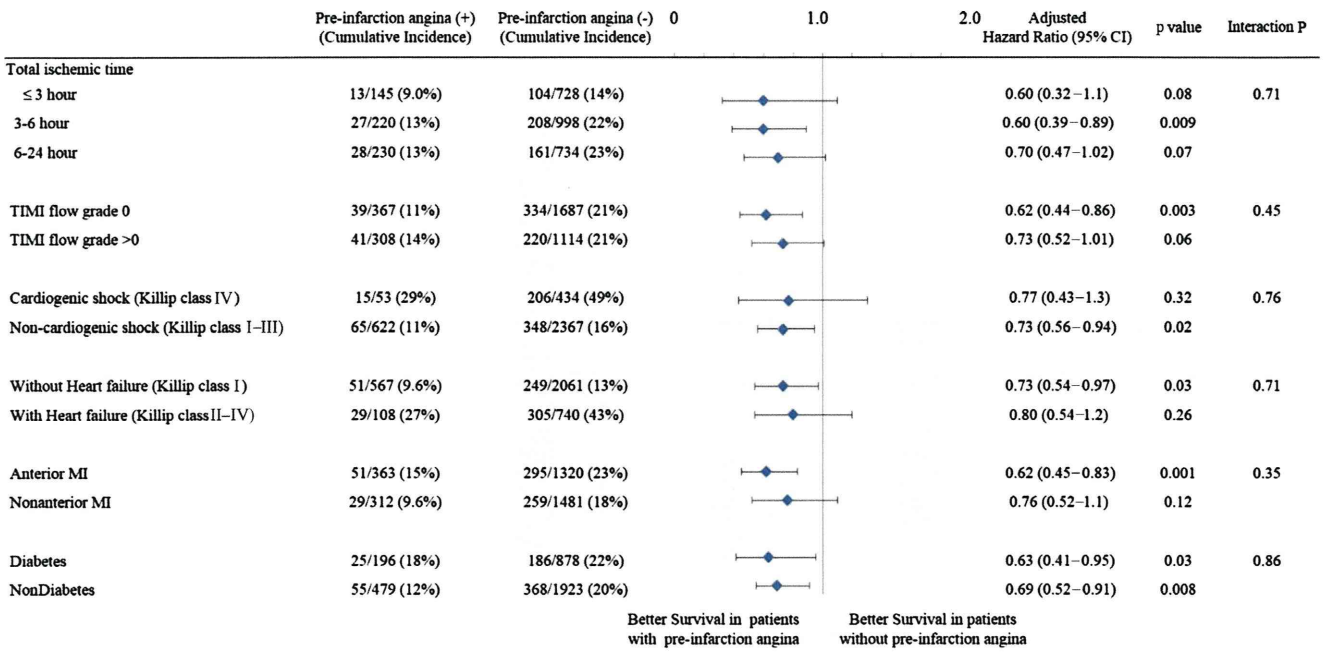

Figure 4. Subgroup analyses; hazard ratio plots for all-cause death.

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[23] 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 al[13] 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 al[9] evaluated infarct size in 430 patients with STEMI who underwent primary PCI by technetium-99m setamibi 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 postconditioning,"[27] with an intermittent ischemia in territories other than coronary circulation during

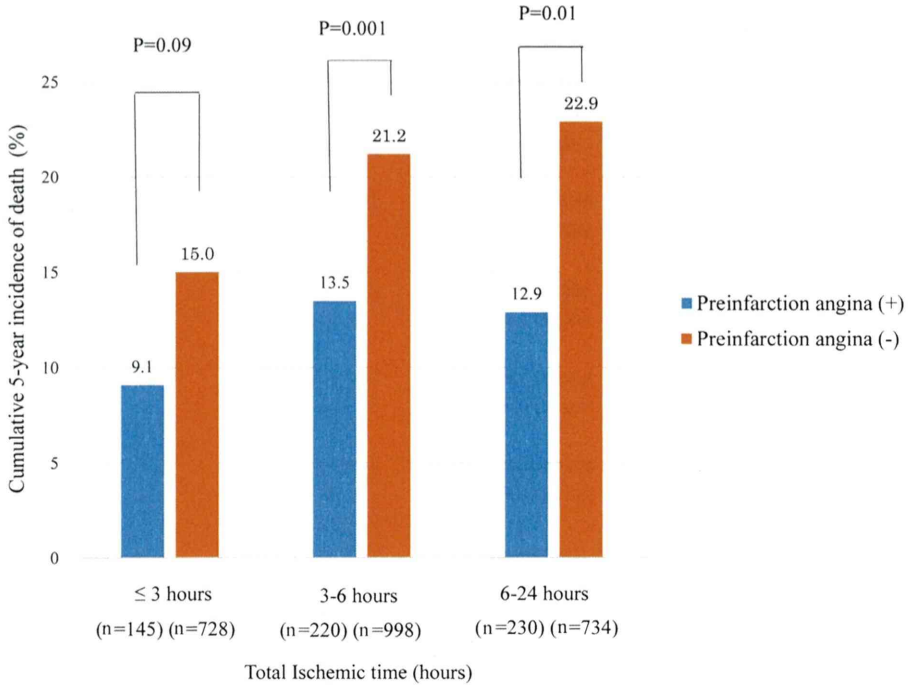

Figure 5. Cumulative 5-year mortality in patients with and without preinfarction AP according to total ischemic time. CI = confidence interval.

