warranted to understand the role of chemotherapy for patients with *EGFR* mutation–positive NSCLC.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Pignon J-P, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552-9.
2. Kris MG, Gaspar LE, Chaft JE, et al. Adjuvant systemic therapy and adjuvant radiation therapy for stage I to IIIA completely resected non-small-cell lung cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline update. J Clin Oncol 2017;35:2960-74.
3. Chouaid C, Danson S, Andreas S, et al. Adjuvant treatment patterns and outcomes in patients with stage IB-IIIA non-small cell lung cancer in France, Germany, and the United Kingdom based on the LuCaBIS burden of illness study. Lung Cancer 2018;124:310-6.
4. Buck PO, Saverno KR, Miller PJE, Arondekar B, Walker MS. Treatment patterns and health resource utilization among patients diagnosed with early stage resected non-small cell lung cancer at US community oncology practices. Clin Lung Cancer 2015;16:486-95.
5. Kelly K, Altorki NK, Eberhardt WEE, et al. Adjuvant erlotinib versus placebo in patients with stage IB-IIIA non-small-cell lung cancer (RADIANT): a randomized, double-blind, phase III trial. J Clin Oncol 2015;33:4007-14.

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Subcutaneous or Transvenous Defibrillator Therapy

TO THE EDITOR: We inquire about the adjudication of shocks in the Prospective Randomized Comparison of Subcutaneous and Transvenous Implantable Cardioverter Defibrillator Therapy (PRAETORIAN) trial conducted by Knops and colleagues (Aug. 6 issue).[1] Of the 83 patients in the subcutaneous implantable cardioverter–defibrillator (ICD) group who had shocks labeled as "appropriate," 11 had shocks for ventricular tachycardia below the cutoff of 180 beats per minute solely because of oversensing of cardiac signals. For example, ventricular tachycardia at a rate of 150 beats per minute could be sensed as 300 beats per minute. Although the device ultimately terminated an arrhythmia in these 11 patients, oversensing can lead to the highly undesirable outcome of shocks while the patient is awake.

The authors acknowledge that these shocks may have been occasionally clinically desirable but they also could be considered to be unnecessary. They cite a post hoc analysis of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)[2] that showed a strong association between any shocks and higher mortality, and the Multicenter Automatic Defibrillator Implantation Trial (MADIT)–Reduce Inappropriate Therapy (MADIT-RIT),[3] which showed that permissive high-rate programming markedly reduced shocks and decreased mortality. These analyses cited by Knops et al. indicate that shocks for slower ventricular tachycardias are inappropriate because they are both painful and associated with increased mortality.

In the original trial protocol (available with the full text of the article at NEJM.org), Knops et al. defined appropriate shocks as those for ventricular tachycardia at a rate of more than 180 beats per minute. We estimate that if approximately half of these oversensed ventricular tachycardias had been labeled as inappropriate, noninferiority would not have been met.

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1. Knops RE, Olde Nordkamp LRA, Delnoy P-PHM, et al. Subcutaneous or transvenous defibrillator therapy. N Engl J Med 2020;383:526-36.
2. Poole JE, Johnson GW, Hellkamp AS, et al. Prognostic importance of defibrillator shocks in patients with heart failure. N Engl J Med 2008;359:1009-17.

3. Moss AJ, Schuger C, Beck CA, et al. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med 2012;367:2275-83.

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TO THE EDITOR: The PRAETORIAN trial involved a smaller cohort of patients with better-preserved ventricular function and intraventricular conduction than those in previous trials of implantable defibrillators.[1-3] In this trial, the subcutaneous ICD was not significantly inferior to a standard transvenous ICD.

Sudden death can result from ventricular tachycardia or ventricular fibrillation or from asystole; the transvenous ICD can address any of these by cardioversion, defibrillation, antitachycardia pacing, or standard pacing. The subcutaneous ICD has only two of these four capabilities and addresses only ventricular tachycardia or ventricular fibrillation, not asystole. Cardiac arrest is often asystolic,[4] particularly when ventricular function is severely impaired or if conduction is disturbed.

The implantation of a device is not a cure but rather the start of a course of therapy. The cost should be calculated from the time of implantation to death. Our local best price for a transvenous ICD equates to approximately $8,600 in U.S. dollars; the subcutaneous ICD costs approximately $15,000. These devices have a projected battery longevity of 15.4 and 7.3 years, respectively, for a corresponding yearly cost of approximately $560 and $2,050. A higher price demands demonstration of clinical superiority; the current subcutaneous ICD offers half the work for thrice the wage.

