

Selecting Antihypertensive Medication in Patients with Essential Hypertension in Malaysia

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INTRODUCTION

Since hypertension is generally asymptomatic, in treating hypertension we are actually seeking to prevent target organ damage and reduce adverse clinical outcome. There have been numerous large clinical trials addressing the question of whether any antihypertensive drug has special protective effects on the cardiovascular and renal systems in addition to the benefit from blood pressure (BP) reduction¹⁻¹⁵. In seeking to correctly interpret the message from these trials, it is important to avoid the confusion that can occur when pharmaceutical companies seek to make the results suit their marketing needs¹⁶⁻¹⁸. The aim of this article is thus to provide an unbiased review of the value of the different antihypertensive drugs for the clinician treating essential hypertension in Malaysia.

The Diuretic: Does ALLHAT contradict ACCOMPLISH?

ALLHAT recruited hypertensive patients over 55 years with at least one other risk factor for coronary disease with the aim to compare the cardiovascular protective efficacy of newer antihypertensive drugs with the diuretic, chlorthalidone^{7, 8}. Out of a total of 42,418 patients, 15,255 were randomized to chlorthalidone, 9,061 patients to doxazosin (α -blocker), 9,048 patients to amlodipine (calcium channel blocker, CCB), and 9,054 patients to lisinopril (angiotensin converting-enzyme inhibitor, ACEI). The arm involving the α -blocker was terminated early after a median follow-up of 3.2 years, when it became clear that doxazosin was not better, and possibly inferior, to the diuretic, chlorthalidone^{8,19}. The primary outcome of fatal coronary heart disease and non-fatal myocardial infarction was equal on both treatment strategies (4-year event rate, doxazosin 7.91%, chlorthalidone 7.76%; RR1.03, 95%CI 0.93-1.15; $p=0.62$). However, the doxazosin arm had more strokes, heart failure and combined cardiovascular events. Compared with the α -blocker, the diuretic arm had more patients achieving target BP control (63% vs 58%) with systolic BP about 2 mm Hg lower. The better clinical outcome may be due to the better BP control with the diuretic.

The remaining 33,357 hypertensive patients on chlorthalidone, amlodipine and lisinopril, had a longer mean follow up of 4.9 years. The six year primary end-point event rate was not significantly different on diuretic (11.5%), CCB (11.3%; 0.98, 0.90-1.07; $p=0.65$), or ACEI (11.4%; 0.99, 0.91-1.08; $p=0.81$). Patients on CCB had higher heart failure compared to diuretic. The ACEI arm had higher heart failure, stroke and combined cardiovascular disease. It is surprising that patients on diuretic had a lower clinical outcome

compared to other more metabolically neutral drugs. It may also be pertinent that the systolic BP was lower on diuretic than on amlodipine (0.8 mm Hg, $p=0.03$) and lisinopril (2mm Hg, $p<0.001$). Subsequent analysis of the ALLHAT population showed that the results hold true whatever the initial glycemic state, renal function status and racial make-up of the patients studied²⁰⁻²³.

Although various secondary clinical end-points favor the diuretic, it is important to note that the primary end-point in all treatments arms were not significantly different. Thus, the over-riding lesson from ALLHAT, the largest clinical hypertensive study ever conducted, must be that there is no major difference between the diuretic, α -blocker, CCB or ACEI in their ability to reduce clinical cardiovascular outcome.

ALLHAT also showed up the adverse metabolic consequences of diuretic therapy. Diabetes occurred more frequently on diuretic (11.6%) than on CCB (9.8%) or ACEI (8.1%); mean fasting glucose level rose more with diuretic (+2.8 mg/dL) than with CCB (+0.6 mg/dL) or ACEI (-0.4 mg/dL). Potassium levels were also significantly lower with diuretic (4.1 mEq/L) compared to CCB (4.4 mEq/L) or ACEI (4.5 mEq/L). Thus, in using diuretics, clinicians must be aware of the need of monitoring to avoid clinically significant hypokalemia, hyponatremia and hyperglycemia²⁴. Nevertheless, since trials have clearly shown diuretics to reduce clinical outcome in diabetic hypertensives, the clinician should not be excessively apprehensive about diuretic use^{21, 25}. An unbiased reading of the trial evidence points to good BP lowering efficacy and cardiovascular protection from diuretic treatment in hypertensive patients.

The more recently published ACCOMPLISH trial randomized 11,506 hypertensive patients either to benazepril plus amlodipine or benazepril plus hydrochlorothiazide, thus testing whether it is better to combine ACEI with CCB or diuretic¹⁵. The trial was pre-terminated after 36 months when the composite primary cardiovascular end-point was clearly lower in the ACEI-CCB arm (9.6% vs 11.8%, RR 0.80, 95%CI 0.72-0.90, $p<0.001$). Since ALLHAT suggested that the CCB was inferior to diuretic, this result from ACCOMPLISH must at first appear confusing. On closer inspection, in ACCOMPLISH, from the same initial BP of 145/80 mm Hg the ACEI-CCB arm ended with the lower systolic (0.9 mm Hg, $p<0.001$) and diastolic BP (1.1 mm Hg, $p<0.001$). Thus the result from ACCOMPLISH is not different from ALLHAT in showing that the arm with the significantly lower achieved BP had the lower clinical outcome. The consistent message

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from both ALLHAT and ACCOMPLISH is to treat to a lower target BP, since patients with the lower achieved BP that had the lower cardiovascular outcome.

