CME Article

Cardiovascular outcomes in the comparative hypertension drug trials: more consensus than controversy

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ABSTRACT

The comparative anti-hypertensive drug trials conducted to assess their cardiovascular protective efficacy actually produce compatible, not conflicting, results. In the last decade, there were 13 major comparative hypertension drug trials with the cardiovascular primary outcome being statistically equivalent in 11 of these 13 trials, involving over 90 percent of the randomised 168,593 patients. Where secondary outcomes favour a drug in these trials, that arm has a significantly lower treated blood pressure as in LIFE, VALUE, ASCOT and ALLHAT. Controversy occurs in seeking to attribute the benefit to drug effect; if the benefit is attributed to the lower achieved blood pressure, then the trials become consistent. The safety and value of diuretics, beta-blockers, calcium-blockers, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers in reducing blood pressure, and in reducing clinical cardiovascular outcomes, is now clearly established. Overall, the importance of tight blood pressure control in reducing cardiovascular outcomes must be emphasised. Physicians should concentrate on achieving good blood pressure control, which often requires a combination of several anti-hypertensive drugs.

Keywords: anti-hypertensive drugs, blood pressure control, cardiovascular outcomes, hypertension, drug trials

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INTRODUCTION

There have been 13 randomised, controlled trials, each recruiting over 500 patients with follow-up of over 2.5 years, conducted in the last decade to assess if any drug is especially valuable in reducing cardiovascular outcomes in hypertension.[1-14] This article aims to objectively review these comparative hypertensive drug trials to derive practical information useful for managing the outpatient hypertensives.

THE INITIAL STUDIES

A sub-study of the United Kingdom Prospective Diabetes Study (UKPDS) looked at hypertension in diabetic patients, comparing captopril with atenolol, and tight conventional blood pressure (BP) control.[1,15] After nine years, in 1,148 patients, diabetic-related clinical events, stroke, myocardial infarction (MI), diabetic death and total mortality were all equivalent on captopril and atenolol. While beta-blockers and angiotensin-converting enzyme inhibitors (ACEI) appear to provide equal cardiovascular protection, tight BP control resulted in lower stroke, heart failure, and diabetic-related death. This suggests that the intensity of BP control is more important than antihypertensive drug type in determining cardiovascular outcomes. Captopril Prevention Project (CAPPP) randomised 10,985 hypertensive patients to captopril or diuretic/beta-blocker.[2] After 6.1 years, MI, stroke or cardiovascular death, individually and its composite primary endpoint, were equal on captopril and diuretic/beta-blocker. Despite a lower incidence of diabetes mellitus, patients on captopril had more strokes. The Swedish Trial in Old Patients with Hypertension-2 (STOP-2) randomised 6,614 patients to conventional treatment (beta-blocker/diuretic), calcium channel blockers (CCB) or ACEI.[3] After 4–6 years, there was no difference in cardiovascular mortality (primary endpoint), MI, stroke, total mortality, diabetes mellitus and heart failure among the conventional therapy, ACEI or CCB groups. Newer and older antihypertensive drugs thus have equivalent cardiovascular protective efficacy.[16] In STOP-2, 46% of patients received two or more drugs, while in UKPDS, about 30% needed three or more drugs for adequate BP control.

RESOLVING THE CALCIUM BLOCKER DEBATE

In the Intervention as a Goal in Hypertension Treatment (INSIGHT) study, among 6,321 hypertensive patients after 51 months, the primary outcome (cardiovascular death, MI, heart failure or stroke), total mortality or cardiovascular death were equal on long-acting nifedipine and co-amiloride.[4] It is the short duration of drug action that caused the excess adverse events in earlier nifedipine

Table 1. Comparative antihypertensive drug trials with cardiovascular primary endpoints.

