Managing CV risk in type 2 diabetes: Towards best practice

Part 3: Antihypertensive agents

Roger Gadsby

Article points

1. Hypertension is a major risk factor for cardiovascular morbidity and mortality in type 2 diabetes.
2. Optimising BP control in this high-risk group is therefore a priority in primary care.
3. Targets for optimal blood pressure control are constantly changing as new evidence becomes available.
4. Inhibitors of the renin-angiotensin system are the treatments of choice for hypertension in type 2 diabetes, based on the cardiovascular and renal benefits demonstrated in current clinical trials.
5. Elevated blood pressure should be intensively targeted early.

Key words

- Type 2 diabetes
- Cardiovascular disease
- Hypertension
- Diabetic nephropathy
- Antihypertensive agents

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Approximately 80 % of all people with type 2 diabetes die prematurely from cardiovascular (CV) complications (Barnett and O'Gara, 2003). Furthermore, approximately 80 % of people with type 2 diabetes are classified as hypertensive (blood pressure [BP] >140/90 mmHg; Barnett and O'Gara, 2003). Hypertension increases the already high risk of CV disease associated with type 2 diabetes (Hypertension in Diabetes Study Group, 1993). Aggressive treatment of CV risk factors, including raised BP, is therefore essential to improve CV outcomes in this high-risk group. The first two parts of this series provided an overview of some of the multifactorial interventions (lipid-lowering agents and oral hypoglycaemic agents [Gadsby, 2006a, 2006b, respectively]) that can, according to evidence-based medicine, improve CV morbidity and mortality in people with type 2 diabetes. In this, the final part in this series, Roger Gadsby focuses on the evidence from clinical studies supporting the use of antihypertensive agents to improve BP control and reduce the incidence of complications experienced by people with type 2 diabetes.

Parts 1 and 2 of this series (Gadsby, 2006a, 2000b, respectively) emphasised that several recognised factors are known to contribute to the increased risk of CV death associated with type 2 diabetes, namely, diabetic dyslipidaemia, hypertension, insulin resistance and hyperglycaemia (Haffner et al, 1999; Turner et al, 1998).

The recently revised General Medical Services contract (GMS-2) focuses on three main therapeutic interventions in people with diabetes: glycaemic control, lipid lowering, and BP reduction. GPs are awarded points according to the percentage of people with diabetes who meet the targets outlined in the GMS-2. These targets include glycosylated haemoglobin (HbA_{1c}) ≤7.5 %, total cholesterol ≤5 mmol/l and BP ≤145/85 mmHg (British Medical Association [BMA] and NHS Employers, 2006). The challenge for primary care practitioners is to implement the best possible standard of care for people with type 2 diabetes in terms of glycaemic control, lipid lowering and BP reduction, along with other CV risk factors, in order to improve CV outcomes.

Evidence from large clinical studies informs best practice and has highlighted the need for

Table 1. Current blood pressure treatment targets for people with type 2 diabetes.

Guideline (year)	Optimal BP target (mmHg)	Audit standard BP target (mmHg)
NICE (2002)	≤135/75*	≤140/80
BHS (2004)	<130/80	<140/80
JBS-2 (2005)	<130/80	<140/80
GMS-2**	≤145/85	≤145/85

** People with type 2 diabetes and microalbuminuria.*
*** BMA and NHS Employers, 2006.*
Abbreviations used: BHS, British Hypertension Society; JBS, Joint British Societies; GMS, General Medical Services contract; NICE, National Institute for Health and Clinical Excellence.

multifactorial interventions in people with type 2 diabetes, and that more than one intervention is often required to treat each risk factor to the target level (Gaede et al, 2003). In particular, as BP targets are tightened they become increasingly more difficult to achieve with one agent, and multiple therapeutic agents are frequently required to reach targets (Donnelly, 2005; National Institute for Health and Clinical Excellence [NICE]/British Hypertension Society [BHS], 2006).

Current guidelines for the management of blood pressure in type 2 diabetes

Guidelines from the BHS (Williams et al, 2004) recommend more aggressive BP treatment targets for people with diabetes (minimum acceptable level of control <140/80 mmHg, optimal BP target <130/80 mmHg) than that recommended in the GMS-2 contract (≤145/85 mmHg). Similarly, NICE also recommends a lower BP target for people with type 2 diabetes (≤140/80 mmHg), and the target is lower again for people with type 2 diabetes and microalbuminuria or proteinuria (≤135/75 mmHg; NICE, 2002).