The ANBP2 study, published a few months after ALLHAT, raised the possibility that ACEI might be better than the diuretic⁹. ANBP2 was a randomized, open-labeled trial of hypertensives above 65 years to initial treatment with an ACEI (n=3044) or a diuretic (n=3039); choice of initiating dose and drug was left to the participating general practitioner. BP reduction was similar over 4.1 years and treatment with ACEI resulted in a lower primary end-point of cardiovascular events or total death that was of borderline significance (ACEI 22.8%, diuretic 24.2%; RR0.89, 95%CI 0.79-1.00; p=0.05). When considering only the 51% of the study population who were females, there was no difference between the ACEI and diuretic groups. Total mortality, coronary event, heart failure and stroke were all similar in the two treatment groups. Thus a fair and careful analysis of ANBP2 shows that it actually confirms the results from ALLHAT, in showing that ACEI and diuretics are almost equivalent in reducing adverse clinical cardiovascular events in hypertensive patients (Table I).

The Calcium Channel Blocker: From foe to friend

A decade ago, concern was raised about the value of CCB since patients on nifedipine apparently had increased cardiovascular events^{26, 27}. This idea has now been proven incorrect with 4 trials, besides ALLHAT, showing the safety and value of various CCB in hypertensive patients. INSIGHT randomized 6321 hypertensive patients to either nifedipine LA or co-amiloride⁴. After 51 months, the composite primary outcome of cardiovascular death, myocardial infarction, heart failure or stroke was equivalent in both arms (6.3% nifedipine, 5.8% co-amiloride; 1.1, 0.91-1.34; p=0.35). In showing the safety of long-acting nifedipine, INSIGHT proved that the increase adverse events noted previously must be due to the short duration of drug action and the inability to provide stable 24-hour BP control. NORDIL randomized 10,881 hypertensive patients to diltiazem or beta-blockers/diuretics⁵. After 4.5 years, there was no difference in the primary end-point of stroke, myocardial infarction and cardiovascular death (diltiazem 16.6 events per 1000 patient-years, beta-blocker/diuretic 16.2 events per 1000 patient-years; RR 1.00, p=0.97).

CONVINCE randomized 16,602 hypertensive patients to verapamil or atenolol/hydrochlorothiazide¹⁰. After three years, the primary outcome of stroke, myocardial infarction or cardiovascular death was equivalent in the two groups (364 verapamil, 365 atenolol/hydrochlorothiazide; RR1.02; p=0.77). When assessed individually, stroke, myocardial infarction, and cardiovascular death were also equal in the verapamil and beta-blocker/diuretic groups. INVEST compared 22,576 hypertensive patients randomized to either a verapamil-based strategy with one based on atenolol¹¹. Trandolapril and hydrochlorothiazide could be added if required; it was anticipated that patients would be on verapamil plus trandolapril or atenolol plus thiazide. After 2.7 years, there was no significant difference in the primary end-point (total mortality, non-fatal myocardial infarction and non-fatal stroke) between the two groups (9.93%

verapamil, 10.17% atenolol; RR 0.98). Over 50% of patients from each group required three or more antihypertensive drugs for adequate BP control. Thus, besides showing the equivalent cardioprotective efficacy of different antihypertensive agents, the most revealing lesson of INVEST is that multiple drugs will be required for adequate BP control. Arguments about which is the best initial antihypertensive agent may thus not be very practical.

JMIC-B which recruited 1650 hypertensive patients with coronary disease and randomized them to either nifedipine-retard or ACEI raised the possibility that the CCB may have anti-atherosclerotic properties¹⁵. After three years, the primary end point (cardiac death, myocardial infarct, angina or heart failure hospitalization, coronary intervention) was 14% with CCB and 12.9% with ACEI (RR1.05, 95%CI 0.81-1.37, p=0.86). Coronary angiography showed no change in coronary lumen on nifedipine, while the minimum luminal diameter reduced significantly on ACEI²⁸. Patients who developed new lesions or whose lesions progressed was also significantly higher in the ACEI group. The idea that CCB may retard the development of atheroma is also suggested by the CAMELOT and PREVENT trials, although these are studies of coronary patients who may not be hypertensive^{29,30}. In CAMELOT, intravascular coronary ultrasound showed significantly less progression of coronary atherosclerosis in patients on amlodipine compared to placebo, with no difference in the atherosclerotic progression between enalapril and placebo. In the PREVENT study, although there was no significant effect on angiographic coronary stenosis, carotid intima-media thickness (IMT) significantly decreased over the study period in patients on amlodipine while IMT progressed in the placebo group.

