Andrew Sindone
Jonathan Erlich
Vlado Perkovic
Michael Suranyi
Henry Newman
Choon Lee
Edward Barin
Simon D Roger

# ACEIs for cardiovascular risk reduction

## Have we taken our eye off the ball?

### Background

Hypertensive patients have an increased risk of cardiovascular (CV) events. There is debate whether angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) offer similar reductions in CV risk.

### Objective

This article discusses some of the recent evidence for the prevention of CV events and mortality with ACEIs and ARBs, and the rationale for using an ACEI as the preferred agent for comprehensive CV risk reduction in specific patient populations.

### Discussion

ACEIs and ARBs are structurally and functionally very different agents; they are not interchangeable. Prescriptions for ARBs are increasing in Australia. However, clinical trial evidence suggests possible advantages of ACEIs over ARBs, particularly in terms of survival benefit. Many patients with hypertension have other CV risk factors that may affect medication choice. The aim of treatment should not be just to lower blood pressure, but to reduce absolute CV risk.

### Keywords

angiotensin-converting enzyme inhibitors; angiotensin receptor antagonists; cardiovascular diseases; risk assessment; hypertension

Treatment of hypertension previously focused on reducing blood pressure as an end in itself. The goal has now shifted toward reducing blood pressure as part of a coordinated approach to reduce absolute cardiovascular (CV) risk using agents shown to have a survival benefit. Australian guidelines for the management of hypertension have grouped angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) as alternative first choice agents (with calcium channel blockers) in uncomplicated hypertension.[1] However, hypertension cannot be managed in isolation: it is the gateway to a cascade of CV risk factors (*Figu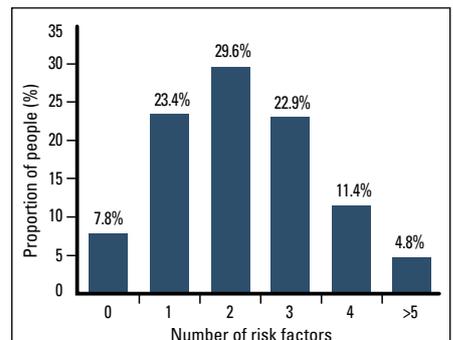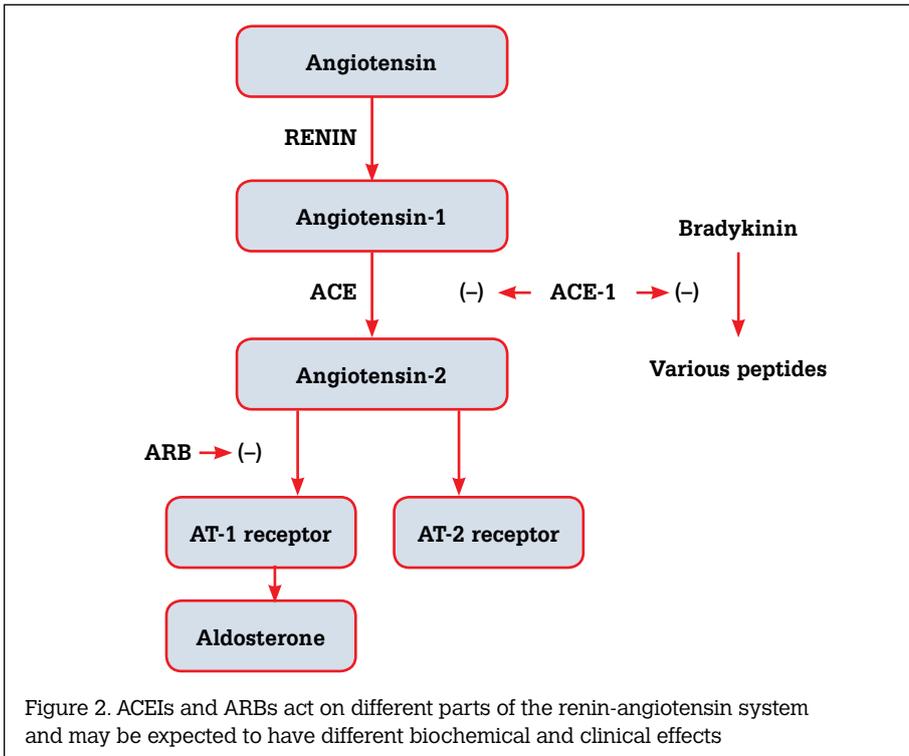re 1*).[2] Absolute CV risk is frequently underestimated and patients presenting with hypertension require absolute risk assessment with the aid of a risk calculator.[3]

