fractional polynomial regression,\(^6\) has been described. Fractional polynomials are a family of models to consider, as covariates, power transformations of a continuous exposure variable restricted to a small, predefined set of integer and noninteger exponents.\(^6\) Such approaches are underused in epidemiologic research and have seldom\(^6\) been compared in a meta-analysis of dose-response aggregate data. Fractional polynomials provide great flexibility for a meta-analysis of dose-response aggregate data and are especially valuable when important nonlinearity is anticipated.\(^2\) Furthermore, they are easier to communicate mathematically, require the estimation of fewer parameters, and are less influenced by arbitrariness in the choice of the model than traditional approaches.

On the basis of the Cholesterol Treatment Trialists’ meta-analysis,\(^7\) Sniderman et al\(^8\) calculated that any potential gain from increasing the dose of atorvastatin calcium from 40 to 80 mg would be small, at best an additional 2\% reduction in clinical events. The increase in dose, unfortunately, would likely be associated with increased adverse effects and decreased adherence. Accordingly, whether net benefit would be demonstrable cannot be assumed. It follows that definitive evidence supporting maximal lowering of LDL-C level or maximal dose of statins is still lacking and that guidelines, if they are to be evidence based, should acknowledge this uncertainty.\(^8\) Although we found, on the basis of flexible (not linear) metaregression, that using statins to reduce LDL-C level by more than approximately 40 mg/dL could produce almost no additional reduction in the risk of major vascular events, further analysis would be required to confirm our findings.

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**Extent and Reporting of Patient Nonenrollment in Influential Randomized Clinical Trials, 2002 to 2010**

Because they assign patients to treatment conditions, randomized clinical trials (RCTs) offer unparalleled internal validity for drawing inferences about the efficacy of a medical treatment. Whether such inferences can be generalized is not always clear because many RCTs enroll a low and unrepresentative proportion of all patients.\(^1\)\(^4\) The challenges of judging the clinical utility of clinical trial results are poor reporting. The study by Gross et al\(^5\) of trials published in leading medical journals from 1999 through 2000 found that only 28\% reported the proportion of screened patients who were enrolled. These deficiencies may have been ameliorated in the past decade because the CONSORT statement was revised in 2001 to require more complete information on the enrollment process in reports of clinical trials,\(^6\) and because many treatment research fields have been showing greater concern about generating knowledge that better informs clinical practice. Accordingly, the present study assessed the extent to which low enrollment rates are still characteristic of widely cited clinical trials, and whether reporting of enrollment information has improved.

**Methods.** A Web of Science search was used to identify the 20 most influential English-language RCTs for each of 14 prevalent chronic disorders (alcohol dependence, Alzheimer disease, breast cancer, colorectal cancer, chronic obstructive pulmonary disorder, depression, diabetes mellitus, drug dependence, human immunodeficiency virus/AIDS, hypertension, ischemic heart disease, lung cancer, nicotine dependence, and schizophrenia) published from 2002 to 2010 (see eTable for search terms and citations returned; http://www.jamainternalmed.com). We sorted the results on citations per year rather than total citations so that recently published trials would still have the chance to rank as influential. Top-cited articles that were not RCTs (eg, major literature reviews) were excluded.
The final data set comprised 280 studies (20 studies for each of 14 conditions). Raters double-coded the studies on the number of patients with the disorder of interest who were screened for trial eligibility, the number who were eligible, and the number of eligible patients who agreed to enroll. When available, the reason for nonenrollment also was recorded. For these studies, we recorded the number of nonenrollments that were due to participants not meeting study eligibility criteria, the number excluded for other reasons (eg, administrative errors), and the number of eligible participants who refused to participate (this included individuals who initially refused to participate and those who initially agreed but then did not return for the start of the study).

Results. Only 145 studies (51.8%) provided sufficient information to allow calculation of the nonenrollment rate. These RCTs had a mean (SD) nonenrollment rate of 40.1% (23.7%). For 6 of the 14 diseases, the influential trials included at least 1 study with a nonenrollment rate higher than 90%.

No association emerged between year of publication and the proportion of patients not enrolled (r = −0.08; P = .37). However, year of publication was positively associated with adequate reporting of enrollment information (odds ratio, 1.19; P = .003). In 2002, only 45% of the trials reported enrollment information, but this proportion rose to 75% by 2010.

Only 35.0% of studies (n = 98) provided sufficient information to categorize reasons for nonenrollment. In these studies, an average of 27.3% of participants did not meet eligibility criteria, 11.2% refused participation, and 3.7% were not enrolled owing to other reasons.

