Age and Effectiveness of Prophylactic Implantable Cardioverter-Defibrillators

TO THE EDITOR: Santangeli and colleagues’ meta-analysis (1) evaluating the effectiveness of implantable cardioverter-defibrillators (ICDs) for primary prevention of sudden cardiac death among young and elderly patients concluded that available data do not definitively show that ICDs improve survival in elderly patients. We agree with the authors that these findings have important clinical implications and might support the theory that cardiac resynchronization therapy alone may be the best device therapy for elderly (>65 years) patients with severe left ventricular dysfunction. However, we would like to raise several points that may shed additional light on the findings and implications of this meta-analysis.

The meta-analysis included data on ICD benefits in different age groups without adjustment for clinical characteristics. Important differences exist in the epidemiology, clinical characteristics, management, and outcome of elderly patients compared with their younger counterparts (2, 3). However, the most important difference is that elderly patients have more comorbid conditions. Thus, the proportion of patients who die of ventricular tachyarrhythmia is lower among elderly patients than younger patients. To explore the effectiveness of ICDs among young and elderly patients, it is important to neutralize the effects of comorbid conditions by adjusting for clinical variables or by setting sudden cardiac death as the primary end point instead of all-cause mortality.

In MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) (4), we showed that after adjustment for multiple clinical variables, the beneficial effects of primary ICD implantation in reducing all-cause mortality were most prominent among patients aged 65 to 74 years (hazard ratio [HR], 0.63 [95% CI, 0.41 to 0.95]; P = 0.03), intermediate among patients 75 years or older (HR, 0.70 [CI, 0.41 to 1.20]; P = 0.20), and lowest among patients younger than 65 years of age (HR, 0.79 [CI, 0.48 to 1.29]; P = 0.35). These results were stronger for the end point of sudden cardiac death, demonstrating a significant benefit for all 3 age groups (4). In addition, our risk score showing a U-shaped pattern for ICD efficacy comprised 5 clinical risk factors, including age older than 70 years (5).

In conclusion, data from MADIT-II have consistently shown that age does not attenuate the benefit of ICD therapy, whereas comorbid conditions, including impaired renal function and atrial fibrillation, do. Therefore, the main implication for clinicians should be to perform appropriate risk assessment before ICD implantation, regardless of a patient’s age. The increasing number of elderly patients who have left ventricular dysfunction and heart failure warrants a prospective, randomized ICD trial in this population.

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Potential Conflicts of Interest: None disclosed.

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an adequately designed, randomized trial of prophylactic device therapy in elderly patients will definitely address this relevant issue.

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Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M10-0999.

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Should Patients With Stroke Wear Compression Stockings?

TO THE EDITOR: Kearon and O’Donnell’s editorial (1) suggests that the lack of evidence in favor of using compression stockings supports the recommendations of the American College of Chest Physicians and the American Heart Association for the use of low-dose unfractionated heparin and low-molecular-weight heparin in patients with acute ischemic stroke and immobility who have no contraindications to anticoagulant therapy. However, this advice assumes that the balance of benefits and harms favors reducing the incidence of venous thromboembolism (VTE) over increasing the incidence of symptomatic intracerebral hemorrhage (SICH). It is unfortunate that data from large trials, such as the IST (International Stroke Trial) (2) and TAIST (Tinzaparin in Acute Ischemic Stroke Trial) (3), suggest that this treatment is as likely to cause SICH as it is to prevent pulmonary embolism.

Prophylactic low-dose anticoagulation may help to treat patients at high risk for VTE in whom the risk for VTE is likely to outweigh the risk for SICH. However, the benefit of this therapy in patients at lower risk, such as those included in trials to date, remains unproved.

Treatment with heparin is costly both in terms of the drug itself and the time and money involved in having a nurse administer it. Although the risk–benefit ratio remains unclear, we do not believe that low-dose heparin should be used routinely for prevention of VTE in most patients with stroke.

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Potential Conflicts of Interest: Professor Philip Bath was the principal investigator of TAIST.

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2. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet. 1997:349:1569-81. [PMID: 9174558]
3. Bath PM, Lindenstrom E, Boysen G, De Deyn P, Friis P, Leys D, et al. Tinzaparin in acute ischaemic stroke (TAIST): a randomised aspirin-controlled trial. Lancet. 2001;358:702-10. [PMID: 11551576]

IN RESPONSE: Dr. Sprigg and colleagues note that they “do not believe that low-dose heparin should be used routinely for the prevention of VTE in most patients with stroke.” We agree that low-dose heparin should not be used routinely in patients with ischemic stroke and did not make such a suggestion (1). As Dr. Sprigg and colleagues also note, “Prophylactic low-dose anticoagulation may help to treat patients at high risk for VTE in whom the risk for VTE is likely to outweigh the risk for SICH.”