Year	Trial	No. patients	Drugs compared	Primary endpoint	RR (95% CI)	p-value
1998	UKPDS	758	Captopril vs. atenolol	Clinical diabetic event, diabetic death, total mortality	1.1 (0.86–1.41) 1.27 (0.82–1.97) 1.14 (0.81–1.61)	0.43 0.28 0.44
1999	CAPPP	10,985	Captopril vs. diuretic / bb	MI, stroke, CV death	1.05 (0.90–1.22)	0.52
1999	STOP-2	6,614 4,418 4,409	New vs. conven ACE I vs. conven CCB vs. conven	CV death CV death CV death	0.99 (0.84–1.16) 1.01 (0.84–1.22) 0.97 (0.80–1.17)	0.89 0.89 0.72
2000	INSIGHT	6,321	Nifedipine LA vs. diuretic	CV death, MI, HF, stroke	1.1 (0.91–1.34)	0.35
2000	NORDIL	10,881	Diltiazem vs. bb / diuretic	Stroke, MI, CV death	1.00 (0.87–1.15)	0.97
2002	LIFE	9,193	Losartan vs. atenolol	CV death, stroke, MI	0.87 (0.77–0.98)	0.021
2002/03	ALLHAT	24,303 24,309 24,314	Amlodipine vs. chlorthalidone Lisinopril vs. chlorthalidone Doxazosin vs. chlorthalidone	Fatal CHD, non-fatal MI Fatal CHD, non-fatal MI Fatal CHD, non-fatal MI	0.98 (0.90–1.07) 0.99 (0.91–1.08) 1.02 (0.92–1.15)	0.65 0.81 0.62
2003	ANBP-2	26,083	ACE I v.s diuretic	CV event, death	0.89 (0.79–1.00)	0.05
2003	CONVINCE	16,602	Verapamil vs. atenolol / thiazide	Stroke, MI, CV death	1.02 (0.88–1.18)	0.77
2003	INVEST	22,576	Verapamil vs. atenolol	Death, non-fatal MI, nonfatal stroke	0.98 (0.90–1.06)	0.57
2004	VALUE	15,245	Valsartan vs. amlodipine	CV event	1.04 (0.94–1.15)	0.49
2004	JMIC-B	1,650	Nifedipine retard vs. ACE I	Cardiac events	1.05 (0.81–1.37)	0.86
2005	ASCOT	19,257	Amlodipine (+ perindopril) vs. Atenolol (+ thiazide)	Non-fatal MI, fatal CHD	0.90 (0.79–1.02)	0.1052

bb: beta-blocker; MI: myocardial infarction; CV: cardiovascular; conven: conventional drugs; ACEI: angiotensin converting enzyme inhibitor; CCB: calcium channel blocker; LA: long-acting; HF: heart failure; CHD: coronary heart disease; RR: relative risk; CI: confident interval

UKPDS : United Kingdom Prospective Diabetes Study Group [1]
CAPPP : Captopril Prevention Project [2]
STOP-2 : Swedish Trial in Old Patients with Hypertension 2 [3]
INSIGHT : Intervention as a Goal in Hypertension Treatment [4]
NORDIL : Nordic Diltiazem Study [5]
LIFE : Losartan Intervention For Endpoint Reduction in Hypertension Study [6]
ALLHAT : Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [7, 8]
ANBP-2 : Second Australian National Blood Pressure Study Group [9]
CONVINCE : Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints [10]
INVEST : International Verapamil-Trandolapril Study [11]
VALUE : Valsartan Antihypertensive Long-Term Use Evaluation [12]
JMIC-B : Japan Multicenter Investigation for Cardiovascular Diseases-B randomized trial [13]
ASCOT : Anglo-Scandinavian Cardiac Outcomes Trial [14]