The fact that CCB has no adverse impact on cardiovascular events, and may even be specially protective, is also shown up in the VALUE and ASCOT-BPLA trials. VALUE randomised 15,245 high risk hypertensives to either the angiotensin-receptor blocker (ARB), valsartan or the CCB, amlodipine¹². After 4.2 years, there was no significant difference in the primary end-point (first cardiac event) between the two groups (10.6% valsartan, 10.4% amlodipine, RR 1.04, 95%CI 0.94-1.15, p=0.49). Although new diabetes was lower with valsartan, myocardial infarction was higher in the valsartan-treated patients (4.8% vs 4.1%; RR1.19; p=0.02). Although BP at trial initiation was similar, attained BP was consistently and significantly lower in the amlodipine group. After correction for the BP difference, the composite of cardiac events, stroke, death or myocardial infarction was similar in the two treatment groups³¹. Furthermore, patients reaching adequate BP control by six months fared better regardless of drug type used. The point made is that the benefit from good BP control is more important than the subtle differences between antihypertensive drugs. The better metabolic profile in the ARB arm did not translate into a reduction in adverse clinical disease. VALUE as did ALLHAT also raise the possibility that drugs targeting the rennin-angiotensin system are less efficacious in reducing BP when compared to the CCB and diuretic^{7,12}.

ASCOT-BPLA recruited 19,257 hypertensive patients with at least three other cardiovascular risk factors and randomized

them to amlodipine (adding perindopril) or atenolol (adding bendroflthiazide)¹⁴. After 5.5 years, the primary end point of non-fatal myocardial infarction and cardiovascular death was similar (5% vs 5%; RR 0.90 95%CI 0.79-1.02; p=0.1052). However, total coronary end-point (RR0.87; p=0.007), total stroke (RR0.77; p=0.0003) and total mortality (RR0.89; p=0.02) were all lower in the amlodipine arm. The achieved BP was lower on amlodipine than on atenolol with an average difference of 2.7/1.9 mm Hg³². Patients on amlodipine also had significantly higher HDL-cholesterol, and lower BMI, triglyceride, creatinine and glucose levels, all of which could contribute to the lower clinical cardiovascular outcome with amlodipine. Multivariate adjustment for all these risk factor differences resulted in the disappearance of the significant cardiovascular event rate difference between the two groups, thus confirming the importance of global risk factor management in seeking to reduce cardiovascular events^{32,33}. The important message from ASCOT-BPLA is that in seeking to lower cardiovascular outcome, tight BP and risk factor management is vital, not that new antihypertensive drugs are superior to older ones^{34,35}.

The rennin-angiotensin antagonists: do they provide special target organ protection?

Strong evidence has emerged on the value of the ARB in preserving renal function in diabetic hypertensives with nephropathy. IDNT randomized 1715 hypertensive patients with nephropathy from type 2 diabetes to irbesartan, amlodipine or a placebo (using other antihypertensive agents) over a mean follow up of 2.6 years³⁶. BP reduction was similar in the three groups. The primary end-point was a composite of doubling of serum creatinine, development of end-stage renal disease (ESRD) or death. Irbesartan reduced the primary end-point by 20% compared to placebo (p=0.02) and by 23% compared to amlodipine (p=0.0006). Another similar trial, IRMA-2, shows that irbesartan retards the development of nephropathy and overt albuminuria in diabetic hypertensive patients with baseline microalbuminuria; full dose irbesartan 300 mg daily is more protective than irbesartan 150 mg daily³⁷. RENAAL assigned 1513 patients, also with type 2 diabetes and nephropathy to losartan or placebo; all patients were allowed other antihypertensive agents as needed for blood pressure control³⁸. The primary end point was a composite of a doubling of serum creatinine, ESRD or death. This was significantly reduced by 16% in the losartan group (p=0.02), driven by a lower doubling of serum creatinine (reduced by 25%, p=0.006) and development of ESRD (reduced by 28%, p=0.002). Clinical cardiovascular event rate between the study groups were not significantly different in both the RENAAL and IDNT trials^{38, 39}. This raises the possibility that the protective role of ARB in retarding renal disease does not hold for cardiovascular disease. It could be that specific drug classes may be more useful in the protection of specific target organ systems, with no one single drug class being superior for every system.