The goal of treating a patient with hypertension is to reduce the risk of fatal and non-fatal CV events and should be based on the available evidence. The most reliable data come from high quality randomised trials and meta-analyses. Despite this, agents with a limited evidence base are often recommended interchangeably with those where clear evidence of benefit has been established. Pharmaceutical Benefits Scheme data show that prescriptions for ARBs are increasing more than ACEIs and other classes for the treatment of hypertension.[4] The evidence for ACEIs and ARBs is quite different, and therefore applying this evidence to all patients, including those with hypertension, is problematic.

## Mechanism of action

ACEIs and ARBs both act on the renin-angiotensin system (RAS), but in very different ways.[5,6] ACEIs decrease synthesis of angiotensin 2 by inhibiting the actions of angiotensin converting enzyme



Figure 1. Multiple CV risk factors are common in Australian adults, with 2 in 3 adults having two or more risk factors[2]

Figure 2. ACEIs and ARBs act on different parts of the renin-angiotensin system and may be expected to have different biochemical and clinical effects

(ACE), whereas ARBs bind directly to one type of angiotensin receptor, AT-1, preventing its activation by angiotensin 2 (*Figure 2*). The RAS is complex, therefore the effects of ACE inhibition and angiotensin receptor blockade may differ. A number of components to the RAS are not angiotensin receptor dependent. In particular, bradykinin leads to an increase in nitric oxide levels,[5] and the recently described peptide angiotensin-(1-7) exerts its effects via the Mas receptor.[7,8] Manipulation of non-angiotensin receptor dependent parts of the RAS system may explain why ACEIs potentially reduce CV morbidity and mortality beyond blood pressure regulation.[5,6]

## Evidence for ACEI use

The landmark HOPE[9] and EUROPA[10] trials demonstrated that ACEI therapy prevents CV events and death in patients with multiple CV risk factors or coronary artery disease. ACEIs have consistent clinical trial evidence of mortality benefit in patients at risk of CV events. A meta-analysis of 39 randomised controlled trials involving 150 943 patients reported that ACEI therapy is significantly superior to placebo in reducing the relative risk of death from any cause, CV death, stroke and myocardial infarction (MI).[6] When compared against placebo or active

alternative drug treatment (including ARBs), ACEIs significantly reduce the relative risk of death from any cause by 9% ($p<0.001$), CV death by 12% ($p<0.001$), and MI by 14% ($p<0.001$) (*Figure 3*).[6] The relative risk of stroke was similar compared with other active treatment ($p=0.31$), but was reduced by 17% compared with placebo ($p<0.05$).[6] This meta-analysis demonstrates that ACEIs and ACEI combinations are an effective evidence based way to initiate CV risk reduction in patients with hypertension.

In patients with chronic heart failure (CHF), ACEIs have been shown to prolong survival in patients with NYHA Class II, III and IV symptoms, compared to placebo.[11–13] They also improve symptom status, physical activity, exercise tolerance and the need for hospitalisation in patients with worsening CHF,[13,14] and increase ejection fraction compared to placebo.[11,13] Studies comparing the use of ACEIs and angiotensin 2 receptor antagonists in heart failure show similar outcomes.[13,15] Angiotensin 2 receptor antagonists have been shown to provide additional morbidity and mortality benefits in patients receiving ACEIs for CHF,[16] but not for heart failure after acute MI.[17] The effect of angiotensin 2 receptor antagonists on mortality alone was not significant in individual trials.[13]

