tomography or cardiac magnetic resonance (CMR), may find wider spread clinical application.

Cardiac fibrosis is recognized as the major substrate for ventricular arrhythmias and the assessment of fibrosis is likely to become central to risk stratification for sudden death in DCM. Combining late gadolinium enhancement (LGE) and T1 mapping with extracellular volume (ECV) quantification, CMR can provide a comprehensive, noninvasive evaluation of the substrate, in terms of both localized and diffuse fibrosis. Both LGE and ECV have been validated histologically against EMB (2,3). Moreover, LGE has shown a strong association with outcomes in DCM, and recent evidences suggest that T1 mapping may add useful prognostic information (4). In consideration of this evidence, CMR might be considered the new gold standard for substrate assessment in patients with chronic heart failure.

Other variables, such as myocardial strain and circulating biomarkers of collagen turnover or galectin 3, have also been associated with myocardial fibrosis. Nowadays, CMR might be used instead of EMB to probe these other markers of fibrosis.

Interestingly, it seems that the LGE status of DCM patients (LGE+ or LGE−) does not change during follow-up (5), thus, continuous reassessment of the fibrotic substrate might be redundant, especially in patients without LGE. This observation, together with the marked differences in prognosis between LGE+ and LGE− patients, may suggest that the presence or absence of LGE identify separate clinical entities within the DCM spectrum.

*Andrea Di Marco, MD
Matthias Schmitt, MD, PhD
Ignasi Anguera, MD, PhD
*Arrhythmia Unit
Heart Institute
Department of Cardiology
Bellvitge University Hospital
Carrer feixa llarga
08907, Barcelona
Spain
E-mail: ayfanciu@hotmail.com

http://dx.doi.org/10.1016/j.jchf.2017.02.015

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Lagan J, Schmitt M, Miller CA. Clinical applications of multi-parametric CMR in myocarditis and systemic inflammatory diseases. Int J Cardiovasc Imaging 2017 Jan 27 [E-pub ahead of print].

2. Iles LM, Ellims AH, Llewellyn H, et al. Histological validation of cardiac magnetic resonance analysis of regional and diffuse interstitial myocardial fibrosis. Eur Heart J Cardiovasc Imaging 2015;16:14–22.

3. Miller CA, Naish JH, Bishop P, et al. Comprehensive validation of cardiovascular magnetic resonance techniques for the assessment of myocardial extracellular volume. Circ Cardiovasc Imaging 2013;6:373–83.

4. Barison A, Del Torto A, Chiappino S, et al. Prognostic significance of myocardial extracellular volume fraction in nonischaemic dilated cardiomyopathy. J Cardiovasc Med 2015;16:681–7.

5. Masci PG, Schuurman R, Andrea B, et al. Myocardial fibrosis as a key determinant of left ventricular remodeling in idiopathic dilated cardiomyopathy: a contrast-enhanced cardiovascular magnetic study. Circ Cardiovasc Imaging 2013;6:790–9.

Observational Versus Randomized

Sliding Toward Nonevidence-Based Medicine

We welcome the provision of additional data in the field of atrial fibrillation (AF) and heart failure (HF), a combination of conditions that results in difficult management decisions and worse outcomes, both for patients with reduced and preserved left ventricular ejection fraction. However, it remains important to adhere to some fundamental aspects of evidence-based medicine. Recent years have seen an abundance of subgroup analyses attempting to answer questions related to treatment effects in nonrandomized studies. These analyses, often using propensity matching or other statistical adjustments, have become commonplace and are often mistakenly considered to be as important as randomized controlled trials (RCTs). Regardless of analysis method, observational data should only be used to generate hypotheses about treatment effects (1,2), and we should resist the temptation to analyze datasets simply because of availability. Ignoring the weaknesses of such studies, and incorrect interpretation, can subsequently lead to confounded conclusions.

