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Beta-Blocker Controversies

BETA-BLOCKERS ARE NOT A GOOD INITIAL CHOICE FOR HYPERTENSION: TRUE OR FALSE?

A meta-analysis (Lindholm et al. 2005) concluded that beta-blockers should not remain the first choice in the treatment of primary hypertension. This analysis included randomized controlled trials (RCTs) with poor methodology.

- In most of the RCTs analyzed by these investigators, atenolol was the beta-blocker used for comparison. Worldwide, atenolol is one of the most prescribed beta-blockers.
- Their analysis indeed suggests that atenolol does not give hypertensive patients adequate protection against cardiovascular disease (CVD). These investigators failed to recognize that beta-blockers possess important and subtle clinical properties. Their analysis does not indicate that other beta-blockers provide the same poor CVD protection as atenolol.

In the second edition of Cardiac Drug Therapy (1988), this author emphasized that beta-blockers are not all alike:

- Those with ISA activity (oxprenolol, pindolol) are not cardioprotective; *see* discussion of ISA activity in Chap. 1.
- Propranolol proved cardioprotective in BHAT (1982), and in the Medical Research Council (MRC 1985) trial of treatment of mild hypertension, but only in nonsmokers (*see* the last section of Chap. 1, Which Beta-Blocker Is Best for Your Patients?)

- Bucindolol, a vasodilatory beta-blocker, surprisingly proved to be of no value for the treatment of heart failure (HF) (Beta-Blocker Evaluation of Survival Trial Investigators 2001) whereas carvedilol (in COPERNICUS (Packer et al. 2002) and CAPRICORN (The CAPRICORN Investigators 2001) significantly *decreased coronary heart disease (CHD) outcomes*.
- Bisoprolol (in CIBIS [CIBIS-II Investigators and Committees 1999]) and metoprolol succinate (in MERIT/HF [MERIT-HF Study Group 1999]) significantly reduced fatal and nonfatal myocardial infarction (MI) and recurrence of HF.
- In CAPRICORN, carvedilol achieved a 50 % reduction in nonfatal MI patients aged mainly >55 years. There was a 30 % reduction in total mortality and nonfatal MI. Carvedilol decreased CHD events in elderly normotensive and hypertensive patients.
- The causation of a fatal or nonfatal MI in patients with CHD is the same in a hypertensive and nonhypertensive individual. Thus calcium antagonist or diuretic therapy used for management of hypertension cannot give more cardioprotection (decrease in fatal and nonfatal MI) than treatment with beta-blockers that are proven in RCTs to prevent outcomes.
- Newer beta-blockers have other possible benefits. Carvedilol and nebivolol are beta-blockers with direct vasodilating and antioxidant properties. Nebivolol stimulates the endothelial L-arginine/nitric oxide pathway and produces vasodilation; the drug increases nitric oxide (NO) by decreasing its oxidative inactivation (Cominacini et al. 2003).
- These two beta-blockers should be subjected to long-term outcome trials in the treatment of primary hypertension.

Atenolol is a hydrophilic beta-blocker that attains low brain concentration. Most important, increased brain concentration and elevation of central vagal tone confers cardiovascular protection (Pitt 1992). **Lipid-soluble** beta-blockers (bisoprolol, carvedilol, metoprolol, propranolol, and timolol) have all been proven in large RCTs to significantly decrease

cardiac deaths; they all attain high brain concentration block sympathetic discharge in the hypothalamus better than water-soluble agents (atenolol and sotalol) (Pitt 1992) Timolol in the Norwegian trial (1981) caused an astounding 67 % reduction in sudden cardiac deaths.

- Äblad et al. (1991), in a rabbit model, showed that although metoprolol (lipophilic) and atenolol (hydrophilic) caused equal beta-blockade, only metoprolol caused a reduction in sudden cardiac death. Metoprolol, but not atenolol, caused a significant increase, which indicates an increase in sympathetic tone.
- Importantly, only the lipophilic beta-blockers (carvedilol, bisoprolol, propranolol, and timolol) have been shown in large RCTs to prevent fatal and nonfatal MI and sudden cardiac death. In the timolol infarction RT, the drug caused a 67 % reduction in sudden deaths. These agents have been shown to quell early morning catecholamine surge and control early morning and exercise-induced excessive rise in blood pressure better compared with atenolol (Neutel et al. 1993; Kokkinos et al. 2006).