In patients who are ACEI intolerant, angiotensin 2 receptor antagonists provide morbidity benefits and a non-significant trend toward mortality benefits in comparison to placebo. Therefore, angiotensin 2 receptor antagonists are recommended as an alternative for patients who experience ACEI-mediated adverse effects, such as cough.[13]

## Evidence for ARB use

Clinical trial data for ARBs are less consistent, particularly regarding mortality benefit. A meta-analysis published in 2011, of 37 randomised controlled trials involving 147 020 patients, reported that ARBs reduce the relative risk of stroke by 10% ($p=0.007$), heart failure by 13% ($p<0.001$), and new onset diabetes by 15% ($p=0.003$) compared with placebo or active treatment. However, ARBs do not reduce the risk of MI (1% reduction, $p=0.055$), CV death (1% reduction, $p=0.090$) or death from any cause (no reduction, $p=0.482$) (*Figure 4*).[18] This meta-analysis included some of the more recent studies, particularly the ONTARGET trial that demonstrated that the ARB telmisartan was not inferior to the ACEI ramipril for reducing the risk of major CV events overall, including CV death.[19]

A pooled analysis, published in 2012, of 20 CV morbidity and mortality trials, where 158 998 patients were randomised to an inhibitor of the RAS system or control, showed a 5% reduction in all-cause mortality and a 7% reduction in CV mortality driven entirely by ACEIs, which were associated with a significant 10% reduction in all-cause mortality, while there was no mortality reduction demonstrated with ARBs.[20] Importantly, the treatment effect between ACEIs and ARBs on all-cause mortality was statistically significantly different,[20] however, these trials were not direct comparisons. Indirect comparisons between studies are problematic as other factors such as co-prescribed therapies, may confound the comparison of the two sets of trials. Comparisons between trials are also subject to epidemiological fallacies and, where available, head-to-head comparisons are preferred.

This meta-analysis[20] can be considered particularly relevant, however, as it included trials in which the majority of patients were hypertensive – the population in which ACEIs and ARBs are primarily initiated and prescribed in the community.
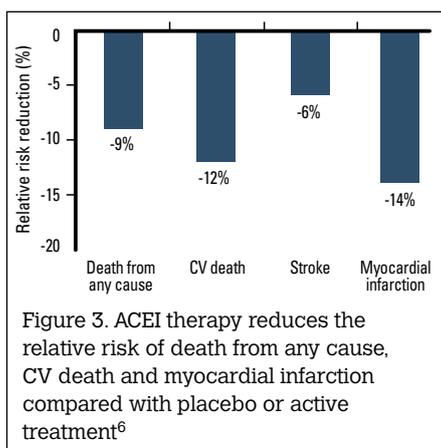
Figure 3. ACEI therapy reduces the relative risk of death from any cause, CV death and myocardial infarction compared with placebo or active treatment[6]
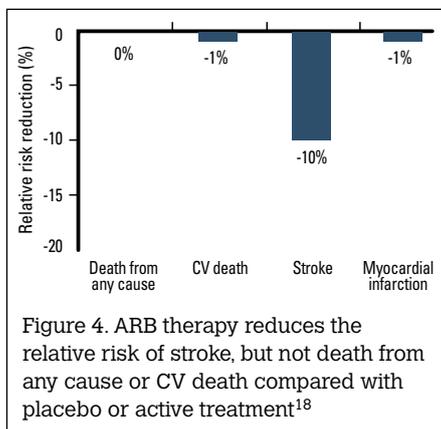


Figure 4. ARB therapy reduces the relative risk of stroke, but not death from any cause or CV death compared with placebo or active treatment[18]

## Direct comparison

The head-to-head ONTARGET trial[19] comparing an ACEI versus an ARB, demonstrated that the ARB telmisartan was not inferior to the ACEI ramipril for reducing the risk of major CV events overall, including CV death,[19] and found fewer side effects in the ARB arm of the trial (mainly due to a reduction in cough).