In line with the BHS guidelines, the Joint British Societies' guidelines on prevention of CV disease in clinical practice have recently recommended an 'audit standard' BP target of <140/80 mmHg and an optimal BP target of <130/80 mmHg for people with diabetes (British Cardiac Society et al, 2005). The disparity between guidelines (summarised in *Table 1*) reflects how targets for optimal BP control are constantly changing as new evidence from clinical outcome studies becomes available.

Previously, the BHS had developed the 'AB/CD' algorithm for the stepwise treatment of hypertension, which was designed to inform better use of logical combinations of drugs and to encourage improved BP control (Williams et al, 2004). Each letter of the BHS algorithm refers to a different BP-lowering drug class (angiotensin-converting enzyme [ACE] inhibitors, angiotensin-II receptor blockers [ARBs], beta-blockers/calcium-channel blockers, or diuretics [thiazide and thiazide-like]). However, in light of the recently published BP-lowering arm of the Anglo–Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA; Dahlof et al, 2005), substantial revisions were made to this algorithm (it has now become 'A/CD' and is discussed in more detail below) as part of a joint initiative by the BHS and NICE (*Figure 1*; NICE/BHS, 2006).

This again highlights how treatment practices are constantly evolving as we gain more compelling clinical data (Williams, 2006).

The recently updated guidelines, issued in June 2006, by NICE/BHS are for the management of people with newly diagnosed hypertension and do not specifically consider treatment of people with hypertension and diabetes. Indeed, the most recent NICE guidelines for the management of BP specifically in people with type 2 diabetes remain those issued in 2002 and they are not expected to be revised until February 2008 (NICE, 2002). It is also important to note that the 2006 revised NICE/BHS guidelines focused only on recommendations for the pharmacological management of hypertension – the BP treatment targets remain unchanged from the previous NICE guidance.

Evidence base for the use of antihypertensive agents

In recent years, much has changed in terms of the evidence base for the reduction of CV risk in people with type 2 diabetes. Large-scale clinical trials in populations with type 2 diabetes or subgroups of larger studies have examined the benefits of antihypertensive agents, in particular inhibitors of the renin-angiotensin system, on CV outcomes. An overview of the key clinical trials that have influenced current best practice for the treatment of hypertension in type 2 diabetes is provided in *Table 2*.

Angiotensin-converting enzyme (ACE) inhibitors

The management of hypertension is a high priority in the treatment of type 2 diabetes and discussions seem primarily focused on how low optimal BP targets should be. The Hypertension in Diabetes Study (HDS) was embedded in the United Kingdom Prospective Diabetes Study (UKPDS) and was designed to investigate whether tight BP control prevents micro- and macrovascular complications in hypertensive people with type 2 diabetes (UKPDS Group, 1998).