It is surprising that the experts who constructed the recent hypertensive guidelines (JNC8 et al. 2014) fail to understand the subtle but important differences that exist between the available beta-blocking agents. These experts do not recommend a beta-blocking drug for the management of hypertension based on an unsound study in which the poorly effective atenolol was administered.

- “The panel did not recommend beta-blockers for the initial treatment of hypertension because in one study use of beta-blockers “atenolol” resulted in a higher rate of the primary composite outcome of cardiovascular death, MI, or stroke compared to use of an ARB”, (JNC8 2014). These experts state “a finding that was driven largely by an increase in stroke (Dahlöf et al. 2002).

The study by Dahlöf et al. did not reveal a significant change in cardiovascular deaths or occurrence of fatal and

nonfatal MI as claimed by this expert panel. 204 losartan and 234 atenolol patients died from cardiovascular disease (0.89, 0.73—1.07, $p=0.206$); 232 and 309, respectively, had fatal or nonfatal stroke (0.75, 0.63—0.89, $p=0.001$); and myocardial infarction (nonfatal and fatal) occurred in 198 and 188, respectively (1.07, 0.88—1.31, $p=0.491$). (Dahlöf et al. 2002) the poorly effective atenolol (see chapter 1) was not a failure.

- To deny the use of a more effective beta-blocking drug [bisoprolol, carvedilol, nebivolol, Toprol XI] as first line or second line in some patients is illogical thinking.
- **Importantly, the duration of action of atenolol varies from 18 to 24 h and fails in some individuals to provide 24 h of CVD protection. The drug leaves an early morning gap, a period crucial for the prevention of fatal MI and sudden cardiac death, information that escapes panel members.**
- The observation that atenolol is less effective than other antihypertensives including vasodilatory beta-blockers at lowering aortic pressure despite an equivalent effect on brachial pressure may partly explain the poor cardioprotection. In the Conduit Artery Function Evaluation (CAFÉ 2006) study, brachial and aortic pressures were measured in a subset of 2,199 patients from ASCOT (PBLA 2005). Despite virtually identical reductions in brachial pressure, the aortic systolic pressure was 4.3 mmHg lower in the amlodipine/perindopril arm versus those on atenolol/bendroflumethiazide.
- **It is clear that beta-blockers are not all alike with regard to their salutary effects, and older beta-blocking drugs including atenolol should become obsolete (Khan 2003).** Beta-blockers are CVD protective provided that bisoprolol, carvedilol, metoprolol, propranolol, or timolol are chosen and not atenolol (Khan 2005). Chockalingam et al. (2012), based on a multicenter study “recommend treatment of symptomatic long QT (LQT1) and LQT2 patients with either propranolol or nadolol, as clearly not all beta-blockers

are equal in their antiarrhythmic efficacy in LQTS. **Propranolol was superior to both nadolol and metoprolol in terms of shortening the cardiac repolarization time, particularly in high-risk patients with markedly prolonged QTc.** A New York–based LQTS Registry indicated that nadolol was the only beta-blocker associated with a significant risk reduction in patients with LQT2 (Abu-Zeitone 2014).

It is poor logic to accept the conclusions drawn from the Lindholm et al. (2005) meta-analysis and the JNC 8 recommendations. In the majority of clinical trials analyzed, atenolol was the beta-blocker administered.

- Nebivolol, bisoprolol carvedilol, or metoprolol succinate extended release [ToprolXL] are recommended for the initial management of mild primary hypertension *depending on the age and ethnicity* of the individual (*see treatment tables and algorithms in Chap. 9, Hypertension Controversies*).

