JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 2, NO. 1, 2009

ISSN 1936-8798/09/$36.00
PUBLISHED BY ELSEVIER INC.
DOI: 10.1016/j.jcin.2008.09.009

EDITORIAL COMMENT

Does Kidney Function Alter the Benefit of Reperfusion Therapy for ST-Segment Elevation Myocardial Infarction?*

Peter B. Berger, MD, FACC,†
Patricia J. M. Best, MD, FACC‡

Danville, Pennsylvania; and Rochester, Minnesota

In the last decade, the importance of chronic kidney disease (CKD) as a cardiovascular risk factor has become clear. The graded risk of CKD is present at all levels of renal function and is a risk factor in those with unrecognized cardiovascular disease or stable coronary disease or after a percutaneous coronary intervention (PCI) or myocardial infarction (1,2). In patients presenting with a myocardial infarction, mild CKD is associated with a 3-fold increase in mortality (1). This risk increases progressively with declining renal function, to a maximum mortality risk in patients with end-stage renal disease (ESRD) that is 15 times higher than in patients with normal renal function. This finding has been substantiated by similar findings in multiple studies, confirming that renal disease is a strong correlate of both early and late mortality (3–7).

See page 26

A frequent limitation of studies investigating the impact of renal disease on post-infarction outcomes is that they often fail to differentiate acute renal failure from CKD. Because renal function before the infarction might not be known and because myocardial infarctions cause acute renal failure in some patients, studies often combine acute and chronic kidney disease in such analyses, leading to an overestimation of the impact of CKD on outcome. In acute myocardial infarction, the development of acute renal failure more frequently occurs in higher-risk patients, such as those with reduced left ventricular function, higher Killip class, anterior wall infarction, a hematocrit <30%, congestive heart failure, shock, and stroke during hospital stay (8). In 1 study, the presence of acute renal failure was independently associated with both short-term and long-term mortality (hazard ratio [HR] at 10 years: 1.15 for mild, 1.23 for moderate, and 1.33 for severe acute renal failure). In other studies, both acute renal failure and the degree of change in creatinine correlated with both the eventual development of ESRD and with mortality (9). Thus, in acute myocardial infarction, both acute renal failure and CKD are strongly correlated with adverse events including death.

Because CKD patients with an acute myocardial infarction have such a high mortality, treatment of the myocardial infarction is even more important than in patients with normal renal function. Reperfusion therapy has been a fundamental component of therapy for ST-segment elevation myocardial infarctions (STEMIs) since the 1980s, when landmark trials such as ISIS-2 (Second International Study of Infarct Survival) and GISSI-1 (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto) demonstrated the ability of fibrinolytic therapy to reduce mortality (10–12). Subsequent studies in the 1990s confirmed the ability of primary PCI to reduce mortality more than fibrinolytic therapy and to reduce re-infarction and stroke to an even greater degree (13,14). Despite the proven effectiveness of reperfusion therapy in the general population, significantly less is known about reperfusion therapy in patients with CKD or ESRD, because these patients have generally been excluded from randomized trials.

Given the high-risk population of patients with CKD and ESRD, it is surprising that reperfusion therapy is so severely underused. Patients with ESRD are only a one-quarter as likely to undergo reperfusion therapy as patients with normal renal function (1). Underuse of reperfusion therapy is present with all levels of renal dysfunction. Even in patients with mild CKD, reperfusion therapy is administered 30% less frequently. Patients with CKD or ESRD undergo coronary angiography 30% less frequently than those with normal renal function and are revascularized only one-half as often (15).

Despite the potential benefits, patients with CKD have a higher complication rate from reperfusion therapy, including bleeding, stroke, infarct-artery re-occlusion, and restenosis (3). In ESRD treated with dialysis, the mortality of a myocardial infarction has been reported to be as high as 59% at 1 year (16). So regardless of the fact that there are more frequent complications from reperfusion therapy, after adjusting for comorbidities, fibrinolytic therapy is associated with a 28% reduction in all-cause mortality in ESRD patients (17). In another study of 5,549 patients with acute myocardial infarction stratified by renal function that included 4,119 patients with at least mild CKD, there was an 11% reduction in mortality with fibrinolytic therapy and a 15% reduction in mortality associated with cardiac catheterization (5). As with patients without CKD, patients with

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From the †Department of Cardiology and Center for Clinical Studies, Geisinger Clinic, Danville, Pennsylvania; and the ‡Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota.