meta-analyses, and long-acting CCBs do not to increase cardiovascular outcomes.[17] Nordic Diltiazem Study (NORDIL) randomised 10,881 patients to diltiazem, or beta-blockers/diuretics.[5] After 4.5 years, there was no difference in the primary endpoint (strokes, MI and cardiovascular death), total mortality, cardiovascular death, MI or heart failure. Incidence of stroke was lower on diltiazem, raising the possibility of CCBs being especially useful for cerebrovascular protection. Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) randomised 16,602 patients to verapamil or to atenolol/hydrochlorothiazide.[10] After three years, the primary outcome (stroke, MI or cardiovascular death), as well as its individual components, were equivalent in the two groups. International Verapamil-Trandolapril Study (INVEST) randomised 22,576 hypertensives with coronary artery disease to a verapamil-based treatment strategy or one based on atenolol.[11] After 2.7 years, despite a lower incidence of diabetes mellitus on verapamil, there was no significant difference in the primary endpoint (total mortality, non-fatal MI and non-fatal stroke) between the two groups. Over 50% of patients from each group required three or more antihypertensive drugs for adequate BP control. Japan Multicenter Investigation for Cardiovascular Diseases-B randomised trail (JMIC-B) recruited 1,650 Japanese hypertensives with coronary disease and randomised them to either nifedipine-retard or ACEI.[13] After three years, the primary endpoint (cardiac death, MI, angina or heart failure hospitalisation and coronary intervention) was similar in both groups. Coronary angiographical assessment of atherosclerosis was retarded on nifedipine, compared to those on ACEI.[18]

Other studies have also suggested that CCBs may have an anti-atherosclerotic effect. CAMELOT randomised coronary patients to placebo, amlodipine or enalapril.[19] Compared with the placebo, the primary endpoint (cardiovascular events) was significantly lower with amlodipine but not with enalapril. In patients with higher BP, intravascular ultrasonography showed less

progression of coronary atherosclerosis on amlodipine compared to placebo, with no difference between enalapril and placebo. The CAMELOT and INVEST results suggest that coronary atherosclerosis is halted and adverse outcomes are at a nadir at systolic BP of about 120 mmH.[20] Over a 36-month period, PREVENT demonstrated a reduction of carotid intima-media thickness of patients on amlodipine compared to placebo, again suggesting an anti-atherosclerotic effect of CCBs.[21]

Anglo-Scandinavian Cardiac Outcomes Trail-Blood Pressure Lowering Arm (ASCOT-BPLA) randomised 19,257 high risk hypertensives to amlodipine (adding perindopril) or atenolol (adding bendroflthiazide).[14] After 5.5 years, the primary endpoint (non-fatal MI and cardiovascular death) was similar in the two groups. However, total coronary endpoint, stroke and mortality were all lower on amlodipine. The fact that BP was lower on amlodipine than on atenolol reinforces the importance of BP control in reducing cardiovascular endpoints. Patients on amlodipine also had a significantly higher HDL-cholesterol, and lower BMI, triglyceride, creatinine and glucose levels; multivariate adjustment for all these differences resulted in the disappearance of cardiovascular event rate differences between the two groups.[22] This confirms the importance of control of all adverse risk factors in seeking to reduce cardiovascular events.[23] The number of patients needed to be treated (NNT) for a year to prevent one cardiovascular event is 220, and to prevent one death, it is 650.[24] This contrasts poorly with the NNT of diuretic antihypertensive therapy to prevent heart failure of 48, beta-blocker after myocardial infarction of 25–80 and statins in secondary prevention trials of 19–56.[25-27] The overall lesson from ASCOT-BPLA is that BP reduction and risk factor control are paramount, with less important differences between different antihypertensive regimes. ASCOT does not prove that newer antihypertensive drugs are superior to older ones.[28,29]