If CLOTS (Clots in Legs Or sTockings after Stroke) Trial 1 (2) had found that graduated compression stockings were very effective at preventing VTE, we would recommend this intervention over low-dose heparin in all patients with stroke, including those at highest risk for VTE. However, it found that graduated compression stockings did not work (2), and therefore, an effective alternative to low-dose anticoagulation to prevent VTE in patients with ischemic stroke does not currently exist. Lack of an alternative to prevent VTE does not mean that low-dose anticoagulation should be used routinely but does strengthen the argument for, as we suggested, “the cautious use of these agents” in patients with acute ischemic stroke and immobility without additional contraindications to anticoagulant therapy.

We propose that the findings of the IST (3) and TAIST (4) are mostly of indirect relevance to this discussion and, indeed, are consistent with our position. TAIST compared high- and intermediate-dose tinzaparin with aspirin in the acute treatment of ischemic stroke (4). This trial did not evaluate whether low-dose tinzaparin, as used to prevent VTE, was beneficial.

The IST compared high-dose unfractionated heparin (12 500 U twice daily) and low-dose unfractionated heparin (5000 U twice daily) with no anticoagulation (3). High-dose therapy was associated with greater harm than benefit. Low-dose therapy was associated with greater benefit than harm; however, we agree that the findings of this subgroup analysis are not definitive. An additional consideration is that if the IST had enrolled only participants with stroke and immobility— that is, persons with a high risk for VTE, a population group similar to those who are the focus of this discussion and that were enrolled in the CLOT Trials—the balance of benefit (reduction
in VTE) to harm (increased intracranial bleeding) may have further favored low-dose heparin.

Finally, both of these trials evaluated the use of heparin in the acute phase of stroke (within 48 hours of onset), when the risk for hemorrhagic transformation is greatest. In patients at increased risk for intracerebral hemorrhage, delayed introduction of low-dose heparin may further alter the balance of benefit to harm. It is hoped that the ongoing CLOTS Trial 3, which is comparing intermittent pneumatic compression with a control group, will identify an effective way to prevent VTE in patients with acute stroke and immobility without increasing the risk for bleeding.

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Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M10-2116.

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Observation

Acute Hepatitis A Virus Infection Without IgM Antibodies to Hepatitis A Virus

Background: Hepatitis A virus (HAV) is the leading cause of acute viral hepatitis in industrialized countries. Diagnosis of acute HAV infection is usually based on detection of anti-HAV IgM antibodies, which are present in more than 99% of affected persons at the onset of illness (1).

Objective: To describe a case of acute HAV infection in a patient without anti-HAV IgM antibodies.

Case Report: A 32-year-old woman with no history of liver disease was hospitalized for deterioration of liver function. Her medical history was unremarkable except for a diagnosis of rheumatoid arthritis 12 years ago, which was treated with several regimens that included a corticosteroid, aurothiopropion sulfonate, methotrexate, and etanercept. Therapy with these drugs became ineffective and was stopped 1 year ago. Infusion therapy with rituximab, 1 g, was administered at that time, 2 weeks later, and 1 year later, according to the usual protocols for rheumatoid arthritis. During this period, she also received azathioprine, 50 mg/d, and prednisolone, 5 mg/d.

Two weeks after her third infusion of rituximab, the patient developed nausea, vomiting, and a temperature of 39.0 °C. Laboratory studies showed normal leukocyte and platelet counts, alanine aminotransferase levels 5.6 times the upper limit of normal, γ-glutamyltransferase levels 4.7 times the upper limit of normal, alkaline phosphatase levels 1.1 times the upper limit of normal, an international normalized ratio of 1.21, serum immunoglobulin titers in the normal range, and negative antiliver autoantibodies.

Results of tests that included RNA amplification were negative for hepatitis C and E viruses. Hepatitis B antibody assays found only antibodies to hepatitis B surface antigen, which suggested that the patient had previously received a hepatitis B vaccine. Results of tests for HAV antibodies using the MONOLISA Anti-HAV EIA kit (Bio-Rad Laboratories, Redmond, Washington) were negative for anti-HAV IgM antibodies and positive for total anti-HAV antibodies, which seemed to rule out acute HAV infection. Results of polymerase chain reaction tests were negative for cytomegalovirus, Epstein–Barr virus, and herpes simplex virus.

