

Figure 4. Subgroup analyses; hazard ratio plots for all-cause death.

preinfarction AP before onset of MI was associated with limited infarct size and improved clinical outcomes possibly through the mechanism of preconditioning effect in patients with AMI mainly in the thrombolytic era. The prevalence of preinfarction AP, however, varied widely from 11% to 69% according to the definitions of preinfarction AP.^{10,13} We defined preinfarction AP as AP within 48 hours of hospital arrival for the index STEMI based on the recent studies suggesting the protective effect of preinfarction AP within 24 to 48 hours before the onset of MI on left ventricular wall motion^{2,3} and on long-term mortality in the thrombolytic era.⁵ The present study was one of the largest scale studies evaluating the clinical significance of preinfarction AP in a large, real-world consecutive series of patients with STEMI who underwent primary PCI within 24 hours of symptom onset. The prevalence of preinfarction AP within 48 hours of arrival at hospital was 19.4% in the present study.

The cardioprotective effects of preinfarction AP in patients with STEMI are still controversial in the primary PCI era. The clinical significance of preinfarction AP was evaluated in several relatively small studies, and most of those studies evaluated infarct size instead of mortality with discordant results in those studies.^{9,13,14} Reiter et al¹³ analyzed 245 patients with STEMI who received PCI with ischemic times between 1 and 6 hours. The occurrence of preinfarction AP within 24 hours of infarction was associated with significantly reduced infarct size, and there was no correlation between the total ischemic time and peak CPK in patients with preinfarction AP. Opposite findings were observed in another studies. De Luca et al⁹ evaluated infarct size in 430 patients with STEMI who underwent primary PCI by technetium-99m sestamibi at 30 days and found no significant difference in infarct size regardless of the presence or absence of preinfarction AP. In the present study, evaluating long-term mortality in a large number of patients,

preinfarction AP was demonstrated to be independently associated with lower long-term mortality.

In several previous studies, protective effects of preinfarction AP were not observed in some subgroups such as patients with nonanterior MI and diabetes mellitus.^{6,24} In contrast to those previous studies, the protective effect of preinfarction AP was consistently observed in all the subgroups evaluated in the present study. The large sample size in the present study might make us possible to find a positive effect of preinfarction AP on long-term mortality in the subgroup analyses.

Furthermore, it was noteworthy that the 5-year mortality in patients with preinfarction AP seemed not to be so much affected by the length of total ischemic time (Figure 5), suggesting that the time course of ongoing myocardial necrosis might be affected profoundly by the preconditioning effect of preinfarction AP. Indeed, the presence of pathological Q waves in admission electrocardiogram rather than total ischemic time was reported to be independently associated with mortality in AMI patients,²⁵ suggesting that extent of myocardial necrosis before reperfusion rather than the total ischemic time might be more crucial in determining the final infarct size. The Presence of preinfarction AP might be associated with lesser extent of myocardial necrosis before reperfusion. Therefore, the presence of preinfarction AP and total ischemic time might be important as the determinants of final infarct size in patients with STEMI.

Another clinical implication of this study is that modifying the time process of myocardial necrosis before reperfusion therapy might be a valuable adjunct to immediate reperfusion therapy emphasized in the current clinical guidelines.²⁶ Of course, it is not possible to intervene patients with STEMI before the onset of chest pain. However, “remote ischemic preconditioning,”²⁷ with an intermittent ischemia in territories other than coronary circulation during

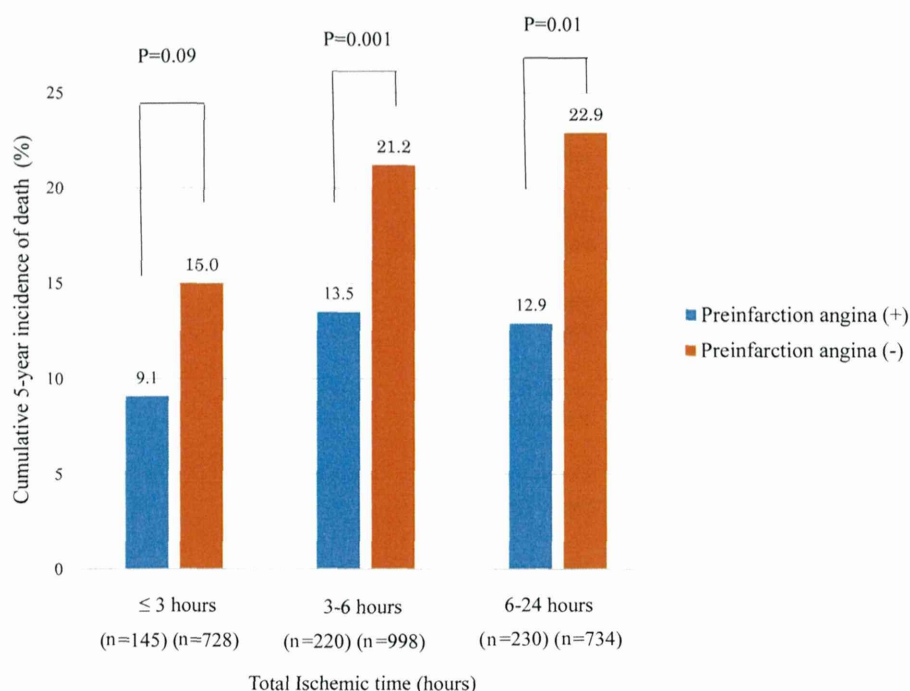


Figure 5. Cumulative 5-year mortality in patients with and without preinfarction AP according to total ischemic time. CI = confidence interval.

the time from onset of MI to coronary reperfusion, has been suggested to limit infarct size of patients with STEMI.²⁸ Further larger clinical trials are warranted to confirm the effect of remote postconditioning on clinical outcome in patients with STEMI who underwent primary PCI.

This study has several limitations. First, we could not exclude the influence of ascertainment bias for preinfarction AP. Although we could not deny the possible under-reporting of preinfarction AP in critically ill patients such as patients with cardiogenic shock, the positive effect of preinfarction AP on long-term mortality was observed after excluding those patients with cardiogenic shock. Second, unmeasured factors other than preinfarction AP could influence the time course of ongoing myocardial necrosis in each subject. Finally, the measured and unmeasured differences in baseline characteristics between patients with and without preinfarction AP might limit the comparability of the groups, although we tried to make statistical adjustment as extensively as possible to minimize the influence of the differences in baseline characteristics.

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Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.amjcard.2014.07.038>.

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