Beta-blockers in Cardiovascular Disease: Do not throw out the baby with the bathwater

H T Ong FAMM, FRCP, FACC, FESC

HT Ong Heart Clinic, 251C Burma Road, Penang 10350, Malaysia

Three decades ago, prior to the use of anti-platelets and reperfusion therapy for patients with myocardial infarction (MI), intravenous beta-blocker was shown to produce a small although clinically significant benefit in reducing the combined end-point of death, cardiac arrest or reinfarction [1]. Subsequently, a review of 29,260 patients in 51 short term trials showed that early beta-blocker use in MI did not significantly reduce mortality (OR 0.96, 95%CI 0.85-1.08) [2]. However, amongst 24,974 patients in 31 long term trials, beta-blocker use was associated with a highly significant reduction in all cause mortality (OR 0.77, 95%CI 0.69-0.85). Amongst the older beta-blockers studied in those trials, propranolol, timolol and metoprolol appeared to be most beneficial. Despite the clear evidence of benefit, beta-blockers remain underutilised through the 1990's even in the United States with only between 21-58 % of eligible MI patients receiving therapy at hospital discharge, and only about 10% receiving adequate doses [3,4].

This issue of the Journal carries a report from an academic tertiary institution in Malaysia, reporting beta-blocker underutilisation at discharge post-MI [5]. Although about 78% of eligible patients received treatment, optimal doses were noted in less than 40%. At a glance, it would appear that beta-blocker coverage post-MI in twenty-first century Malaysia is better than in twentieth century America. Yet an optimal dosing rate of below 40% cannot be acceptable and as the authors rightly point out, more physician education is needed to improve this. Beta-blockers are not contraindicated in heart failure but in fact results in reduction of morbidity and mortality, although initiating doses must be low [6]. Patients with asthma or chronic obstructive airway disease can tolerate beta-blockers, although dose used should be low, increase gradual and beta-1 selective agents should be chosen [7,8]. The concern about poor quality of life, depression and sexual dysfunction with beta-blockers may be exaggerated since a robust review of over 35,000 patients from 15 trials showed no increase in depression, with only minimal increases in fatigue (1 per 57 patient-year) and sexual dysfunction (1 per 199 patient- year) [9]. Although beta-blockers do adversely affect the lipid profile and glycemic control, it is important to remember that the real benefit it produces in reducing mortality post-MI is far more important to the patient than any adverse laboratory report.

Recently however, the value of beta-blockers in hypertension and coronary disease has been called into question. In a meta-analysis of over 24,000 hypertensive patients aged 52-70 years, Carlberg found atenolol to be no different from placebo for total mortality (RR 1.01, 95%CI 0.89-1.15), cardiovascular mortality (RR 0.99, 0.83-1.18), MI (RR 0.99, 0.83-1.19) and stroke (RR 0.85, 0.72-1.01)[10]. It was also inferior to other anti-hypertensive drugs with higher total mortality (RR 1.13, 1.02-1.25), cardiovascular mortality (RR 1.16, 1.00-1.34) and stroke (RR1.30, 1.12-1.50) in patients on atenolol. Another meta-analysis of 13 trials recruiting over 105,000 hypertensive patients found betablockers to be inferior to other drugs in reducing stroke (RR 1.16, 1.04-1.30)[11]. A recent Cochrane review of over 95,000 hypertensive patients in 13 trials showed that beta-blockers do not reduce mortality and are inferior to other antihypertensive drugs suggesting that they should not be initiating drugs in hypertension [12]. An observational study of patients in the REACH registry looked at the association between beta-blocker use and subsequent cardiovascular events over a median of 44 months in patients with prior MI, in those with stable coronary disease without MI and in those with only risk factors for coronary disease [13]. Beta-blocker use was not associated with lower cardiovascular outcome in any of the 3 groups studied.