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1. The AVID Investigators. Causes of death in the antiarrhythmics versus implantable defibrillators (AVID) trial. J Am Coll Cardiol 1999;34:1552-9.
2. Greenberg H, Case RB, Moss AJ, et al. Analysis of mortality events in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II). J Am Coll Cardiol 2004;43:1459-65.
3. Poole JE, Olshansky B, Mark DB, et al. Long-term outcomes of implantable cardioverter-defibrillator therapy in the SCD-HeFT. J Am Coll Cardiol 2020;76:405-15.
4. Stevenson WG, Stevenson LW, Middlekauff HR, Saxon LA. Sudden death prevention in patients with advanced ventricular dysfunction. Circulation 1993;88:2953-61.

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TO THE EDITOR: Knops and colleagues report that subcutaneous ICDs were noninferior to transvenous ICDs with respect to device-related complications and inappropriate shocks. We have concerns about their trial design.

First, noninferiority testing should assess efficacy for interventions with superior safety or interventions that offer an obvious benefit, such as convenience.[1] With regard to subcutaneous ICDs, the evaluation of superiority for safety outcomes (e.g., inappropriate shocks and complications) or noninferiority for efficacy (e.g., shock efficacy and mortality) would have been more informative. The testing of noninferiority for safety outcomes risks acceptance of a therapy of uncertain and potentially inferior efficacy.

Second, the choice of composite for the primary outcome is debatable. Subcutaneous ICDs led to fewer complications and more inappropriate shocks than transvenous ICDs, as expected.[2] The combination of these two outcomes trending in opposite directions for subcutaneous ICDs and transvenous ICDs decreased the between-group difference and increased the likelihood of a finding of noninferiority.[1,3] Thus, we recommend interpreting the two components of the primary composite outcome of this trial separately when assessing the risks and benefits of choosing a subcutaneous ICD instead of a transvenous ICD.

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1. Mulla SM, Scott IA, Jackevicius CA, You JJ, Guyatt G. How to use a noninferiority trial. In: Guyatt G, Rennie D, Meade MO, Cook DJ, eds. Users' guides to the medical literature: a manual for evidence-based clinical practice. 3rd ed. New York: McGraw-Hill Education, 2015:75-86.
2. Olde Nordkamp LRA, Knops RE, Bardy GH, et al. Rationale and design of the PRAETORIAN trial: a Prospective, RAndomizEd comparison of subcuTaneOus and tRansvenous ImplANtable cardioverter-defibrillator therapy. Am Heart J 2012;163:753.e2-760.e2.

3. Ferreira-Gonzalez I, Montori VM, Busse JW, et al. Composite end points. In: Guyatt G, Rennie D, Meade MO, Cook DJ, eds. Users' guides to the medical literature: a manual for evidence-based clinical practice. 3rd ed. New York: McGraw-Hill Education, 2015:207-18.

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TO THE EDITOR: The PRAETORIAN trial conducted by Knops et al. showed noninferiority of the subcutaneous ICD to the transvenous ICD with respect to device-related complications or inappropriate shocks in patients who had a class I or IIa indication for an ICD but no requirement for pacing. In this trial, 43% of the patients had a first-generation device and 57% had a second-generation device (Table S3 in the Supplementary Appendix, available with the full text of the article at NEJM.org). Since there is a lower incidence of inappropriate shocks with the second-generation subcutaneous ICD than with the first-generation subcutaneous ICD,[1] it would be informative to provide a comparative analysis of the cumulative incidence of inappropriate shocks with the two devices.

In addition, considering the greater battery longevity of second-generation subcutaneous ICDs,[2] longer-term follow-up in this trial might show superiority of second-generation subcutaneous ICDs with respect to device-related complications. Finally, several patients in the subcutaneous ICD group underwent an upgrade to a cardiac resynchronization therapy defibrillator (CRT-D) during the median 4-year follow-up (Table S4 of the article). Accordingly, it appears likely that a device upgrade to a CRT-D within several years may have been warranted in some patients in the subgroup of patients with a low left ventricular ejection fraction (<35%), high New York Heart Association class (III or IV), and wide QRS duration (≥120 msec). This finding may suggest that the exclusion criteria of this trial were incomplete.

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No potential conflict of interest relevant to this letter was reported.

1. Willy K, Reinke F, Bögeholz N, et al. Outcome differences and device performance of the subcutaneous ICD in patients with and without structural heart disease. Clin Res Cardiol 2020;109:755-60.
2. Ali H, Lupo P, Cappato R. The entirely subcutaneous defibrillator — a new generation and future expectations. Arrhythm Electrophysiol Rev 2015;4:116-21.

