JACC VOL. 65, NO. 2, 2015
JANUARY 20, 2015:217–23

was completed in 4 patients with incessant VT: before the diagnosis of TB in 1 patient and during anti-TB treatment in the remaining 3 patients. Patients were followed up at 1, 3, and 6 months after the initiation of anti-TB treatment and when clinically warranted. The response was assessed after the intensive phase of anti-TB treatment in terms of clinical improvement, change in ejection fraction by echocardiography, and change in 18-fluorodexoyglucose uptake by PET/CT.

There was significant improvement in ejection fraction (mean 46.7 ± 14.4% to 50.8 ± 16.1%; p = 0.009). All patients but 1 became free of VT. In a follow-up PET/CT (n = 11), abnormal metabolic activity resolved completely in the myocardium in 4 patients and in the lymph nodes in 9 patients (Table 1). There were no deaths.

Our observations suggest that TB can present as idiopathic VT or unexplained ventricular dysfunction; patients may not have constitutional symptoms. Biopsy targeting fluorodeoxyglucose-avid lymph nodes rather than endomyocardial biopsy is more useful in making a clinical diagnosis. It may be prudent to investigate all patients with unexplained VT or left ventricular dysfunction and lymphadenopathy for myocardial TB, especially in those areas where the prevalence of TB is high. By subjecting the biopsy specimen to mycobacterial culture, TB polymerase chain reaction and histopathologic examination will help in distinguishing between TB and sarcoidosis—another granulomatous condition that may present in a similar fashion (4). This report serves to highlight the fact that myocardial TB may be more common than believed. Early diagnosis is important to prevent morbidity and mortality.

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http://dx.doi.org/10.1016/j.jacc.2014.09.087

Please note: Dr. Narasimhan has received research grants from Biosense Webster, Inc., Medtronic, Inc., and St. Jude Medical, Inc.; and a fellowship grant from Medtronic, Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. The authors thank John G. Cleland, Foundation Chair of Cardiology at the University of Hull, for useful suggestions.

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Increased Mortality by Digoxin in Patients With Atrial Fibrillation?

In the TREAT-AF (Retrospective Evaluation and Assessment of Therapies in AF) study (1), the effect of digoxin on overall mortality in patients with incident atrial fibrillation (AF) was studied. In this observational study, after adjustment for potential confounders with the Cox proportional hazards model and propensity score analyses, digoxin was associated with an increased risk (21% to 24%) of death. The investigators extensively discussed the potential limitations of their study, but I have 2 questions about the design choices.

First, the investigators stated that patients were placed in the digoxin group versus the reference group on the basis of use of digoxin within the first 90 days after the diagnosis of AF. Digoxin is the first choice for therapy in patients with AF complicated by heart failure and the second choice in patients whose first choices for treatment of AF, beta-blockers and calcium channel antagonists, are not effective enough. When only the first 90 days are used for exposure classification, there may be a substantial misclassification of digoxin in both the digoxin group and the reference group. The fact that the medication possession ratio of digoxin was only calculated for the digoxin group does not take into account such misclassification.

Second, the investigators stated that they adjusted for the medication possession ratio in the multivariate Cox analysis. I do not understand this: how can you adjust for a variable that is zero in all patients in the reference group and a certain number between zero and one in the digoxin group? I believe the appropriate analysis would be to stratify the digoxin group with different medication possession ratios and compare these with the reference group.

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http://dx.doi.org/10.1016/j.jacc.2014.09.081

Please note: Dr. de Boer is a member of 2 steering committees of projects that are financed by GlaxoSmithKline and 2 umbrella organizations: the European Federation of Pharmaceutical Industries and Associations and the Association of the European Self-Medication Industry. These relationships are not relevant to the contents of this letter.

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1. Turakhia MP, Santangeli P, Winkelmayer WC, et al. Increased mortality associated with digoxin in contemporary patients with atrial fibrillation: findings from the TREAT-AF study. J Am Coll Cardiol 2014;64:660–8.

REPLY: Increased Mortality by Digoxin in Patients With Atrial Fibrillation?

Dr. de Boer brings up some important design considerations regarding our analysis of the TREAT-AF (Retrospective Evaluation and Assessment of Therapies in AF) study (1). He correctly argues that there can be misclassification of digoxin exposure in our design. Our observational study was designed as an intention-to-treat analysis, comparing the strategies of use and nonuse of digoxin as initial or early therapy in patients with newly diagnosed atrial fibrillation (AF) (1). Although we found that 80% of patients in the digoxin arm were still on therapy at 1 year, there is a strong possibility of digoxin exposure in the control arm after 90 days. However, we believe this would not represent "misclassification" in an intention-to-treat design but rather crossover of therapy. Generally, crossover would bias toward the null and therefore would not likely account for the observed difference in outcomes.

Therapy crossover is common in management of AF and complicates analysis and interpretation of randomized trials. Crossover may be motivated by observed and unobserved confounders, which can further complicate analysis and may in part explain the seemingly incongruent results of 2 secondary analyses of digoxin using the same AFFIRM (AF Follow-Up Investigation of Rhythm Management) trial data set (2,3). Separating patients into exposed and unexposed blocks of person-time without adjusting for time-varying confounders could exaggerate treatment effect (or harm) (4). On the other hand, contemporary approaches such as marginal structural models that incorporate time-varying data can bias toward the null from overadjustment or model misspecification (5).

For these reasons, we elected to study a new disease cohort using an intention-to-treat design that evaluated digoxin as an initial treatment strategy. Our decision to adjust for adherence rather than to stratify was to account for variation in adherence in the overall point estimate. We agree that further work to explore the heterogeneity of treatment effects across strata of adherence and time course of therapy would be valuable and complementary.

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Patent Foramen Ovale and Paradoxical Systemic Embolism

Can We Determine High-Risk Characteristics by Echocardiography?

We read with interest the review paper on paradoxical embolism by Windecker et al. (1). It was suggested, on the basis of available evidence from published reports, that device closure of patent foramen ovale (PFO) should be considered in patients with first-time cryptogenic stroke, particularly in those with high-risk criteria, such as presence of an atrial septal aneurysm (ASA), large PFO, Eustachian valve, or Chiari network. The viewpoints of