with regard to the risk of death from any cause with the number of patients enrolled. Moreover, any such benefit was likely to decline with time, as seems to have been the case.

What are the implications of these findings for clinical practice? The results of the DANISH trial probably represent the most optimistic estimate of the benefit of ICD therapy in patients with nonischemic heart failure who receive evidence-based treatment. Patients enrolled in trials are usually younger and have fewer coexisting conditions than do those in the community and, as a consequence, have a relatively higher risk of death from cardiovascular causes than from noncardiovascular causes.[6,7] In keeping with this observation, there was a suggestion of a differential response according to age in the present trial, with a possible benefit of ICD therapy with regard to death from any cause among younger patients (<68 years of age). The background rate of death from cardiovascular causes and sudden cardiac death could also be reduced even more in practice by further optimizing pharmacologic therapy, with greater use of mineralocorticoid-receptor antagonists and new treatments shown to reduce risk in heart failure, as well as the use of coronary revascularization in patients with ischemic cardiomyopathy.[8,9] Consequently, the absolute benefit of ICDs in a typical and well-treated population with heart failure might be small. ICDs are expensive and not without adverse effects. It is, therefore, desirable to avoid their use in patients who are unlikely to obtain a worthwhile benefit. These considerations highlight the need to target ICDs to the patients most likely to benefit — that is, those who remain at high absolute risk for sudden cardiac death despite receiving the best available pharmacologic and device therapy. The results of the DANISH trial, coupled with the generally infrequent use of ICDs globally, should open a debate about whether it is ethical to conduct new ICD trials involving the highest-risk patients. The challenge is how to identify such patients.[10]

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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Antibiotic Prophylaxis for Cesarean Delivery — When Broader Is Better

Robert A. Weinstein, M.D., and Kenneth M. Boyer, M.D.

Approximately 4 million babies are born each year in the United States. Of these infants, about a third are delivered by cesarean section. One of the many concerns about cesarean deliveries is the high risk of maternal infectious complications, which are 5 to 10 times more frequent than with vaginal deliveries.[1] During cesarean delivery, the endometrial cavity and operative field may be seeded

with pathogens, carried from the birth canal or the skin, that put mothers at risk for endometritis (incidence without prophylaxis, 4 to 18%) and of surgical-site infections (incidence without prophylaxis, 7 to 10%).[2] To reduce these risks, prophylactic administration of an intravenous periprocedural antibiotic, usually cefazolin, is routinely recommended. Such an infusion reduces these rates by about half.[3] Stringent adherence to infection-control protocols and broader antibiotic regimens might yield further reductions.[4]

In this issue of the *Journal*, Tita and colleagues[5] present the results of a randomized trial comparing the addition of broad-spectrum prophylaxis with adjunctive azithromycin (a macrolide antibiotic) to standard prophylaxis for cesarean deliveries at 14 U.S. hospitals. Approximately 2000 women with singleton pregnancies at 24 or more weeks of gestation and who were in labor or whose membranes had ruptured were randomly assigned to receive a single 500-mg dose of azithromycin or placebo intravenously before the cesarean incision, in addition to the intravenous dose of cefazolin that is routinely recommended at each center. Women with scheduled cesarean deliveries, who are at lower risk for infection than are those undergoing nonelective cesarean section, were excluded.

The rate of the primary composite outcome (endometritis, wound infection, or other infections occurring within 6 weeks after delivery) was significantly lower in the azithromycin group than in the placebo group (6.1% vs. 12.0%, P<0.001), with significant differences in rates of endometritis (3.8% vs. 6.1%, P=0.02) and wound infection (2.4% vs. 6.6%, P<0.001). The rates of a number of other clinically important maternal outcomes, including unscheduled return office visits, hospital readmissions, and receipt of postpartum antibiotics, were also significantly lower in the azithromycin group. Neonatal outcomes, which were tracked up to 3 months, were similar in the two trial groups.

To what can we attribute the marked benefit of adjunctive azithromycin? One plausible factor is the broader spectrum of coverage provided by the drug. The authors' hypothesis in designing the trial was that the addition of azithromycin would provide microbiologic activity against common components of the vaginal mucosal microbiome that usually are not detected by routine cultures. Earlier studies showed that genital or placental colonization with *Ureaplasma urealyticum* significantly increased the risk of postpartum endometritis and wound infection.[6,7] Standard prophylaxis with cefazolin does not have activity against such pathogens. Unfortunately, the study does not include the type of specialized culture data that would help to confirm this hypothesis.