BETA-BLOCKERS ARE NOT RECOMMENDED FOR TREATMENT OF ELDERLY HYPERTENSIVES: TRUE OR FALSE?

Messerli et al. (1998) concluded that this statement is truly based on their meta-analysis, which included the poorly run MRC trial in the elderly (1992).

- **The MRC Working Party (1992) confirmed that 25 % of patients were lost to follow-up and more than half the patients were not taking the therapy assigned by the end of the study.**
- **How can a learned expert use this unsound study result? But nonetheless it has convinced the world not to use beta-blockers in the elderly hypertensive. This statement is in major textbooks and editorials are taught to students and interns.**
- There was no difference in total mortality between atenolol and diuretic therapy, but, surprisingly, diuretics reduced

coronary heart disease (CHD) events, and atenolol did not. This is a spurious finding; to this date we do not use diuretics to effectively treat patients with CHD, but we do use beta-blockers. Atenolol, the beta-blocker used, is a poorly effective beta-blocker as outlined earlier in this chapter, and its use should be curtailed (Khan 2003).

- **The spurious and misleading finding nevertheless led Messerli et al. (1998) to publish an article in the Journal of the American Medical Association entitled “Are β -Blockers Efficacious as First-Line Therapy for Hypertension in the Elderly?”**
- These analysts concluded that beta-blockers should not be first-line therapy for elderly hypertensives. Unfortunately, this faulty expert opinion of Messerli and colleagues (1998) has gained access to notable textbooks and journals. It appears that virtually all internists and guideline providers (UK and USA) share this faulty opinion, which has been spread worldwide.

The beta-blocker hypertension controversy, including appropriate use in elderly hypertensive patients, is discussed fully in Chaps. 8 and 9, and algorithms are provided indicating which initial drug is best depending on the age and ethnicity of the hypertensive patient.

BETA-BLOCKERS CAUSE GENUINE DIABETES MELLITUS: TRUE OR FALSE?

A small presumed increased risk for the development of type 2 diabetes caused by beta-blocker therapy in hypertensive individuals has become a concern. Many national guidelines have been changed based on this notion. Thus, worldwide, many hypertensive patients and diabetics are denied treatment with a beta-blocking drug.

- Insulin secretion is probably partly β_2 mediated. Glucose-sulfonylurea-stimulated insulin secretion is partially inhibited by beta-blockers (Loubatiere et al. 1971).

- Clinically, however, no significant worsening of glycemic control is seen when beta-blockers are combined with these agents.
- Long-term beta-blocker therapy may increase blood glucose concentration by approximately 0.2–0.5 mmol/L (~3–9 mg/dL), as observed in RCTs with follow-up beyond 5 years, but this mild increase in fasting glucose levels does not prove a diagnosis of type 2 diabetes.
- The increase in blood glucose observed in some subjects may be due to *benign reversible glucose intolerance or genuine diabetes in prediabetics*.

In **ASCOT-BPLA** (2005), baseline glucose concentration for amlodipine and the atenolol-based regimen was 6.24 versus 6.4 mmol/L.

- At follow-up 5 years later, levels for the atenolol regimen were only 0.2 mol/L higher than in the amlodipine group.
- Without clearly confirming a diabetic state, the investigators proclaimed that beta-blockers caused a 30 % increase in diabetes.
- The diagnosis of diabetes mellitus was not confirmed by a 2 h glucose assessment.
- It is surprising that *The Lancet*, a peer-reviewed journal, would print such erroneous conclusions.
- Physicians who incorrectly label individuals as diabetics are in line for medicolegal action.

UKPDS (1998) studied 1,148 hypertensive patients with type 2 diabetes to determine whether tight control of blood pressure with either a beta-blocker or an ACE inhibitor has a specific advantage or disadvantage in preventing the macrovascular and microvascular complications of type 2 diabetes.

- At 9-year follow-up, blood pressure lowering with captopril or atenolol was similarly effective in reducing the incidence of major diabetic complications.
- Glycated hemoglobin concentration was similar in the two groups over the second 4 years of study (atenolol 8.4 % versus captopril 8.3 %; see Figs. 1–3 and Chaps. 9 and 22).