ALLHAT: THE RETURN OF THE DIURETIC

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trail (ALLHAT) is the largest hypertensive trial ever conducted with 15,255 patients randomised to chlorthalidone, 9,061 to doxazosin, 9,048 to amlodipine, and 9,054 to lisinopril.[7,8] Compared with the α-blocker, systolic BP was about 2 mmHg lower and more patients achieved target BP control on chlorthalidone (63% vs. 58%).[30] Although the primary outcome (fatal coronary heart disease and non-fatal MI) was equal in both groups, the doxazosin arm had more stroke, heart failure and combined cardiovascular events. Systolic BP was higher on amlodipine (0.8 mmHg, $p = 0.03$) and lisinopril (2 mmHg, $p < 0.001$) than on chlorthalidone. The primary endpoint was similar on diuretic, CCB, or ACEI. Compared to the diuretic, the CCB arm had a higher incidence of heart failure, while the ACEI arm had a higher incidence of heart failure, stroke and combined cardiovascular disease; the results were similar whatever the initial glycaemic state, renal function status and racial make-up of the patients studied.[31-34] Over 60% of patients in ALLHAT required two or more drugs for good BP control.[35]

In ALLHAT, although diabetes mellitus occurred more frequently and fasting glucose rose on diuretics, these metabolic abnormalities did not result in more cardiovascular events. Even among diabetic patients, heart failure was more common on doxazosin, amlodipine and lisinopril, compared to those on chlorthalidone.[31,32] Since it is the ultimate aim of hypertensive therapy to reduce clinical disease, and not just to improve laboratory profiles, ALLHAT should put to rest apprehension about diuretic use and has led to suggestions that diuretics be the first line antihypertensive agents, in both diabetic and non-diabetic patients.[36-38]

ARE RENIN-ANGIOTENSIN ANTAGONISTS ESPECIALLY PROTECTIVE?

Second Australian National Blood Pressure Study Group (ANBP-2) compared patients on an ACEI (n = 3,044) to those on a diuretic (n = 3,039).[9] Treatment with ACEI resulted in a lower incidence of the primary endpoint (cardiovascular events or total death) of borderline significance (ACEI 22.8%, diuretic 24.2%, relative risk [RR] 0.89, 95% confidence interval [CI] 0.79–1.00, $p = 0.05$); this difference disappeared in females. There was no difference in total mortality, first cardiovascular event or death. Thus, ANBP-2 actually confirms the results from ALLHAT, showing that ACEI and diuretics are equivalent in reducing cardiovascular events in hypertension.[39]

In Losartan Intervention For Endpoint reduction in hypertension study (LIFE), 9,193 hypertensives with left ventricular hypertrophy were randomised to either losartan or atenolol.[6] Losartan treatment saw a marked reduction in stroke that produced a significant reduction in the composite primary endpoint (death, MI or stroke). The results of LIFE should be taken together with data from other trials. No other study showed up a special benefit from the renin-angiotensin antagonists in preventing stroke. In fact, ACEI was weaker than the comparator drug in preventing stroke in both CAPPP and ALLHAT.[2,7] Reviews suggest that among antihypertensive drugs, it is the diuretic and CCB that may be more useful in stroke reduction.[40,41] The treated systolic BP was lower with losartan (1.1 mmHg, $p = 0.017$), and the clinical benefit could arise from the better BP reduction. Recent meta-

analyses showed that beta-blockers are less useful in the older patient, and among beta-blockers, atenolol has the weakest evidence supporting its value in cardiovascular event reduction.[42,43] Thus, rather than showing a special role for angiotensin receptor blockers (ARB), LIFE actually confirms the importance of BP reduction, and reveals the weaker cardiovascular protective effect of atenolol in older hypertensive patients.