A special renal protective effect of the ACEI amongst non-diabetic hypertensive patients with nephropathy has also been noted. In AASK, 1094 African-Americans with hypertensive nephrosclerosis were randomized to therapy with ramipril, amlodipine or metoprolol^{40, 41}. The primary

outcome was rate of change of glomerular filtration rates (GFR), with the secondary outcome being the composite of reduction of GFR by 50% or 25ml/min per 1.73 m², development of ESRD or death. Amongst patients with proteinuria above 300 mg/day or baseline GFR less than 40ml/min per 1.73 m², compared to amlodipine, the ramipril group had a significantly slower decline of GFR. In the overall population, there was no significant difference in the primary end-point between the ramipril, amlodipine or metoprolol groups. However, compared to amlodipine, ramipril reduced the secondary composite clinical endpoint by 38% (p=0.007). Compared to metoprolol, ramipril also reduced secondary clinical outcome by 22% (p=0.04). Thus, AASK clearly show the superiority of ACEI over betablocker and CCB in retarding renal deterioration of African Americans with hypertension, a group previously thought to be less responsive to the ACEI. It also suggested that a CCB may be detrimental in patients with baseline proteinuria above 300 mg/day or moderate impairment of renal function (GFR < 40ml/min per 1.73 m²).

Clinical trials comparing ACEI with other antihypertensive drugs generally showed no difference in cardiovascular outcomes (Table II). In UKPDS, 758 hypertensive diabetics had their BP tightly controlled with either captopril or atenolol¹. Both treatment arms had similar BP reduction and after 9 years, there was no difference in the primary outcome of diabetic-related clinical events (RR for captopril 1.10; p=0.43), stroke (1.12; p=0.74), myocardial infarction (1.20; p=0.35), or total mortality (1.14; p=0.44). In contrast, cardiovascular events were much higher in patients treated to less strict BP levels compared to this group on tight BP control⁴². CAPP randomized 10,985 hypertensive patients to either captopril or conventional therapy with diuretics/beta blockers². After 6.1 years, the composite primary end point of myocardial infarction, stroke or cardiovascular death was 11.1 per 1000 patient-years with captopril and 10.2 per 1000 patient-years with conventional treatment (RR 1.05, 95%CI 0.90-1.22; p=0.52). The captopril group had a slightly but significantly higher BP at randomization and throughout the study period, and patients on captopril had a higher incidence of strokes. STOP-Hypertension 2 recruited 6614 older hypertensive patients and randomized them to conventional therapy (beta-blockers or diuretics), CCB or ACEI³. Reduction in BP was similar in the three groups. After 4-6 years, there was no difference in cardiovascular mortality, the primary end point, between conventional therapy (19.8 per 1000 patient-years), ACEI (20.5 per 1000 patient-years) or CCB (19.2 per 1000 patient-years). Cardiovascular mortality, myocardial infarction, stroke, total mortality, diabetes and heart failure were also all similar in these three groups.

As mentioned above, in ALLHAT, JMIC-B and VALUE, the clinical primary end-point was similar whether patients were on a rennin-angiotensin antagonist or its comparator drug^{7, 12, 13}. Furthermore, in both ALLHAT and VALUE, the arm with the significantly lower achieved BP developed lower secondary clinical end-points. It is important to recall this fact in interpreting the LIFE trial which randomized 9193 hypertensive patients with left ventricular hypertrophy to either losartan or atenolol⁶. There was a marked reduction of

stroke in the losartan group (RR 0.87; $p=0.001$), and this caused a significant reduction in the composite primary end-point of death, Myocardial Infarction or stroke (11% vs 13%; RR 0.87, 0.77-0.98; $p=0.021$). The mean systolic BP was lower on losartan (1.1 mmHg, $p=0.017$) and it is possible that the clinical benefit resulted from the better BP control in the losartan arm. No other comparative study involving the rennin-angiotensin antagonist had shown up a special cerebrovascular protective effect; in fact, ACEI was weaker than the comparator drug in preventing stroke in both CAPPP and ALLHAT^{2,7}. Furthermore, recent reports suggest that beta-blockers, especially atenolol, may be less useful in the older hypertensive, and are specially weak in preventing stroke^{43,44,45}. Thus, LIFE actually confirms the importance of BP reduction and the weaker efficacy of atenolol instead of showing a special cardiovascular protective effect of losartan.

The idea that the ACEI/ARB may be useful as cardioprotective agents came not from comparative drug trials in hypertensive patients, but from placebo-controlled trials in patients at high risk for cardiovascular events. In all these trials, the arm on active ACEI/ARB treatment ended up with a lower BP compared to the placebo arm. Thus, the reduction in clinical outcome could arguably be attributed to the benefit from the lower achieved BP in the treatment group. Furthermore, these trials have not consistently shown a positive effect from rennin-angiotensin antagonist treatment. HOPE, EUROPA and JIKEI showed significant reduction of cardiac outcome while PROGRESS, PEACE, CAMELOT, TRANSCEND and PROFESS did not⁴⁶⁻⁵³. In CAMELOT, compared to the placebo group, cardiovascular outcome was not significantly affected with enalapril yet was significantly lower in patients on amlodipine. Furthermore, progression of coronary atherosclerosis was retarded with amlodipine but showed no difference between the enalapril and placebo groups⁵¹. Thus, CAMELOT suggests that it is the CCB, and not ACEI, that has an anti-atherosclerotic effect. It is also interesting to compare how strikingly similar the results of PROFESS are to those of PROGRESS^{48,53}. In PROGRESS, amongst patients only on perindopril, the BP reduction was 5/3 mm Hg, with stroke (RR 0.95) and major vascular event (RR 0.96) reduction not significantly different from placebo. In PROFESS, the BP reduction of 4/2 mm Hg produced a non-significant reduction of stroke (RR 0.95) and cardiovascular event (RR 0.94). In PROGRESS, it was the addition of indapamide that produced a larger BP reduction (12/5 mm Hg) and resulted in a highly significant reduction in stroke (RR 0.52). Thus, PROFESS confirms the impression of PROGRESS that the rennin-angiotensin antagonists when used alone are not potent BP reducing drugs, and do not have special stroke reducing or cardiovascular protective effects.

