59 900 had diabetes. Among patients with diabetes, 20.3% had hypertension [6]. The majority of patients with diabetes and hypertension in this analysis also had dyslipidaemia as defined by the National Cholesterol Education Program.

Hypertension substantially increases the risk of microvascular and macrovascular complications in patients with diabetes, and it is recommended that all patients with hypertension be screened for diabetes [7]. Hypertension causes structural abnormalities of the microvessels [8], thus compounding the detrimental effects of hyperglycaemia on the microvasculature (particularly hypertrophic remodelling), which leads to the well-known microvascular complications of diabetes: retinopathy, nephropathy and questionably neuropathy [8].

Atherosclerosis is accelerated in patients with diabetes. The combination of diabetes and hypertension increases arterial stiffness, which often precedes the occurrence of macrovascular events such as myocardial infarction or stroke [9]. Obesity and hyperlipidaemia also contribute to elevate the rate of macrovascular complications in patients with type 2 diabetes [10].

The presence of nephropathy is important in patients with diabetes [11]. The terms 'normoalbuminuria', 'microalbuminuria' and 'macroalbuminuria' are arbitrary points on a continuum of albumin excretion that correlate with increasing CV risk. Microalbuminuria, defined as an albumin excretion rate of 30–300 mg/24 h, is a particularly important CV risk factor in patients with diabetes. It is increasingly recognized that lower levels of albuminuria than are currently used should be considered as an indicator of vascular inflammation [12]. The incidence of microalbuminuria is more common in patients with diabetes, suboptimal glycaemic control and hypertension [13]. Moreover, microalbuminuria is a significant and independent predictor of all-cause mortality, CV mortality and morbidity (including stroke, MI and congestive cardiac failure). Note that if the ACR method is used to detect microalbuminuria, then gender differences should be taken into account. For example, European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines define microalbuminuria as an ACR of $\geq$22 mg/g for men and an ACR of $\geq$31 mg/g for women [14].

The prevalence of type 2 diabetes, which makes up 97% of the population with diabetes, is increasing. In the USA, the prevalence increased from 5 to 6.5% over the period 1988–2002 according to data from the National Health and Nutrition Examination Survey (NHANES) [15]. This estimate is in close agreement with the estimated global prevalence of 6% [16]. The increasing prevalence of diabetes and hypertension in the USA is linked to an increasing prevalence of chronic kidney disease [17]. The ageing population and the general increase in affluence and obesity will likely conspire to further increase the global prevalence of diabetes and the health burden associated with complications of the disease.

Challenges in Treating Hypertension in Diabetes

Management of hypertension in patients with diabetes is complex. Extensive vascular remodelling in patients with diabetes, as reflected by increases in the media : lumen ratio, may interfere with the efficacy of antihypertensive

drugs that increase vascular compliance through vasorelaxation. Diabetic nephropathy alters the pharmacokinetics of many drugs, and great care must be taken not only in adjusting the dose of medications prescribed for patients with renal dysfunction but also in considering their potential to ameliorate or exacerbate the progression of nephropathy. A large number of medications are prescribed for patients with diabetes; thus, it is important to consider potential drug–drug interactions and the potential for interference with control of glucose and lipid levels. Perhaps, the greatest challenge in managing hypertension in patients with diabetes is achieving the more stringent BP targets that are recommended for patients with diabetes. It is essential that clinicians involved in the care of patients with diabetes appreciate the importance of achieving tight control of BP in these individuals.

Tight BP Control in Patients with Diabetes and Hypertension

Tight control of BP in patients with diabetes and hypertension significantly reduces morbidity and mortality rates [18,19]. In the UKPDS, tight BP control, defined as an SBP/DBP of <150/85 mmHg, significantly reduced the risk of diabetes-related end-points by 24%, deaths from diabetes by 32% and microvascular complications by 37%. After 9 years of follow-up, the group assigned to tight BP control had a 47% reduction in risk of a decrease in vision by three or more lines in both eyes of the Early Treatment of Diabetic Retinopathy Study [19]. A total of 758 patients enrolled in the UKPDS were assigned to tight BP control and 390 patients to less tight control (<180/105 mmHg) and were treated for a median duration of 8.4 years. The mean SBP/DBP maintained during the trial was 144/82 mmHg in those on tight control and 154/87 mmHg in those on less tight control. Importantly, there was no difference in the degree of glycaemic control between patients receiving tight and less tight BP control in the study. Compared with the conventional group, the risk in the intensive group was 12% lower [95% confidence interval (95% CI) 1–21, $p = 0.029$] for any diabetes-related end-point. Most of the risk reduction in the any diabetes-related aggregate end-point was because of a 25% risk reduction (95% CI 7–40, $p = 0.0099$) in microvascular complications [20].

The UKPDS established the importance of tight BP control and provided the impetus for clinicians to focus more attention on control of this risk factor in patients with diabetes, although it must be noted that the definition of tight control in the trial was much less stringent than that recommended in contemporary guidelines. Moreover, the recent 10-year follow-up data from this study further support the notion that the protection seen from tight BP control was lost when the lower pressure was not maintained over time, while unlike BP control, benefits of intensive glycaemic control did not lose their effect when not maintained [21]. It is noteworthy that glycaemic control can lower BP, and for every molecule of glucose that is filtered and reabsorbed, one molecule of sodium is also absorbed [22]. The current definition of tight control more closely reflects that used in the Hypertension Optimal Treatment (HOT) study, the results of which have had a lasting influence on the management of hypertension [18].

The HOT study confirmed that the risk of CV events decreases in proportion to reductions in BP. A total of 18 790 patients with hypertension were randomized to a target DBP of ≤90, ≤85 or ≤80 mmHg in the trial. The lowest incidence of major CV events occurred in patients assigned to the lowest BP stratum. Among patients with diabetes, who comprised 8% of the overall study population, there was a highly significant 51% reduction in the incidence of major CV events in patients randomized to the lowest stratum (≤80 mmHg) compared with the least stringent stratum (≤90 mmHg) [18]. Major adverse CV events included in the composite end-point included fatal and non-fatal MI, fatal and non-fatal stroke and all other CV deaths. Antihypertensive treatment was generally well tolerated in the trial and was associated with improvements in patients' sense of well being [23].