- Clearly, beta-blocker therapy did not cause worsening of diabetes control during the lengthy 9-year follow-up. Importantly, for most clinical trials, follow-up is usually 1–4, rarely 5 years.

Gress et al. (2000) conducted a prospective study of 12,550 adults 45–64 years old who did not have diabetes. A health evaluation conducted at baseline included assessment of medication use. The incidence of type 2 diabetes was assessed after 3 and 6 years by assessment of fasting serum glucose. Individuals with hypertension treated with beta-blockers had a 28 % higher risk of subsequent diabetes.

- The diagnosis of diabetes mellitus versus *benign reversible glucose intolerance* was not clarified. Thus this analysis is flawed.

Padwal and colleagues (2004) conducted a systematic review of antihypertensive therapy and the incidence of type 2 diabetes.

- Data from the highest quality studies indicated that diabetes incidence is unchanged or increased by beta-blocker and thiazide diuretics and unchanged or decreased by ACE inhibitors and calcium antagonists.
- **The authors concluded that current data are far from conclusive. These investigators warned that poor methodologic quality limits the conclusions that can be drawn from the several nonrandomized studies quoted by many.**
- Most important, in the studies analyzed by Padwal et al., the increase in diabetic incidence reported is presumptive because type 2 diabetes was not proved by appropriate diagnostic testing.

In most studies, including LIFE (Lindholm et al. 2002), post hoc analysis suggests that increased risk of new-onset diabetes is confined to individuals with an elevated blood glucose at baseline and family predisposition to diabetes.

This finding strongly suggests that in prediabetics, beta-blockers bring to light type 2 diabetes at an earlier point in time but do not cause diabetes in nondiabetic individuals.

STOP-2 (Hansson et al. 1999), a large RCT, showed no difference between ACE inhibitors and beta-blockers in preventing cardiovascular events and no difference in incidence of diabetes.

- **Clinicians and Trialists should ask whether the reported increased incidence of diabetes is real, or are there other explanations for the observed minimal increase in fasting glucose concentrations observed. Murphy et al. (1982) holds the key.** Murphy et al. (1982) completed a lengthy 14-year follow-up in hypertensive patients treated with diuretics that caused a major increase in the incidence of glucose intolerance.
- *This effect, however, was promptly reversed in most (60%) of the patients on discontinuation of the diuretic. Thus, these individuals developed benign reversible glucose intolerance.*
- **It is important for clinicians to note that these patients were not classified as diabetics by these learned investigators. Similar findings have been reported when beta-blocker therapy is discontinued.**
- The study of Murphy et al. shows without doubt that diuretics do not cause genuine diabetes mellitus and this information should be made known to Trialists and experts in the field who continue to issue misleading medical reports.
- Trialists and those who claim to be experts in the field must be warned not to label individuals as diabetic solely on a fasting glucose level range of 6.4–7.0 mmol/L (115–125 mg/dL) without further diagnostic confirmation in patients treated with a beta-blocker, a diuretic, or a combination of both.
- ACE inhibitors do not reduce diabetic risk as proclaimed by some (*see* Chap. 3).
- It is unclear whether long-term treatment with beta-blockers and diuretics increases glucose levels 0.2–0.9 mmol/L (3–10 mg/dL) in normal subjects or mainly in prediabetics.

- **In some subjects with prediabetes or a positive family history of type 2 diabetes, beta-blockers and diuretics might bring the diabetic state to light at an earlier point in time, and thus energetic treatment can commence. This presents a reassuring, rather than alarming, scenario.**
- It must be reemphasized that the finding of glucose intolerance does not necessarily mean a diabetic state exists. Beta-blockers do not cause type 2 diabetes, as proclaimed by several trialists and notable clinicians.
- In non-prediabetics, beta-blockers may cause mild glucose intolerance that is benign and reversible on discontinuation of these agents.