The ONTARGET trial sought to answer two questions about the role of the rennin-antagonists in high risk patients, whether an ARB is similar to an ACEI in therapeutic efficacy, and whether their combination could produce even better clinical results⁵⁴. Patients with vascular disease or diabetes are randomized to 10 mg ramipril ($n=8576$), 80 mg telmisartan ($n=8542$) or both ($n=8502$); 69% of patients were hypertensive. From the same initial level of 142/82 mm Hg, after six weeks BP fell to 135/78 mm Hg on ramipril, 134/77 mm Hg on telmisartan, and 132/76 mm Hg on combination therapy. The primary end-point was a composite of

cardiovascular death, Myocardial Infarction, stroke and heart failure hospitalization. After a median of 56 months, compared to ramipril there was no difference in the primary end-point with telmisartan (RR 1.01, 95% CI 0.94-1.09) or combination therapy (0.99, 0.92-1.07). While the combination of ramipril and telmisartan better reduced proteinuria compared to ramipril alone, major renal outcomes (need for dialysis, doubling of serum creatinine and death) were surprisingly higher in the combination group (14.5% vs 13.5%; 1.09, 1.01-1.18; $p=0.037$)⁵⁵. Furthermore, adverse side effects were highest with combination therapy. ONTARGET thus shows that ARB and ACEI are equivalent in their clinical efficacy. It also shows that there is no added benefit from combining them. If indeed attacking the rennin-angiotensin system is especially useful in preventing cardiac disease, then the combination of ARB with ACEI should logically result in even lower cardiovascular event rates. By showing that combining ARB and ACEI did not produce any reduction in cardiovascular outcome compared to ACEI monotherapy, ONTARGET thus shows it unlikely that there is a special cardiovascular protective effect from antagonizing the rennin-angiotensin system. The higher adverse effect with combination treatment in ONTARGET also highlights the potential dangers in excessively antagonizing the rennin-angiotensin system. It may be that patients respond best when different strategies are used for treatment, and excessively targeting a single pathway will result in less clinical benefit with higher risk of adverse consequences.

Beta-blockers: an objective appraisal

The National Institute of Health and Clinical Excellence together with the British Hypertension Society in their 2006 guidelines relegated beta-blockers to fourth line antihypertensive drugs behind the diuretic, ACEI/ARB and CCB⁵⁶. However, hypertension guidelines of the European Society of Hypertension/ European Society of Cardiology published a year later did not concur, and still considered beta-blockers equivalent to the other anti-hypertensive drug groups⁵⁷. It is thus best for all clinicians to understand the trials and meta-analyses and decide which conclusion is more appropriate!

The two trials which suggested that beta-blockers may be inferior to other antihypertensive drugs are LIFE and ASCOT-BPLA^{6,14}. In LIFE, atenolol was inferior to losartan in reducing stroke, while in ASCOT-BPLA, atenolol was inferior to amlodipine in reducing coronary events, stroke and total mortality. However, achieved BP was higher in the atenolol group in both trials, while numerous adverse risk factors also ended-up elevated on atenolol in ASCOT-BPLA. In fact, correction for the BP and cardiovascular risk factor differences between the atenolol and amlodipine groups in ASCOT-BPLA resulted in the disappearance of clinical outcome difference these groups³². Amongst beta-blockers, there is evidence that atenolol being hydrophilic is less cardio-protective than other beta-blockers^{58,59}. In a subset of 2199 patients in the ASCOT-BPLA trial, the central aortic systolic BP on atenolol was 4.3 mm Hg higher than on amlodipine although peripheral brachial artery BP in the two groups were similar⁶⁰. This inability of atenolol to lower central BP may partly account for its poorer ability to reduce cardiovascular events.