Valsartan Antihypertensive Long-term Use Evaluation (VALUE) randomised 15,245 patients to valsartan and amlodipine to study the incidence of cardiac events for the same BP reduction.[12,44] However, the attained BP was lower on the CCB. After 4.2 years, there was no significant difference in the primary endpoint of the first cardiac event. Diabetes mellitus was lower, but MI was higher on valsartan. After correction for the BP difference, the composite of cardiac events, stroke, death or MI was similar in the two groups.[45] Patients reaching adequate BP control by six months fared better regardless of drug type used, thereby reinforcing the point that the benefit from good BP control is more important than differences between antihypertensive drugs. The better metabolic profile in the ARB arm did not translate into a reduction in clinical disease. The very large studies, VALUE and ALLHAT, suggest that drugs targeting the rennin-angiotensin system do not provide special cardiovascular protection.[7,12]

Surveys have shown that discontinuation of anti-hypertensive drug treatment is high, and is an important reason accounting for poor control of hypertension.[46,47] Having few adverse effects and a favourable influence on quality of life, the ARBs have higher compliance and lower discontinuation rates.[48-51] Furthermore, diuretics and beta-blockers adversely influence metabolic parameters as shown up in the ALLHAT and ASCOT-BPLA trials.[7,14] Thus, patients on diuretics and beta-blockers have to be closely monitored to ensure that in seeking BP control, other cardiovascular risk factors are not adversely altered.[52] In seeking to promote better compliance, the favourable side-effect profile of the ARB must be weighed against their higher costs. Studies have also consistently shown that the more money a patient has to spend on medication, the higher the discontinuation rate.[53,54] As hypertension is asymptomatic and requires long-term therapy, it may be important to discuss these cost and side-effects issues with the patient in the hope of achieving better cooperation and ultimate compliance.

CONCLUSION: LESSONS FROM THE LITERATURE

The important question of whether any hypertensive drug confers special cardiovascular protective effects in addition to the benefit from BP reduction has not yet been clearly answered. There is thus a need to objectively review the numerous comparative antihypertensive drug trials addressing this question.[1-14] The conclusion from these trials, with differing methodology and endpoints, can be confusing to the non-specialist. This situation is worsened when pharmaceutical companies seek to interpret the results to best suit the marketing needs of their products.[55-57] By describing and presenting the results of these trials in an unbiased manner, this paper hopes to assist the clinician in reconciling them, to seek points of agreement with the aim of drawing important and practical lessons for hypertension management.

Since the primary endpoint is by definition the main purpose of any study, it is useful to look at the primary endpoints addressed by the 13 trials reviewed above. As shown in Table I, there was no significant difference in the cardiovascular primary endpoint in 11 of these 13 trials, involving 91% of the randomised 168,593 patients.[1-5,7,8,10-14] Thus, the major lesson from these trials must be that there cannot be major differences between the different antihypertensive drug groups. Given the very large number of patients studied in these well-conducted trials, if there were any specially useful, or detrimental, cardiovascular effect of a particular class of antihypertensive drug, it would have been obvious by now. This conclusion of equivalent value among different antihypertensive drug groups is in agreement with the earlier meta-analysis by Staessen et al, who reviewed 15 trials involving 120,574 hypertensive patients, and found that, after correcting for different achieved BP levels, all antihypertensive drugs have an equivalent reduction of myocardial infarction, cardiovascular mortality and total mortality.[58] Similarly, the Blood Pressure Lowering Treatment Trialists' Collaboration, after analysing different drug regimes in eight trials recruiting 37,872 patients, found only borderline differences in clinical outcomes, in contrast to the clear benefit when treatment was compared to placebos.[59]

In the two trials reviewed above where there was a significant difference in the primary endpoint between treatment groups, the difference in ANBP-2 just reached a p-value of 0.05, while the result in LIFE was driven by a lower stroke incidence on ARB treatment that is not noted in any of the other studies involving ARB or ACEI.[6,9] In LIFE (losartan vs. atenolol), ALLHAT (doxazosin, amlodipine, lisinopril vs. chlorthalidone), VALUE (amlodipine vs. valsartan) and ASCOT (amlodipine vs. atenolol), where a secondary cardiovascular endpoint was lower in one of the treatment arms, it was always the arm with the lower achieved BP that saw the better clinical outcome.[6-8,12,14] Thus, instead of trying to work out why

antihypertensive drugs could exert apparently different cardiovascular protective efficacy in different trials, the simple and consistent message is that the lower the achieved BP, the lower the adverse clinical cardiovascular outcome. This lesson to treat to lower target BP is also reinforced by the results from the ACEI-placebo studies, where the arm on treatment had lower BP and significantly lower cardiovascular events.[60-62]

