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EDITORIAL COMMENT

Better Late Than Never

A Welcome Publication of Tardy Clinical Trial Results*

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This issue of *JACC: Heart Failure* includes a report of results from the REVIVE (Randomized EValuation of Intravenous leVosimendan Efficacy) trials of the calcium sensitizer levosimendan in patients with acute decompensated heart failure (ADHF) (1), more than 7 years after these trials were completed. The fundamental findings from the 100-patient pilot study (REVIVE) and the 600-patient randomized controlled trial (REVIVE II) are that levosimendan improved symptoms compared with placebo in patients with ADHF but at the cost of an increase in the incidence of major adverse cardiovascular events. The REVIVE article, however, also represents a milestone for the cardiovascular community, who should rejoice in the fact that the REVIVE investigators have finally decided to come out of the data cellar.

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The publication of this trial fulfills a pair of critical obligations on the part of the investigators and sponsors, who were given the privilege to conduct human experiments in a society that is increasingly sensitized to the harm that can be done when results of trials are not presented in an accurate and timely fashion. The first obligation is to the study participants, who signed a consent form waiving some of their freedoms in order to participate in an experiment as "subjects" in a clinical trial whose purpose is explicitly defined by the U.S. Department of Health and Human Services as "the creation of generalizable knowledge" (2). The second is to their clinical and scientific colleagues, who have been forced to make decisions about drug development and clinical practice in the setting of ADHF in the absence of a complete and accurate peer-reviewed accounting of the results derived from these trials.

Findings from REVIVE. In a general sense, the findings from the REVIVE trials are widely known, because they have been discussed for years in the absence of a primary publication, following an abstract presentation at the 2005 American Heart Association Scientific Sessions (3,4). The study sponsors (Abbott Laboratories and Orion Pharma) and investigators conceived an interesting design that focused on testing whether levosimendan improved clinical status compared with placebo in addition to standard therapy for ADHF. The results convincingly demonstrate that clinical status was improved by levosimendan: less "rescue" intervention was needed, length of stay was shorter, and B-type natriuretic peptide levels were lower. The price exacted by these improvements, however, was significant: more hypotension, arrhythmia, and tachycardia and a numerically higher death rate. The different direction of symptomatic measures and some biomarkers (tending toward benefit) and death and other biomarkers (tending toward detriment) underscores the critical importance of accruing adequate numbers of "hard" events to generate definitive information about likely risk–benefit tradeoffs.

It is sad to reflect that, to this day, we still cannot accurately characterize the balance of risk and benefit of levosimendan on clinical outcomes in ADHF, because of a hodge-podge of clinical trials in various states of publication and a paucity of well-designed, adequately powered trials with an appropriate balance of clinical leadership and sponsor input. Interestingly, in 2010, a cost-effectiveness analysis of REVIVE was presented in the peer-reviewed published literature. The study, which focused on a trial subgroup that was not powered to assess mortality effects, advanced the claim that levosimendan is cost effective compared with standard care in the subgroup (5). The publication of a non–pre-specified subgroup analysis without first making available the full trial results in a peer-reviewed venue constitutes an example of a publication fostered by commercial interests without appropriate academic participation.

Obligations to research participants. Experiments on human subjects, of course, have multiple purposes, but all have at least 1 thing in common: the obligation of those who fund and conduct such experiments to fulfill their promises to the participants. The patients randomized into the REVIVE II trial were critically ill and had a very high degree of expected mortality and morbidity—much higher than any known form of cancer. The study sponsors and investigators promised to provide public access to the knowledge gained

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from the voluntary participation of these patients. The results of the study were obviously disappointing and, in concert with other data, inadequate for achieving marketing approval in the United States and parts of Western Europe. But despite this, the drug was marketed in "over 40 countries" (6) and selected, highly biased segments of the data were included in accessible documents.

Some patient advocates and researchers have argued for liberation of data gathered from human experiments almost immediately upon completion of the given study, but most reasonable people would grant some time for the investigators and sponsors—whether government or industry—to assimilate the findings into a comprehensible report and a manuscript that then receives peer review before publication. One cannot help wondering, given the stellar track record of the REVIVE investigators, what offences have been promulgated by less accomplished investigators and sponsors. It just does not seem right to say: "We did an experiment on you, but we didn't like the result, so we didn't publish the results in a form that would really inform the many doctors who might put patients at risk in the future."

Obligations to colleagues. Care providers and scientists who participate in the development, evaluation, and use of therapies do so because they want to offer patients better treatments to relieve suffering. Doctors caring for patients, experts deciding on clinical practice guidelines, and regulators making decisions about indications for treatment all depend on transparent knowledge about human research to make wise decisions not only about what to prescribe to patients but also about the risks and benefits to future research participants. Unfortunately, an ample body of evidence pointing to entrenched reporting and publication bias suggests this trust might be misplaced (7). One can easily see that a person reviewing the published data on levosimendan would find numerous positive reports but no primary record of the REVIVE trials—until now. Yet, the drug has been available in "over 40 countries," with reported net sales of €44 million in 2011 (8).

Preemptive approaches. Major forces are in motion to develop systematic approaches to ensuring that clinical trial results become available to the public in a more complete, transparent, and timely fashion. ClinicalTrials.gov, a registry initially developed to enable patients with life-threatening illness to find relevant trials, has evolved into a comprehensive source for information on what clinical trials are done as well as the fundamental design and top-line results of those trials. In the United States, it is now illegal to fail to register most clinical trials or to neglect to report relevant results—including adverse events—in the structured format of ClinicalTrials.gov (9).

This expanded role for ClinicalTrials.gov is one facet of efforts designed to culminate in a system in which all investigators, care providers, patients, and study participants are engaged in a cycle that embeds research and continuous learning as a routine aspect of care delivery—the "learning health care system" of the Institute of Medicine (10). Although the Institute of Medicine has progressively defined a vision for the learning health system, a major series of publications in the Hastings Center Report (11,12) has proposed a significant change in societal expectations with regard to the moral obligations of all constituents. The ethicists who authored these papers propose that patients, providers, administrators, and payers alike are considered to have a moral duty to participate in the creation of generalizable knowledge as a routine element of clinical care.

The revival of the REVIVE trials is welcome news, and Packer et al. (1) are to be congratulated for their perseverance in publishing and "reviving" these results. With the full dissemination of these findings, the participants in the REVIVE trials have been shown well-deserved respect, and the colleagues of the investigators in drug development and clinical practice now have a record of a human experiment that heretofore had been partially secret. As the broad movement for expanding access to the results of scientific investigations gains strength, the clinical and research communities must work together to create a learning health system in which failings such as those seen in the REVIVE trials become a rare exception rather than a common occurrence.

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