

ity reserve when there is limited oxygen available to the myocardium. Perhaps surgical reduction of left ventricular chamber size only changes the position, but not the area, of the left ventricular pressure–volume loop as cardiac-output needs fluctuate during activities of daily living in patients with ischemic cardiomyopathy.

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Valsartan and Recurrent Atrial Fibrillation

TO THE EDITOR: Disertori et al. (April 16 issue)¹ describe the effects of valsartan on the recurrence of atrial fibrillation. The disappointing results of the trial may be explained by two important limitations. First, no data were provided concerning how long patients were known to have had either atrial fibrillation or underlying heart disease. We would expect that the extent of remodeling would become more severe and even irreversible in patients with a longer history of atrial fibrillation or underlying heart disease. In patients with a shorter history, however, remodeling processes are less advanced, providing more opportunities for blockade of the renin–angiotensin–aldosterone system (RAAS) to be effective.² Second, RAAS blockade was probably started too late in the trial — namely, when sinus rhythm was already obtained. Upstream therapy requires more time to influence remodeling processes, and it would have been better if valsartan had been started several weeks before instead of at least 2 days after obtaining sinus rhythm.³ Thus, the question still remains whether RAAS blockade is effective in maintaining sinus rhythm if it is started as soon as possible after presentation with atrial fibrillation.

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to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation: a prospective and randomized study. *Circulation* 2002;106:331-6.

TO THE EDITOR: Disertori et al. report that they found no significant reduction in the incidence of recurrent atrial fibrillation among patients receiving valsartan, as compared with those receiving placebo. The study is basically a secondary prevention trial. Previous studies have presented positive results for the use of angiotensin II receptor blockers (ARBs) for the secondary prevention of atrial fibrillation in a relatively small number of patients.¹ In contrast, previous trials and meta-analyses involving more than 50,000 patients have suggested more pronounced effects of angiotensin-converting–enzyme (ACE) inhibitors or ARBs for the primary prevention of atrial fibrillation.^{2,3} In primary prevention trials, ACE inhibitors and ARBs might prevent the occurrence and progression of structural and electrical remodeling as the substrate for atrial fibrillation,⁴ but the remodeling process might be completed and irreversible in the secondary prevention setting. Thus, a large, randomized, prospective, placebo-controlled, multicenter trial to test an ARB for the primary prevention of atrial fibrillation would be mandatory before concluding that ARBs are not effective in preventing this condition. In such a trial, an evaluation of changes in cardiac-chamber dimensions would be useful in assessing the mechanism of prevention of atrial fibrillation.

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THE AUTHORS REPLY: Smit and Van Gelder raise the question of the timing of the administration of valsartan in the evaluation of its effects. We reported the results of two additional analyses involving patients who were in sinus rhythm at 15 days (as prespecified in the protocol)¹ and at 8 weeks (a post hoc analysis) after randomization. No trend in favor of valsartan was apparent. In the 8-week analysis, atrial fibrillation recurred at 1 year in 42.7% of patients in the valsartan group, as compared with 44.0% of those in the placebo group (hazard ratio, 0.96; 96% confidence interval, 0.80 to 1.14; $P=0.62$).

With respect to the duration of the history of atrial fibrillation, we do not have this information for the patients in our study. However, we performed a subgroup analysis as to whether the duration of the last episode of atrial fibrillation had an effect on the results. We did not observe

any difference in the effect of valsartan between patients with episodes lasting more than 48 hours and those with shorter episodes.

As Tomoda correctly points out, the efficacy of RAAS blockade in the primary prevention of atrial fibrillation is still an open issue, with current evidence coming from post hoc analyses of large trials, databases, and overviews. Thus, a large, randomized clinical trial of such therapy in the primary prevention of atrial fibrillation may be appropriate. However, such a trial is likely to be difficult to carry out because of the broadening range of use of RAAS inhibitors in a variety of cardiovascular conditions.

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1. Disertori M, Latini R, Maggioni AP, et al. Rationale and design of the GISSI-Atrial Fibrillation trial: a randomized, prospective, multicentre study on the use of valsartan, an angiotensin II AT1-receptor blocker, in the prevention of atrial fibrillation recurrence. *J Cardiovasc Med (Hagerstown)* 2006;7:29-38.

Telaprevir for Chronic HCV Infection

TO THE EDITOR: McHutchison et al. and Hézode et al. (April 30 issue) found an important effect of adding telaprevir to current antiviral therapy.^{1,2} Nevertheless, the results of the Protease Inhibition for Viral Evaluation (PROVE) trials (ClinicalTrials.gov numbers, NCT00336479 and NCT00372385) are disappointing, since they demonstrate the risk of serious side effects resulting from high dosing of a new molecule, with profound consequences for efficacy. Combined data from all telaprevir regimens in both trials show a significant difference in sustained virologic response between patients completing and those discontinuing treatment (78% and 25%, respectively; $P<0.001$). Although telaprevir had an acceptable initial side-effect

profile, the extended administration of high doses of telaprevir was accompanied by a high rate of treatment discontinuation, mainly because of unexpected rash and more severe anemia.

The first study of telaprevir showed similar initial viral declines with different dosages; viral breakthrough occurred in the lower dosing regimen.³ The fear of selection of telaprevir-resistant variants can be negated, since mutant viruses are sensitive to peginterferon.⁴

We are concerned that major decisions in the development of new antiviral agents are primarily based on the reduction of hepatitis C virus (HCV) RNA levels and on the highest tolerated doses in short phase 1 trials. Subsequent trials