CKD would be expected to derive greater benefit from primary PCI than from fibrinolytic drugs and might have even relatively greater benefit, given the higher mortality risk and the greater bleeding risk in CKD patients treated with fibrinolytic therapy. Before the current study by Medi et al. (18) in this issue of *JACC: Cardiovascular Interventions,* 1 of the few studies to address this was a study from the 2002 ACSIS (Acute Coronary Syndrome Israeli Survey), which included only 132 patients with CKD (19). In that small study, there was a trend toward a higher, not lower, mortality risk at 7 days with primary PCI compared with fibrinolytic therapy (HR: 3.8; 95% confidence interval: 0.9 to 26.7) and 30 days (HR: 7.3; 95% confidence interval: 1.8 to 50.4). In another nonrandomized study of 4,758 patients with acute coronary syndromes including 36% STEMI analyzed by renal function where 3,592 had at least mild CKD, they found a long-term mortality reduction in those with CKD treated with PCI (20). This mortality reduction was greater than that seen with coronary artery bypass surgery.

The study by Medi et al. (18) is now the largest to evaluate reperfusion strategy in patients with an acute STEMI in which a detailed analysis of renal function was included. In this post hoc analysis of the prospective GRACE (Global Registry of Acute Coronary Events), 12,532 STEMI patients were evaluated, of whom 3,450 had at least moderate CKD. The investigators reported that patients with greater degrees of CKD were less likely to receive reperfusion therapy, as had been reported in many smaller studies. They found that 3.7% of patients with normal renal function or mild CKD did not receive reperfusion therapy, which rose to 15.1% with moderate CKD, and 31.5% with severe CKD. However, the principle and new finding was that primary PCI was associated with a lower adjusted in-hospital mortality compared with fibrinolytic therapy in the normal renal function group (odds ratio: 0.51) and in those with moderate CKD (odds ratio: 0.66). In the severe CKD group the odds ratio was 0.72, but this failed to reach statistical significance. As has been reported in many other studies, primary PCI was also associated with a lower risk of stroke, which remained true at all levels of renal function. Despite this finding primary PCI was not associated with a statistically significant benefit compared with no therapy in those with CKD. At 6 months, in patients with normal renal function and in those with moderate CKD, there was a significant reduction in mortality associated with primary PCI compared with no reperfusion therapy. In patients with severe CKD, the mortality at 6 months was increased with either PCI or fibrinolytic therapy compared with no reperfusion therapy. Thus, this study exemplified the complexity of reperfusion therapy and the limited knowledge in patients with CKD. This study suggests that patients with moderate, but not severe, CKD might benefit from primary PCI in an acute STEMI. Additionally, this study demonstrates less risk of complications of stroke with primary PCI in patients with moderate or severe CKD when compared with fibrinolytic therapy.

In-hospital and long-term therapy with aspirin, beta blocker drugs, statin drugs, and angiotensin-converting enzyme inhibitor drugs is an essential part of the treatment for myocardial infarction. Such therapy is under-prescribed by up to 50% in CKD patients (4,5,21-23). Despite a paucity of prospective randomized trials that included patients with CKD after a myocardial infarction, retrospective data suggest that CKD patients derive a similar benefit from aspirin, beta blocker drugs, and statin drugs as patients without CKD (21,24). They might receive even greater benefit from angiotensin converting enzyme inhibitor drugs (25). Unfortunately, as with reperfusion therapy, patients with the greatest renal dysfunction and highest mortality after myocardial infarction are prescribed the least medical therapy.

Patients with CKD at all levels are at increased risk of dying from myocardial infarction. Aggressive therapy is warranted. When choosing reperfusion, primary PCI might have greater benefit in patients with moderate CKD compared with fibrinolytic therapy, with lower risk of stroke. However, in those with severe CKD this study did not establish an optimal reperfusion strategy. Medi et al. (18) are to be congratulated for performing the largest study to date to address the most appropriate method of reperfusion therapy for CKD patients, which has added to our understanding of appropriate reperfusion therapy in CKD. However, further studies will be necessary to fully understand the role of each revascularization therapy in the high-risk patient with CKD.

Reprint requests and correspondence: Dr. Patricia J. M. Best, Division of Cardiovascular Diseases, Mayo Clinic, Gonda 5, 200 First Street SW, Rochester, Minnesota 55905. E-mail: best.patricia@mayo.edu.

REFERENCES

1. Wright RS, Reeder GS, Herzog CA, et al. Acute myocardial infarction and renal dysfunction: a high-risk combination. Ann Intern Med 2002;137:563–70.
2. Best PJ, Lennon R, Ting HH, et al. Even mild renal insufficiency is associated with increased mortality after percutaneous coronary interventions. J Am Coll Cardiol 2002;39:1113–9.
3. Sadeghi HM, Stone GW, Grines CL, et al. Impact of renal insufficiency in patients undergoing primary angioplasty for acute myocardial infarction. Circulation 2004;108:2769–75.
4. Masoudi FA, Plomondon ME, Magid DJ, Sales A, Rumsfeld JS. Renal insufficiency and mortality from acute coronary syndromes. Am Heart J 2004;147:623–9.
5. Keough-Ryan TM, Kiberd BA, Dipchand CS, et al. Outcomes of acute coronary syndrome in a large Canadian cohort: impact of chronic renal insufficiency, cardiac interventions, and anemia. Am J Kid Dis 2005;46:845–55.
6. Shlipak MG, Heidenreich PA, Noguchi H, Chertow GM, Browner WS, McClellan MB. Association of renal insufficiency with treatment