Two large meta-analyses of beta-blockers in hypertension added to doubts about their value in cardiovascular protection^{61,62}. Carlberg and colleagues studied the effects of atenolol on cardiovascular outcomes in hypertensive patients with mean age ranging from 52-70 years. Atenolol did not reduce myocardial infarction, stroke, cardiovascular and total mortality when compared to placebo. Compared to other anti-hypertensive drugs, despite equivalent degrees of blood pressure reduction, atenolol treatment was associated with higher total mortality (RR 1.13, 1.02-1.25), cardiovascular mortality (RR 1.16, 1.00-1.34) and strokes (RR1.30, 1.12-1.50). The meta-analysis by Lindholm and colleagues was more comprehensive, involving 13 trials recruiting 105951 patients comparing beta-blockers with other antihypertensive drugs, and 7 trials involving 27,433 patients comparing beta-blockers with placebo. Although the overall message was that beta-blockers were inferior to other antihypertensive drugs in stroke prevention (RR 1.16, 1.04-1.30), the results were different when the beta-blockers were divided into atenolol and non-atenolol beta-blockers. Compared to other anti-hypertensive drugs, atenolol was associated with higher stroke and total mortality. Non-atenolol beta-blockers were not inferior to other hypertensive drugs in stroke, myocardial infarction and total mortality. Thus, rather than suggesting that all beta-blockers are inferior to other hypertensive drugs in reducing cardiovascular events, these meta-analyses actually reinforce the impression that it is atenolol which has the inferior effect. While the evidence is still not conclusive, a cautious clinician should always ask whether a non-atenolol beta-blocker is available when contemplating beta-blocker therapy.

Another meta-analysis highlights the possibility that the older hypertensive patient may be different from younger ones⁶³. Amongst patients with mean baseline age less than 60 years, beta-blockers reduced major cardiovascular outcomes compared to placebo (19,414 patients, RR0.86, 0.74-0.99) and were equivalent to other antihypertensive drugs (30,412

patients, RR 0.97, 0.88-1.07). In patients of mean baseline age 60 years and above, beta-blockers were equivalent to placebo (8,019 patients, RR 0.89, 0.75-1.09) and were less effective in reducing cardiovascular outcomes compared to other antihypertensive drugs (79,775 patients, RR1.06, 1.01-1.10). These results are clinically reasonable, since the pathophysiology of hypertension is different between the younger and older patient^{64,65}. By acting to reduce cardiac output, beta-blockers may be more useful in the younger hypertensive with a higher sympathetic drive but who has essentially normal vascular resistance⁶⁶. Unfortunately another meta-analysis contradicts this, and asserts that different anti-hypertensive drug classes do not have differing effects amongst older or younger hypertensive patients⁶⁷. This problem of contradicting publications is also evident with one report suggesting that beta-blocker induced slowing of heart rate is detrimental in hypertension, and another showing that heart rate reduction is associated with lowering of adverse outcomes in patients with ischemic heart disease^{68,69}. Since hypertension predisposes to ischemic heart disease, one of these two reports obviously cannot be correct!

Symptomatic relief of angina pectoris from beta-blocker therapy has been known since the 1960s⁷⁰. Their prognostic benefit in patients with myocardial ischemia has also been conclusively demonstrated by the mortality reduction in secondary prevention of patients after a myocardial infarction⁷¹. The demonstration of an anti-atherosclerotic effect of metoprolol provides a patho-physiological rationale for the prognostic benefit beta-blockers produce in ischemic heart disease^{72,73}. Bisoprolol, carvedilol and metoprolol have been established as a drug that improves prognosis and reduces mortality in heart failure^{74, 75, 76}. In heart failure treatment, initiation of therapy with beta-blockers is gentle, with low doses increased at gradual intervals. The demonstration that bucindolol does not produce the same mortality reduction as carvedilol in similar patients highlights the fact that not all beta-blockers are the same⁷⁷.

Table I: Hypertension drugs trials comparing diuretic with other drugs showing
i) primary clinical outcome usually similar in both treatment arms
ii) the arm with the lower achieved BP has significantly lower clinical outcome

Trial	ALLHAT	ALLHAT	ANBP-2	ACCOMPLISH
Year	2002	2002	2003	2008
Type of Patient				
Number	24309	24309	26083	11506
Follow-up (yr)	4.9	4.9	4.1	3
Drugs compared	lis vs c'done	amlo vs c'done	ACEI vs diu	ben/amlo vs ben/c'zide
Entry BP (mmHg)	146/84	146/84	168/91	145/80
BP difference during study (mmHg)	lisinopril SBP 2 higher	amlodipine SBP 0.8 higher	NS	ben/amlo SBP 0.9 lower DBP 1.1 lower CVS events
Primary End Point	Fatal CHD nonfatal MI	Fatal CHD nonfatal MI	CVS event total mortality	CVS events
RR, 95% CI; Significance	0.99, 0.91-1.08; NS	0.98, 0.90-1.07; NS	0.89, 0.79-1.00; p=0.05	0.80, 0.72-0.90; p<0.001
Other significant differences	lisinopril Stroke higher CCF higher	amlodipine CCF higher	In males RR 0.83; p=0.02 In females RR 0.98; p=0.98	ben/amlo MI, revas lower

Yr: year; NS: not significant; BP: blood pressure; lis: lisinopril; c'done: chlorthalidone; amlo: amlodipine; ACEI: angiotensin converting enzyme inhibitor; diu: diuretic; ben: benazepril; c'zide: chlorothiazide; SBP: systolic blood pressure; DBP: diastolic blood pressure; MI: Myocardial Infarction; CVS: cardiovascular; CHD: coronary heart disease; RR: relative risks; CI: confidence intervals; NS: not significant; CCF: congestive cardiac failure; revas: revascularization

ALLHAT : The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

ANBP-2 : Second Australian National Blood Pressure Study Group

ACCOMPLISH : The Avoiding Cardiovascular Events Through Combination Therapy in Patients with Systolic Hypertension Trial

Table II: Trials comparing angiotensin converting enzyme inhibitors/ angiotensin receptor blockers with other regimes in hypertensive patients show
i) no significant difference in primary end-point in most studies and
ii) group with lower blood pressure had lower adverse clinical outcome regardless of treatment strategy.