The collective results of UKPDS and HOT provide convincing evidence that tight BP control significantly reduces the risk of microvascular and macrovascular end-points in patients with type 2 diabetes and hypertension [18,19]. For this reason, tight BP control has become a prominent message in contemporary treatment guidelines.

Treatment Guidelines for Patients with Diabetes and Hypertension

There are several major treatment guidelines that provide recommendations for the management of hypertension in patients with diabetes (table 1) [24]. Each of these guidelines provides treatment goals and drug therapy recommendations that are based on clinical trial data, including those from the landmark UKPDS and HOT studies [19]. Guidelines differ as to whether their recommendations are based on categorical treatment thresholds, as, for example, in JNC 7 [24] and the American Diabetes Association (ADA) treatment guidelines that also define a specified BP threshold [25,26], or on an

Table 1 Major recommendations of treatment guidelines related to management of hypertension in patients with diabetes

	ADA [26]	JNC 7 [24]	AACE [73]	ESH/ESC [14]	NKF [11,74]	WHO/ISH [75]	NICE [76]
Type of diabetes considered	Type 1 or 2	Type 2	Type 2	Type 2	Type 2	Type 2	Type 2
Recommended BP target (mmHg)	<130/80	<130/80	≤130/80	<130/80	<130/80	<130/80	<140/80; <130/80 if kidney, eye or cerebrovascular disease
Recommended initial antihypertensive treatment	ACEI or ARB (±thiazide diuretic if required)	Any of: a thiazide diuretic, BB, ACEI, ARB, CCB	First or second choice: ACEI, ARB or thiazide diuretic; second or third choice: BB, CCB	Any effective and well-tolerated drug, combination therapy frequently needed	ACEI or ARB (± diuretic) is preferred, BB or CCB is added if further BP lowering or CVD risk reduction is required	First choice: diuretics in the absence of a compelling indication for another class	First choice is an ACEI; add CCB or diuretic if target not achieved; after triple therapy, add α-blocker, BB or potassium-sparing diuretic
Other comments	ACEIs delay progression of nephropathy (type 1) and macroalbuminuria (type 2); ARBs delay progression of microalbuminuria nephropathy (type 2)	ACEIs and ARBs have favourable effects on the progression of diabetic nephropathy	Use of low-dose thiazide diuretics requires adequate potassium replacement	ACEIs or ARBs are preferred when microalbuminuria is present, should be part of any combination when monotherapy is insufficient to achieve target BP	ACEIs or ARBs are indicated in all patients with diabetic kidney disease regardless of BP	Nephropathy is a compelling indication for an ACEI (type 1 diabetes) or ARB (type 2 diabetes)	First choice for person of African-Caribbean descent is an ACEI + CCB or diuretic. For any patient who is ACEI intolerant, substitute an ARB for the ACEI

AACE, American Association of Clinical Endocrinologists; ACEI, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; ARB, angiotensin II receptor blocker; BB, β-blocker; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; ESH/ESC, European Society of Hypertension/European Society of Cardiology; JNC 7, The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; NICE, National Institute for Health and Clinical Excellence; NKF, National Kidney Foundation; WHO/ISH, World Health Organization/International Society of Hypertension.

estimation of the risk of CV events, as, for example, in the recently updated ESH/ESC guidelines [14]. Tight control of BP is a consistent theme across the various guidelines in order to reduce diabetes-related mortality, progression of diabetic nephropathy, microvascular and macrovascular complications and CV disease. Thus, a target BP threshold of <130/80 mmHg is recommended for patients with diabetes and hypertension, and the higher targets recommended in earlier guidelines are no longer considered acceptable. ACEIs, β-blockers, calcium channel blockers (CCBs), ARBs and diuretics have all shown benefit in treating hypertension in patients with diabetes. Traditional or vasoconstrictor β-blockers such as atenolol or metoprolol as well as diuretics are not the preferred first-line choice because they result in an increase in insulin resistance and may show most benefit when used in combination with other antihypertensive agents [14]. However, β-blockers do have particular benefit in patients with a recent MI as well as ischaemic heart disease. Because we assume that the majority of patients with hypertension and type 2 diabetes have significant coronary artery disease, β-blockers with peripheral vasodilatory capabilities that decrease insulin resistance should be used more frequently in such patients. The preferred initial treatment varies, although more recent guidelines and those that focus specifically on patients with diabetes make strong and specific recommendations regarding the use of ACEIs or ARBs as initial monotherapy and as part of combination therapy. This recommendation is based on the beneficial effects of these agents in patients with diabetic nephropathy [4,11,14,26,27], and they have been shown to prevent the appearance of microalbuminuria and reduce CV risk [28,29]. In patients with type 2 diabetes and chronic kidney disease, ACEIs and ARBs can delay deterioration in glomerular filtration rate and increases in albuminuria.

Aliskiren is the first of a new class of oral direct renin inhibitors effective in lowering BP and reducing albuminuria. Dual blockage of the renin–angiotensin–aldosterone system (RAAS) was studied in the 'Aliskiren in the Evaluation of proteinuria in Diabetes' trial [30]. A 20% reduction of urinary ACR was noted in the aliskiren group when compared with placebo, with a reduction of 50% or more in 24.7% of patients who received aliskiren compared with 12.5% of those receiving placebo. A smaller study of 15 patients with type 2 diabetes initiated on 300 mg of aliskiren [31] demonstrated a 17% reduction in the urinary ACR in 2–4 days and 44% at 28 days [31].

In clinical practice, it is generally assumed that RAAS blockade is less effective in lowering BP in African Americans compared with Caucasians; however, an antihypertensive treatment effect is noted in African Americans as well as Caucasians using an ARB alone or in combination with the use of a thiazide diuretic [32].

Most patients with diabetes and hypertension require more than one antihypertensive agent – some patients may require three or more – to achieve recommended SBP/DBP targets recommended in contemporary hypertension treatment guidelines. Thus, it is necessary to choose agents from different classes with complementary modes of action. If combination therapy is required to lower BP to <130/80 mmHg, then the ADA recommends that a diuretic, CCB or β-blocker should be added to existing ACEI or ARB therapy [27]. Guidelines clearly stated that combination of two or more antihypertensive agents should be used initially to achieve BP goals if BP is >20/10 mmHg above the goal of <130/80 mmHg.

