The Aggressive Cholesterol Therapy to Inhibit Vein Graft Events trial: To continue or not? How to answer the question

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How do you make the decision to continue or not?

Central Message

Clinical trials have oversight for patient safety. How do we decide to stop a trial early when guidelines change? The decision is difficult for investigators committed to innovation and discovery.

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In this month's issue of the Journal, Kulik and colleagues¹ report the results of the Aggressive Cholesterol Therapy to Inhibit Vein Graft Events (ACTIVE) trial. In a pilot multicenter double-randomized trial, 173 patients who had undergone coronary artery bypass grafting (CABG) with saphenous vein graft were randomly allocated to receive atorvastatin either 10 mg (low intensity) or 80 mg (high intensity) daily for 1 year. The primary outcome was saphenous vein graft occlusion at 1 year; this outcome did not differ between the two groups, even though the higher dose therapy significantly lowered the low-density lipoprotein cholesterol levels after surgery by 26.1%.¹ Oversight was provided by individual site institutional review boards, the US Food and Drug Administration, and Health Canada. A data and safety monitoring board was not explicitly mentioned in the publication. The trial was stopped prematurely in 2016 and did not reach the target of 200 subjects because of recruitment difficulties and changes in the 2013 American College of Cardiology and American Heart Association guideline regarding statin use.^{2,3} The guideline changes included a class 1, grade A recommendation to place all patients undergoing CABG on a high-dose statin regimen.³

Important questions are raised by the ACTIVE study as to when a trial should be terminated prematurely. Previously, 2 trials of induction therapy closed prematurely when several studies (International Adjuvant Lung Cancer Trial, Cancer and Leukemia Group B 9633) demonstrated an advantage relative to adjuvant chemotherapy after surgery.^{4,5} The investigators believed that induction therapy trials could no longer ethically accrue patients to the surgery-only arm, because adjuvant chemotherapy had been demonstrated to confer a significant survival benefit.^{4,5} Recent recommendations have included providing better

guidance for data and safety monitoring boards in trials involving cardiovascular disease and introducing independent advisory bodies, training modules, and mentorship programs to provide unbiased, consistent, and integrity-based oversight.^{6,7} The institutional review boards, US Food and Drug Administration, and Health Canada provided oversight for the ACTIVE clinical trial, but they may not have been aware that the recommendations for statin therapy changed during the trial because no adverse events occurred. Is it the responsibility of the investigators, the data and safety monitoring boards, the institutional review boards, or oversight agencies to review changing guidelines while a trial is active? We know of no regulations or guidelines that address that question. Another important question is whether a trial should be discontinued on the basis of changes in clinical guidelines that are updated with peer-reviewed iterations. Are guidelines merely recommendations, or should they be rigidly applied to ongoing clinical trials? Clinical adoption of the 2013 American College of Cardiology and American Heart Association guidelines was only modest, despite an impressive projected decrease in cardiovascular disease.^{8,9} The argument could also be made that early trial closure "wastes" the contributions of patients.¹⁰

The Belmont Report established 3 basic ethical principles to guide clinical research: respect for persons, beneficence, and justice.¹¹ Grade A recommendations have a “high certainty based on evidence that the net benefit is substantial” and seem to rigorously uphold research ethics, but important questions remain.¹² The ACTIVE investigators have not disregarded their responsibilities, but blurred lines of recommendations and guidelines as they apply to clinical research do not sufficiently clarify the lines of responsibility for making important research decisions.

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