In the case of the paper by Cadrin-Tourigny et al. (3), the patients were not randomized to receive beta-blockers, and hence there was confounding at both the patient and physician level that hampers external validity. Physicians typically give beta-blockers to patients at lower risk, confirmed in this study as being younger in age, with more nonischemic cardiomyopathy, less time in AF, and higher use of anticoagulation and defibrillator therapy (all factors associated with lower mortality). Although a propensity-matched analysis can be useful to mitigate minor differences in demographic characteristics, it was not designed to account for different patient populations or for exposures that interact with the outcome. The limitations of propensity-matched analysis have been demonstrated for digoxin therapy

(the inverse of beta-blockers, in which clinicians tend to prescribe to higher risk patients), where propensity-matching was unable to replicate the results of RCTs (4). Confounding may also explain why Cadrin-Tourigny et al found such discrepant findings for death and hospitalization. Furthermore, only 57% of their population was actually in AF at the time of analysis. We have already shown how effective beta-blockers are in preventing AF (and therefore subsequent adverse outcomes) for patients with AF in sinus rhythm (5). A few methodological issues also arise on detailed review, including the divergence in matched groups, omission of paroxysmal versus persistent AF from the standardized difference plot (with clearly >10% difference), and misrepresentation in the abstract about the sample size (n = 655 [not 1,376], with just 95 deaths without beta-blockers and 136 deaths on beta-blockers).

We considered the requirement for AF on the baseline electrocardiography a strength of our previous analysis, which demonstrated a significant interaction in beta-blocker efficacy according to heart rhythm using data from double-blind, placebo-controlled RCTs in patients with HF and predominantly reduced left ventricular ejection fraction (5). Using systematic, carefully checked, and harmonized individual patient data from 10 trials, we identified no significant benefit from beta-blockers in >3,000 patients with concomitant AF, consistent across all outcomes studied and based on a published design paper and pre-specified analysis plan.

Where, as a body of clinical scientists, do we go from here? The answer lies in new RCTs, rather than more analyses of observational data.

*Dipak Kotecha, MD, PhD
Douglas G. Altman, DSc
Giuseppe Rosano, MD, PhD
Marcus D. Flather, MD

*University of Birmingham
Institute of Cardiovascular Sciences
The Medical School
Vincent Drive
Birmingham B15 2TT
United Kingdom
E-mail: d.kotecha@bham.ac.uk

http://dx.doi.org/10.1016/j.jchf.2017.02.013

Please note: Dr. Kotecha is the Chief Investigator for RATE-AF (Rate Control Therapy Evaluation in Permanent Atrial Fibrillation trial; NCT02391337) and the lead for BB-meta-HF (Beta-blockers in Heart Failure Collaborative Group study; NCT00832442); has received research grants from Menarini; has received professional development support from Daiichi-Sankyo; and has received lecture fees from AtriCure. Dr. Flather has received personal fees from AstraZeneca; and has received grants from Novartis, all outside the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Vandenbroucke JP. Observational research, randomised trials, and two views of medical science. PLoS Med 2008;5:e67.

2. Greenland S. Randomization, statistics, and causal inference. Epidemiology 1990;1:421–9.

3. Cadrin-Tourigny J, Shohoudi A, Roy D, et al. Decreased mortality with beta-blockers in patients with heart failure and coexisting atrial fibrillation: an AF-CHF substudy. J Am Coll Cardiol HF 2017;5:99–106.

4. Ziff OJ, Lane DA, Samra M, et al. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. BMJ 2015;351:h4451.

5. Kotecha D, Holmes J, Krum H, et al. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. Lancet 2014;384:2235–43.

REPLY: Observational Versus Randomized

Sliding Toward Nonevidence-Based Medicine

We thank Dr. Kotecha and colleagues for their interest in our study (1). However, we feel obliged to correct several inaccurate and misleading statements, including the catchy but deceptive title. Although Dr. Kotecha and colleagues portrayed their pooled analysis (2) as above the fray of observational research, it should be pointed out that their study was also observational. Despite the care with which it was planned, a post hoc analysis of selected trials is retrospective in nature and subject to several limitations, including search, selection, and publication biases, heterogeneity issues, constraints related to pooling nonuniformly defined variables across studies, and incomplete data. Such limitations have led to the observation that meta-analyses provide discordant results to subsequent large trials in 35% of cases (3).

More specific to the population in question, our AF-CHF (Atrial Fibrillation-Congestive Heart Failure) trial explicitly focused on patients with atrial fibrillation (AF) and heart failure. Inclusion criteria were detailed and AF history was comprehensively characterized. In contrast, studies included in the analysis by Kotecha et al. (2) were not designed to assess a population with AF. As a result, the investigators retrospectively relied on a single nonadjudicated baseline electrocardiogram to define a population with AF. That they consider this “a strength” is misguided, perhaps reflecting an over-simplistic view of a complex entity with a variable disease course. Although all subjects in the AF-CHF trial had electrocardiographically documented and adjudicated AF at entry, the proportion in AF at any given time fluctuated throughout the study.

Another important point of clarification is the suggestion that “confounding may also explain why