Control of BP in Patients with Diabetes

The proportion of patients achieving target BP is generally low and, given the serious risks associated with hypertension, a cause for concern. Many factors contribute to low rates of BP control in the general population, including the lack of symptoms and the need for lifestyle changes and a high degree of adherence with drug therapy on the part of the patient, clinical inertia on the part of physicians [33] and inadequate access to care on the part of the health-care system. The connection between insulin resistance and compensatory hyperinsulinaemia seen with hypertension may be explained by a number of mechanisms linking these disturbances, such as activation of the sympathetic nervous system [34] or enhancement of renal sodium reabsorption [35], and contribute to even lower success rates. The high prevalence of hypertension in patients with diabetes, the presence of other CV risk factors, for example obesity, and the need for multiple medications, for example antihyperglycaemic agents, make compliance with management of hypertension and achievement of the low BP targets a particular challenge. Interestingly, during recent years, a considerable number of animal and human studies have shown that the use of specific antidiabetic agents such as thiazolidinediones was associated with usually small but significant reductions of BP levels [36]. In the contrary, the particular antihypertensive agent chosen to treat hypertension in patients with diabetes may itself have implications regarding the issue of lower success rates in the past. More specifically, conventional, non-vasodilating β-blockers and diuretics are associated with detrimental effects on insulin sensitivity and glycaemic control [37] and,

consequently, could result in a worsening of the patient's diabetic condition, resulting in discontinuation of antihypertensive therapy. Exceptions to this observation with β-blockers are those with vasodilating properties, that is carvedilol and nebivolol. In a large, multicentre trial, carvedilol was compared with metoprolol and shown not to worsen glycaemic control or insulin resistance [38]. This has also been observed with nebivolol in a smaller study [39].

Epidemiological studies provide evidence of low rates of BP control in patients with diabetes and the need for more aggressive therapy [40]. Recent data from the NHANES survey show that the prevalence of hypertension increased significantly between 1988 and 2002, as has the prevalence of diabetes. Although significantly more treated patients with diabetes and hypertension achieved a BP of <130/85 mmHg in the most recent survey (36% in 2001–2002 vs. 29% in 1988–1991), the overall control rates continue to be low and are particularly dismal in certain important subgroups with a high prevalence of diabetes (e.g. 8% in middle-aged Mexican-American men) [15].

Publication of evidence-based treatment guidelines does not necessarily increase BP control rates. For example, publication of updated JNC treatment guidelines in 1997 and 2003 did not lead to substantial increases in the number of patients, including patients with diabetes, with well-controlled BP during the period 1995–2005 according to a recent analysis of the US National Disease and Therapeutics Index (IMS HEALTH) data [41].

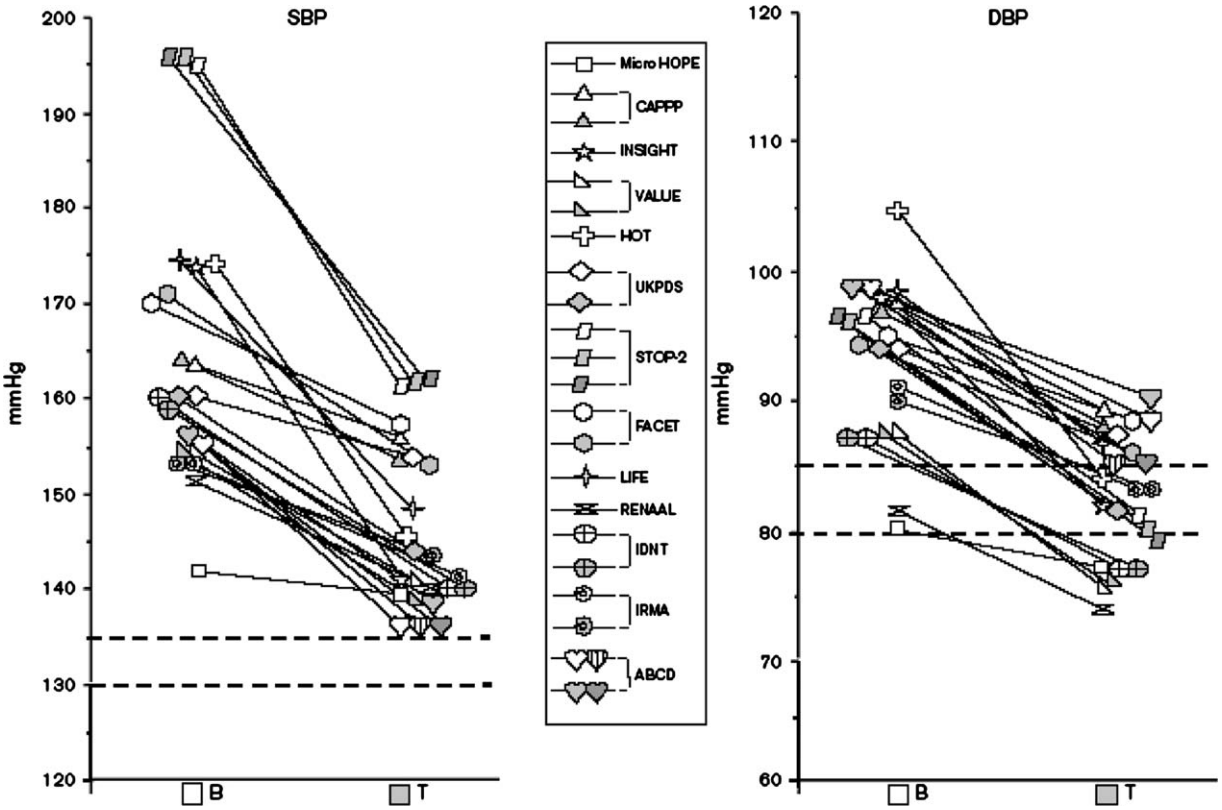

Fig. 1 Effects of antihypertensive drug treatment on systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients with diabetes and hypertension in several trials. Reproduced with permission from Mancia and Grassi [42]. Note: values at trial entry and during treatment are shown for each trial. Dashed horizontal lines refer to goal blood pressure values indicated by international guidelines to be achieved during treatment. ABCD, Appropriate Blood pressure Control in hypertensive and normotensive type 2 Diabetes mellitus; CAPPP, The Captopril Prevention Project; FACET, Fosinopril versus Amlodipine Cardiovascular Events Trial; HOT, Hypertension Optimal Treatment; IDNT, Irbesartan Diabetic Nephropathy Trial; INSIGHT, Intervention as a Goal in Hypertension Treatment; IRMA, Irbesartan in Type 2 Diabetes with Microalbuminuria; LIFE, Losartan Intervention For Endpoint; MicroHOPE, substudy of the HOPE (Heart Outcomes Prevention, Evaluation); RENAAL, Reduction in End points in NIDDM (non-insulin-dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan; STOP-2, Swedish Trial in Old Patients -2; VALUE, Valsartan Anti-hypertensive long term Use Evaluation; UKPDS, UK Prospective Diabetes Study.

