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Mortality in Patients With Atrial Fibrillation and Heart Failure

We read with interest the paper by Nieuwlaat et al. (1) on patients with atrial fibrillation (AF) and heart failure (HF) from the observational Euro Heart Survey. We have recently reported a large series of patients (n = 1,269) with both AF and HF and a similar number of deaths (n = 247) during follow-up (2).

The Euro Heart Survey was a declarative multicenter registry, whereas we performed a single-center systematic continuous analysis retrieving information from the computerized codification system filled in for each patient using the International Classification of Diseases-10th Revision of the World Health Organization (3). It is interesting to note that in both studies the characteristics of the patients were very similar in many aspects (type of AF, association or not with left ventricular systolic dysfunction, medication during follow-up), although the way of collecting a large amount of data was somewhat different.

However, and in contrast to the results presented by Nieuwlaat et al. (1), we found that in unselected patients with AF and HF, treatments with beta-blocker alone or with beta-blocker plus digoxin were associated with a significant decrease in the risk of death. We think this may have some interest because very few studies have been published to date addressing the effect of beta-blockers in HF patients having AF. Beyond the older age of the patients and the continuous collection of data in our study, we do not have clear explanation for these different results. We were somewhat surprised by the listing of the multivariable determinants of all-cause mortality in patients with AF and HF in the Euro Heart Survey because it appears that a major bleeding is presented as a strong predictor of death during follow-up. The parameters included in this type of multivariate analysis should only include baseline characteristics of the patients. A severe event during follow-up is obviously associated with a higher risk of mortality. Because a history of major bleeding at baseline is not presented, we are wondering if Nieuwlaat et al. (1) have included a major bleeding during follow-up as a predictor of mortality. If this is the case, this inappropriate way of performing the analysis may have affected the final results on the predictors of all-cause mortality.

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Reply

We thank Dr. Smit and colleagues and Drs. Fauchier and Gorin for their interest in our paper (1) regarding the characteristics, management, and prognosis of patients with the combination of atrial fibrillation (AF) and heart failure (HF) in the Euro Heart Survey.

First, we would like to clarify that the variable "major bleeding" in the multivariable analyses concerns a history of major bleeding at baseline, rather than major bleeding during study follow-up. We want to congratulate Fauchier et al. (2) on their interesting study showing improved survival of patients with AF and HF who receive a beta-blocker. However, we did not find a benefit of beta-blockers in our prospective survey, which was also the case in subanalyses of the CIBIS II (The Cardiac Insufficiency Bisoprolol Study II) (3) and MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure) (4) trials as pointed out by Dr. Smit and colleagues. There are multiple potential reasons for these different results, among which are study setting, selection of the population, study design, and follow-up duration. Only randomized controlled trials specifically designed to test the effect of beta-blockers among these patients can clarify this issue. The same argument holds for the rate control target issue as raised by Dr. Smit and colleagues. The AF guidelines indicate that rhythm versus rate control studies usually used a rate control target of ≤60 to 80 beats/min and is reasonable (5). However, it is unknown whether aiming for ≤80 beats/min produces superior therapeutic effects compared with a lower or higher target. The RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation) trial (6) will indeed shed more light on this issue for permanent AF patients.

No or inconclusive research evidence can be a reason for suboptimal implementation of therapies. Until stronger evidence is available, we will have to rely on guideline recommendations optimally weighing the evidence as extrapolated from more general trial patient groups, observational studies such as ours, and expert opinion. Inadequate guideline adherence is a multifactorial problem of which lack of firm evidence is an important, but not the only, aspect. Ever-growing research evidence will clarify management issues that are of importance, but implementing this evidence optimally in local practice is another issue (7). Understanding the causes for gaps between guidelines and practice and finding effective ways to close them is an essential next step in the continuous feedback loop between research and practice (8). We hope that our survey and the discussions by Dr. Smit and colleagues and Drs. Fauchier and Gorin will stimulate further research to improve the care and outcomes for patients with AF and HF.

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Peripheral Blood Monocyte Subset Assessment in Non–ST-Segment Elevation Myocardial Infarction Is Required

We read with great interest both the research paper by Tsujioka et al. (1) and the editorial comment by Shantsila and Lip (2) outlining the role of monocytes in myocardial infarction (MI). We agree that understanding the role of different monocyte population subsets during acute coronary syndromes (ACS) might provide important clinical information; however, much more work is required, and there is a need to express some cautionary notes. An important limitation in the paper by Tsujioka et al. (1) and others referenced by Shantsila and Lip's editorial (2) in considering the kinetics of monocyte chemoattractant protein (MCP)-1 release (3) are the small sample sizes (n = 36 and n = 23 for MI, respectively). Thus, interpretation must be restrained. Our data from 216 patients with ACS do not support the association of the early release kinetics of MCP-1 (the ligand for chemokine [C-C motif] receptor 2 [CCR-2]). Thus, the idea that it is related to the "prompt up-regulation of CCR-2 expressing CD14+CD16- monocytes" might not be correct (2). In our larger ACS population, we found no time-dependent increase in MCP-1 measurement during the first 12 h after the onset of symptoms (4). In addition, Tsujioka et al. (1) present data indicating that there was an increase in the $CD14^{+}CD16^{+}$ subgroup (these cells lack CCR-2; refer to Figs. 3B and 4D in Tsujioka et al. [1]) in that at admission the levels were lower in the MI group as compared with the stable angina group, with subsequent peak levels in the MI group significantly higher (1). However, this cell subpopulation did not correlate with myocardial salvage (1). Moreover, the data are from patients with ST-segment myocardial infarction (STEMI), which tend to be larger infarctions. Data in a more diverse group, including those with smaller events diagnosed with cardiac troponin—which is recommended by the guidelines groups (5)—would be important to see whether differences exist between those groups (1).

If monocyte subgroups are important in non-STEMI, they might prove extremely useful in deciding on the timing of invasive intervention. Non-STEMI patients benefit from early intervention but not necessarily immediate intervention (6). Perhaps data related to monocyte activity and expression would help to differentiate those who might benefit immediately from those who can wait for some hours. Such considerations will require detailed information on the effects of invasive interventions on monocyte subgroups as well as whether serial monitoring is required for risk stratification. These are important issues, which when addressed will shed additional light on the role of monocytes and their laboratory use in risk stratification for patients presenting with ACS.

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Reply

We are grateful to Drs. Kavsak and Jaffe for their valuable comments and suggestions to our study (1). They pose a question regarding the kinetics of monocyte chemoattractant protein (MCP)-1 release. They found no time-dependent increase in MCP-1 measurement during the first 12 h after the onset of symptoms in 216 patients with acute coronary syndromes (2). On the contrary, Matsumori et al. (3) have