Hypertension Control in Chronic Kidney Disease: Don't Miss the Forest for the Trees

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Hypertension is common in Malaysia, with a prevalence of up to 41% in the urban adult population [1]. It has been estimated that up to 90% of adults over the age of 50 will develop hypertension in their lifetime [2]. Besides stroke, heart failure and coronary artery disease, hypertension leads to chronic kidney disease (CKD) and end-stage renal failure (ESRF). Awareness of hypertension amongst patients in Malaysia at 35% is poor, while good control is only achieved in 26% of treated patients [3,4]. It is thus important that all doctors seek to improve hypertension awareness and control so as to reduce adverse cardiovascular and renal outcomes which take up so much of our healthcare resources today.

This issue of the MJM carries a retrospective review of 107 patients with hypertension and ESRF admitted to a tertiary hospital over a 2 year period (5). Although data from a small population with ESRF in a single centre may not apply to the much larger number of hypertensive patients with CKD, important lessons can be drawn from this study. Hypertension control rate below 30% in this referral unit emphasises the need for physician, and patient, to work harder to control blood pressure (BP). Since hypertension is asymptomatic and drugs do have adverse effects, compliance can only be improved if the patient understands the importance of continuous treatment [6]. Furthermore, lifestyle changes have been shown to reduce BP, while emotion such as impatience and hostility can result in elevation [7,8]. Thus hypertension cannot be controlled unless the patient is motivated. Time should be spent highlighting the adverse consequences of hypertension, the need for lifestyle changes and the benefit as well as potential adverse effect of the drugs used. The educated, responsible patient will ultimately be a well controlled hypertensive.

The authors' conclusions about the value of the different hypertensive drug regimen is open to debate given their retrospective case-record based methodology and the absence of standardisation of dose and type of hypertensive drug used. However, their study emphasises that good BP control requires a combination of different types of antihypertensive drugs consistent with world-wide reports [9,10]. Since there is a plateauing of therapeutic effect with increasing drug concentration, it is more sensible to add another agent rather than to keep increasing doses once a drug reaches recommended dosing. The many antihypertensive drug trials have also shown that a combination of 2 to 3 drugs will usually be required for adequate BP control. The 2011 Malaysian Clinical Practice Guideline on management of CKD states that, in the absence of proteinuria, any class of antihypertensive drug - angiotensin-converting enzyme inhibitor (ACEI), angitensin receptor blocker (ARB), beta-blocker, calcium channel blocker (CCB), diuretic and alpha-blocker - can be used to control BP in these patients [11].

Proteinuria increases progression of CKD and is a marker of increased risk for cardiovascular events [12]. ACEI and ARB are both useful to reduce proteinuria and retard progression of nephropathy in hypertensive patients [13]. Recently ONTARGET confirmed the equivalent therapeutic protective effect of the ARB, telmisartan, and the ACEI, ramipril, in 25,620 high risk patients, 69% of whom were hypertensive [14,15]. However, major renal outcomes (need for dialysis, doubling of serum creatinine and death) were higher in patients on combination telmisartan-ramipril compared to those on ramipril alone (14.5% vs 13.5%; 1.09, 1.01-1.18; p=0.037). Similarly, adverse drugs effects necessitating discontinuation including syncope, hypotension and diarrhoea were significantly higher with combination therapy. The ALTITUDE trial was prematurely terminated because renal failure and hyperkalemia were higher when aliskerin, a direct renin inhibitor, was added to diabetic nephropathics already on ARB or ACEI [16]. Thus while ARB or ACEI should be first-line anti-hypertensive drugs used in patients with renal impairment and proteinuria, their use together should not be encouraged and excessive antagonism of the renin-angiotensin system can have detrimental clinical effects.

Since patients with CKD are susceptible to adverse cardiovascular events, it is important to appreciate the effect of ACEI and ARB on the cardiovascular system. We performed a meta-analysis of 10 randomised placebo-controlled trials with either ACEI (5 trials, 38,988 patients) or ARB (5 trials, 38645 patients) in patients with a combination of cardiovascular risk factors to assess treatment effect on all cause mortality, cardiovascular mortality and nonfatal myocardial infarction (MI) [17-26]. As shown in Figure 1, compared to placebo, ACEI treatment significantly reduced all cause mortality (7.67% vs 8.6%; RR 0.89, 95% CI 0.84-0.95; p=0.0008), cardiovascular mortality (4.31% vs 5.09%; RR 0.85, 0.78-0.93; p=0.0003), and nonfatal MI (5.55% vs 6.79%; RR 0.82, 0.76-0.88; p<0.00001). However compared to placebo, ARB treatment did not reduce all cause mortality (7.48% vs 7.45%; RR 1.00, 0.94-1.08; p=0.89), cardiovascular mortality (3.05% vs 3.15%; RR 0.97, 0.86-1.08; p=0.54) and

