from RCTs. Examination of the reasons behind this contra-
diction by the regulatory agency may help to improve the
reliability of this new program.

Ilke Sipahi, MD
Seden Celik, MD
Nurdan Tozun, MD

**Author Affiliations:** Department of Cardiology, Acibadem University Medical
School, Istanbul, Turkey (Sipahi, Celik); Harrington Heart and Vascular Institute,
University Hospitals Case Medical Center, Case Western Reserve University
School of Medicine, Cleveland, Ohio (Sipahi); Department of Internal Medicine,
Acibadem University Medical School, Istanbul, Turkey (Tozun).

**Corresponding Author:** Ilke Sipahi, MD, Department of Cardiology, Acibadem
University Medical School, Acibadem Maslak Hospital, Buyukdere Cad 40,
34457 Istanbul, Turkey (ilkesipahi@gmail.com).

**Published Online:** November 18, 2013. doi:10.1001/jamainternmed.2013.12217.

**Author Contributions:** Dr Sipahi had full access to all of the data in the study
and takes responsibility for the integrity of the data and the accuracy of the data
analysis.

**Study concept and design:** Sipahi.

**Acquisition of data:** Sipahi.

**Analysis and interpretation of data:** All authors.

**Drafting of the manuscript:** Sipahi.

**Critical revision of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** Sipahi.

**Administrative, technical, or material support:** Sipahi.

**Study supervision:** Tozun.

**Conflict of Interest Disclosures:** None reported.

1. Southworth MR, Reichman ME, Unger EF. Digabitrin and postmarketing

2. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and
   Investigators. Dabigatran versus warfarin in patients with atrial fibrillation.


4. Schulman S, Kearon C, Kakkar AK, et al; RE-MEDY Trial Investigators;
   RE-SONATE Trial Investigators. Extended use of dabigatran, warfarin, or

   http://www.fda.gov/downloads/AdvisoryCommittees/CommitteeMeetingMaterials /
   Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM226009.pdf. Accessed
   July 2013.

   boehringer-ingelheim.com/content/dam/internet/opi/clinicaltrial

**Editor’s Note**

**Multiple Data Sources, the Best Way to Gather Safety Information About Medications**

The US Food and Drug Administration’s (FDA) Mini-Sentinel Program is an important initiative to identify adverse
effects of new medications during the postapproval period. The system links
electronic data from a variety of health care providers so as to rapidly determine the safety
of medications in use.

The system is especially useful for identifying adverse effects that might not be apparent in randomized clinical
trials because they are rare, occur in patient groups not

**Digitalis Use in Contemporary Clinical Practice: Refitting the Foxglove**

Over 200 years after William Withering wrote the classic mono-
graph, *An Account of the Foxglove and Some of Its Medicinal
Uses,*1 the indications for and optimal dosing of digitalis gly-
cosides (primarily prescribed as digoxin) continue to be de-
bated. Convincing evidence regarding the purported benefits
of digoxin was unavailable until the Digitalis Investigation
Group (DIG) trial, published in 1997.2 This study was
approved by the institutional review board at each partici-
pating center.

The DIG trial was a large-scale, international, prospec-
tive trial that randomized 6800 ambulatory adult patients
with symptomatic heart failure (HF) to digoxin treatment or
placebo. Enrolled patients were receiving concomitant
HF therapy with diuretics (81% of patients) and angiotensin-
converting enzyme (ACE) inhibitors (94% of patients). Nota-
bly, patients with atrial fibrillation were excluded from the
trial. Treatment with digoxin had no significant reduction
in all-cause mortality, although it led to a 28% relative
risk reduction for hospital admission for worsening
HF within a mean follow-up of approximately 3 years
(Box).

Little is known about the patterns of digoxin use for the
treatment of HF since the publication of the DIG trial, and
the use of digoxin in HF therapy remains controversial.
Concern about digitalis toxicity, along with the advent of
other agents shown to confer a mortality benefit, such as

---
