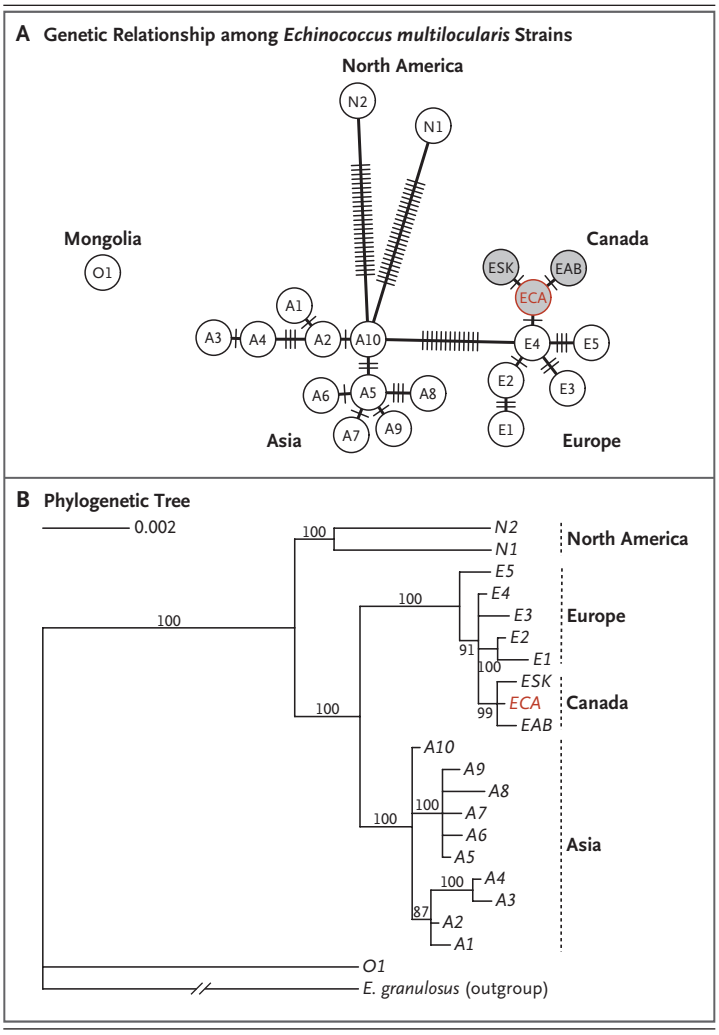

Figure 1. Genetic Relationship between Historic and Newly Identified Strains of *Echinococcus multilocularis*, According to Geographic Location.

Panel A shows the genetic relationship among the previously described strains of *Echinococcus multilocularis* worldwide in the GenBank sequence database and the newly identified endemic strains (ECA, EAB, and ESK) in 77 parasite specimens obtained from the animal reservoir in Alberta and southern Saskatchewan in Canada. One of these strains (ECA, shown in red) caused at least five of seven cases of human alveolar echinococcosis that were diagnosed from 2013 to 2018 in Alberta on the basis of histopathological, serologic, and polymerase-chain-reaction assays. The other North American samples were previously described in specimens obtained in the United States. Panel B shows the phylogenetic tree inferred by partitioned Bayesian analysis performed on concatenated mitochondrial DNA, with the use of *E. granulosus* as an outgroup. The 0.002 scale bar denotes the genetic distance in nucleotide substitutions per site.

of the strain was not possible, and the patient's travel history, although suggestive of local acquisition, was not conclusive.

These data support the hypothesis that the establishment of a European-like strain of *E. multilocularis* in animal hosts in Canada may result in the emergence of human alveolar echinococcosis in North America.

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Early or Delayed Cardioversion in Recent-Onset Atrial Fibrillation

TO THE EDITOR: Pluymaekers et al. (April 18 issue)[1] evaluated the occurrence of spontaneous cardioversion in patients with recent-onset (<36 hours) atrial fibrillation. The proposed "wait-and-see" approach included cardioversion within 48 hours in the absence of spontaneous resump-

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tion of sinus rhythm, and delayed cardioversion was actually necessary in 28% of the patients randomly assigned to this strategy. We think that the idea of waiting for spontaneous cardioversion of atrial fibrillation is interesting, but for practical reasons, better patient targeting would be required. In two previous prospective, randomized trials, we found that in patients with recent-onset atrial fibrillation, spontaneous cardioversion can be predicted with the use of two clinical factors that are easily identified on admission: absence of underlying heart disease[2] and age of 60 years or less.[3] In addition, in a prospective trial, Danias et al.[4] found that a duration of atrial fibrillation of less than 24 hours was a statistically significant predictor of spontaneous conversion to sinus rhythm. In view of these findings, we think that the wait-and-see approach would be best applied to patients who are most likely to have spontaneous conversion, thus limiting the need for delayed cardioversion.

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TO THE EDITOR: Pluymaekers et al. showed that a wait-and-see approach was noninferior to early cardioversion in maintaining sinus rhythm after 1 month in patients who presented to the emergency department with symptomatic atrial fibrillation. The authors' delayed approach consisted of scheduling follow-up outpatient visits the day after presentation. If atrial fibrillation remained present, patients were referred back to the emergency department for cardioversion.

Unfortunately, such an approach may prove impractical in many hospitals with limited resources and could affect health care expenditures. The longer duration of the index visit (a median of 30 minutes) with early cardioversion should be weighed against the greater number of visits to the outpatient clinic with the wait-and-see approach.

