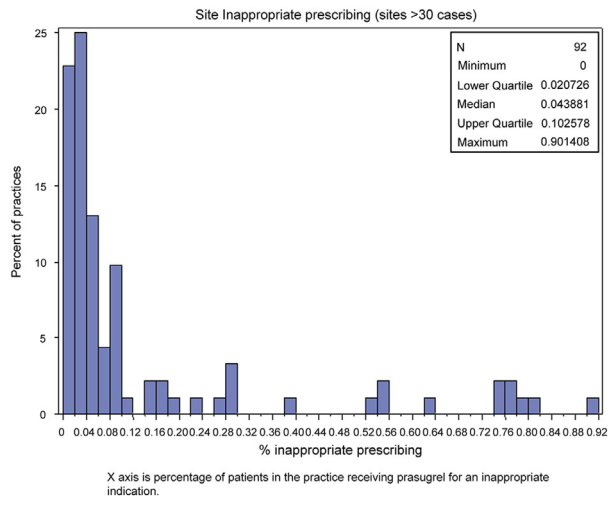

Figure 1 **Practice-Level Variation in Inappropriate Prasugrel Prescribing**

Percentage of patients in individual practices receiving prasugrel inappropriately ranged from 0% to 90% (median: 4.4% [interquartile range: 2% to 10%]). The median rate ratio was 2.89 (95% confidence interval: 2.75 to 3.03), indicating significant practice-level variation.

motivated for quality improvement and, therefore, inappropriate and nonrecommended rates may be higher in nonparticipating practices. Data on the contraindications to clopidogrel, reason for choosing prasugrel instead of clopidogrel, dosage of prasugrel pertaining to patients weighing <60 kg, results of platelet function studies, and ischemic and bleeding outcomes are not collected in the PINNACLE registry, and analyses pertaining to these variables, therefore, could not be performed.

Almost 1 in 5 patients receiving prasugrel had an inappropriate or nonrecommended indication with significant practice-level variation. Our findings suggest opportunities to improve evidence-based prasugrel prescribing.

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Placebo in Autologous Cell-Based Interventions

Hard Pill to Swallow?

To the Editor: Cell-based strategies are under intense investigation in the pursuit to develop new effective treatment protocols for ischemic heart disease (IHD). These strategies have been mainly based on the use of tissue-specific autologous stem/progenitor cells such as cells from bone marrow, adipose tissue, or the heart itself (1). Several of these cell types have reached the

phase of clinical testing (2,3). Clinical trials, in particular trials investigating cell-based interventions, entail inherent scientific and ethical challenges. Due to the combination of the relative lack of experience with cell-based interventions, the complexity, the variability (especially when autologous cells are used), and the invasive character, traditional ethical issues get a new perspective. One of these issues is the choice for the comparator (4).

Treatment effect is generally assessed in clinical trials by means of superiority of the novel intervention over standard clinical care or placebo. Placebo is used to conceal intervention allocation both for the patient and investigator-physician (5). In pharmaceutical clinical trials, the placebo is often a capsule or tablet indistinguishable from the investigational new drug. However, in clinical trials assessing autologous cell interventions for heart disease, proper blinding can only be achieved when participants allocated to the placebo group undergo the identical harvesting procedure (e.g., bone marrow aspiration in the case of bone marrow mononuclear cells) as well as a sham delivery procedure to the heart undistinguishable from the cell delivery procedure. If the interventional cardiologist is not involved in the follow-up and/or outcome analysis, the sham procedure may not necessitate an actual injection with a placebo solution identical to the cell suspension. Either way, in contrast to placebo tablets, autologous cell interventions expose the control group to risk and harm, raising ethical concerns.

To date, little is known about the extent to which sham interventions in cell-based trials are performed. To address this question, we conducted a systematic review on published reports of randomized clinical trials (RCTs) investigating efficacy of autologous cell interventions in patients with IHD. We assessed how RCTs were designed regarding cell harvesting and/or cardiac sham delivery, whether this depended on the type and stage of cardiac disease, and the adverse events rate in sham procedure patients. A search syntax was developed based on relevant synonyms for domain, which is patients with IHD, and determinant, which is cell intervention delivered to the heart (i.e., intracoronary delivery or intramyocardial injection). The outcome—efficacy of cell intervention—was deliberately withheld from our search syntax to avoid potential reporting and retrieval bias. A systematic literature search was conducted in MEDLINE and EMBASE on the 13th of May 2013. Two reviewers (S.K., J.W.) independently screened title and abstract of studies in accordance of in-/exclusion criteria (see the Online Appendix). The selected articles were crosschecked to identify relevant studies missed by the initial search using ISI Web of Science.