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Fig. 1: Meta-analysis of trials comparing angiotensin-converting enzyme inhibitors (ACE) and angiotensin receptor blockers ARB with placebo.
1a. Effect on total mortality.
1b. Effect on cardiovascular mortality.
1c. Effect on non-fatal myocardial infarction. (See text for references to trials)

Fig. 1a: Total mortality

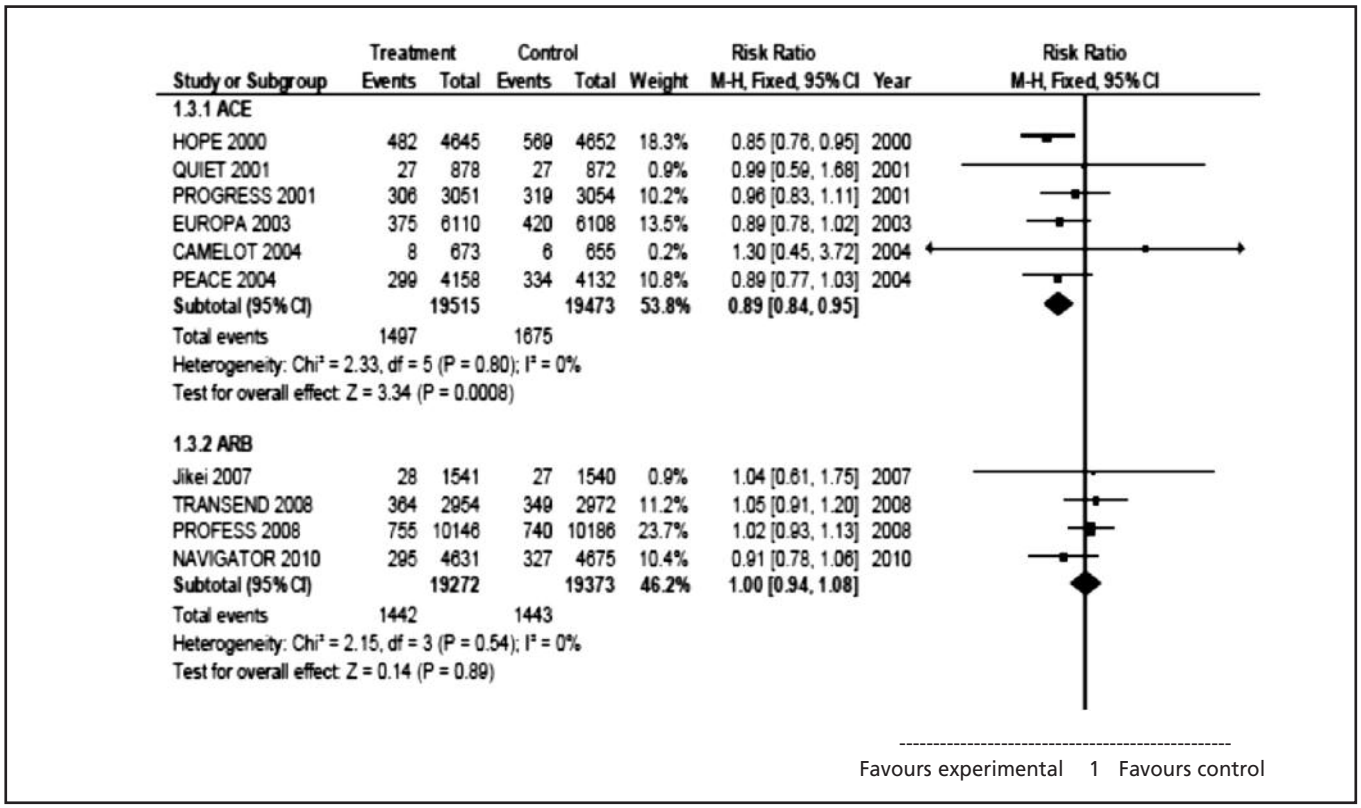


Fig. 1b: Cardiovascular mortality

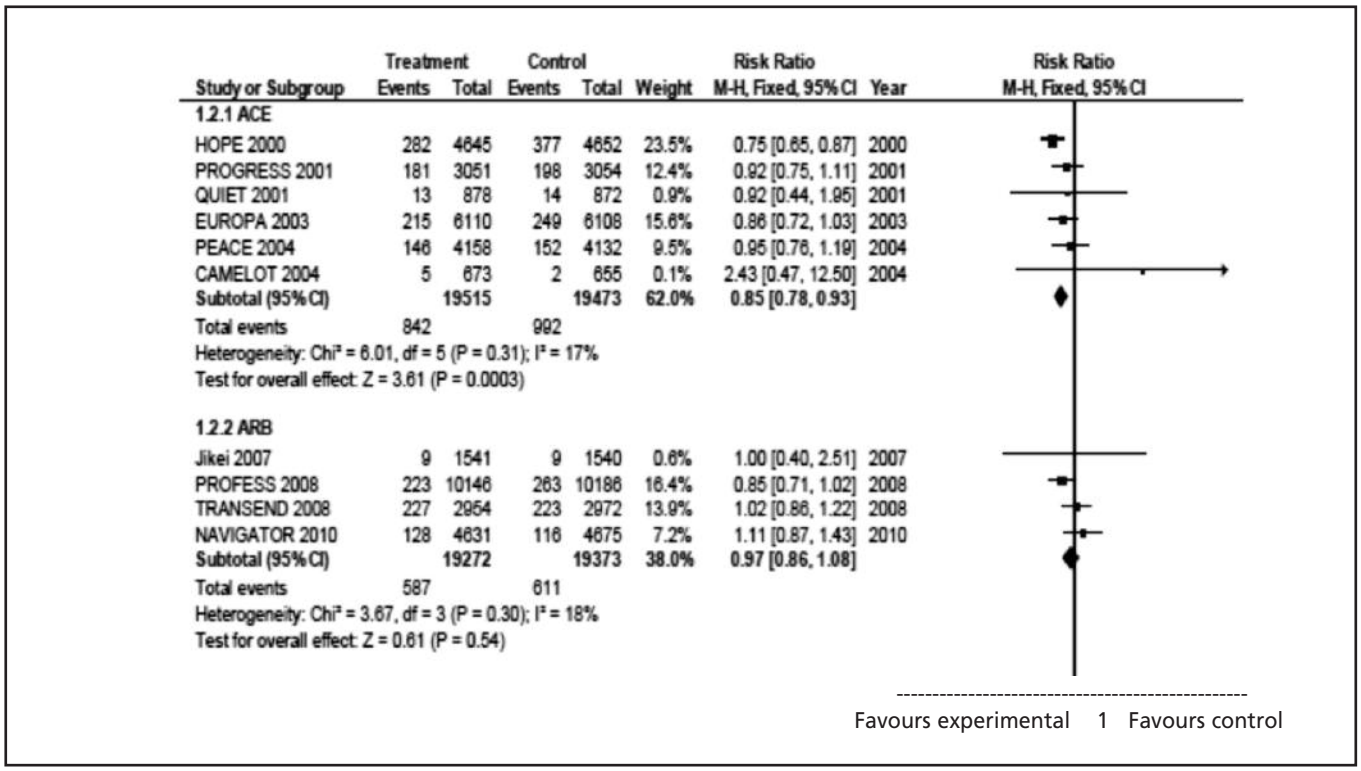
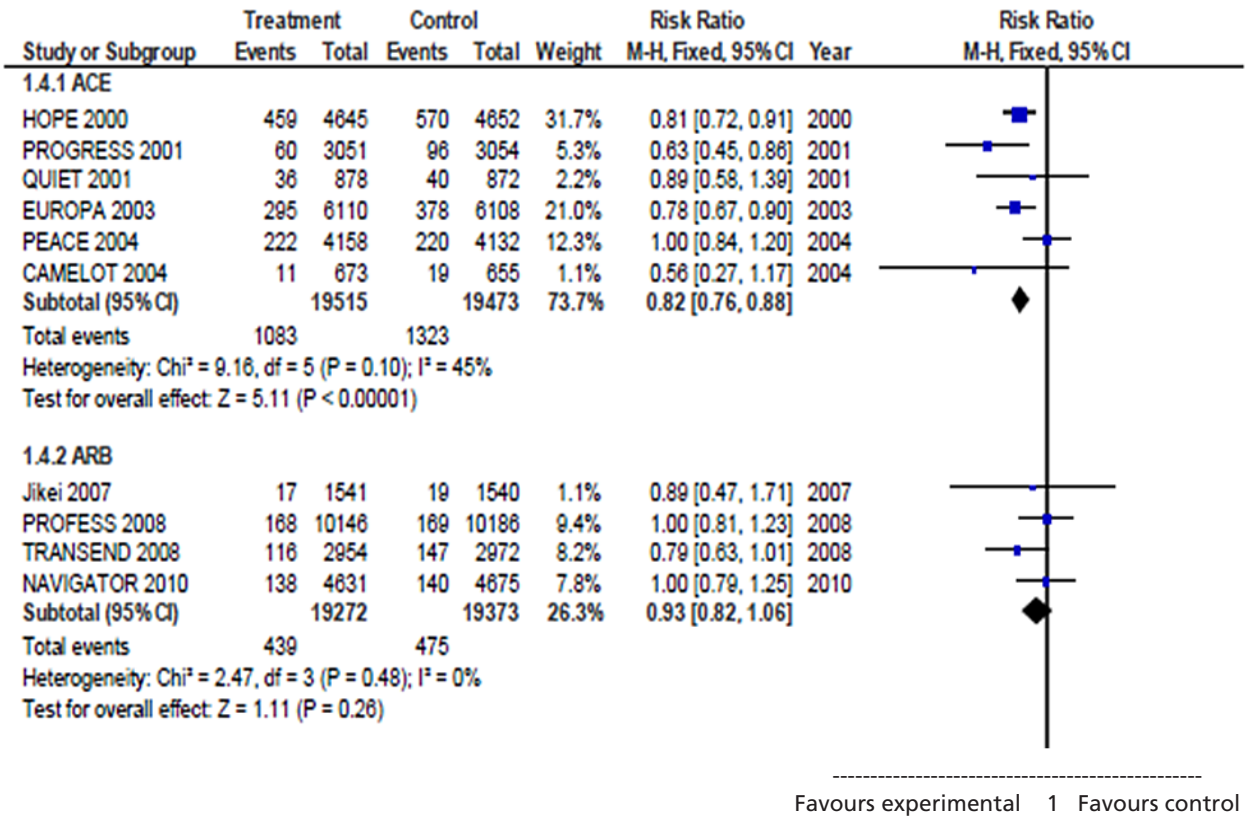