Furthermore, an early pharmacologic cardioversion strategy may test the safety and efficacy of antiarrhythmic drugs, which can then be prescribed for administration by the patient (i.e., the "pill-in-the-pocket" approach), thus further reducing the future likelihood of emergency department visits.[1-3]

In addition, early cardioversion may improve patients' immediate satisfaction with their care.[4] Therefore, it would have been interesting to assess quality of life directly after patients were sent home and at other times before 4 weeks had passed.

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TO THE EDITOR: The results of the trial by Pluymaekers et al., in which delayed cardioversion was found to be noninferior to early cardioversion in patients presenting to the emergency department with recent-onset atrial fibrillation,

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encourage shared decision making. Practices in North America differ from those in Dutch hospitals. The authors favor a delayed approach because it reduces the use of physician-mediated cardioversion, which requires an anesthesiologist, cardiologist, or both. In North America, however, emergency physicians provide sedation and perform cardioversion unassisted.[1-3] The authors reported that a wait-and-see approach effected a 30-minute reduction in the duration of the initial visit but that a next-day clinic visit and a second emergency visit were needed for 28% of patients assigned to this approach. The authors assert that the approach was "not necessarily more time consuming." Yet in North America, these next-day visits would certainly be time consuming, and policy makers are actively seeking to reduce, not increase, visits to an overtaxed emergency system. For many patients (and their employers), the additional time away from work imposes an economic burden, and in the United States, each visit requires an out-of-pocket copayment. Add to this the known increase in the risk of thromboembolism associated with delayed cardioversion in patients who are not receiving anticoagulation therapy,[4] and our preference for early rhythm control becomes intelligible.

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THE AUTHORS REPLY: Boriani and Biffi comment that our wait-and-see approach might be enhanced by the application of more stringent patient selection. As many as 69% of patients had spontaneous conversion to sinus rhythm less than 48 hours after the onset of atrial fibrillation. Application of their selection rules raises this figure only slightly, to 80%, indeed reducing delayed cardioversions. However, the number of early cardioversions would increase dramatically. In our population, their algorithm lacks sensitivity, and its application would have unduly withheld the wait-and-see approach from 167 of the 218 initial wait-and-see patients (77%), of whom 65% had spontaneous cardioversion. Obviously, further studies are needed to improve the rules guiding conversion prediction and the effect these rules have on the use of early cardioversion.

We agree with Compagnucci and colleagues that the adoption of a wait-and-see approach precludes observation of responses to antiarrhythmic drugs (conduction abnormalities, ventricular arrhythmias, or a Brugada pattern on electrocardiography) that are "diagnostic."[1] Surely, their approach enhances the safety and applicability of pill-in-the-pocket cardioversion of recurrent atrial fibrillation.[2] However, patients who qualify for drug treatment nowadays usually undergo catheter ablation. Immediate patient satisfaction may be higher with early conversion, but our trial shows that it is not maintained after 30 days. Above all, the positive initial reaction of the patient fuels an excess of attention by attending physicians to short-term rhythm control, a practice that may lead to antiarrhythmic overtreatment and serve as a distraction from the installation of appropriate cardiovascular risk management, including anticoagulation therapy.[3]

We agree with Vinson and Atzema that cardioversion strategies and local logistics vary greatly[4] but disagree that the wait-and-see approach increases the burden of care on the emergency department. Our approach undeniably frees up capacity and reduces unplanned cardioversions. In addition, pathways to the treatment of atrial fibrillation can be simplified, since the wait-and-see strategy enables planning for cardioversion, which may then be performed in outpatient facilities rather than overcrowded emergency departments. Our findings may feed restructuring processes intended to improve and reduce the variability in the logistics of cardioversion. It is also important to note that our

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approach allows for the avoidance of potentially harmful treatment in two thirds of patients. The argument concerning the increased risk of stroke with delayed cardioversion does not hold. With or without cardioversion, it is mandatory to assess the risk of stroke and to initiate or continue appropriate anticoagulation therapy indefinitely in all high-risk patients. Unfortunately, this fact is often overlooked.[3] In contrast, in low-risk patients, cardioversion may be performed safely within 48 hours without anticoagulation therapy.[5]

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

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Verubecestat for Prodromal Alzheimer's Disease

TO THE EDITOR: Egan et al. (April 11 issue)[1] report adverse neurologic effects, including decreased memory and cognition, in a trial of verubecestat involving patients with prodromal Alzheimer's disease. Henley et al.[2] observed similar findings in a trial of atabecestat involving patients with presymptomatic Alzheimer's disease.

These compounds inhibit β-site amyloid precursor protein–cleaving enzyme (BACE). With support from the National Institute on Aging, we conducted neurobiologic studies of verubecestat and two other BACE inhibitors (lanabecestat and LY2886721). All three compounds inhibited long-term potentiation, an electrophysiologic correlate of memory, in mouse hippocampus. Two of the three inhibitors decreased paired-pulse facilitation, a measure of presynaptic neurotransmitter release, and all three impaired burst-induced short-term plasticity, which reflects both presynaptic and postsynaptic mechanisms (Fig. 1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

These data, along with those from other studies,[3-5] may provide a mechanistic explanation for the impaired memory and cognition that were reported in the two human trials: BACE inhibitors interfere with the physiologic processing of known neuronal substrates of BACE (e.g., Scn2b and Sez6) that are required for neurotransmission. It may be useful to identify BACE-1 inhibitors that selectively decrease the processing of amyloid precursor protein more than that of other substrates to potentially enable safer long-term inhibition of this amyloid-generating protease.

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Dr. Selkoe reports being a director of and consultant to Prothena Biosciences. No other potential conflict of interest relevant to this letter was reported.

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