Learning From Clinical Randomized Trials

— Individualized Therapy is Important in the Management of Atrial Fibrillation —

Yoshinori Kobayashi, MD; Akira Fujiki, MD*; Kazutaka Aonuma, MD**

Atrial fibrillation (AF) is the arrhythmia most commonly encountered in the clinical practice. Cardiologists usually have plenty experience with the management of AF, which has various etiologies and pathophysiology. Thus, the determination of treatment of AF is frequently made case-by-case, either by referring to practice guidelines or sometimes empirically. On the first visit of an AF patient to an outpatient clinic, we evaluate the patient's status, including symptoms experienced during AF, type of AF (paroxysmal, persistent or permanent), clinical background, presence of any basic heart disease, degree of atrial remodeling, risk factors for thromboembolic events and other complications. Of the 2 representative therapeutic methods (ie, rhythm-control or rate-control), we decide which is the most appropriate for the patient. For younger generation, symptomatic patients with paroxysmal AF, the majority of cardiologists choose the rhythm-control strategy, where as for the asymptomatic elderly patient with persistent AF, they are likely to choose the rate-control strategy. Why do we make decisions like these? Because we know how the patient will respond to the specific treatment and how quality of life (QOL) will be improved according to which strategy is chosen.

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To date, there have been a number of randomized clinical trials^{1–4} investigating which strategy leads to a better outcome, mostly with regard to mortality and morbidity, including heart failure, stroke and bleeding events. These trials have shown that the prevalence of their endpoints are comparable for both strategies, which totally differs from the prior expected result by the investigators that the rhythm-control strategy would be superior to the rate-control strategy. Why did such a discrepancy occur? One reason might be that each strategy was randomly assigned to the patients, irrespective of their overall status.

In this issue of the *Circulation Journal*, the results of the

J-RHYTHM study “Optimal treatment strategy in patients with paroxysmal atrial fibrillation” are published.⁵ This is the first randomized multicenter study in the field of arrhythmia management performed in Japan. What the investigators found was that the rhythm-control strategy was associated with fewer primary endpoints than the rate-control strategy when physical/psychological disabilities requiring an alteration in the assigned strategy (cross-over) were included in the endpoint criteria. However, mortality and cardiovascular morbidity were rarely and equally documented in both strategies. The lesser prevalence of the major endpoints in J-RHYTHM, as compared with previous studies, might be related to the characteristics of the patients enrolled, in respect to the lack of structural heart disease and history of CHF, and few risk factors for stroke (CHADS2 score). The rate-control strategy was associated with a higher prevalence of cross-over events than the rhythm-control strategy, which at least in a part correlated with a greater improvement in the QOL score (AFQOL 1) in the rhythm-control group.

What we learn from J-RHYTHM is primarily that paroxysmal AF in this patient population can be safely treated with class I antiarrhythmic agents. The second important observation is that the occurrence of a cross-over is higher in the rate-control group. Thus rhythm-control might be the more suitable therapy in this patient population. Focusing on the cross-over events between the treatment strategies, the AFFIRM trial¹ demonstrated a greater incidence of cross-over in the rhythm-control group than in the rate control group (37.5% vs 14.9%, respectively), which is the reverse relationship to that in the J-RHYTHM study, implying that patients with a greater comorbidity, for whom the rate control is commonly selected, were included in the AFFIRM trial, because the cross-over of the treatment strategy was a result of objective patient or physician matters. Recently, the report of a randomized study with similar design targeting a restricted patient population with congestive heart failure (AF-CHF study⁶) revealed that both (rhythm- and rate-control) groups showed a similar outcome for both the primary endpoint (death from cardiovascular causes) and secondary endpoints (death from any cause, stroke, worsening heart failure etc). It should be noted that the occurrence of a cross-over was higher in the rhythm-control group than in the rate-control group (21% vs 10%, respectively), similar to the AFFIRM trial. In this particular study, more patients with persistent (long-standing AF for up to 6 months) were included than those with paroxysmal AF (approximately 70% vs 30%, respectively). Most of the patients with persistent AF were supposed to be followed up with rate-control therapy at the time of the trial inclusion, because the rate of patients taking digitalis or β -blockers was relatively high (65% and 80%, respectively). It can be speculated that in

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Department of Internal Medicine, Division of Cardiology, Nippon Medical School, Tokyo, *Second Department of Internal Medicine, University of Toyama, Toyama and **Division of Cardiovascular Sciences, Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan

Mailing address: Yoshinori Kobayashi, MD, Department of Internal Medicine, Division of Cardiology, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan. E-mail: kobaya-y@nms.ac.jp

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such patients it was difficult to maintain sinus rhythm, even with amiodarone and optimal medical therapy for heart failure. In fact, the most common reason for the cross-over events in the rhythm-control group was the inability to maintain sinus rhythm.

From observations from all the previous randomized trials,^{1–6} it can be inferred that appropriate selection of the treatment strategy in a case-by-case fashion (ie, individualized therapy) might be the most important factor in the management of AF, rather than choosing only the rhythm-control or rate-control strategy. The J-RHYTHM study enable us to revisit the importance of this substantial strategy in the overall management of AF.

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