When premature is not premature—the ASCOT study

Franz H. Messerli* and Tina Sichrovsky

Department of Cardiology, St Luke’s-Roosevelt Hospital Center, Columbia University, 1000, Tenth Avenue, Suite 3B-30, New York 10019, NY, USA

Received 28 April 2005; revised 4 August 2005; accepted 4 August 2005; online publish-ahead-of-print 18 August 2005

"Controversy is the Lifeblood of Science"

Sir George Pickering

Almost 3 years ago, in the aftermath of the ALLHAT study, the New York Times was carrying the headlines ‘Older way to treat hypertension found best’. ALLHAT, the largest study ever done, showed no difference in primary outcome (coronary heart disease) among the three treatment arms but seemed to favour chlorthalidone over amlodipine or lisinopril with regard to some secondary endpoints. Clearly, these headlines will need to be amended in view of the recent premature termination of the ASCOT trial. The primary objective of ASCOT was to compare the effects on fatal and non-fatal coronary heart disease of a so-called ‘conventional’ treatment, i.e. a beta-blocker (atenolol), combined, if needed, with a thiazide diuretic, to a more contemporary regimen of a calcium antagonist (amlodipine) and, if needed, an ACE-inhibitor (perindopril). In a prospective randomized open-blinded endpoint design (PROBE), a total of 19 000 patients were randomized to the two antihypertensive strategies. The study was launched in 1997 and stopped about 1 year before schedule because the contemporary treatment arm showed significant cardiovascular benefits when compared with the beta-blocker/diuretic regimen.

Specifically, when compared with atenolol/thiazide, amlodipine/perindopril resulted in a 15% reduction of all-cause mortality, coronary events, and all cardiovascular events and procedures. Fatal and non-fatal stroke were reduced by 25%, as was cardiovascular mortality. Importantly, the risk of new onset diabetes was more than 30% lower with the contemporary regimen than with the traditional one. It seems unlikely that the small difference in blood pressure (2.9/1.8 mmHg) between the two treatment arms would fully explain the observed benefits with amlodipine/perindopril (numbers based on preliminary presentation, for exact values see ASCOT-trial, ahead of print publication in Lancet).

For cognitive physicians these findings are not entirely unexpected, but in view of the current guidelines for antihypertensive therapy, nothing short of revolutionary. Time and again, in various guidelines such as the reports of JNC 5, JNC 6, and JNC 7, physicians were told, despite lack of evidence and even evidence to the contrary, that conventional therapy (beta-blockers and diuretics) was just as efficacious (and considerably more cost effective) than contemporary therapy, such as calcium antagonists and blockers of the renin–angiotensin system. While this has been documented for low doses of chlorthalidone, there has never been any study showing a reduction in heart attacks, strokes, or all-cause mortality with a beta-blocker-based therapy in uncomplicated hypertension. On the contrary, a variety of studies attested to the inefficacy of this drug class for the prevention of cardiovascular events in hypertensive patients, despite the fact that blood pressure was lowered to a similar extent with beta-blockers as with other drug classes. In many of these studies, a beta-blocker-based therapy was not only inefficacious, but elicited unacceptable side effects such as fatigue, dyspnoea, cold intolerance, and bradycardia. This means that as of today, in the US alone, about eight million hypertensive patients are still exposed to cost, inconvenience, and adverse effects of a therapeutic regimen that has never shown to be effective.

The ASCOT study takes us a big step further in that it not only shows the superiority of a calcium antagonist-based regimen over a beta-blocker-based one, but does so in patients, who apart from hypertension, had at least three additional risk factors such as smoking, diabetes, cerebrovascular or peripheral vascular disease, and microalbuminuria. This indicates that even in patients with more advanced hypertensive cardiovascular disease, a beta-blocker-based therapy should be avoided in favour of a calcium antagonists/ACE-inhibitor one. ASCOT also provides powerful evidence for the safety of dihydropyridine calcium antagonists, specifically of amlodipine. This is no small feature given that as little as 4 years ago the same New York Times was needlessly alarming their readers with statements such as ‘The use of such drugs known as calcium channel blockers is leading to nearly 85 000 unnecessary heart attacks and cases of heart failure each year worldwide’. Safety and efficacy of calcium antagonists

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

*Corresponding author. Tel: +1 212 523 7373; fax: +1 212 523 7765. E-mail address: fmesserli@aol.com

© The European Society of Cardiology 2005. All rights reserved. For Permissions, please e-mail: journals.permissions@oupjournals.org
have been hotly debated for more than a decade. A few recent wrinkles from an observational study not withstanding,9 ASCOT together with ALLHAT, VALUE,10 and ACTION11 put this controversy to rest and allow us to (finally) turn the page.

Of note, ASCOT and most other studies were done with atenolol and much less is known about the efficacy of other beta-blockers in hypertension. Conceivably, vasodilating compounds such as carvedilol and celiprolol may have benefits not shared by other members of this heterogeneous drug class. Beta-blockers have been, are, and will remain a cornerstone in the cardiovascular armamentarium. They are invaluable drugs for the treatment of coronary heart disease, congestive heart failure, and many arrhythmias. However, to extrapolate from these benefits in well-defined disease states to hypertensive cardiovascular disease is inappropriate and the first line use of beta-blockers for this indication should be discouraged. ASCOT was terminated prematurely. This is fortunate, because for patients who still are treated with less effective or even ineffective drugs, prematurely means long overdue.

Conflict of interest: F.H.M. has received honoraria for speaking on behalf of Pfizer and other companies.

References
2. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Disease in Insulin-Resistant Adults (ALLHAT). JAMA 1997;277:96-108.