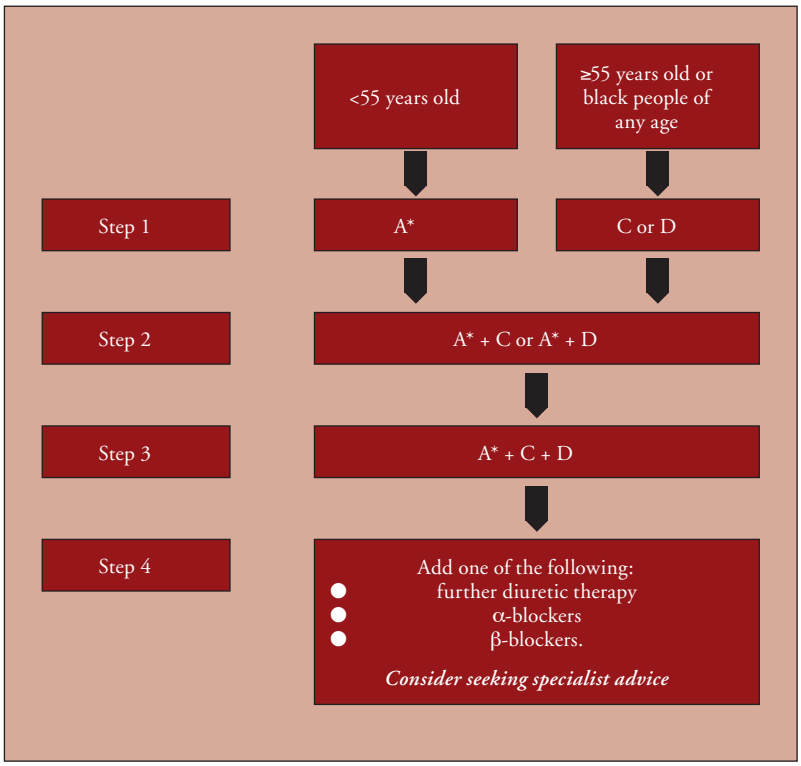

Figure 1. Revised BHS/NICE treatment algorithm for people with newly diagnosed hypertension (NICE/BHS, 2006). These guidelines do not apply to people with type 2 diabetes. Abbreviations used: A, angiotensin-conevrting enzyme (ACE) inhibitor (or angiotensin-II receptor blocker if ACE inhibitor is not tolerated); C, calcium -hannel blocker; D, thiazide-type diuretic.

Participants randomised to tight BP control (target BP <150/85 mmHg) received either the ACE inhibitor captopril or the beta-blocker atenolol, plus other agents if the BP control criteria were not met. Those allocated to less tight BP control (target BP <180/105 mmHg) were not treated with an ACE inhibitor nor a beta-blocker. The final mean BP was significantly lower in the tight control group (144/82 mmHg) than in the less tight control group (154/87 mmHg; $P<0.0001$).

Those assigned to the tight BP control group had significant reductions in diabetes-related complications (24%; $P=0.0046$), diabetes-related death (32%; $P=0.019$), stroke (44%; $P=0.013$) and microvascular disease (37%; $P=0.0092$). The HDS concluded that intensive treatment of hypertension with an ACE inhibitor or β-blocker significantly reduces the risk of diabetes-related death and

Page points

1. NICE guidelines for the management of BP in people with type 2 diabetes are not expected to be revised until 2008.
2. The 2006 revised NICE/BHS guidelines only focused on recommendations for the pharmacological management of hypertension. The BP treatment targets remain those from 2002.
3. The HDS concluded that intensive treatment of hypertension with an ACE inhibitor or beta-blocker significantly reduces the risk of diabetes-related death and complications in people with type 2 diabetes.

complications in people with type 2 diabetes. Moreover, the reductions in BP achieved were similar to the recently issued GMS-2 contract target BP of ≤145/85 mmHg.

Further evidence for the beneficial effects of an ACE inhibitor on CV morbidity and mortality in diabetes came from MICRO-HOPE, a substudy of the Heart Outcomes Prevention Evaluation (HOPE) study (HOPE, 2000). MICRO-HOPE demonstrated that treatment of people with diabetes and a history of CV disease (or at least one other CV risk factor) with ramipril significantly reduced the risk of myocardial infarction (MI), stroke and CV death by 25% ($P=0.0004$). The authors stated that the observed CV benefits of ramipril were greater than those attributable to BP reductions alone, providing strong evidence for the use of an ACE inhibitor to reduce CV morbidity and mortality in people with type 2 diabetes.

There has been some controversy concerning this conclusion since there were small but significant differences in BP in favour of the ramipril group by the end of the study (systolic BP was reduced by 1.92 mmHg in the ramipril group compared with an increase of 0.55 mmHg in the placebo group, $P=0.0002$; diastolic BP decreased by 3.30 mmHg in the ramipril group compared with a decrease of 2.30 mmHg in the placebo group, $P=0.008$). However, after adjustment for these changes in BP, ramipril still had the same effects on the primary outcome. The controversy surrounding the degree to which the outcome was influenced by the BP differences between the groups polarised opinion into those who felt that it was mostly due to changes in BP and others who felt there was a specific non-BP-related benefit.

Angiotensin-II receptor blockers

ARBs have been shown to be at least as efficacious as ACE inhibitors in terms of achieving and maintaining BP control and are generally used in the treatment of people who are intolerant to ACE inhibitors (Himmelmann et al, 2001). Preventing or delaying the development of diabetic nephropathy is another major goal in the treatment of type 2 diabetes.