In addition, the study population was at increased risk for infection. Cesarean delivery was nonelective, and in 73% of the women, the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) was 30 or more, and obesity is associated with a doubling in the risk of infectious complications. Although actual doses are not specified, cefazolin may have been underdosed in women with increased BMI values,[8] so that azithromycin improved outcomes on the basis of the additive effects of the two drugs against common surgical pathogens, such as staphylococcus species. In support of this hypothesis, information provided in the Supplementary Appendix accompanying the article (available at NEJM.org) indicates that routine bacterial cultures, when done, were much less frequently positive in the azithromycin group (P=0.001).

The fact that azithromycin concentrates in and is retained for several days in myometrium and adipose tissue provides a rationale for the efficacy of treatment with a single preoperative dose for this surgical site.[9] In a post hoc analysis (with details also provided in the Supplementary Appendix of the article), the addition of azithromycin provided greater benefit in women whose incisions were closed with staples than among those whose incisions were closed with sutures (P=0.02 for interaction). Although post hoc findings must be interpreted with caution, the use of staples is generally discouraged because of an increased risk of infection.[4,10] Pharmacologic data indicating that azithromycin only minimally crosses the placenta into the fetal circulation suggest limited exposure for the infant,[9] although longer follow-up of newborns could provide reassurance that the risks of macrolide complications, such as pyloric stenosis and hearing impairment, are not increased.

Therefore, should azithromycin now be recommended as a routine adjunct to cefazolin for prophylaxis of infectious complications in cesarean deliveries? Before broad recommendations are made, the following issues should be considered. First, the high prevalence of obesity and frequent use of staples in the trial population indicate a

high-risk group who may have been particularly likely to benefit from azithromycin. Second, should the potential pharmacologic benefit of higher doses of cefazolin alone be evaluated further before the addition of a second agent? Third, the collection of prospective microbiologic data would help to test the hypothesis that the prevention of infections caused by vaginal ureaplasma species or similar pathogens accounts for the observed benefit of azithromycin; such data collection could also assist in assessing the effect of broader prophylaxis on maternal and infant microbiomes.

Time will tell whether such findings result in changes in routine antibiotic prophylaxis before cesarean deliveries. However, on the basis of this well-designed, pragmatic, multicenter trial, it seems likely that a single adjunctive 500-mg dose of intravenous azithromycin would reduce a number of infectious complications for some women without established infections who are undergoing nonelective cesarean section.

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Balancing the Evidence Base on Coronary Stents

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The development of percutaneous coronary intervention (PCI) transformed the treatment of obstructive coronary artery disease by creating a less invasive revascularization option to coronary-artery bypass grafting.[1] In the first decade of PCI, clinical outcomes associated with the use of balloon catheters were limited by operator learning curves, early interventional equipment, inadequate antithrombotic therapy, acute vessel closure requiring emergency bypass surgery in 6% of patients, and target-lesion restenosis within 6 months in half the patients. In the second decade, bare-metal stents mostly solved the problem of acute closure by scaffolding the arterial wall and reduced restenosis rates to approximately 20% but created the new challenge of in-stent restenosis. In the third decade, the use of first-generation drug-eluting stents further reduced restenosis rates to less than 5% for most coronary stenoses but was associated with delayed arterial healing and the risk of late stent thrombosis. Now in the fourth decade of PCI, changes in stent design and metal composition, surface polymer coating, and antiproliferative agents have created a second generation of drug-eluting stents that may have better outcomes and a lower risk of stent thrombosis than either their first-generation predecessors or bare-metal stents.[2-4]

The clinical advantages of bare-metal stents over balloon angioplasty, of drug-eluting stents over bare-metal stents, and of second-generation over first-generation drug-eluting stents are obvious to any interventional cardiologist who has performed PCI during the past 25 years. PCI has now evolved into an outpatient procedure with very low complication rates, and recurrent patient symptoms are usually due to progressive disease rather than to target-lesion restenosis or stent thrombosis. At the same time, the investigators in the Norwegian Coronary Stent Trial (NORSTENT),