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What Ever Happened to Cardioprotection With β-Blockers?

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The take-home message of the provocative article by Tsujimoto et al[1] is that "using nationally representative data, all-cause mortality in diabetic participants was higher in those taking β-blockers than in those not taking β-blockers." This was also true for the subset of diabetic patients with coronary heart disease. However, in nondiabetic patients there was no mortality difference between those taking β-blockers and those not taking β-blockers, and in nondiabetic patients with coronary heart disease, β-blockers were associated with lower mortality rates.

In view of the fact that we have used β-blockers for many decades in a variety of cardiovascular diseases for what has been called "cardioprotection," these results are sobering. Until recently, there has been general consensus that the evidence for the use of β-blockers in patients after myocardial infarction (MI) is ironclad, based as it is on multiple randomized clinical trials.[2,3] Long-term β-blockade for perhaps a year or so following discharge after an MI has been considered to be of proven value because for many such patients mortality reductions of approximately 25% may be achieved. Unfortunately, under the umbrella of cardioprotection ("we need to protect your heart"), the solid evidence gathered in these post-MI trials has been uncritically extrapolated to other indications, such as hypertension, diabetes, chronic kidney disease, and even cerebrovascular disease. Despite the lack of evidence, the marketing of β-blockers for such comprehensive cardioprotection proved to be exceedingly successful, and many of these ill-documented β-blocker indications have persisted in the minds of physicians up to today.

We should remember though that these post-MI trials were conducted 3 to 4 decades ago, at a time when β-blockers were considered contraindicated for the treatment of heart failure, as is documented by the statement of Ezra Amsterdam et al[4,p105]: "Congestive heart failure, the most serious untoward effect associated with propranolol therapy, follows from the negative inotropic effects of the drug…The previous presence of congestive heart failure is considered to preclude the use of propranolol…" The simple fact that β-blockers are a cornerstone in today's treatment of heart failure[5] should convince even the most skeptical among us that times have changed and most likely will continue to do so.

What then are the changes that have occurred regarding β-blockade in patients after MI? Two major changes have taken place:

1. As Tsujimoto et al[1] note, aggressive reperfusion therapy has drastically reduced the possible benefits of β-blocker therapy. A reperfused, viable myocardium has little in common with a necrotic or scarred myocardium, as was commonly encountered before reperfusion therapy.[6] The presence of necrosis and scar tissue generates arrhythmias because of reentry mechanisms and might well enhance the ability of β-blockers to prevent arrhythmias and sudden death. Thus, in post-MI patients who are adequately revascularized and have normal left ventricular systolic function, there is little in the way of a pathogenetic process for β-blockers to target and thereby exert cardioprotection.

2. Currently, most patients with a previous MI not only use a β-blocker but also are prescribed aspirin, new oral anticoagulants, lipid-lowering agents, and blockers of the renin-angiotensin system. If nothing else, these powerful drugs have significantly reduced the overall risk in post-MI patients and, as a consequence, made it more difficult to document the possible benefits of β-blockers.

This brings up the next question as to the difference in mortality rates between diabetic and nondiabetic patients. As the authors point out, there has not been a randomized controlled trial to assess the effectiveness of β-blockers in diabetic patients.[1] The simple observation that titration of blood pressure to less than 120 mm Hg, as was performed in ACCORD (Action to Control Cardiovascular Risk in Diabetes),[7] conferred no benefits in diabetic hypertensive patients, whereas SPRINT (Systolic Blood Pressure Intervention Trial)[8] reported such titration to be exceedingly beneficial in nondiabetic individuals, teaches us that outcome evidence gathered in nondiabetic patients cannot be extrapolated to diabetic patients. Why then should β-blockers increase mortality rates in diabetic patients? Most differences in mortality rates between diabetic patients taking and not taking β-blockers emerged after several years only, supporting the hypothesis that the adverse effects of the drug class on glucose metabolism, lipid metabolism, hypertension control, and weight gain may lead to an increased risk of mortality.

β-Blocker–associated weight gain may be of particular concern and remains an underappreciated issue among clinicians. In a systematic analysis of 8 randomized controlled hypertension trials involving 7048 patients, β-blockers caused an average weight gain of 1.2 kg compared with control subjects, with most of the weight gain occurring within the first few months of starting therapy.[9] In β-blocker–treated patients, the adjusted mean body weight was 9 to 17 kg higher in those attending the diabetes and hypertension clinic compared with patients not treated with β-blockers.[10] We hypothesize that long-term β-blockade causes weight gain by blunting energy expenditure. For obvious reasons, weight gain is more worrisome in diabetic patients than in nondiabetic patients.

Tsujimoto et al[1] rightly point out that β-blockers may increase central blood pressure and that this prohypertensive effect can be expected to be more pronounced in a stiffer arterial tree, such as in diabetic patients. The increase in central pressure is related to the decrease in heart rate, and the slower the heart rate, the greater the increase in central pressure. For obvious reasons, not all β-blockers are created equal, and the vasodilating agents have little if any effect on central pressure.

Finally, we should point out that despite careful adjustment and propensity score matching, confounding by indication is a real possibility that cannot be fully accounted for. We do not know the exact clinical circumstances that triggered a β-blocker prescription in these patients. The fact that the point estimate suggests harm even in the diabetic subgroup with heart failure should raise caution, if not suspicion, because it goes against all evidence from randomized clinical trials. We wholeheartedly agree with the authors' last sentence that prospective randomized trials are needed "to assess whether β-blockers are effective in reducing mortality and coronary events in diabetic patients receiving optimal medical treatment."[1] Until then, the only ironclad indication for cardioprotection with β-blockers remains heart failure with reduced ejection fraction,[11,12] the very indication that decades ago was the only contraindication for β-blocker therapy.[4] "Tempora mutantur, nos et mutamur in illis" ("Times change, and we change with them") (Caspar Huberinus [1500-1553], commonly misattributed to Ovid's *Metamorphoses*).

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