The IRbesartan in patients with type 2 diabetes and MicroAlbuminuria (IRMA-2) study investigated the effect of the ARB irbesartan on the development of diabetic nephropathy in hypertensive people with type 2 diabetes and persistent microalbuminuria (Parving et al, 2001). Treatment with irbesartan (300 mg/day) was associated with a 70% decrease in progression to overt diabetic nephropathy compared with placebo ($P<0.001$). Interestingly, the renoprotective effect of irbesartan was independent of its BP-lowering effects.

Further evidence for the beneficial effect of ARBs on reducing the rate of progression of renal disease in people with type 2 diabetes was provided in the Reduction of Endpoints in NIDDM with the Angiotensin-II Antagonist Losartan (RENAAL) study (Brenner et al, 2001). People with type 2 diabetes receiving losartan had a 16% reduction in the combined endpoint of a doubling of serum creatinine concentration, progression to end-stage renal failure and death ($P=0.02$). Again, the beneficial effects of an ARB exceeded those attributable solely to a change in BP in people with type 2 diabetes and nephropathy.

Antihypertensive agents that can

Table 2. Summary of large-scale clinical outcome studies in populations (or subgroups) with type 2 diabetes.

Study acronym	Number of people randomised*	Drug (dose)	Comparator	Endpoint
HDS	1148	Captopril (25–50mg bd) Atenolol (50–100mg)	Target BP <180/105 mmHg Target BP <150/80 mmHg	24% reduction in any diabetes-related complication** 32% reduction in any diabetes-related death** 44% reduction in stroke**
MICRO-HOPE	3577	Ramipril(10 mg)	Placebo	25% reduction in MI, stroke and CV death**
IRMA-2	590	Irbesartan (150 or 300 mg)	Placebo	70% reduction in overt diabetic nephropathy**
RENAAL	1513	Losartan (50–100 mg)	Placebo	16% reduction in a doubling of serum creatinine concentration, progression to end-stage renal failure and death**

** All of whom had type 2 diabetes.*
*** Significant reduction.*
Abbreviations used; HDS, The Hypertension in Diabetes Study; IRMA-2, IRbesartan in patients with type 2 diabetes and MicroAlbuminuria Study; MICRO-HOPE, a substudy of the Heart Outcomes Prevention Evaluation (HOPE) study; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin-II Antagonist Losartan study.

Page points

1. Impaired renal function is itself a risk factor for CV disease.
2. The CALM study compared the effects of candesartan (ARB) or lisinopril (ACE inhibitor), or both, in people with microalbuminuria, hypertension and type 2 diabetes.
3. The combination of candesartan plus lisinopril was more effective than monotherapy in reducing BP and microalbuminuria and was well tolerated.
4. These findings support the use of dual blockade of the renin-angiotensin system in the management of raised BP and prevention of diabetic renal disease.

prevent or delay the development of diabetic nephropathy provide a major improvement in the treatment of type 2 diabetes. The importance of the evidence gained from IRMA-2 and RENAAL has been reflected in the GMS-2 contract (it is recommended that people with diabetes are tested for microalbuminuria, and that those with proteinuria or microalbuminuria are treated with an ACE inhibitor or an ARB).

The studies described above indicate that the ACE inhibitor and ARB classes of drugs can be renoprotective in people with diabetes. It is important to remember that impaired renal function is itself a risk factor for CV disease (Yuyun et al, 2005). For example, microalbuminuria doubles the risk of a CV event in people with type 2 diabetes even after adjusting for traditional risk factors (Karalliedde and Viberti, 2004). The UKPDS and Hypertension Optimal Treatment (HOT) trials also demonstrated that intensive lowering of BP in people with hypertension (with or without diabetes) reduces adverse CV outcomes (Hansson et al, 1998; UKPDS Group, 1998).

Evidence to support a dual blockade of the renin-angiotensin system in the treatment of people with type 2 diabetes comes from the Candesartan And Lisinopril Microalbuminuria (CALM) study (Mogensen et al, 2000). The CALM study assessed and compared the effects of candesartan (an ARB) or lisinopril (an ACE inhibitor), or both, in people with microalbuminuria, hypertension and type 2 diabetes. Candesartan was shown to be as effective as lisinopril in reducing BP and microalbuminuria. Importantly, the combination treatment (candesartan plus lisinopril) was shown to be more effective than monotherapy in reducing BP and was well tolerated. Given the increasing importance of aggressive BP reduction in people with diabetes and renal disease, plus the observed additive effect of dual blockade of the renin-angiotensin system on BP reduction, these findings support such an approach in the management of raised BP and prevention of diabetes-related renal disease.