Importantly, BP control rates in patients with diabetes lagged behind those in patients without diabetes, and the gap widened over time [41].

The findings of large-scale epidemiological studies of BP control rates in the community mirror the results of well-controlled clinical trials in which the majority of patients with diabetes and hypertension do not achieve BP targets (figure 1) [42]. Thus, there is a substantial gap between the recommendations in evidenced-based treatment guidelines for hypertension and the rate of BP control achieved in the community. This is because of a relative lack of evidence from clinical trials in people over the age of 70 years. Only three trials have a mean age over 70 years that deal with outcomes in patients with hypertension, but all suggest obtaining a SBP below 140 mmHg if possible.

RAAS Inhibition in Patients with Diabetes and Hypertension

Since the inception of ACEIs, no outcomes studies have been performed to assess kidney disease progression in patients with type 2 diabetes. All studies thus far have analysed markers of disease progression, that is change in proteinuria and glomerular filtration rate [43]. With the introduction of ARBs, clinical outcome trials on nephropathy progression end-points were performed. These led to indications for slowing of nephropathy progression for two different ARBs, losartan and irbesartan [44,45].

Suitable antihypertensive agents for patients with type 2 diabetes must provide marked and sustained reductions in BP so that patients can attain the recommended target SBP/DBP (<130/80 mmHg). Ideally, any antihypertensive agent used in patients with diabetes should not interfere with glycaemic control or worsen serum lipid levels but should delay the onset and slow the progression of diabetic nephropathy.

Prior to the introduction of ARBs, there was a general lack of consensus regarding the optimal class of antihypertensive agent for patients with diabetes. Several classes of agents compared well with ACEIs, particularly in their BP-lowering efficacy [10]. ARBs produce reductions in BP that are significantly greater than placebo and comparable to ACEIs, and importantly, patients are more likely to persist with ARB therapy than with ACEI therapy because of better tolerability [46]. Moreover, ACEIs and ARBs produce similar BP-dependent reductions in the incidence of stroke, coronary heart disease and heart failure [47]. ARBs improve markers of renal function, including glomerular filtration rate and urinary ACR, and in head-to-head comparisons with ACEIs, ARBs demonstrate a similar effectiveness in reducing proteinuria [48]. These findings suggest that ARBs can prevent or retard the progression of diabetic nephropathy.

In the Diabetics Exposed to Telmisartan and Enalapril study, which included 250 patients with normal kidney function, type 2 diabetes, hypertension, BMI >25 kg/m^2 and normoalbuminuria to microalbuminuria, telmisartan 80 mg/day produced similar reductions in SBP and DBP over 5 years compared with enalapril 20 mg/day [49]. Similarly, there was no difference between telmisartan and enalapril in the change in glomerular filtration rate, serum creatinine concentration or urinary albumin excretion at the end of treatment [49,50].

ARBs have renoprotective effects in patients with type 2 diabetes, hypertension and overt nephropathy, defined as an elevated urinary ACR and an elevated serum creatinine level [44,45]. In the Reduction in End points in NIDDM (non-insulin-dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan (RENAAL) trial, the incidence of the composite end-point of a doubling in serum creatinine, onset of ESRD or death was lower after 4 years of treatment with losartan than placebo. This randomized, double-blind trial enrolled 1513 patients with type 2 diabetes, hypertension and nephropathy [51]. The incidence of a doubling in serum creatinine and ESRD, but not mortality, was significantly lower in patients randomized to losartan than to placebo, as was the urinary albumin : creatinine excretion ratio at the end of treatment. Importantly, there was no difference in BP between the two study groups during treatment because use of antihypertensive agents other than ACEIs and ARBs was allowed in patients randomized to placebo. Nephropathy was defined as a baseline urinary ACR $\geq$300 (or urinary protein excretion $\geq$0.5 g/day) and serum creatinine level of 1.3–3.0 g/dl. The results of the study suggest that the nephroprotective effect of losartan is attributable to factors other than the BP-lowering effects of the drug [44].

Consistent with the findings of RENAAL, irbesartan was significantly more effective than amlodipine or placebo in preventing the same composite end-point (doubling in serum creatinine, onset of ESRD or death) in 1715 patients with type 2 diabetes, hypertension and nephropathy in the randomized, double-blind Irbesartan Diabetic Nephropathy Trial (IDNT). During a mean follow-up of 2.6 years, the relative risk of reaching the primary end-point among recipients of irbesartan was 20% lower than in patients randomized to placebo ($p = 0.02$) and 23% lower than in those randomized to amlodipine ($p = 0.006$). The mean SBP/DBP was similar in patients randomized to irbesartan (140/77 mmHg) and amlodipine

(141/77 mmHg), both of which were significantly ($p = 0.001$) lower than in those randomized to placebo (144/80 mmHg) [45].

ARBs also retard progression of renal disease in patients with diabetes and microalbuminuria but not with overt nephropathy [52]. In the Irbesartan in Type 2 Diabetes with Microalbuminuria (IRMA II) trial, the proportion of patients who progressed from microalbuminuria to macroalbuminuria was lower following 2 years of treatment with irbesartan 150 mg/day (9.7%) or 300 mg/day (5.2%) than placebo [53]. The trial studied 590 patients with type 2 diabetes and hypertension and with a baseline urinary albumin excretion rate of 20–200 μg/min and nephropathy defined as an increase in urinary albumin excretion rate to ≥200 μg/min and an increase of ≥30% over baseline. Indeed, urinary albumin excretion decreased by 24 and 38%, respectively, in patients treated with irbesartan 150 and 300 mg/day but by just 2% in those treated with placebo ($p < 0.001$ for both irbesartan groups combined vs. placebo). The mean trough SBP/DBP throughout the trial was 143/83, 141/83 and 144/83 mmHg, respectively, in patients treated with irbesartan 150 and 300 mg/day and placebo [53].