Another meta-analysis by Volpe et al,[21] published in 2009, compared ARBs with other medications that lower blood pressure, including beta-blockers, diuretics, calcium channel blockers and ACEIs as well as placebo. This meta-analysis analysed patients with hypertension, high CV risk, stroke, coronary disease, renal disease, and heart failure, and showed no difference in risk of MI with ARBs compared to the other treatments, but also no significant difference compared to placebo. The blood pressure lowering arm of the ASCO trial also demonstrated that beta-blockers and diuretics are less efficacious in reducing CV risk when compared to ACEIs and calcium channel blockers.[22] Volpe et al[22] concluded: 'The present meta-analysis indicates that the risk of MI is comparable with use

of ARBs and other antihypertensive drugs in a wide range of clinical conditions'.[21]

In addition, no reduction in the risk of MI with ARBs compared to placebo was found. This may be consistent with the results of the TRANSCEND study,[23] which evaluated the effect of an ARB in high risk patients intolerant of ACEIs and showed no significant reduction in CV events. Conversely, the HOPE study,[9] which utilised an ACEI in a similar study design, did show a reduction in CV events, although the background population demographics and co-prescribed medications did differ between the two trials. Neither the meta-analysis by Volpe et al nor the ONTARGET study showed a reduction in MI when ARBs and ACEIs were combined. On the basis of these results, the combination of ARBs and ACEIs is no longer recommended for reduction of CV risk in patients with significantly increased CV risk.

## Specific populations – diabetic kidney disease

Different considerations come into play when considering type 2 diabetes and kidney disease. While the evidence base for the prevention of new onset albuminuria is stronger for ACEIs,[24–26] the prevention of kidney failure in patients with established nephropathy has been demonstrated in trials using ARBs.[27,28] Both classes may therefore have a role individually, but it may be prudent to favour the class or the specific drug that has been demonstrated to be beneficial for particular patient subgroups. There are no head-to-head comparison trials between ACEIs and ARBs in diabetic patients with established kidney disease. Clinicians have to weigh up the risk of a patient dying from a CV event (where ACEIs have consistent clinical evidence of mortality benefit)[6] versus the risk of heading toward end stage renal failure requiring dialysis and/or transplantation (where two ARBs have shown clinical benefit against amlodipine[28] or non-ACEI antihypertensive agents).[27] Renal impairment is an independent risk factor for CV disease.[29] While caution is required in employing drugs that manipulate the RAS, there are clear benefits to be obtained from ACEI therapy, even in patients with mild renal impairment.[9]

## What do the guidelines say?

Different clinical guidelines make different recommendations,[1,13,29–31] making it confusing

to determine the optimal treatment for individual patients. Hypertension guidelines may be at odds with other CV risk factor guidelines, including cholesterol lowering, diabetic guidelines, or other non-CV strategies to reduce risk.[1,29–31]

ACEIs and ARBs are bundled together in some guidelines, as though these drug classes are interchangeable.[1,31] This is not based on evidence, as the trials on which the guidelines are based often utilise only one class of drug. Extrapolation to all drug classes that impact on the RAS may not be clinically appropriate.

The Australian National Vascular Disease Prevention Alliance has recently published the *Guidelines for the assessment and management of absolute CV risk*,[32] which is an excellent resource for general practitioners in this context.

## Practical challenges

The evidence of a possible survival advantage of ACEIs over ARBs[6,18] is often overshadowed by concern over the risk of cough. The incidence of ACEI induced cough has been reported to be 5–35% among patients receiving treatment with these agents, however a much lower incidence (up to 3%) has been described in studies where the cause of the chronic cough in patients receiving ACEIs has been evaluated.[33] Following simple initial screening, the tolerability and adherence to ACEIs is comparable to ARBs in large populations.[26,34]