Trial	UKPDS	CAPP	STOP-2
Year	1998	1999	1999
Type of Patient	hypertensive	hypertensive	hypertensive
Number	758	10985	4418
Follow-up (yr)	9	6.1	4.6
Drugs compared	cap vs atenolol	cap vs diu/bb	ACEI vs conven
Entry BP (mmHg)	159/93	162/100	194/98
BP difference during study (mmHg)	NS	captopril BP higher 2/2	NS
Primary End Pt	1) clinical diabetes event 2) diabetes death 3) total mortality	MI, stroke, CV death	CV death
RR, 95% CI; Significance	1) 1.1, 0.86-1.41; NS 2) 1.27, 0.82-1.97; NS 3) 1.14, 0.81-1.61; NS	1.05, 0.90-1.22; NS	1.01, 0.84-1.22; NS
Other significant outcome differences	nil	Captopril group 43% higher stroke, p = 0.004	nil
Trial	LIFE	VALUE	JMIC-B
Year	2002	2004	2004
Type of Patient	Hypertensive	Hypertensive	hypertensive
Number	9193	15245	1650
Follow-up (yr)	4.8	4.2	3
Drugs compared	losartan vs atenolol	amlodipine vs valsartan	ACEI vs nifedipine
Entry BP (mmHg)	174/98	155/88	145/82
BP difference during study (mmHg)	losartan	valsartan	ACEI
Primary End Point	SBP lower 1.1, p = 0.017 CV death, stroke, MI	BP higher 2.1/1.7, p<0.0001 CV event	BP higher 4/1, P<0.01 Cardiac event
RR, 95% CI; Significance	0.87, 0.77-0.98; p = 0.021	1.04, 0.94-1.15; NS	1.05, 0.81-1.37; NS
Other significant outcome differences	losartan group 25% stroke reduction p = 0.001	valsartan group 19% higher MI, p = 0.02	ACEI group coronary stenosis worsen

Yr: year; cap: captopril; diu: diuretic; bb: betablocker; ACEI: angiotensin converting enzyme inhibitor; conven: conventional; NS: not significant; BP: blood pressure; pt: point; MI: Myocardial Infarction ; CV: cardiovascular; chlor: chlorthalidone; SBP: systolic blood pressure; CHD: coronary heart disease
 UKPDS : United Kingdom Prospective Diabetes Study Group
 CAPP : Captopril Prevention Project
 STOP-2 : Swedish Trial in Old Patients with Hypertension 2
 JMIC-B : Japan Multicenter Investigation for Cardiovascular Diseases-B randomized Trial
 LIFE : Losartan Intervention For Endpoint Reduction in Hypertension Study
 VALUE : Valsartan Antihypertensive Long-Term Use Evaluation Trial

Table III: Discontinuation rate of antihypertensive drugs in the comparative trials.

TRIAL	ACEI	ARB	ACEI+ARB	BB	CCB	DIU
ONTARGET, n=25620	25%	23%	29%	-	-	-
LIFE, n=9193	-	23%	-	27%	-	-
VALUE, n=15245	-	26%	-	-	24%	-
ALLHAT, n=33357	27%	-	-	-	20%	20%
UKPDS, n=758	22%	-	-	35%	-	-
JMIC-B, n=1650	9%	-	-	-	5%	-

ACEI : Angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: Calcium Channel Blocker; DIU: diuretic; BB: betablocker
 ONTARGET : Ongoing Telmisartan Alone and in Combination with Ramipril Global Trial
 LIFE : Losartan Intervention For Endpoint Reduction in Hypertension Study
 VALUE : Valsartan Antihypertensive Long-Term Use Evaluation
 ALLHAT : Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
 UKPDS : United Kingdom Prospective Diabetes Study Group
 JMIC-B : Japan Multicenter Investigation for Cardiovascular Diseases-B randomized trial

Furthermore, in contrast to secondary prevention, acute treatment with beta-blockers early in acute myocardial infarction has consistently been shown to have a neutral prognostic effect^{71,78}. Thus, cardiovascular event reduction with beta-blocker therapy requires choosing the correct beta-blocker in the appropriate clinical situation so that its benefit can be realized while avoiding its adverse effects.