The results of RENAAL, IDNT and IRMA II demonstrate collectively that ARBs retard the progression of diabetic nephropathy across a wide spectrum of disease (i.e. from microalbuminuria to overt nephropathy). In addition, data from these studies provide insight into optimal BP levels in patients with type 2 diabetes and the efficacy of ARBs reducing the risk of important clinical end-points.

In the IDNT trial, the SBP during treatment predicted outcomes. SBP >149 mmHg was associated with a 2.2-fold increase in the risk of doubling serum creatinine or progression to ESRD when compared with SBP <134 mmHg. The relative risk of reaching a renal end-point was lower in patients treated with irbesartan than with amlodipine at all SBP levels (figure 2) [54]. Improvement in renal outcomes and survival were obtained with progressive reductions in SBP to a threshold of 120 mmHg, below which all-cause mortality increased. Importantly, the observed improvements were independent of baseline renal function. Although the finding of increased mortality in patients with SBP of <120 mmHg is likely attributable to co-morbid conditions (e.g. hypovolaemia associated with nephrotic syndrome) rather than to BP [55], these data suggest that the optimal SBP in patients with type 2 diabetes and nephropathy is in the range of 120–130 mmHg.

There have been few direct comparisons of the antihypertensive efficacy of different ARBs [56], although the most recently approved agent in this class, olmesartan medoxomil, has been compared with several other

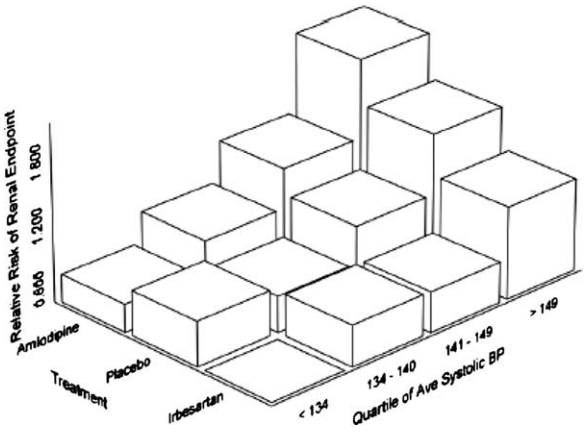

Fig. 2 Simultaneous impact of quartile of achieved systolic blood pressure (BP) and treatment modality on the relative risk for reaching a renal end-point (doubling of baseline serum creatinine level or end-stage renal disease, defined as a serum creatinine level of 6.0 mg/dl or renal replacement therapy) Reproduced with permission from: Pohl *et al.* [54].

ARBs. In a randomized, double-blind multicentre study in 696 patients with hypertension, a higher percentage of those treated for 12 weeks with olmesartan medoxomil 20–40 mg/day (18.2%) than with losartan 50–100 mg/day (11.3%) or valsartan 80–320 mg/day (11.1%) achieved the target SBP/DBP of <130/85 mmHg [57]. Among the subgroup of 53 patients with diabetes in the study by Giles *et al.* [57], olmesartan medoxomil produced the greatest reductions in BP at week 8 (figure 3),

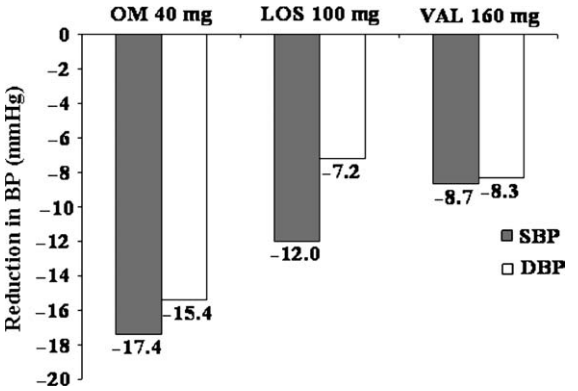

Fig. 3 Mean reduction from baseline to week 8 in seated cuff diastolic BP with olmesartan medoxomil (n = 18), losartan (n = 11) and valsartan (n = 13) in patients with diabetes, glucose intolerance or hyperglycaemia [58]. BP, blood pressure; DBP, diastolic blood pressure; LOS, losartan; OM, olmesartan medoxomil; SBP, systolic blood pressure; VAL, valsartan.

with more recipients in the olmesartan medoxomil 40 mg/day group achieving SBP/DBP goal of <130/80 mmHg at week 8 compared with losartan 100 mg/day or valsartan [58]. At week 12, similar changes from baseline in mean SBP and DBP were shown for all three agents in the diabetes subgroup; however, the proportion of these patients achieving the SBP/DBP goal of <130/80 mmHg was not reported.

ARBs are very well tolerated drugs. Adverse events are generally mild in severity and transient in duration. Few laboratory abnormalities have been attributed to these agents, and discontinuation rates in clinical trials have generally been similar in patients treated with ARBs or placebo [59]. ARBs have a low potential for pharmacokinetic drug–drug interactions compared with other classes of antihypertensive agents; hence, they can be safely administered with all other major antihypertensive drug classes [60,61].

An overview of important ongoing studies evaluating the use of ARBs in patients with diabetes is presented in table 2.

Pleiotropic Effects of ARBs Relevant to Patients with Diabetes and Hypertension

While it is critical to attain BP control, which accounts for more than 90% of the protective effect of this class, the RAAS also plays a crucial role in circulatory homeostasis and endothelial function [10,59]. The endocrine and autocrine/paracrine effects of angiotensin II include vasoconstriction, enhanced susceptibility to thrombosis, superoxide production, vascular smooth muscle growth, myocyte hypertrophy, fibrosis, remodelling of tissues and stimulation of other hormonal mediators that drive CV and renal pathology [59]. Hence, pharmacological modulation of the RAAS produces significant CV and renal benefits in patients.

Activation of the RAAS is prominent in patients with diabetes. Sympathetic overactivity stimulates the RAAS, which, in turn, promotes retention of sodium and leads to increases in intravascular volume and peripheral vascular resistance. This underscores the importance of RAAS blockade for the management of hypertension in patients with diabetes [62].