## Conclusion

Although ACEIs and ARBs are equally effective in lowering blood pressure,[5] ACEIs have more consistent data of mortality benefit in the setting of prior MI, coronary artery disease or heart failure.[6,18] ACEIs (alone or in combination with a diuretic) have the most direct evidence of benefit in preventing recurrent stroke.[35] Selecting a class for renal protection in patients with type 2 diabetes is more complex. Therefore it may be prudent to favour the class, and perhaps the specific drug, that has demonstrated benefit in particular patient subgroups, with ACEIs being initially utilised for CV risk reduction and ARBs being used initially for the prevention and treatment of diabetic nephropathy. Renal impairment is an independent risk factor for CV disease[29] and even patients with mild renal impairment can benefit from ACEI therapy.[9] ARBs

also have a role in patients who cannot tolerate ACEIs because of cough or angioedema.

ACEIs and ARBs are distinct classes that are not interchangeable, and their prescription should be based on clinical evidence. Disparities in the prescription of ACEIs and ARBs require evaluation, discussion and reflection on whether we are doing the best by our patients in the light of the evidence.

## Key points

- High blood pressure is the gateway to a cascade of CV risk.
- The aim of treatment in the long term should be to reduce absolute CV risk.
- ACEIs and ARBs are not interchangeable; they are structurally and functionally different.
- Clinical trial data are more consistent for ACEIs than ARBs, particularly for mortality benefit.
- ACEIs should be the preferred agent in the setting of previous MI, coronary artery disease or heart failure because of documented mortality reduction.

## Authors

Andrew Sindone BMed(Hons), MD, FRACP, FCSANZ, is a cardiologist and Director, Heart Failure Unit and Department of Cardiac Rehabilitation, Concord Hospital, New South Wales. andrew.sindone@email.cs.nsw.gov.au

Jonathan Erlich BMedSc, MBBS, FRACP, PhD, is Senior Lecturer, University of New South Wales and a nephrologist, Prince of Wales Hospital, Sydney, New South Wales

Vlado Perkovic MBBS, FRACP, PhD, is a nephrologist, Royal North Shore Hospital, Sydney, New South Wales

Michael Suranyi MBBS, FRACP, PhD, is a nephrologist, Liverpool Hospital, Sydney, New South Wales

Henry Newman MBBS, FRACP, FCSANZ, is a cardiologist, Liverpool Hospital, Sydney, New South Wales

Choon Lee MBBS(Hons), FRACP, FRCPA, is visiting cardiologist, Nepean Hospital, Sydney, New South Wales

Edward Barin MBBS, MMed, FRACP, FCSANZ, is a cardiologist and Director, Cardiac Rhythm Management Unit, Royal North Shore Hospital, Sydney, New South Wales

Simon D Roger MD, FRACP, is Director of Renal Medicine, Gosford Hospital, New South Wales.

## References

1. National Heart Foundation of Australia. Guide to management of hypertension 2008. Updated December 2010. Available at www.heartfoundation.org.au/SiteCollectionDocuments/HypertensionGuidelines2008to2010Update.pdf [Accessed 11 February 2013].
2. Australian Institute of Health and Welfare. Living dangerously, Australians with multiple risk factors for cardiovascular disease. AIHW bulletin no. 24. Cat. no. AUS 57. Canberra: AIHW, 2005.
3. National Vascular Disease Prevention Alliance. Absolute cardiovascular disease risk assessment. Quick reference guide for health professionals, 2009. Available at www.cvdcheck.org.au [Accessed 12 September 2012].
4. Medicare Australia. Pharmaceutical Benefits Scheme Item Reports, 2002-12. Available at www.medicareaustralia.gov.au/statistics/pbs_item.shtml [Accessed 16 October 2012].
5. Epstein BJ, Gurns JG. Angiotensin receptor blockers versus ACE inhibitors: prevention of death and myocardial infarction in high-risk populations. Ann Pharmacother 2005;39:470–80.
6. Strauss MH, Hall AS. Angiotensin receptor blockers may increase risk of myocardial infarction: unraveling the ARB-MI paradox. Circulation 2006;114:838–54.
7. Rabelo LA, Alenina N, Bader M. ACE2-angiotensin-(1-7)-Mas axis and oxidative stress in cardiovascular disease. Hypertens Res 2011;34:154–60.
8. Zimmerman D, Burns KD. Angiotensin-(1-7) in kidney disease: a review of the controversies. Clin Sci (Lond) 2012;123:333–46.
9. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. 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;342:145–53.
10. Fox KM, EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003;362:782–88.
11. National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk. 2012. Available at http://strokefoundation.com.au [Accessed 11 February 2013].
12. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. N Engl J Med 1991;325:293–302.
13. Krum H, Jelinek M, Stewart S, Sindone A, Atherton J. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2011 Available at www.heartfoundation.org.au/sitecollectiondocuments/chronic_heart_failure_guidelines_2011.pdf [Accessed 11 February 2013].
14. The CONSENSUS Trial Study Group. Effects of enal-