The next question to answer is, what target BP to aim for in seeking to best reduce cardiovascular outcomes? The mean BP at the end of study in the arm with the lower clinical cardiovascular outcome was 146/79 mmHg in LIFE, 134/75 mmHg in ALLHAT, 137/78 mmHg in VALUE, and 136/77 mmHg in ASCOT.[6-8,12,14] Epidemiological reviews suggest that lowest risk of cardiovascular disease in communities with or without diabetes mellitus occur at systolic BP of less than 120 mmHg.[20,63-65] The hypertension guidelines all define normal BP to be under 135/80 mmHg, with optimal BP of under 120/80 mmHg.[66-69] Thus, it is reasonable to try to achieve normal BP in most patients, and to reach optimal BP in those at high risk of cardiovascular disease or with evidence of target organ damage from hypertension.

It is however important that some caution be sounded as physicians are urged to seek tight BP control. In a meta-analysis of three trials that compared intensive with less intensive BP control, intensive control significantly reduced stroke and coronary heart disease, but not heart failure, cardiovascular or total mortality.[59] The African American Study of Kidney disease (AASK) trial, recruiting African-Americans with baseline hypertensive nephrosclerosis, saw no slowing in progression of renal disease among patients treated to a lower mean BP of 128/78 mmHg, compared to those treated to a mean of 141/85 mmHg.[70] In the Prevention of Events with Angiotensin-Converting Enzyme (PEACE) trial, which studied 8,290 patients with stable coronary artery disease, from an initial mean BP of 133/78 mmHg, further reducing the BP by 4.4/3.6 mmHg with an ACEI, produced no significant cardiovascular benefit.[71] A review of data from the INVEST trial suggest that a J curve does exist for BP levels, with a nadir at 119/84 mmHg and adverse outcomes increasing significantly in patients treated to a diastolic below 70 mmHg.[72] Thus, physicians must always consider the overall status of the presenting hypertensive patient, and in pursuing guideline targets, avoid over-aggressive intervention which may be especially undesirable in the elderly, whose coronary, cerebral or renal circulation have impaired autoregulation.

Keeping in mind that the main lesson is to seek good BP control, in selecting antihypertensive drugs, physicians should also be guided by prior data showing a particular drug to be useful for coexisting clinical conditions. Therapy for hypertensive patients with angina pectoris should include a beta-blocker or CCB, given their definite antianginal and possible antiatherosclerotic effects.[18,19,21,73] Patients with a prior myocardial infarction should be on a beta-blocker.[74] Hypertensives with a poor left ventricular function should be on diuretics as well as an ACEI and beta-blocker.[7,75,76] If the patient had a prior stroke, or is at special risk of stroke, the balance of evidence calls for therapy with a CCB or diuretic.[40,41] For renal protection, especially in the setting of diabetic proteinuria, ARB or ACEI are best suited to prevent and delay nephropathy.[70,77-79] This approach in choosing the antihypertensive drug according to the clinical disease and target organ most at risk of damage is logical and in keeping with the guidelines.[66-69]

In the hypertensive patient who is free of clinical disease, a case can be made for diuretics to be the first line drugs, although CCB, ARB and ACEI can also claim evidence to support its use. In the older patient, beta-blockers, especially atenolol, should not be drug of first choice.[42,43,80] The comparative hypertension drug trials show that multiple drugs are required for adequate BP control in most patients. Thus, physicians should not be too preoccupied about how to initiate treatment, but to remember to add drugs till adequate control is achieved. Given the present poor control rates in hypertension, the challenge of hypertension management to the physician, and patient, is to successfully use a combination of drugs to normalise and optimise BP levels.[81,82]