Reductions in morbidity and mortality have been obtained with ARBs in clinical trials. Losartan reduced the risk of the combined end-point of CV death, stroke and MI by 13% compared with atenolol over a mean of 4.7 years, despite similar reductions in BP in the randomized, double-blind Losartan Intervention For Endpoint (LIFE) study [63]. The benefit of losartan over atenolol in the LIFE study was also evident in the subgroup of 1195 patients with diabetes and hypertension enrolled in the trial [64]. Although atenolol is a less efficacious β-blocker than other agents in the class, particularly with regard to its antiarrhythmic effects [65], the CV benefits demonstrated by losartan in the LIFE study remain clinically significant.

In addition to the demonstrated BP-lowering and renoprotective effects of ARBs, drugs in this class also improve insulin sensitivity in patients with diabetes [66–69] when compared with conventional β-blockers, such as atenolol, that are associated with increases in insulin resistance [37]. For example, the incidence of new-onset diabetes was significantly lower in patients treated with losartan than with atenolol in the LIFE study [66]. A systematic review of 22 clinical trials involving 143 153 patients with hypertension who did not have diabetes at the time of randomization showed that the risk of new-onset diabetes was lowest for ARBs and ACEIs, followed in rank order by CCBs, vasoconstricting β-blockers and diuretics [70].

The beneficial effects of ARBs in improving insulin sensitivity and reducing the risk of new-onset diabetes were thought to be associated with the partial agonist activity at PPARγ, demonstrated *in vitro* for telmisartan [71]. A small randomized study in patients with type 2 diabetes and hypertension demonstrated improvement over baseline in blood glucose, haemoglobin A1c and adiponectin levels and in the homeostasis model assessment index after 4 months of treatment with telmisartan 80 mg/day than with amlodipine 10 mg/day in 40 patients. All patients in this study were receiving metformin at baseline and were started on rosiglitazone 4 mg/day at the beginning of the study. The two drugs produced similar and significant reductions in mean BP after 4 months when compared with baseline [72]. This effect, however, has not been shown in large, appropriately powered studies in man as the insulin-sensitizing effect of telmisartan is very weak, that is approximately one-eighth the effect of a thiazolinedione.

Most patients with diabetes and hypertension require more than one antihypertensive agent – some patients may require three or more – to achieve recommended SBP/DBP targets recommended in contemporary hypertension treatment guidelines. Thus, it is necessary to choose agents from different classes with complementary modes of action. Choosing a regimen that does not produce burdensome side-effects and allows for achievement of stringent target SBP/DBP goals is probably more important than a specific drug strategy [26].

Conclusions

Hypertension is a common and important CV risk factor in patients with diabetes, the prevalence of which is

Table 2 Major ongoing trials of ARBs in patients with diabetes

Trial	ARB	Comparator	Patient characteristics	Number of patients (duration of follow-up)	End-point	Results expected
INNOVATION [77] r, db, mc	Telmisartan	Placebo	Hypertensive and normotensive Japanese patients with type 2 diabetes and urinary ACR of 100–300 mg/g creatinine	1855 (52 weeks)	Overt nephropathy (urinary ACR >300 mg/g creatinine and 30% higher than baseline)	NA
ORIENT [78] r, db, mc	Olmesartan medoxomil	Placebo	Japanese and Chinese patients with type 2 diabetes and overt proteinuria (urinary ACR ≥300 mg/g creatinine) and serum creatinine 1.0–2.5 mg/dl)	400 (4 years)	Time to doubling of SCr or onset of ESRD (SCr >5.0 mg/dl, the need for chronic dialysis or renal transplantation) or death	2009
ROADMAP [79] r, db, mc	Olmesartan medoxomil	Placebo	Type 2 diabetes, hypertension and normoalbuminuria	4400 (5 years)	Goal BP = 130/80 mmHg Primary end-point: microalbuminuria Secondary end-points: fatal and non-fatal CV events, microvascular complications	2012
PHIDIAS (NCT00456963) r, db, mc	Losartan	Enalapril	Untreated patients aged 40–75 years, SBP 130–139 mmHg and/or DBP 85–89 mmHg, fasting glucose 100–125 mg/dl and waist circumference ≥102 cm (males) or ≥88 cm (females)	6000 (3 years)	Onset of frank diabetes (fasting glucose ≥126 mg/dl) and hypertension (SBP ≥140 or DBP ≥90 mmHg)	2012
K-CAT (NCT00492128) r, mc	Losartan/amlodipine	Losartan/HCTZ or losartan	Hypertension. Includes a subset of patients with diabetes and chronic kidney disease	3 months	Change in SBP, achievement of goal BP	NA
NAGOYA-HEART (NCT00129233) r, mc	Valsartan	Amlodipine	Japanese patients with hypertension, type 2 diabetes or impaired glucose tolerance	Not specified	Fatal or non-fatal MI, fatal or non-fatal stroke, hospitalization for HF, coronary revascularization, sudden cardiac death	NA

ACR, albumin : creatinine ratio; ARB, angiotensin receptor blocker; BP, blood pressure; db, double-blind; DBP, diastolic blood pressure; ESRD, end-stage renal disease; HCTZ, hydrochlorothiazide; HF, heart failure; K-CAT, Kanagawa Combination Anti-hypertensive therapy; mc, multicentre; INNOVATION, Investigation on type 2 Diabetic Nephropathy; MI, myocardial infarction; NA, not available; NAGOYA-HEART, Hypertensive Events and ARB Treatment; ORIENT, Olmesartan Reducing incidence of End stage renal disease in diabetic Nephropathy Trial; PHIDIAS, Prevention of Diabetes and Hypertension; r, randomized; ROADMAP, Randomized Olmesartan And Diabetes Microalbuminuria Prevention Study; SBP, systolic blood pressure; SCr, serum creatinine concentration.

increasing. Tight control of BP in patients with diabetes significantly reduces morbidity and mortality rates and is recommended in contemporary treatment guidelines for patients with diabetes. The target SBP/DBP in patients with diabetes is <130/80 mmHg, and it often takes three or more antihypertensive agents to achieve this goal. ARBs produce reductions in BP that are comparable to ACEIs; have renoprotective effects in patients with diabetes, hypertension and overt nephropathy and retard progression of renal disease in patients with microalbuminuria but not with overt nephropathy. The equivalent antihypertensive effects of ARBs compared with other agents, combined with the nephroprotective effects and better tolerability of ARBs when compared with other antihypertensive drug classes, support recommendations for the use of these agents in patients with type 2 diabetes and hypertension.

Acknowledgements

We express thanks to Blair Jarvis, MSc, and Alan Klopp, PhD, for their editorial assistance in the preparation of this manuscript. Funding for editorial assistance was provided by Daiichi Sankyo Inc.