Still this is not yet the time to discard beta-blockers in cardiovascular disease. Khan and McAlister reviewed 145,811 patients enrolled in 21 hypertension trials and suggested that the effect of beta-blockers in the older hypertensive patient may be different from younger ones [14]. In patients 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 those 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). There is also good evidence that beta-blockers have an anti-atherosclerotic effect. BCAPS randomised 793 patients with ultrasonic carotid plaques to long-acting metoprolol 25 mg daily, fluvastatin 40 mg daily or placebo [15]. Over 36 months, metoprolol patients had a lower rate of progression of IMT thickness compared to placebo, and also had significantly reduced combined cardiovascular end-point (8 vs 19, p=0.031). In an analysis of 1515 patients with coronary disease recruited into 4 trials, atheroma volume as assessed by intravascular ultrasound (IVUS) was significantly reduced at follow-up in patients who received beta-blockers (-2.4 mm/yr, p<0.001), but did not change in patients not receiving beta-blockers (-0.4 mm/yr, p=0.86) [16]. Compatible with the anti-ischemic and anti-atherosclerotic effects, patients with ischemic heart disease undergoing high-risk vascular surgery who were put on beta-blockers had a lower

Corresponding Author: HT Ong Heart Clinic, 251C Burma Road, Penang 10350, Malaysia
Email: ongheanteik@gmail.com

Table I: Outline of therapeutic role of beta-blockers in cardiovascular disease and hypertension

Disease condition	Therapeutic Pointers on beta-blocker use
Stable Ischemic Heart Disease (IHD)	1. First line drug 2. Anti-anginal and atherosclerosis reducing effect 3. Pre-operative prophylaxis in those at high cardiac risk
Myocardial Infarction (MI)	1. Reduces mortality post-MI with long-term use 2. Should be initiated before discharge 3. Not first line drug in early MI, when reperfusion and anti-platelets of primary importance
Heart Failure	1. First line drug in all forms of systolic heart failure 2. Not all beta-blockers have been shown to be useful 3. Mortality reduction proven with bisoprolol, carvedilol and metoprolol. 4. Morbidity reduction proven for bisoprolol, carvedilol, metoprolol and nebivolol.
Primary Hypertension	1. First line anti-hypertensive drug in patients with associated stable IHD, post-MI or heart failure 2. First line anti-hypertensive drug in patients with high sympathetic drive 3. Equivalent to other anti-hypertensive drug in patients below 60 yr 4. Inferior to other drugs in patients above 60 yr or isolated systolic hypertension

peri-operative and 2 year follow-up cardiovascular event rate [17,18]. In patients with systolic heart failure, 3 beta-blockers - bisoprolol, carvedilol and metoprolol - have been clearly shown to reduce mortality and morbidity, while nebivolol reduces morbidity [19].

In considering the role of beta-blockers in cardiovascular therapeutics, it is important to adopt a balanced approach and not to throw out the baby with the bathwater [20]. As outlined in table I, beta-blockers are first line drugs for treatment of symptomatic stable ischemic heart disease and for reducing mortality post-MI [21]. In patients undergoing vascular surgery who are at high cardiac risk owing to coronary artery disease, ischemia on preoperative testing or multiple risk factors, titrated beta-blocker treatment is recommended [22]. They are also first line treatment for all patients with systolic heart failure [23]. In patients with primary hypertension and associated heart failure, stable coronary disease or after MI, beta-blockers are an essential part of their drug regimen. Beta-blockers are inferior to other anti-hypertensive drugs in older hypertensive patients (above 60 years) and in isolated systolic hypertension, although even the clinical guidelines are not unanimous on this issue [24, 25]. In younger patients, and in those in whom hypertension is associated with a hyperactive sympathetic drive (clinically shown by a tachycardia), beta-blockers remain an important part of the therapeutic regimen.

Clinicians must decide on appropriateness of beta-blocker use depending on what the trial evidence actually says, and not be like models changing their fashion to suit the latest trend. New data must be analysed while remembering and reassessing previous publications. Data on hypertension and a longitudinal observational study of patients with various atherosclerotic disease should not lead to the dismissal of numerous randomised placebo-controlled MI trials [2,12,13]. Reduction of mortality after MI with long term beta-blocker use should remain undoubted. It is thus indeed timely for Ong and colleagues to remind us that beta-blockers are underutilised in post-MI patients even in a tertiary academic centre in the 21st century [5]. After all, good medical practice is not just about keeping up-dated, it is also about correctly applying all previous knowledge.

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