Fig. 1c: Nonfatal Myocardial Infarction



HOPE	Heart Outcomes Prevention Evaluation
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
QUIET	Quinapril Ischemic Event Trial
EUROPA	European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease
CAMELOT	Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis
PEACE	Prevention of Events with Angiotensin Converting Enzyme Inhibitors
JIKEI	Valsartan in a Japanese Population with Hypertension and other Cardiovascular Disease
TRANSCEND	Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease
PROFESS	Telmisartan to Prevent Recurrent Stroke and Cardiovascular Events
NAVIGATOR	Nateglinide and Valsartan in impaired glucose tolerance outcomes research

nonfatal MI (2.28% vs 2.45%; RR 0.93, 0.82-1.06; p=0.26). The suspicion that ARB is not cardio protective is supported by the ROADMAP trial of 4447 diabetic patients, which showed that although olmesartan managed to delay onset ofmicroalbuminuria, it resulted in significantly higher fatal cardiovascular events[27]. Patients with normal systolic function who are at high risk of adverse clinical cardiovascular events should be on an ACEI, and the ARB cannot be considered equally useful alternatives.

Two major clinical trials raise interesting issues about usingCCB and diuretics in hypertensive patients with renal disease[28]. The AASK (African-American Study of Kidney disease and hypertension) trial which compared metoprolol or amlodipine with ramipril in 1094 African-Americans with hypertensive kidney disease showed that ramipril was best atreducing proteinuria and progression of renal disease.Amongst those with proteinuria above 300mg/day ormoderate renal impairment (glomerular filtration rate [GFR] <40mL/min per 1.73m2), amlodipine treatment in fact hastened decline in renal function[29,30]. In ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial), the largest hypertensive trial ever conducted involving 42,418 patients, chlorthalidone better reduced and BP and better reduced clinical cardiovascular events compared to lisinopril, amlodipine or the alpha-blocker doxazocin[31,32]. Yet patients on the diuretic had a morerapid deterioration of GFR, and more metabolic abnormalities, over the 4 year trial period. Therefore, while

CCB and diuretics can be used in CKD patients whose BP is inadequately controlled, monitoring is needed to ensure thatrenal function and proteinuria do not significantly deteriorate[33]. The commonly used beta-blocker, atenolol, ishydrophilic, excreted fully in the urine and will need doseadjustment with deteriorating renal function. Atenolol maybe less able to reduce clinical cardiovascular events inhypertensive patients and it is thus preferable to usemetoprolol if there is a need for beta-blockade in hypertensive patients with CKD[34,35].

Although discussing the special benefit and adverse effect of the different classes of antihypertensive drug is intellectually stimulating, in managing the hypertensive patient with CKD, it is vital to avoid missing the forest for the trees. Patients with CKD are prone to hypertension induced clinical morbidityand mortality and the main aim of therapy must be to seek good drug compliance and BP control. Multiple drugs are often needed for adequate BP control. Nevertheless three large trials, ACCORD (Action to Control Cardiovascular Riskin Diabetes), INVEST (International Verapamil-TrandolaprilStudy) and AASK, have suggested that intensive BP control is not associated with lower clinical events, increases drug-induced adverse effects and may even increase total mortality[30,36,37]. It is thus reasonable to strive for BP below 140/90 mmHg but probably not below 120/80 mm Hg[11]. ACEI and ARB should be amongst the drugs used in patients with kidney disease, especially when proteinuria is present. All other antihypertensive drug classes can be added as necessary, but patients with renal disease may be particularly susceptible to drug-induced adverse effects which must be constantly remembered.

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