When added to an ACE inhibitor (and other treatments) candesartan has also been shown to provide clinically important reductions in CV events in people with chronic heart failure and reduced left-ventricular ejection fraction (McMurray et al, 2003).

β-blockers

The ASCOT-BPLA study was designed to compare the effects of the following treatment combinations: a beta-blocker (atenolol) with a thiazide (bendroflumethiazide) versus a calcium-channel blocker (amlodipine) with an ACE inhibitor (perindopril), on the primary prevention of CV disease in people with hypertension with at least three other CV risk factors (Dahlof et al, 2005). A total of 27% of participants in each treatment arm had type 2 diabetes at baseline.

The trial did not reach its primary endpoint because it was stopped prematurely owing to the higher incidence of CV events and deaths in the beta-blocker/thiazide arm. Furthermore, there was a statistically significant 30% increase in new-onset diabetes in those allocated the atenolol-based regimen compared with the amlodipine-based regimen ($P<0.001$). The finding that the amlodipine-based regimen prevented more CV events and induced less diabetes than the atenolol-based regimen has led to a re-evaluation of the current treatment guidelines for hypertension.

The BHS has collaborated with NICE to review the guidelines and re-evaluate the treatment algorithm for people newly diagnosed with hypertension. The final revised guidelines were announced in June 2006 (NICE/BHS, 2006). As a result of these revisions, beta-blockers are no longer recommended as a routine initial therapy for people newly diagnosed with hypertension (*Figure 1*; NICE/BHS, 2006). The previous 'AB/CD' treatment algorithm for hypertension described by the BHS in 2004 has now become 'A/CD', based on the findings from the ASCOT-BPLA study. This alteration in the guidelines has had only a marginal effect on the order in which the different classes of drugs are used in people with hypertension and diabetes, as beta-blockers were usually third- or fourth-line agents in this group before the ASCOT-BPLA trial was published.

Best practice

The combination of hypertension and diabetes doubles the risk of developing micro- and macrovascular disease, and doubles the risk of mortality, compared with people without diabetes (Hypertension in Diabetes Study Group, 1993). Optimising BP control in this at-risk population is therefore a priority in primary care (as reflected in the GMS-2 contract) and antihypertensive therapy may provide greater benefit in this high-risk group than in the general population.

The debate about which antihypertensive agent should be used first line in people with type 2 diabetes has intensified with the results

Table 3. Recommended angiotensin-converting enzyme (ACE) inhibitor doses used in treating hypertension.

ACE inhibitor	Recommended doses†	NHS cost for 28 days therapy*
Captopril (Capoten[1])	Starting dose: 12.5 mg BD†† Maximum: 50 mg BD	£1.52 £2.11
Cilazapril (Vascace[2])	Starting dose: 1 mg OD†† Maximum: 5 mg OD	£6.01 £13.28
Enalapril (Innovace[3])	Starting dose: 5 mg OD Maximum: 40 mg OD	£1.54 £3.78
Fosinopril (Staril[4])	Starting dose: 10 mg OD Maximum: 40 mg OD	£4.20 £10.46
Lisinopril (Carace[5]; Zestril[6])	Starting dose: 5 mg OD Maximum: 80 mg OD	£1.30 £7.92
Perindopril (Coversyl[7])	Starting dose: 4 mg OD†† Maximum: 8 mg OD	£10.95** £10.95**
Quinapril (Accupro[8])	Starting dose: 10 mg OD†† Maximum: 80 mg OD	£2.79 £7.98
Ramipril (Tritace[9])	Starting dose: 1.25 mg OD Maximum: 10 mg OD	£1.76 £2.79
Trandolapril (Gopten[10])	Starting dose 500 µg OD Maximum: 4 mg OD	£2.80 £11.64

† British National Formulary No. 52, September 2006.
†† Initial dose of captopril in elderly patients is 6.25 mg BD (cost £0.76 per 28-day supply); initial dose of cilazapril in elderly patients is 500µg OD (cost £3.65/28-day supply); initial dose of perindopril in elderly patients is 2 mg OD (cost £10.95 per 28-day supply); initial dose of quinapril in elderly patients is 2.5 mg OD (cost £1.15/28-day supply).
** NHS electronic Drug Tariff, December 2006.*
*** For a 30-day supply.*
1. Squibb, Uxbridge.
2. Roche, Welwyn Garden City.
3. MSD, Hoddesdon.
4. Squibb, Uxbridge.
5. Bristol-Myers Squibb, Uxbridge.
6. AstraZeneca, Luton.
7. Servier, Wexham.
8. Pfizer, Walon-on-the-Hill.
9. Aventis Pharma, Guildford.
10. Abbot, Maidenhead.