Discussion. Highly cited clinical trials do not enroll an average of 40.1% of identified patients with the disorder being studied, primarily owing to eligibility criteria. Low enrollment rates can lower external validity because, by definition, eligibility criteria create trial research samples that differ from real-world patient samples. The larger the proportion of patients not enrolled, the more likely it is that the results of the study will not reflect what the intervention would produce in front-line clinical practice. Although exclusion criteria are sometimes essential in trials, including to protect patient safety, we add our voices to those of others who have suggested that treatment researchers use them as minimally as possible and only with good justification.

On a more positive note, from 2002 through 2010, the proportion of clinical trials reporting complete enrollment information increased from 45% to 75%. Improved reporting may reflect the accrued influence of the CONSORT guidelines, as more authors and editors become aware of them, as well as the impact of numerous studies and editorials raising concerns about unrepresentative research samples.

We close with an important caution. Gandhi et al found that publications of trial results tend to underreport the number of exclusion criteria that were in the approved protocol. Furthermore, in some trials, insufficient effort is put into tracking data on nonenrollment. Therefore, even though we have identified high rates of nonenrollment, our results may nonetheless underestimate the degree to which this is a reality of current clinical trial research.

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noncommunicable diseases in developing countries: focus on research capacity building

In a well-conceived study, Damasceno et al demonstrated that the etiology of acute heart failure in sub-Saharan Africa differed from that in developed countries. In particular, the causes were often nonspecific in nature, with hypertension being the most predominant etiological factor. It is therefore likely that the best practices in prevention and management of acute heart failure will also differ, and appropriate treatment guidelines will hinge on future studies conducted within sub-Saharan Africa.

Not only is this finding paramount for cardiovascular disease prevention, it also has broader implications for the utility of research capacity building in reducing noncommunicable diseases (NCDs). The 2011 report of the United Nations High Level Meeting on Non-Communicable Diseases highlighted many interventions for addressing the global burden of NCDs, such as investment in research. However, given the potential for remarkable differences in the etiology of NCDs between developing and developed countries, we further suggest that investment in research represents an integral first step. With this approach, we suspect that the unique etiological phenotype of NCDs in developing countries will come to light, and prevention strategies will have to be remodeled based on these findings.

Certainly, awaiting the results of seminal research studies cannot delay the broader effort to reduce NCDs, and there are situations where significant gains can be made without further research into the etiological basis for disease. For instance, the relationship between tobacco use and lung cancer is well established and is unlikely to vary among countries. Also, transferring insights from international efforts in human immunodeficiency virus/AIDS to the realm of NCDs can be done without a baseline research infrastructure dedicated to NCDs. Hence, investment in research is one element, albeit a crucial element in our view, of the first steps taken to curb the global burden of NCDs.

With the advent of global austerity measures, identifying areas to allocate funds will be a challenge. We propose that stakeholders consider the important role of research in delivering effective health care. The work by Damasceno et al is one study that can reshape cardiovascular disease prevention efforts in Africa. Appropriate research investments by regional, national, and international stakeholders will facilitate the generation of future studies.

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In reply

We thank the authors for their kind comments on our multicenter outcome cohort study on acute heart failure in 9 African countries. We fully agree with their views that investment in health research is essential to curb the growing burden of noncommunicable diseases (NCDs), as well as to secure the public good of research and development in Africa and other developing regions of the world.

Since 1991, research productivity in sub-Saharan Africa has grown, with the importance of NCDs as a contributor to morbidity and mortality in Africans increasingly recognized. This has lead to a number of initiatives supporting research in NCDs in Africa. First, the National Institutes of Health (NIH) Millennium Promise Award on Noncommunicable Disease supports the training of researchers with masters or doctoral degrees and postdoctoral fellows from Africa in any basic science and clinical or public health research related to NCD. Similarly, the University of Cape Town has established a center to combat NCDs through investment in research and training. Second, the Pan African Pulmonary Hypertension Cohort Study (PAPUCO), in 10 African centers, is now under way and facilitates the training of 4 African PhD students (http://www.hatter.uct.ac.za). A similar multicenter prospective registry on rheumatic heart disease has been initiated as part of the Stop Rheumatic Heart Disease A.S.A.P. Programme of the Pan African Society of Cardiology (PASCAR). Finally, we have initiated 2 multinational randomized clinical trials in cardiovascular disease. A larger randomized study investigating the Bi-treatment With Hydralazine/Nitrates vs Placebo in Africans Admitted With Acute Heart Failure” (B-AHEF) and the Investigation of the Management of Pericarditis (IMPI) Trial, a study being conducted in 8 African countries, with recruitment of 1400 participants with pericarditis expected before the end of this year.

There is a renaissance in health research in sub-Saharan Africa that is largely led by academics, with the support of external funders. More government-led capacity building and training initiatives in NCDs are, however, required to promote research and address the public health challenges facing the continent. This increased investment in health re-