april on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;3161:1429–35.

15. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. Lancet 2000;355:1582–87.

16. McMurray JJ, Ostergren J, Swedberg K, et al. 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 2003;362:767–71.

17. Pfeffer MA, McMurray JJ, Velaquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 2003;349:1893–906.

18. Bangalore S, Kumar S, Wetterslev J, Messerli FH. Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147 020 patients from randomised trials. BMJ 2011;342:d2234.

19. Yusuf S, Teo KK, Pogue J, et al for the ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547–59.

20. van Vark LC, Bertrand M, Akkerhuis KM, et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158 998 patients. Eur Heart J 2012;33:2088–97.

21. Volpe M, Tocci G, Sciarretta S, Verdecchia P, Trimarco B, Mancia G. Angiotensin II receptor blockers and myocardial infarction: an updated analysis of randomized clinical trials. J Hypertension 2009;27:941–46.

22. Dahlöf B, Sever PS, Poulter NR, for the ASCOT investigators. 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 2005;366:895–906.

23. Yusuf S, Teo K, Anderson C, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors (TRANSCEND): a randomised controlled trial. Lancet 2008;372:1174–83.

24. Strippoli GF, Craig M, Deeks JJ, Schena FP, Craig JC. Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. BMJ 2004;329:828.

25. Ruggenenti P, Fassi A, Ilieva AP, et al for the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. Preventing microalbuminuria in type 2 diabetes. N Engl J Med 2004;351:1941–51.

26. Patel A, ADVANCE Collaborative Group, MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;370:829–40.

27. 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;345:861–69.

28. 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;138:542–49.

29. Chadban S, Howell M, Twigg S, et al. National evidence based guideline for diagnosis, prevention and management of chronic kidney disease in type 2 diabetes. Canberra: Diabetes Australia and the NHMRC, 2009.

30. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand. Reducing risk in heart disease: guidelines for preventing cardiovascular events in people with coronary heart disease 2007 (Updated 2008). Available at www.heartfoundation.org.au/SiteCollectionDocuments/Reduce-risk-in-heart-disease-guideline.pdf [Accessed 11 February 2013].

31. Diabetes Australia. Diabetes management in general practice. 17th edition, 2011/12. Available at www.racgp.org.au/download/documents/Guidelines/Diabetes/201107diabetesmanagementingeneralpractice.pdf [Accessed 11 February 2013].

32. National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk. 2012. Available at http://strokefoundation.com.au/health-professionals/nvdpa-alliance/ [Accessed 11 February 2013].

33. Dicpinigaitis PV. Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. Chest 2006;129:169–73S.

34. Simons LA, Ortiz M, Calcino G. Persistence with anti-hypertensive medication: Australia-wide experience, 2004-2006. Med J Aust 2008;188:224–27.

35. National Stroke Foundation. Clinical guidelines for stroke management 2010. Melbourne, Australia. Available at http://strokefoundation.com.au/site/media/clinical_guidelines_stroke_management_2010_interactive.pdf [Accessed 11 February 2013].

correspondence **afp@racgp.org.au**