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THE AUTHORS REPLY: As noted by Mandrola et al., the definitions of appropriate and inappropriate shocks in the PRAETORIAN trial were changed early in the course of the trial. This change took place in July 2011 (4 months after enrollment began), when our trial transitioned from its initial single-center pilot phase to become a multicenter trial. The original definition of an "appropriate" shock included shock therapy for ventricular tachycardia of more than 180 beats per minute; the revised definition included "shock therapy for ventricular tachycardia." The rate cutoff of 180 beats per minute was removed from the definition to allow for variations in programming zones and to be consistent with definitions in other large ICD trials. Since any ventricular tachycardia could be clinically relevant, the definition of shocks used in the SCD-HeFT and the MADIT trials was also used in the PRAETORIAN trial. In the SCD-HeFT, "ICD shocks that followed the onset of ventricular tachycardia or ventricular fibrillation were considered to be appropriate."[1] In the MADIT trials, inappropriate therapy was defined as "therapy delivered for nonventricular tachyarrhythmias."[2] Since the causal association between ICD therapy, including antitachycardia pacing, and death in these trials is uncertain and complex, these citations do not suggest that shock therapy for slower ventricular tachycardia is inappropriate.

With regard to the comments of Gallagher et al.: more ICDs were implanted in the PRAETORIAN trial than in the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial, the MADIT-II trial, and the SCD-HeFT. Also, a median ejection fraction of 30% overall is not a well-preserved ejection fraction, and the 81% of patients with a primary prevention indication in our trial had a mean ejection fraction of 28% — well below the mean ejection fraction of 32% in the AVID trial. Our trial showed no between-group difference in the numbers of patients with sudden cardiac death; this finding suggests that asystolic cardiac arrest was not frequent. Moreover, the subcutaneous ICD supplies post-shock pacing for up to 30 seconds. Finally, Gallagher

et al. refer to costs associated with the subcutaneous ICD. However, a thorough cost-efficacy analysis should compare both the costs of the implant itself and implantation of the device and the costs of device-related complications and hospitalizations. For example, our trial showed 50% fewer device infections in the subcutaneous ICD group than in the transvenous ICD group. Treatment for a patient with an infected ICD costs more than £20,000 (approximately $27,500 in U.S. dollars) in the United Kingdom and more than $40,000 in the United States.[3]

The PRAETORIAN trial investigated the difference in safety outcomes between the transvenous ICD and the subcutaneous ICD, since efficacy was established in previous trials.[4] Noninferiority and superiority analyses for the primary end point were scheduled and performed. Kim et al. correctly point out that inappropriate shocks and complications have diverging trends. However, we did not anticipate this divergence in our design.[5] The PRAETORIAN-XL trial, a substudy of the PRAETORIAN trial, is under way to assess these outcomes separately in the prolonged follow-up period (an additional 4 years).

We agree with Sato and Nojiri that a large percentage of the subcutaneous ICDs in the PRAETORIAN trial were first-generation devices, which have a higher incidence of inappropriate shocks than later-generation devices. Follow-up is under way to investigate end points with newer algorithms and later-generation devices.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Poole JE, Johnson GW, Hellkamp AS, et al. Prognostic importance of defibrillator shocks in patients with heart failure. N Engl J Med 2008;359:1009-17.
2. Moss AJ, Schuger C, Beck CA, et al. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med 2012;367:2275-83.
3. Brough CEP, Rao A, Haycox AR, Cowie MR, Wright DJ. Real-world costs of transvenous lead extraction: the challenge for reimbursement. Europace 2019;21:290-7.
4. Lewis GF, Gold MR. Safety and efficacy of the subcutaneous implantable defibrillator. J Am Coll Cardiol 2016;67:445-54.
5. Olde Nordkamp LR, Knops RE, Bardy GH, et al. Rationale and design of the PRAETORIAN trial: a Prospective, RAndomizEd comparison of subcuTaneOus and tRansvenous ImplANtable cardioverter-defibrillator therapy. Am Heart J 2012;163:753.e2-760.e2.

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Women Physicians and Promotion in Academic Medicine

TO THE EDITOR: The article by Richter et al. (Nov. 26 issue)[1] highlights the persistence of gender inequity and confirms the lack of advancement of women in academic medical leadership.[2,3] Equity in health leadership is both a fundamental social justice issue and a population health issue.[4,5] We propose that the time has come to move beyond describing the problems. It is time for effective large-scale change to move the dial on this issue. Building the evidence base on best practices to support gender equity is vital in order to achieve effective, long-term, sustainable career advancement for women in health, including those in academic medicine.[4,5] Women cannot simply be expected to be more like their male colleagues to succeed. There is also a recognized need to move away from individual women having to battle entrenched barriers to career advancement, toward policy-, systems-, and organization-level approaches; this shift would enhance the ability and motivation of women to advance in their careers and provide opportunities for them to do so.[2,3]

We are currently leading a competitive Australian initiative funded by the National Health and Medical Research Council for the advancement of women in health leadership. This initiative engages health services, professional colleges, and government. Through collaborative implementation research, we aim to strengthen evidence on effective organizational change and to translate this new knowledge into strategies, policies, and practice in order to address gender inequity in health care leadership.

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