Treatment with all of the patient’s medications was withdrawn, but her liver function continued to worsen. A transjugular liver biopsy showed conserved portal tracts without fibrosis but with significant inflammatory infiltration composed of lymphocytes, neutrophils, and eosinophils, which suggested viral or toxic liver injury. On hospital day 25, we transferred her to the transplantation unit. Her international normalized ratio was 1.65, and alanine aminotransferase levels were 134 times the upper limit of normal. She developed cardiac arrest several hours after transfer and died.

Results of repeated anti-HAV IgM antibody assays performed on blood samples obtained 2 days before the patient died were positive. Further analysis of blood samples obtained on admission and kept frozen found HAV RNA and low avidity for HAV-specific IgG antibodies (avidity index, 20%), which suggested a recent infection. Blood samples obtained 1 year before admission and kept frozen were negative for total anti-HAV antibodies.

Discussion: We could not initially diagnose this patient’s acute HAV infection because of the absence of anti-HAV IgM antibodies. In addition, the presence of anti-HAV IgG antibodies suggested a resolved HAV infection and excluded early-phase acute HAV infection, when HAV antibodies are not detectable (2). However, immunocompromised patients may have an impaired adaptive immune response to infection; for example, the absence of anti–hepatitis C virus antibodies have been reported in patients co-infected with HIV and hepatitis C virus (3).

This patient had an atypical immune response to HAV, despite serum immunoglobulin titers within the normal range. Rituximab is a chimeric monoclonal antibody that targets CD20+ B cells and differentially affects serum antibody titers, especially those of IgM antibodies (4). The generation of anti-HAV IgM antibodies after acute infection requires cooperative interaction of antigen-specific T cells and B cells. We therefore believe that rituximab depleted this patient’s B cells, which led to an impaired immune response just as it can lead to an impaired response to vaccination (5).

In conclusion, physicians should consider administering HAV vaccine before prescribing rituximab. Also, physicians should try to diagnose acute HAV infection in immunocompromised patients, es-
especially those receiving rituximab, by using polymerase chain reaction tests instead of anti-HAV IgM antibody assays.

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Potential Conflicts of Interest: Dr. Mallet: Board membership: Merck; Consultancy: Gilead Science; Payment for lectures, including service on speakers’ bureaus: Roche, Bristol-Myers Squibb, Gilead Science, Merck; Patents (planned, pending, or issued): INSERM.

Reproducible Research Statement: Study protocol and statistical code: Not available. Data set: Available from Dr. Mallet (e-mail, vincent.mallet@cch.aphp.fr) after establishing written agreement with the authors.

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CORRECTIONS

Correction: Surveillance for Hepatocellular Carcinoma in the United States

In the recent article by Davila and colleagues (1), the row labels "Men" and "Women" in Table 1 were switched. This has been corrected in the online version.

Reference
1. Davila JA, Henderson L, Kramer JR, Kanwal F, Richardson PA, Duan Z, et al. Utilization of surveillance for hepatocellular carcinoma among hepatitis C virus-infected veterans in the United States. Ann Intern Med. 2011;154:85-93. [PMID: 21242565]

Correction: Recommended Adult Immunization Schedule: United States, 2011

The recent immunizations guidelines (1) contained a few errors. In Figure 2, there is no recommendation for vaccination for human papillomavirus in pregnant women. The word “seasonal” is no longer used to qualify influenza now that there is no longer pandemic vaccine. Also in Figure 2, the phrase “for females” has been removed in the recommendation for human papillomavirus. The first sentence of the fifth paragraph on page 168 should read as follows: “The meningococcal conjugate vaccine (MCV4) footnote (footnote 9) has language added to indicate that a 2-dose series of meningococcal conjugate vaccine is recommended. . . . ” (i.e., the word “conjugate” has been added to the second mention of meningococcal vaccine). In footnote 9 of the figure, “conjugate” should also appear in the phrase, “Medical: A 2-dose series of meningococcal conjugate vaccine is recommended for adults. . . . ” These changes have been made in the online version.

Reference
1. Advisory Committee on Immunization Practices. Recommended adult immunization schedule: United States, 2011. Ann Intern Med. 2011;154:168-73. [PMID: 21282696]
**CORRECTION: ACUTE HEPATITIS A VIRUS INFECTION**

The authors of a recent letter (1) should be listed in the following order:

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This has been corrected in the online version.

Reference

1. Chakvetadze C, Gaussec L, Mallet V, Hannoun L, Pol S. Acute hepatitis A virus infection without IgM antibodies to hepatitis A virus. Ann Intern Med. 2011;154:507-8. [PMID: 21464358]