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 2, NO. 1, 2009
JANUARY 2009:34–6

and outcomes after myocardial infarction in elderly patients. Ann Intern Med 2002;137:555–562.
7. Al Suwaidi J, Reddan DN, Williams K, et al. GUSTO-IIb, GUSTO-III, PURSUIT. Global Use of Strategies to Open Occluded Coronary Arteries. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. PARAGON-A Investigators. Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network. Prognostic implications of abnormalities in renal function in patients with acute coronary syndromes. Circulation 2002;106:974–80.
8. Parikh CR, Coca SG, Wang Y, Masoudi FA, Krumholz HM. Long-term prognosis of acute kidney injury after acute myocardial infarction. Arch Intern Med 2008;168:987–95.
9. Newsome BB, Warnock DG, McClellan WM, et al. Long-term risk of mortality and end-stage renal disease among the elderly after small increases in serum creatinine level during hospitalization for acute myocardial infarction. Arch Intern Med 2008;168:609–16.
10. Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. The European Myocardial Infarction Project Group. N Engl J Med 1993;329:383–9.
11. Collins R, Peto R, Baigent C, Sleight P. Aspirin, heparin, and fibrinolytic therapy in suspected acute myocardial infarction. N Engl J Med 1997;336:847–60.
12. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Lancet 1994;343:311–22.
13. Zahn R, Schiele R, Schneider S, et al. Decreasing hospital mortality between 1994 and 1998 in patients with acute myocardial infarction treated with primary angioplasty but not in patients treated with intravenous thrombolysis. Results from the pooled data of the Maximal Individual Therapy in Acute Myocardial Infarction (MITRA) Registry and the Myocardial Infarction Registry (MIR). J Am Coll Cardiol 2000;36:2064–71.
14. Weaver WD, Simes RJ, Betriu A, et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. JAMA 1997;278:2093–8.
15. Charytan D, Mauri L, Agarwal A, Servoss S, Scirica B, Kuntz RE. The use of invasive cardiac procedures after acute myocardial infarction in long-term dialysis patients. Am Heart J 2006;152:558–64.
16. Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. N Engl J Med 1998;339:799–805.
17. Herzog CA. Dismal long-term survival of dialysis patients after acute myocardial infarction: can we alter the outcome? Nephrol Dial Trans 2002;17:7–10.
18. Medi C, Montalescot G, Budaj A, et al., on behalf of the GRACE Investigators. Reperfusion in patients with renal dysfunction after presentation with ST-segment elevation or left bundle branch block: GRACE (Global Registry of Acute Coronary Events). J Am Coll Cardiol Intv 2008;2:26–33.
19. Dragu R, Behar S, Sandach A, et al. Should primary percutaneous coronary intervention be the preferred method of reperfusion therapy for patients with renal failure and ST-elevation acute myocardial infarction? Am J Cardiol 2006;97:1142–5.
20. Keeley EC, Kadakia R, Soman S, Borzak S, McCullough PA. Analysis of long-term survival after revascularization in patients with chronic kidney disease presenting with acute coronary syndromes. Am J Cardiol 2003;92:509–14.
21. McCullough PA, Sandberg KR, Borzak S, Hudson MP, Garg M, Manley HJ. Benefits of aspirin and beta-blockade after myocardial infarction in patients with chronic kidney disease. Am Heart J 2002;144:226–32.
22. Krause MW, Massing M, Kshirsagar A, Rosamond W, Simpson RJ Jr. Combination therapy improves survival after acute myocardial infarction in the elderly with chronic kidney. Renal Failure 2004;26:715–25.
23. Tessone A, Gottlieb S, Barbash IM, et al. Underuse of standard care and outcome of patients with acute myocardial infarction and chronic renal insufficiency. Cardiology 2007;108:193–9.
24. Berger AK, Duval S, Krumholz HM. Aspirin, beta-blocker, and angiotensin-converting enzyme inhibitor therapy in patients with end-stage renal disease and an acute myocardial infarction. J Am Coll Cardiol 2003;42:201–8.
25. Tokmakova MP, Skali H, Kenchaiah S, et al. Chronic kidney disease, cardiovascular risk, and response to angiotensin-converting enzyme inhibition after myocardial infarction: the Survival And Ventricular Enlargement (SAVE) study. Circulation 2004;110:3667–73.

Key Words: chronic renal failure ■ myocardial infarction ■ percutaneous coronary intervention ■ thrombolytic therapy.