So what is the role of beta-blockers in managing hypertension? Beta-blockers should be used in hypertensive patient with concomitant angina, prior myocardial infarction or heart failure. In younger patients who often have a higher sympathetic drive, beta-blockers should remain first line anti-hypertensives, together with the diuretics, CCB, ACEI and ARB; choice of drug(s) depends on the clinical circumstances of the individual patient. In the older hypertensive, beta-blockers should be avoided unless another clinical condition necessitates its use. Beta-blockers may not all be equivalent in cardiovascular protective effects, and there is evidence to suggest that atenolol is inferior to other drugs in reducing stroke and total mortality in older patients.

CONCLUSION: APPLYING LESSONS FOR MALAYSIA

The large comparative hypertensive drug trials generally recruited few Asian patients – in ALLHAT, less than 5% of recruited patients were Asians⁷. However, hypertensive studies of similar design in Asia or Europe have produced similar results and there is thus no reason to believe that Malaysian hypertensive patient would respond differently to the trial population studied^{79,80}. The hypertension prevalence rate in Malaysia is 42% of which only 26% achieves proper control, emphasizing the need to adequately treat this widespread problem⁸¹. An uncomplicated interpretation of the comparative drug trials to derive practical lessons will undoubtedly aid in achieving better hypertension control.

An unbiased review thus shows that there was no significant difference in the cardiovascular primary end point in most of the large comparative hypertension drug trials conducted^{1-5, 7, 8, 10-14}. In LIFE (losartan vs atenolol), ALLHAT (doxazosin, amlodipine, lisinopril vs chlorthalidone), VALUE (amlodipine vs valsartan), ASCOT (amlodipine vs atenolol) and ACCOMPLISH (benazepril plus amlodipine vs benazepril plus hydrochlorothiazide), where major cardiovascular end-points were noted to be lower in one of the treatment arms, it was always the arm with the lower achieved BP that saw the better clinical outcome^{6, 7, 8, 12, 14, 15}. Thus, instead of trying to work out why antihypertensive drugs could exert apparently different cardiovascular protective effect in different trials, the simple and consistent message is that the lower the achieved BP, the lower the adverse clinical cardiovascular outcome.

Choice of initiating antihypertensive agent logically should be guided by the presence of clinical disease or target organ damage. Hypertensive patients with angina should have a betablocker or CCB, given their definite anti-anginal and possible anti-atherosclerotic effects^{29,30,72,73}. Those with a prior myocardial infarction should be on a betablocker, and if the infarction is anterior or has led to left ventricular dysfunction, an ACEI or ARB is needed as well^{71, 82, 83}. Hypertensives with poor left ventricular function or heart failure should be on diuretic, ACEI and beta-blocker^{7, 84, 85}. If

the patient has had a prior stroke, or is at special risk of stroke, the balance of evidence calls for therapy with CCB, diuretic or ARB; the beta-blocker would be least useful^{6, 86, 87}. For renal protection, especially in the setting of diabetic proteinuria, an ARB or an ACEI is best to prevent and delay nephropathy^{36, 37, 38, 40, 41}. The rennin-angiotensin antagonists also increase insulin sensitivity and should be preferred hypertensive drugs in diabetics struggling to achieve good glycemic control^{2, 7, 12, 14}. This approach in choosing the anti-hypertensive drug according to the target organ most at risk of damage is in keeping with the published guidelines^{56, 57, 88, 89}. The comparative hypertension drug trials also show that multiple drugs are required for adequate BP control. Thus, rather than argue over which drug to use in initiating therapy, the practical message is to seek tight blood pressure control using a combination of several antihypertensive drugs. This position is supported by the results of various meta-analyses which have consistently shown better clinical outcome comparing drugs with placebo, but only borderline differences when comparing different classes of antihypertensive drugs^{90, 91}.

Since hypertension treatment is long term, it is important to minimize treatment induced adverse effects so as to promote compliance. It is interesting to compare the discontinuation rate of the anti-hypertensive drugs in various trials (Table III). Although some reviews suggest that compliance is best with ARB, they are still not free of adverse effects with a discontinuation rate in excess of 20%^{92, 93}. In fact, in VALUE, the CCB was better tolerated than the ARB which had a significantly higher incidence of dizziness, headache, angina, diarrhea, and syncope¹². Contrary to the perception that diuretics are poorly tolerated, in ALLHAT the discontinuation rate on diuretic was lower than on ACEI, and equivalent to CCB⁷. Given the present poor control rate of hypertension, the challenge for all physicians is not to rigidly follow guidelines, but to seek best compliance in every individual patient with a combination of drugs that optimize BP control with the least adverse effects^{94, 95}. Compliance could partly be enhanced by simplifying treatment. Trials comparing combination pills with the same medication as separate pills showed better adherence and clinical outcome with combination pills⁹⁶. Cost containment is also important in seeking increased compliance. In fact, generic cardiovascular drugs have been shown to be clinically equivalent to originals, and generic substitution of patented anti-hypertensive medication has actually reduced the non-adherence rate^{97, 98}.

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