A total of 56 RCTs were identified that were published between 2001 and 2013. In total 3,610 patients were included in these studies, of which 2,189 (61%) received autologous cells, compared to 1,421 (39%) controls. In 75% of studies, bone marrow mononuclear cells were the investigational cell type. Diagnosis was acute myocardial infarction (MI) in 2,463 patients (982 controls [40%]), compared to 1,147 patients (439 controls [38%]) with chronic IHD (i.e., refractory angina or post-MI heart failure).

Combined cell harvesting and sham cardiac delivery, thereby ensuring patient and investigator blinding, was performed in 22 of the 56 studies (39%). Analysis divided for IHD type revealed that 11 of 36 studies (31%) used sham delivery in acute MI and 11 of 20 studies (55%) in chronic IHD (chi-square; $p = 0.09$). Apparently, use of placebo is generally not preferred in the acute setting of MI in contrast with an elective cell intervention procedure for chronic IHD. Furthermore, in 1 study, participants allocated to the control group underwent cell harvesting but no sham cardiac injections, while the rest of the studies used usual care as a comparator.

Out of 22 studies that used placebo, adverse events in controls were reported in 5 studies (23%), all of which investigating bone marrow cells. A combined endpoint analysis of major cardiovascular events revealed that intracoronary infusion of a placebo solution did not lead to heightened mortality or serious morbidity in these 5 studies. With regard to the cell harvesting procedure no adverse events were reported.

Three major conclusions emanate from our study: 1) 39% of RCTs investigating efficacy of autologous cell intervention used a double-blind trial design based on a sham procedure; 2) trials using sham delivery were less frequently observed in acute MI compared to chronic IHD; and 3) 23% of these trials reported data on (minor) adverse events. This report shows that the choice for the control group for cell-based interventions in cardiology differs among research groups, which could be related to diverging views on scientific necessity and ethical acceptability of sham. The diversity in the choice of the comparator group, shown by this empirical report, supports the need to clarify when and under what conditions sham is scientifically necessary and ethically acceptable, and when another comparator is more appropriate in clinical trials investigating cell-based interventions for cardiology and other medical fields. This will, among others, probably correlate with the study population, and the risk profile of the sham procedure. Hence, this report can function as a starting point to formulate guidelines for researchers that aim to set up a cell-based randomized trial.

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APPENDIX

For supplemental references, a figure, and a table, please see the online version of this article.

Letters to the Editor

Application of the Gompertz Method for Evaluating Survival Gains in Patients Receiving Cardiac Resynchronization Therapy

In the paper by Finegold et al. (1), the methods used for the survival analysis have been described with insufficient detail. It appears, however, that lifespan gains were calculated through a separate analysis of each individual trial, were then "weighted according to study size," and finally were "averaged across all trials."

This step of the survival analysis, which is described by Finegold et al. (1) in their Results section and not in the Methods, needs to be clarified in at least 2 aspects. First, the weighting process is essential to any meta-analysis, because in this way, between-trial variations are explored and confidence intervals for differences are estimated. So, one question is why the results were presented exclusively on the basis of the pooled (or "average") survival gain, without any information on the gains calculated for each individual trial and without any measure of statistical variability. Second, in the calculation of the trial-specific lifespan gains, the authors state that they "used the Gompertz method for this." However, fitting a Kaplan-Meier curve to the Gompertz equation is a complex task from a mathematical and statistical viewpoint (2,3), and it is unfortunate that no details were provided on this point.

If these inconsistencies are clarified, this paper can be viewed as an important contribution in this field, mainly for reasons of cost-effectiveness. Given that the gain of 1 month can be valued at approximately €5,000 according to common benchmarks (4–7), this study shows that the clinical benefit of this procedure is not, as suggested by short-term data, only approximately 1 month (equivalent to €5,000, which would not even cover the device cost) but could be as high as 6.5 months (equivalent to more than €30,000, which is much more than the cost of the device).

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Reply

Application of the Gompertz Method for Evaluating Survival Gains in Patients Receiving Cardiac Resynchronization Therapy

We thank Dr. Messori and colleagues for asking for clarification on the Methods used in our recent paper.

We should clarify that our Figure 2 used an average weighted solely by the sample size of the 5 trials, because this seemed appropriate weighting for combining rates across trials. The reason