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The Great Debate of 2008—How Low to Go in Preventive Cardiology?

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THE DEBATES OF 2008 HAVE ALREADY BEEN QUITE intense. During this election year, politicians and pundits alike, reviewing the same set of information, have formulated remarkably different conclusions and recommendations for national policy. The field of preventive cardiology has likewise been witness to its own debate. Spurred by a series of important yet somewhat unexpected clinical trial results, the question of "how low to go" in cardiovascular risk-factor modification has been hotly disputed.

This debate is not new and traditionally has been waged between the "true believers," those with a strong a priori conviction that more aggressive pharmacological treatment will reduce future events, and the "therapeutic nihilists," those who require unequivocal proof before acceptance. In recent years, the true believers have had the upper hand. Epidemiologic data have consistently concluded that lower levels of lipids, blood pressure, and glucose all correlate with less cardiovascular disease. Similarly, among patients with established cardiovascular disease, intensive lipid lowering with statins has been demonstrated to reduce future cardiac events.[1] Thus, national treatment guidelines have progressively lowered their thresholds for initiation of drug therapy as well as the target levels to be achieved.[2,3] Yet the benefit of aggressive pharmacological therapy for primary prevention is less clear, even among high-risk subgroups.[4,5] Additionally, while statin therapy appears beneficial for hypertensive patients,[6] the ideal targets for low-density lipoprotein cholesterol (LDL-C) or blood pressure lowering in these patients have not been defined. Here lies the doubt of the nihilists: "Where is the evidence that intensive lowering is necessarily better or even safe?"

In this issue of *JAMA*, Howard and colleagues[7] report the results of the Stop Atherosclerosis in Native Diabetics Study (SANDS), which compared aggressive therapy of systolic blood pressure and LDL-C lowering to standard therapy among American Indian patients with type 2 diabetes mellitus. This is one of the first studies to assess the role of aggressive risk factor modification in a high-risk primary prevention setting. The study was well-designed and rigorously conducted with patient follow-up every 3 months for up to 3 years. The authors also examined these questions in a traditionally understudied population. The results showed that patients receiving intensive management had significant regression of carotid intimal medial

See also p 1678.

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thickness (IMT) and reduced left ventricular mass compared with patients treated with standard strategies. In contrast to the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT),[8] there appeared to be no synergistic effect between lipid and blood pressure lowering on these separate surrogates—aggressive LDL-C lowering was associated with IMT regression, but was not a predictor of left ventricular mass reduction; conversely, aggressive systolic blood pressure lowering was associated with left ventricular mass reduction, but not with IMT regression. Importantly, while the study was not powered to address clinical outcomes, intensively managed patients had no significant reduction in cardiovascular events after 3 years of follow-up relative to patients receiving standard treatment. In fact, more adverse effects (hypotension, hyperkalemia) were observed in the group receiving aggressive blood pressure treatment.

Some of the obstacles facing primary prevention trials are highlighted in SANDS. Given low annual event rates, primary prevention trials often require large sample sizes and long-term follow-up to assess hard clinical outcomes. Comparing event differences becomes particularly challenging when the question moves from a placebo-based comparison to one that assesses the incremental effect of more aggressive vs standard therapy. In an attempt to expedite evidence development, many have turned to surrogate markers, intermediate end points in the biological pathway, as more readily measurable alternatives to clinical outcomes. However, surrogate end points often fail if they are not in the direct causal pathway of the effect of the intervention or if the intervention causes harm independent of the disease process.

Even though surrogate end points such as IMT and left ventricular hypertrophy have evidence associating them with both cardiovascular risk factors and outcomes,[9,10] there is a paucity of evidence showing that changes in these markers will accurately predict future cardiovascular events.[11] For example, the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study found that vitamin supplementation delayed carotid IMT progression, but had no effect on reducing clinical events.[12] Similarly, while cholesterol lowering has been well associated with carotid IMT regression, the ENHANCE trial recently reported that aggressive lipid lowering may not necessarily correlate with IMT reduction, at least in a small short-term evaluation.[13] In addition, tighter blood glucose control has been associated with delayed IMT progression, yet the ACCORD trial found that more aggressive glycemic control led to an excess of deaths relative to standard management.[14]

Without doubt, these trials underscore the need to look not just at surrogate markers, but at the ultimate clinical expression of the intervention—patient outcomes. However, there are no easy solutions for improving the throughput of trials with hard clinical end points. Enriching the study population with high-risk populations can increase event rates, but this is not always predictable (as evidenced by the unexpectedly low event rates in SANDS), and doing so can limit study generalizability. Longer and larger studies are ideal, yet using current trial methodologies, can be quite costly. SANDS,[7] with only 500 patients, cost approximately $12 million, whereas a 10 000-patient clinical end point–driven trial may cost in excess of $200 million. Thus, methods to improve trial efficiency with better tools to identify eligible patients, quicker site activation, streamlined electronic data collection, and remote monitoring are needed to make trials more practical and affordable.

What are the take-home messages from SANDS? For the true believers, the study confirms that aggressive lipid and hypertension treatment has a favorable effect on proven "early markers" of disease. Thus, with longer duration of follow-up (which will hopefully be the case), the study would most assuredly demonstrate improved patient outcomes. For the therapeutic nihilists, however, SANDS took high-risk patients with type 2 diabetes, studied them under idealized circumstances, and still found no clinical benefit after 3 years of follow-up. In fact, an aggressive approach involved greater polypharmacy and costs and had a higher risk of adverse effects.

In contrast to these extremes and while awaiting longer-term data, a practical middle-of-the-road approach might be to support intensive lipid lowering with statin therapy in patients with diabetes, because this is supported by prior large, randomized, clinical, end point–driven trials,[15] and has relatively few adverse effects or patient risks. For intensive blood pressure management, however, more data are needed because the benefits are not assured and there are modest, but measurement-negative effects on patients' finances and well-being. The blood pressure lowering group of the ACCORD trial,[16] comparing a goal of lower than 120 mm Hg vs lower than 140 mm Hg, as well as the recently announced National Heart, Lung, and Blood Institute's Systolic Blood Pressure Intervention Trial (SPRINT), comparing aggressive vs standard blood pressure management in a large end point–driven trial, should provide these much needed data.

Finally, believers or not, all clinicians can support the pressing need to better assist patients in effectively modifying their risk factors to whatever goal deemed appropriate. Even in the rigorous National Heart, Lung, and Blood Institute's protocol-driven study environment of SANDS, with concomitant patient education and dedicated study physician and nursing care, blood pressure and lipid targets were reached in fewer than half of all patients. Now in community practice, only a third of patients with hypertension and hyperlipidemia are meeting standard treatment goals.[17] This problem would only be magnified if future evidence mandates more stringent goals. Thus, novel strategies to facilitate patient engagement in their disease management are needed.[18,19]

In conclusion, SANDS is an important step forward in discovering whether lower goals are truly better for primary prevention. While the study results can be interpreted to support both viewpoints on the ideal target of therapy, such debates are healthy and will ultimately drive physicians to search for more definitive evidence as well as to seek system-wide strategies to effectively reach therapeutic goals in community practice.

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