References

1 Ford ES, Ajani UA, Croft JB *et al*. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. N Engl J Med 2007; **356:** 2388–2398.
2 Fox CS, Coady S, Sorlie PD *et al*. Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. Circulation 2007; **115:** 1544–1550.
3 Fuller H, Stevens LK. Prevalence of hypertension among diabetic patients and its relation to vascular risk. Diabetes Hypertension Study Group. J Hum Hypertens 1991; **5:** 237–243.
4 Hypertension in Diabetes Study (HDS): I. Prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardiovascular and diabetic complications. J Hypertens 1993; **11:** 309–317.
5 The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1997; **157:** 2413–2446.
6 Johnson ML, Pietz K, Battleman DS, Beyth RJ. Prevalence of comorbid hypertension and dyslipidemia and associated cardiovascular disease. Am J Manag Care 2004; **10:** 926–932.
7 Screening for high blood pressure: U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med 2007; **147:** 783–786.
8 Rizzoni D, Agabiti Rosei E. Small artery remodeling in hypertension and diabetes. Curr Hypertens Rep 2006; **8:** 90–95.
9 Tedesco MA, Natale F, Di Salvo G *et al*. Effects of coexisting hypertension and type II diabetes mellitus on arterial stiffness. J Hum Hypertens 2004; **18:** 469–473.
10 Ravid M, Rachmani R. Cardiovascular protection in patients with type 2 diabetes mellitus: considerations about the tightness of blood pressure control and the choice of treatment. Eur J Intern Med 2005; **16:** 154–159.
11 K/DOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis 2007; **49** (Suppl. 2): S1–S179.
12 Wachtell K, Olsen MH. Is it time to change the definition of normal urinary albumin excretion? Nat Clin Pract Nephrol 2008; **4:** 650–651.
13 Karalliedde J, Viberti G. Microalbuminuria and cardiovascular risk. Am J Hypertens 2004; **17:** 986–993.
14 Mancia G, De Backer G, Dominiczak A *et al*. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007; **25:** 1105–1187.
15 Cheung BM, Ong KL, Man YB, Lam KS, Lau CP. Prevalence, awareness, treatment, and control of hypertension: United States National Health and Nutrition Examination Survey 2001–2002. J Clin Hypertens (Greenwich) 2006; **8:** 93–98.
16 Adeghate E, Schattner P, Dunn E. An update on the etiology and epidemiology of diabetes mellitus. Ann N Y Acad Sci 2006; **1084:** 1–29.
17 Coresh J, Selvin E, Stevens LA *et al*. Prevalence of chronic kidney disease in the United States. JAMA 2007; **298:** 2038–2047.
18 Hansson L, Zanchetti A, Carruthers SG *et al*. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998; **351:** 1755–1762.
19 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998; **317:** 703–713.
20 Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; **352:** 837–853.
21 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; **359:** 1577–1589.
22 Bell DSH. Hypertension, diabetes, insulin resistance, and postprandial hyperglycemia. Drug Dev Res 2006; **67:** 595–596.
23 Wiklund I, Halling K, Ryden-Bergsten T, Fletcher A. Does lowering the blood pressure improve the mood? Quality-of-life results from the Hypertension Optimal Treatment (HOT) study. Blood Press 1997; **6:** 357–364.

24 Chobanian AV, Bakris GL, Black HR *et al.* Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003; **42:** 1206–1252.

25 Arauz-Pacheco C, Parrott MA, Raskin P. Hypertension management in adults with diabetes. Diabetes Care 2004; **27** (Suppl. 1): S65–S67.

26 American Diabetes Association. Standards of medical care in diabetes–2007. Diabetes Care 2007; **30:** S4–S41.

27 American Diabetes Association. Standards of medical care in diabetes–2008. Diabetes Care 2008; **31** (Suppl. 1): S12–S54.

28 Yusuf S, Sleight P, Pogue J *et al.* Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000; **342:** 145–153.

29 Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001; **345:** 1667–1675.

30 Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK. Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med 2008; **358:** 2433–2446.

31 Persson F, Rossing P, Schjoedt KJ *et al.* Time course of the antiproteinuric and antihypertensive effects of direct renin inhibition in type 2 diabetes. Kidney Int 2008; **73:** 1419–1425.

32 Bakris GL, Smith DH, Giles TD *et al.* Comparative antihypertensive efficacy of angiotensin receptor blocker-based treatment in African-American and white patients. J Clin Hypertens (Greenwich) 2005; **7:** 587–595; quiz 596–587.

33 Phillips LS, Branch WT, Cook CB *et al.* Clinical inertia. Ann Intern Med 2001; **135:** 825–834.

34 Moan A, Nordby G, Rostrup M, Eide I, Kjeldsen SE. Insulin sensitivity, sympathetic activity, and cardiovascular reactivity in young men. Am J Hypertens 1995; **8:** 268–275.

35 Strazzullo P, Barbato A, Galletti F *et al.* Abnormalities of renal sodium handling in the metabolic syndrome. Results of the Olivetti Heart Study. J Hypertens 2006; **24:** 1633–1639.

36 Sarafidis PA, Nilsson PM. The effects of thiazolidinediones on blood pressure levels – a systematic review. Blood Press 2006; **15:** 135–150.

37 Sarafidis PA, Bakris GL. Antihypertensive treatment with beta-blockers and the spectrum of glycaemic control. QJM 2006; **99:** 431–436.

38 Bakris GL, Fonseca V, Katholi RE *et al.* Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. JAMA 2004; **292:** 2227–2236.

39 Poirier L, Cleroux J, Nadeau A, Lacourciere Y. Effects of nebivolol and atenolol on insulin sensitivity and haemodynamics in hypertensive patients. J Hypertens 2001; **19:** 1429–1435.

40 Berlowitz DR, Ash AS, Hickey EC *et al.* Hypertension management in patients with diabetes: the need for more aggressive therapy. Diabetes Care 2003; **26:** 355–359.

41 Wang YR. Lack of effect of guideline changes on hypertension control for patients with diabetes in the U.S., 1995-2005. Diabetes Care 2007; **30:** 49–52.

42 Mancia G, Grassi G. Systolic and diastolic blood pressure control in antihypertensive drug trials. J Hypertens 2002; **20:** 1461–1464.