Page points

1. The findings of the ASCOT-BPLA study led to a re-evaluation of the current treatment guidelines for hypertension.
2. The revised guidelines from NICE and the BHS no longer recommend beta-blockers as routine initial therapy for people newly diagnosed with hypertension.

Table 4. Recommended angiotensin-II receptor blocker (ARB) doses used in treating hypertension.

ARB	Recommended doses†	NHS cost for 28 days therapy*
Candesartan (Amias[1])	Starting dose: 8 mg OD	£9.89
	Maximum: 32 mg OD	£16.13
Eprosartan (Teveten[2])	Starting dose: 600 mg OD††	£14.31
	Maximum: 800 mg OD	£15.77
Irbesartan (Aprovel[3])	Starting dose: 150 mg OD††	£12.57
	Maximum: 300 mg OD	£16.91
Losartan (Cozaar[4])	Starting dose: 50 mg OD††	£18.09
	Maximum: 100 mg OD	£24.20
Olmesartan (Olmetec[5])	Starting dose: 10 mg OD	£10.95
	Maximum: 40 mg OD††	£17.50
Telmisartan (Micardis[6])	Starting dose: 40 mg OD	£11.34
	Maximum: 80 mg OD	£14.18
Valsartan (Diovan[7])	Starting dose: 80 mg OD††	£16.44
	Maximum: 160 mg OD	£21.66

† *British National Formulary, September 2006.*
†† *Initial dose of eprosartan in elderly patients (>75 years) is 300 mg OD (cost £11.63/28-day supply); initial dose of irbesartan in elderly patients is 75 mg OD (cost £10.29/28-day supply); initial dose of losartan in elderly patients is 25 mg OD (cost £18.09/28-day supply); maximum dose of olmesartan in elderly patients is 20 mg OD (cost £12.95/28-day supply); initial dose of valsartan in elderly patients is 40 mg OD (cost £14.76/28-day supply).*
* *NHS electronic Drug Tariff, December 2006.*
1. *Takeda, High Wycombe.*
2. *Solvay, Southampton.*
3. *Bristol-Myers Squibb and Sanofi-Synthlabo, Uxbridge and Guildford, respectively.*
4. *MSD, Hoddesdon.*
5. *Sankyo, Amersham.*
6. *Boehringer Ingelheim, Bracknell.*
7. *Novartis, Camberley.*

Page points

1. ACE inhibitor-based regimens (or ARB-based if ACE inhibitor is not tolerated due to cough) should form the foundation of antihypertensive treatment in people with type 2 diabetes.
2. Antihypertensive agents with evidence of renoprotective or cardioprotective effects, should be considered over those that do not have such strong evidence.

of the recently published ASCOT-BPLA study (Dahlof et al, 2005). The debate is, in the author's opinion, somewhat sterile when it comes to people with diabetes as many will require several agents to control their BP, so whichever one is used first becomes academic.

However, there is no doubt, from the evidence to date, that ACE inhibitor-based regimens (or ARB-based if ACE inhibitor is not tolerated due to cough) should form the foundation of antihypertensive treatment in people with type 2 diabetes. The recommended dose ranges and costs of the many currently available ACE inhibitors and ARBs in the UK are summarised in *Tables 3* and *4*, respectively. Selection should be based on both efficacy – agents that are able to provide sustained, 24-hour BP control should be favoured (Lacourciere and Asmar, 1999) – and cost. In addition, antihypertensive agents that provide 'added-value' (that is, benefits beyond those attributable to BP pressure reductions alone) with evidence of renoprotective or cardioprotective effects, or protective effects of both, in people with type 2 diabetes should be considered over those that do not have such strong evidence.