DO ALL BETA-BLOCKERS CAUSE BENIGN GLUCOSE INTOLERANCE?

The GEMINI trial (2004) compared the effects of two different beta-blockers on glycemic control as well as other cardiovascular risk factors in a cohort with glycemic control similar to the UKPDS.

- Carvedilol stabilized HbA_{1c}, improved insulin resistance, and slowed development of micro-albuminuria in the presence of renin-angiotensin system (RAS) blockade compared with metoprolol.
- Carvedilol treatment had no effect on HbA_{1c} (mean [SD] change from baseline to end point, 0.02 % [0.04 %]; 95 % CI, -0.06–0.10 %; $p=0.65$), whereas metoprolol increased HbA_{1c} (0.15 % [0.04 %]; 95 % CI, 0.08–0.22 %; $p<0.001$).
- HOMA-IR was reduced by carvedilol and increased with metoprolol, which resulted in a significant improvement from baseline for carvedilol (-9.1 %, $p=0.004$) but not metoprolol which lowers insulin resistance (GEMINI 2004), an effect that correlated with HbA_{1c}. This finding supports the effect of carvedilol on reducing insulin resistance, which has been previously shown by Giugliano et al. (1997) in more time-intensive insulin clamp studies.

- Treatment with carvedilol was associated with improvement in total cholesterol and a smaller increase in triglyceride levels relative to metoprolol (GEMINI 2004).

BETA-BLOCKERS SHOULD NOT BE GIVEN TO PATIENTS DURING THE EARLY HOURS OF ACUTE MI: TRUE OR FALSE?

The results of COMMIT/CCS-2: Clopidogrel and metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study (2005) may cause changes in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines. In this huge RC, patients received aspirin and were randomized to receive clopidogrel 75 mg/day or placebo; within these two groups, patients were then randomized to inappropriately large doses of metoprolol (*15 mg IV in three equal doses followed by 200 mg/day orally*) or placebo. Patients were randomized within 24 h of suspected acute MI and demonstrating ST elevation or other ischemic abnormality.

- Metoprolol produced a significant 18 % reduction in reinfarction (2.0 % versus 2.5 %; $p=0.001$) as well as a 17 % reduction in ventricular fibrillation (2.5 % versus 3.0 %; $p=0.001$); there was no effect on mortality. Metoprolol, however, significantly increased the relative risk of death from cardiogenic shock, by 29 %, with the greatest risk of shock occurring primarily on d 0–1.
- Cardiogenic shock was understandably more evident in patients in Killip class II and III; this adverse effect was largely iatrogenic because the dose of metoprolol was excessive and given to patients in whom these agents are contraindicated.
- Oral beta-blocker therapy is preferred, and IV use is cautioned against, particularly in patients with pulmonary edema or systolic blood pressure (BP) < 100 mmHg. In this study, a large dose of metoprolol was given IV to patients with systolic BP < 95 mmHg and in those with Killip class II and III.

- Study cochair Rory Collins emphasized that it may generally be prudent to wait until a heart attack patient's condition has stabilized before starting beta-blocker therapy. This RCT persuaded some nonthinking cardiologists to not use metoprolol in patients with acute MI.
- The advice should be restated: do not give beta-blockers to patients who are hemodynamically unstable or in whom heart failure is manifest. Most patients with acute MI can be given metoprolol at an appropriate dose within the early hours of onset of acute MI (Khan Khan 2007)
- The METOCARD-CNIC: Effect of metoprolol in cardio-protection during an acute myocardial infarction trial
- The study randomized 270 patients with Killip class II anterior STEMI presenting early after symptom onset (<6 h) to pre-reperfusion IV metoprolol or control group
- In patients with anterior Killip class <or equal to 11 ST elevation MI undergoing PCI, early IV metoprolol before reperfusion resulted in higher long-term left ventricular ejection fraction.
- This administration reduced the incidence of severe left ventricular dysfunction and implantable cardioverter defibrillator indications and fewer admissions for heart failure (Pizarro et al. 2014). See Chap. 22.

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