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 underreporting 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.

Acknowledgments: The authors appreciate the support and collaboration of the co-investigators participating in the CREDO-Kyoto AMI Registry. The authors are indebted to the outstanding effort of the clinical research coordinators for data collection.

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.

1. Ottani F, Galvani M, Ferrini D, Sorbello F, Limonetti P, Pantoli D, Rusticali F. Prodromal angina limits infarct size. A role for ischemic preconditioning. *Circulation* 1995;91:291–297.
2. Ottani F, Galvani M, Ferrini D, Nicolini FA. Clinical relevance of prodromal angina before acute myocardial infarction. *Int J Cardiol* 1999;68(Suppl 1):S103–S108.
3. Andreotti F, Pasceri V, Hackett DR, Davies GJ, Haider AW, Maseri A. Preinfarction angina as a predictor of more rapid coronary thrombolysis in patients with acute myocardial infarction. *N Engl J Med* 1996;334:7–12.
4. Anzai T, Yoshikawa T, Asakura Y, Abe S, Akaishi M, Mitamura H, Handa S, Ogawa S. Preinfarction angina as a major predictor of left ventricular function and long-term prognosis after a first Q wave myocardial infarction. *J Am Coll Cardiol* 1995;26:319–327.
5. Ishihara M, Sato H, Tateishi H, Kawagoe T, Shimatani Y, Kurisu S, Sakai K, Ueda K. Implications of prodromal angina pectoris in anterior wall acute myocardial infarction: acute angiographic findings and long-term prognosis. *J Am Coll Cardiol* 1997;30:970–975.
6. Kosuge M, Kimura K, Kojima S, Sakamoto T, Ishihara M, Asada Y, Tei C, Miyazaki S, Sonoda M, Tsuchihashi K, Yamagishi M, Ikeda Y, Shirai M, Hiraoka H, Inoue T, Saito F, Ogawa H. Effects of preinfarction angina pectoris on infarct size and in-hospital mortality after coronary intervention for acute myocardial infarction. *Am J Cardiol* 2003;92:840–843.
7. Kloner RA, Shook T, Przyklenk K, Davis VG, Junio L, Matthews RV, Burstein S, Gibson M, Poole WK, Cannon CP, McCabe CH, Braunwald E. Previous angina alters in-hospital outcome in TIMI 4. A clinical correlate to preconditioning? *Circulation* 1995;91:37–45.
8. Kloner RA, Shook T, Antman EM, Cannon CP, Przyklenk K, Yoo K, McCabe CH, Braunwald E. Prospective temporal analysis of the onset of preinfarction angina versus outcome: an ancillary study in TIMI-9B. *Circulation* 1998;97:1042–1045.
9. De Luca G, Parodi G, Sciagra R, Bellandi B, Comito V, Vergara R, Migliorini A, Valenti R, Antoniucci D. Preinfarction angina does not affect infarct size in STEMI patients undergoing primary angioplasty. *Atherosclerosis* 2013;226:153–156.
10. Zahn R, Schiele R, Schneider S, Gitt AK, Seidl K, Bossaller C, Schuler G, Gottwik M, Altmann E, Rosahl W, Senges J. Effect of preinfarction angina pectoris on outcome in patients with acute myocardial infarction treated with primary angioplasty (results from the Myocardial Infarction Registry. *Am J Cardiol* 2001;87:1–6.

11. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986;74:1124–1136.
12. Cohen MV, Liu GS, Downey JM. Preconditioning causes improved wall motion as well as smaller infarcts after transient coronary occlusion in rabbits. *Circulation* 1991;84:341–349.
13. Reiter R, Henry TD, Traverse JH. Preinfarction angina reduces infarct size in ST-elevation myocardial infarction treated with percutaneous coronary intervention. *Circ Cardiovasc Interv* 2013;6:52–58.
14. Kosuge M, Kimura K, Kojima S, Sakamoto T, Ishihara M, Asada Y, Tei C, Miyazaki S, Sonoda M, Tsuchihashi K, Yamagishi M, Ikeda Y, Shirai M, Hiraoka H, Inoue T, Saito F, Ogawa H. Beneficial effect of preinfarction angina on in-hospital outcome is preserved in elderly patients undergoing coronary intervention for anterior acute myocardial infarction. *Circ J* 2005;69:630–635.
15. Shiomi H, Nakagawa Y, Morimoto T, Furukawa Y, Nakano A, Shirai S, Taniguchi R, Yamaji K, Nagao K, Suyama T, Mitsuoka H, Araki M, Takashima H, Mizoguchi T, Eisawa H, Sugiyama S, Kimura T. Association of onset to balloon and door to balloon time with long term clinical outcome in patients with ST elevation acute myocardial infarction having primary percutaneous coronary intervention: observational study. *BMJ* 2012;344:e3257.
16. Miki T, Miura T, Tsuchida A, Nakano A, Hasegawa T, Fukuma T, Shimamoto K. Cardioprotective mechanism of ischemic preconditioning is impaired by postinfarct ventricular remodeling through angiotensin II type 1 receptor activation. *Circulation* 2000;102:458–463.
17. Ishihara M, Inoue I, Kawagoe T, Shimatani Y, Kurisu S, Hata T, Nakama Y, Kijima Y, Kagawa E. Ischaemic preconditioning effect of prodromal angina pectoris is lost in patients with prior myocardial infarction. *Heart* 2006;92:973–974.
18. Kimura T, Morimoto T, Furukawa Y, Nakagawa Y, Kadota K, Iwabuchi M, Shizuta S, Shiomi H, Tada T, Tazaki J, Kato Y, Hayano M, Abe M, Tamura T, Shirotani M, Miki S, Matsuda M, Takahashi M, Ishii K, Tanaka M, Aoyama T, Doi O, Hattori R, Tatami R, Suwa S, Takizawa A, Takatsu Y, Takahashi M, Kato H, Takeda T, Lee JD, Nohara R, Ogawa H, Tei C, Horie M, Kambara H, Fujiwara H, Mitsudo K, Nobuyoshi M, Kita T. Long-term safety and efficacy of sirolimus-eluting stents versus bare-metal stents in real world clinical practice in Japan. *Cardiovasc Interv Ther* 2011;26:234–245.
19. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, Buller N, Bonser R, van den Brand MJ, van Herwerden LA, Morel MA, van Hout BA. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med* 2001;344:1117–1124.
20. Ghali WA, Quan H, Brant R, van Melle G, Norris CM, Faris PD, Galbraith PD, Knudtson ML. Comparison of 2 methods for calculating adjusted survival curves from proportional hazards models. *JAMA* 2001;286:1494–1497.
21. Jesel L, Morel O, Ohlmann P, Germain P, Faure A, Jahn C, Coulbois PM, Chauvin M, Bareiss P, Roul G. Role of pre-infarction angina and inflammatory status in the extent of microvascular obstruction detected by MRI in myocardial infarction patients treated by PCI. *Int J Cardiol* 2007;121:139–147.
22. Billinger M, Fleisch M, Eberli FR, Garachemani A, Meier B, Seiler C. Is the development of myocardial tolerance to repeated ischemia in humans due to preconditioning or to collateral recruitment? *J Am Coll Cardiol* 1999;33:1027–1035.
23. Noda T, Minatoguchi S, Fujii K, Hori M, Ito T, Kanmatsuse K, Matsuzaki M, Miura T, Nonogi H, Tada M, Tanaka M, Fujiwara H. Evidence for the delayed effect in human ischemic preconditioning: prospective multicenter study for preconditioning in acute myocardial infarction. *J Am Coll Cardiol* 1999;34:1966–1974.
24. Ishihara M, Inoue I, Kawagoe T, Shimatani Y, Kurisu S, Nishioka K, Kouno Y, Umemura T, Nakamura S, Sato H. Diabetes mellitus prevents ischemic preconditioning in patients with a first acute anterior wall myocardial infarction. *J Am Coll Cardiol* 2001;38:1007–1011.
25. Wong CK, Gao W, Raffel OC, French JK, Stewart RA, White HD. Initial Q waves accompanying ST-segment elevation at presentation of acute myocardial infarction and 30-day mortality in patients given streptokinase therapy: an analysis from HERO-2. *Lancet* 2006;367:2061–2067.
26. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;127:e362–425.
27. Kloner RA. Current state of clinical translation of cardioprotective agents for acute myocardial infarction. *Circ Res* 2013;113:451–463.
28. Crimi G, Pica S, Raineri C, Bramucci E, De Ferrari GM, Klersy C, Ferlini M, Marinoni B, Repetto A, Romeo M, Rosti V, Massa M, Raisaro A, Leonardi S, Rubartelli P, Oltrona Visconti L, Ferrario M. Remote ischemic post-conditioning of the lower limb during primary percutaneous coronary intervention safely reduces enzymatic infarct size in anterior myocardial infarction: a randomized controlled trial. *JACC Cardiovasc Interv* 2013;6:1055–1063.