The choice of which ACE inhibitor or ARB to try first will depend on the prescriber's experience and familiarity with individual drugs within these groups and also the costs of the drugs. The number of dose titrations required to reach the evidence-based dose needed for renal protection (which is usually the maximum dose) is also a factor that may be considered. It is important to titrate up the dose of ACE inhibitor or ARB to the dose used in the trials which demonstrated renal protection.

Concordance with medication is another important consideration, especially in people with type 2 diabetes and associated co-morbidities. There are now a number of fixed-dose combination tablets of ACE inhibitor (or ARB) and a thiazide available. The use of such combinations can help to reduce tablet load, which in turn can aid concordance with therapy.

In practice, and in line with increasing evidence, many people with type 2 diabetes start with an ACE inhibitor (or ARB if ACE inhibitor is not tolerated because of cough), but will require further antihypertensive treatments. Treatment is then stepwise, with a thiazide (e.g. bendrofluazide) introduced second-line, then a calcium-channel blocker and then a beta-blocker. If four therapies do not control BP there are a number of other agents (e.g. alpha-blockers) that can be used as fifth-line therapy.

Future strategies

A recent meta-analysis of randomised clinical trials investigating BP-lowering regimens in people with and without diabetes was performed by the Blood Pressure Lowering

Page points

1. The TROPHY study found a significant relative risk reduction for developing new-onset hypertension in those patients taking candesartan.
2. Future studies are required to determine whether lowering targets for BP reduction even further could impact on CV morbidity and mortality and for which patient groups this would be most appropriate.
3. Despite current best practice the incidence of CV morbidity and mortality is still two-fold greater in people with type 2 diabetes than in the general population.

Treatment Trialists' Collaboration (Turnbull et al, 2005). As part of the analyses, there was some evidence to suggest that people with diabetes achieve greater reductions in the risk of major CV events ($P = 0.03$ by Chi Squared test of homogeneity) and CV deaths ($P = 0.02$ by Chi Squared test of homogeneity) with regimens targeting lower BP goals than do those without diabetes. These findings suggest that more aggressive and intensive BP-lowering strategies are justified in people with diabetes.

Hypertension is a major risk factor for CV morbidity and mortality in people with type 2 diabetes; it is therefore important to target raised BP early. The real question will be how early?

The recently published TRial Of Preventing HYpertension (TROPHY) study investigated whether treatment of pre-hypertension (where mean baseline BP as measured at clinic visit with an automated device, 134/85 mmHg) with candesartan over 4 years could prevent or delay progression to clinical hypertension (Julius et al, 2006). At the end of the study there was a significant 15.6% relative risk reduction for developing new-onset hypertension in those patients taking candesartan ($P<0.007$). Future studies are required to determine whether driving down targets for BP reduction even further could impact on CV morbidity and mortality and for which special patient groups this would be most appropriate.

Conclusion

Inhibitors of the renin-angiotensin system are the treatments of choice for hypertension in people with type 2 diabetes, based on the CV and renal benefits demonstrated in current clinical trial evidence. When BP pressure targets are no longer achieved with monotherapy, treatment combinations should be used in line with the revised BHS/NICE treatment algorithm. BP-lowering agents and other therapeutic agents that have additional beneficial effects beyond those attributable to their primary function should form the basis of future best-practice management of people with type 2 diabetes in order to improve outcomes. The GMS-2 contract encourages us to not only improve glycaemic control in people with type 2 diabetes but also provide optimal, evidence-based treatment of other risk factors. Despite current best practice, the incidence of CV morbidity and mortality is still two-fold greater in people with type 2 diabetes than in the general population.

Compared with microvascular complications, CV disease is the biggest killer in people with type 2 diabetes and aggressive BP-lowering approaches may confer greater benefits on CV outcomes in these individuals than in those without diabetes. Elevated BP should be intensively treated early as achieving BP control is more important than the choice of therapy. In the meantime, we must look to optimise our care with informed decision-making using the tools that are available to us. ■

CONFLICT OF INTEREST: The author has participated in advisory boards for Takeda UK Ltd.