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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME MULTIPLE CHOICE QUESTIONS (CODE SMJ 200808A)

	True	False
Question 1. Regarding hypertension drug trials:		
(a) There was no significant difference in the cardiovascular primary end-point in most trials comparing different classes of anti-hypertensive drugs.	☐	☐
(b) In trials which demonstrated a significant difference in secondary clinical outcomes, it was the arm with the lower final blood pressure that had the lower outcomes.	☐	☐
(c) Most hypertensive patients will need two or more drugs for good blood pressure control.	☐	☐
(d) Choice of anti-hypertensive drugs should be guided by the need to treat or prevent target organ damage and associated clinical condition.	☐	☐
Question 2. In the ALLHAT study, patients in the diuretic arm:		
(a) had no significant difference in the primary end-point outcome compared to those on ACEI or CCB.	☐	☐
(b) had the lowest blood pressure compared to those on ACEI or CCB at the trial conclusion.	☐	☐
(c) had a lower incidence of heart failure compared to those on ACEI and CCB.	☐	☐
(d) had an increase in glucose levels compared to those on ACEI or CCB.	☐	☐
Question 3. Patients on calcium channel blockers:		
(a) have been shown to have slower progression of coronary atherosclerosis compared to those on ACEI.	☐	☐
(b) had a lower incidence of myocardial infarction compared to those on ARB in the VALUE study.	☐	☐
(c) ended the trial with a better metabolic cardiovascular risk factor profile compared to those on atenolol in the ASCOT-BPLA trial.	☐	☐
(d) have been shown to have equivalent cardiovascular outcomes compared to beta-blocker/diuretic whether the CCB used was verapamil, diltiazem or long-acting nifedipine / amlodipine.	☐	☐
Question 4. Regarding ACEI / ARB:		
(a) Incidence of diabetes is lower in patients treated with ACEI / ARB compared to those on other anti-hypertensive drugs.	☐	☐
(b) ARB / ACEI are especially useful in patients with diabetic proteinuria.	☐	☐
(c) ACEI / ARB treated patients had equivalent primary cardiovascular end-point when compared to other hypertensive drugs in the UKPDS, CAPPP, STOP- Hypertensive 2, ALLHAT, JMIC-B and VALUE trials.	☐	☐
(d) Patients on ACE / ARB ended up with poorer blood pressure control compared to other antihypertensive drugs in the ALLHAT and VALUE trials.	☐	☐
Question 5. Regarding beta-blockers:		
(a) Patients on beta-blockers had equivalent primary cardiovascular end-point outcome compared to those on CCB the ASCOT-BPLA trial.	☐	☐
(b) Atenolol may be less useful in reducing cardiovascular events compared to other beta-blockers.	☐	☐
(c) Beta-blockers may be less useful amongst older hypertensive patients.	☐	☐
(d) Beta-blockers are especially useful in patients with angina, prior myocardial infarction or heart failure.	☐	☐

Doctor's particulars:

Name in full: _____

MCR number: _____ Specialty: _____

Email address: _____

SUBMISSION INSTRUCTIONS:
(1) Log on at the SMJ website: http://www.sma.org.sg/cme/smj and select the appropriate set of questions. (2) Select your answers and provide your name, email address and MCR number. Click on "Submit answers" to submit.

RESULTS:
(1) Answers will be published in the SMJ October 2008 issue. (2) The MCR numbers of successful candidates will be posted online at www.sma.org.sg/cme/smj by 15 October 2008. (3) All online submissions will receive an automatic email acknowledgment. (4) Passing mark is 60%. No mark will be deducted for incorrect answers. (5) The SMJ editorial office will submit the list of successful candidates to the Singapore Medical Council.

Deadline for submission: (August 2008 SMJ 3B CME programme): 12 noon, 25 September 2008.