43 Bakris GL, Weir M. ACE inhibitors and protection against kidney disease progression in patients with type 2 diabetes: what's the evidence. J Clin Hypertens (Greenwich) 2002; **4:** 420–423.

44 Brenner BM, Cooper ME, de Zeeuw D *et al.* Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001; **345:** 861–869.

45 Lewis EJ, Hunsicker LG, Clarke WR *et al.* Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001; **345:** 851–860.

46 Matchar DB, McCrory DC, Orlando LA *et al.* Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. Ann Intern Med 2008; **148:** 16–29.

47 Turnbull F, Neal B, Pfeffer M *et al.* Blood pressure-dependent and independent effects of agents that inhibit the renin-angiotensin system. J Hypertens 2007; **25:** 951–958.

48 Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. Ann Intern Med 2008; **148:** 30–48.

49 Barnett AH, Bain SC, Bouter P *et al.* Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med 2004; **351:** 1952–1961.

50 Barnett A. Preventing renal complications in type 2 diabetes: results of the diabetics exposed to telmisartan and enalapril trial. J Am Soc Nephrol 2006; **17:** S132–S135.

51 Bakris GL, Weir MR, Shanifar S *et al.* Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study. Arch Intern Med 2003; **163:** 1555–1565.

52 Berl T, Hunsicker LG, Lewis JB *et al.* Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy. Ann Intern Med 2003; **138:** 542–549.

53 Parving HH, Lehnert H, Brochner-Mortensen J *et al.* The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001; **345:** 870–878.

54 Pohl MA, Blumenthal S, Cordonnier DJ *et al*. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: clinical implications and limitations. J Am Soc Nephrol 2005; **16:** 3027–3037.
55 Ruggenenti P, Remuzzi G. What blood-pressure level provides greatest renoprotection in patients with diabetic nephropathy and hypertension? Nat Clin Pract Nephrol 2006; **2:** 250–251.
56 Maillard MP, Wurzner G, Nussberger J *et al*. Comparative angiotensin II receptor blockade in healthy volunteers: the importance of dosing. Clin Pharmacol Ther 2002; **71:** 68–76.
57 Giles TD, Oparil S, Silfani TN, Wang A, Walker JF. Comparison of increasing doses of olmesartan medoxomil, losartan potassium, and valsartan in patients with essential hypertension. J Clin Hypertens (Greenwich) 2007; **9:** 187–195.
58 Neutel J, Lee Y, Walker F. Efficacy of olmesartan medoxomil (OLM), losartan potassium (LOS) and valsartan (VAL) in diabetic patients. Am J Hypertens 2005; **18:** A69
59 Volpe M, Ruilope LM, McInnes GT, Waeber B, Weber MA. Angiotensin-II receptor blockers: benefits beyond blood pressure reduction? J Hum Hypertens 2005; **19:** 331–339
60 Unger T, Kaschina E. Drug interactions with angiotensin receptor blockers: a comparison with other antihypertensives. Drug Saf 2003; **26:** 707–720.
61 Bohler S, Pittrow D, Bramlage P, Kirch W. Drug interactions with angiotensin receptor blockers. Expert Opin Drug Saf 2005; **4:** 7–18.
62 Perin PC, Maule S, Quadri R. Sympathetic nervous system, diabetes, and hypertension. Clin Exp Hypertens 2001; **23:** 45–55.
63 Dahlof B, Devereux RB, Kjeldsen SE *et al*. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; **359:** 995–1003.
64 Lindholm LH, Ibsen H, Dahlof B *et al*. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; **359:** 1004–1010.
65 Bangalore S, Sawhney S, Messerli FH. Relation of beta-blocker-induced heart rate lowering and cardioprotection in hypertension. J Am Coll Cardiol 2008; **52:** 1482–1489.
66 Lindholm LH, Ibsen H, Borch-Johnsen K *et al*. Risk of new-onset diabetes in the Losartan Intervention For Endpoint reduction in hypertension study. J Hypertens 2002; **20:** 1879–1886.
67 Jin HM, Pan Y. Angiotensin type-1 receptor blockade with losartan increases insulin sensitivity and improves glucose homeostasis in subjects with type 2 diabetes and nephropathy. Nephrol Dial Transplant 2007; **22:** 1943–1949.
68 de Vinuesa SG, Goicoechea M, Kanter J *et al*. Insulin resistance, inflammatory biomarkers, and adipokines in patients with chronic kidney disease: effects of angiotensin II blockade. J Am Soc Nephrol 2006; **17:** S206–S212.
69 Iwai M, Chen R, Imura Y, Horiuchi M. TAK-536, a new AT1 receptor blocker, improves glucose intolerance and adipocyte differentiation. Am J Hypertens 2007; **20:** 579–586.
70 Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. Lancet 2007; **369:** 201–207.
71 Benson SC, Pershadsingh HA, Ho CI *et al*. Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARgamma-modulating activity. Hypertension 2004; **43:** 993–1002.
72 Negro R, Hassan H. The effects of telmisartan and amlodipine on metabolic parameters and blood pressure in type 2 diabetic, hypertensive patients. J Renin Angiotensin Aldosterone Syst 2006; **7:** 243–246.
73 American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of hypertension. Endocr Pract 2006; **12:** 193–222.
74 K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 2004; **43:** S1–S290.
75 Whitworth JA. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens 2003; **21:** 1983–1992.
76 NICE. The National Collaborating Centre for Chronic Conditions. National Institute for Health and Excellence. Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update). London: Royal College of Physicians. Available from URL: http://www.nice.org.uk/nicemedia/pdf/CG66diabetesfullguideline.pdf. 2008; 1–279.
77 Makino H, Haneda M, Babazono T *et al*. The telmisartan renoprotective study from incipient nephropathy to overt nephropathy – rationale, study design, treatment plan and baseline characteristics of the incipient to overt: angiotensin II receptor blocker, telmisartan, Investigation on Type 2 Diabetic Nephropathy (INNOVATION) Study. J Int Med Res 2005; **33:** 677–686.
78 Imai E, Ito S, Haneda M, Chan JC, Makino H. Olmesartan reducing incidence of endstage renal disease in diabetic nephropathy trial (ORIENT): rationale and study design. Hypertens Res 2006; **29:** 703–709.
79 Haller H, Viberti GC, Mimran A *et al*. Preventing microalbuminuria in patients with diabetes: rationale and design of the Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study. J Hypertens 2006; **24:** 403–408.