Barnett AH, O'Gara G (2003) *In Clinical Practice Series: Diabetes and the Heart*. Churchill Livingstone, London

Brenner BM, Cooper ME, de Zeeuw D et al (2001) Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *New England Journal of Medicine* **345**(12): 861–9

British Cardiac Society, British Hypertension Society, Diabetes UK et al (2005) JBS-2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* **91**(Suppl 5): v1–v52

British Medical Association and NHS Employers (2006) Revisions to the GMS contract 2006/2007. http://www.bma.org.uk/ap.nsf/content/revisionnGMSFeb20062 (accessed 28.11.2006)

Dahlof B, Sever PS, Poulter NR et al; ASCOT Investigators (2005) Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* **366**(9489): 895–906

Donnelly R (2005) Managing cardiovascular risk in patients with diabetes. *British Journal of Diabetes and Vascular Disease* **5**(6): 325–9

Gadsby R (2006a) Managing CV risk in type 2 diabetes: Towards best practice. Part 1: Lipid-modulating agents. *Diabetes and Primary Care* **8**(2): 69–80

Gadsby R (2006b) Managing CV risk in type 2 diabetes:

Towards best practice. Part 2: Oral glucose-lowering agents. *Diabetes and Primary Care* **8**(3): 134–46

Gaede P, Vedel P, Larsen N et al (2003) Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *New England Journal of Medicine* **348**(5): 383–93

Haffner SM, D'Agostino R Jr, Mykkanen L et al (1999) Insulin sensitivity in subjects with type 2 diabetes. Relationship to cardiovascular risk factors: the Insulin Resistance Atherosclerosis Study. *Diabetes Care* **22**(4): 562–8

Hansson L, Zanchetti A, Carruthers SG et al (1998) 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* **351**(9118): 1755–62

Heart Outcomes Prevention Evaluation (HOPE) Study Investigators (2000) Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* **355**(9200): 253–9

Himmelmann A, Keinanen-Kiukaanniemi S, Wester A et al (2001) The effect duration of candesartan cilexetil once daily, in comparison with enalapril once daily, in patients with mild to moderate hypertension. *Blood Pressure* **10**(1): 43–51

Hypertension in Diabetes Study Group (1993) Hypertension in Diabetes Study (HDS): II. Increased risk of cardiovascular complications in hypertensive type 2 diabetic patients. *Journal of Hypertension* **11**(3): 319–25

Julius S, Nesbitt SD, Egan BM et al (2006) Feasibility of treating prehypertension with an angiotensin-receptor blocker. *New England Journal of Medicine* **354**(16): 1685–97

Karalliedde J, Viberti G (2004) Microalbuminuria and cardiovascular risk. *American Journal of Hypertension* **17**(10): 986–93

Lacourciere Y, Asmar R (1999) A comparison of the efficacy and duration of action of candesartan cilexetil and losartan as assessed by clinic and ambulatory blood pressure after a missed dose, in truly hypertensive patients: a placebo-controlled, forced titration study. Candesartan/Losartan study investigators. *American Journal of Hypertension* **12**(12 Pt 1–2): 1181–7

McMurray JJ, Ostergren J, Swedberg K et al (2003) Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* **362**(9386): 767–71

Mogensen CE, Neldam S, Tikkanen I et al (2000) Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. *BMJ* **321**(7274): 1440–4

National Institute for Health and Clinical Excellence (2002) *Management of Type 2 Diabetes: Management of blood pressure and blood lipids (Inherited Guideline H)*. NICE, London

NICE/British Hypertension Society (2006) Clinical Guideline 34: Hypertension. Management of hypertension in adults in primary care: Partial update. http://www.nice.org.uk/CG034guidance (accessed 28.11.2006)

Parving HH, Lehnert H, Brochner-Mortensen J et al; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group (2001) The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *New England Journal of Medicine* **345**(12): 870–8

Turnbull F, Neal B, Algert C et al; Blood Pressure Lowering Treatment Trialists' Collaboration (2005) Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Archives of Internal Medicine* **165**(12): 1410–9

Turner RC, Millns H, Neil HA et al (1998) Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *BMJ* **316**(7134): 823–8

UK Prospective Diabetes Study (UKPDS) Group (1998) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* **317**(7160): 703–13

Williams B (2006) Evolution of hypertensive disease: a revolution in guidelines. *Lancet* **368**(9529): 6–8

Williams B, Poulter NR, Brown MJ et al; British Hypertension Society (2004) Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *Journal of Human Hypertension* **18**(3): 139–85

Yuyun MF, Adler AI, Wareham NJ (2005) What is the evidence that microalbuminuria is a predictor of cardiovascular disease events? *Current Opinion in Nephrology and Hypertension* **14**(3): 271–6