Acute coronary syndrome in ESRD patients

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CASE PRESENTATION

A 55-year-old male with end-stage renal disease (ESRD) secondary to diabetic nephropathy on hemodialysis for 2 years via a tunneled catheter line was admitted to the Brigham & Women's Hospital with chest pain. The chest pain was localized to the midline, radiated to the left arm, and was present at rest with no diaphoresis. His cardiac enzymes were elevated (troponin-I of 11.46 ng/ml and creatinine kinase-MB of 30.7 ng/ml) and his electrocardiogram (EKG) showed nonspecific ST–T wave changes that were unchanged from previous EKG 6 months earlier. He had a history of coronary artery disease (CAD) status post coronary artery bypass graft (CABG) 10 months earlier, type 1 diabetes mellitus since the age of 6 years, and peripheral neuropathy, blindness secondary to proliferative retinopathy, gastroparesis, neurogenic bladder, peripheral vascular disease (above-knee amputation of right limb), hypertension, and hypercholesterolemia. He had a failed living-related renal transplant because of recurrent diabetic nephropathy and chronic allograft nephropathy after 15 years. He had no history of stroke. His medications included aspirin, metoprolol, simvastatin, gemfibrozil, insulin, calcium acetate, sevelamer, epoeitin alfa, methadone, and hydromorphone hydrochloride. There was no significant family history of cardiovascular or renal disease. On physical examination, he was alert and afebrile, with a blood pressure of 135/60 mmHg, heart rate of 70 beats per minute, respiratory rate of 14 breaths per minute, with an oxygen saturation of 100% on room air and jugular venous pressure of 7 cm. His tunneled catheter site on the right side of the neck was clean, with no tenderness or erythema. Cardiac examination revealed distant heart sounds with no murmurs. The rest of the examination was unremarkable.

CLINICAL DIAGNOSIS

A clinical diagnosis of acute coronary syndrome (ACS) (a non-ST-elevation myocardial infarction (MI)) was made.

CLINICAL FOLLOW-UP

The patient was admitted with a provisional diagnosis of non-ST-elevation MI. He was managed medically with aspirin, beta-blockers, statin, and heparin. However, he did not receive clopidogrel, thrombolytics, or emergent catheterization because of substantial comorbidities and because it was unclear if any further intervention would be beneficial. He remained chest pain-free during the hospital stay. Subsequently, he underwent an echocardiogram 4 days after admission that showed an ejection fraction of 55–60% with no wall-motion abnormalities and a moderate enlargement of the left atrium. These findings were similar to an echocardiogram performed 6 months earlier. Five days after admission, a cardiac catheterization was performed (Figure 1), which revealed a left dominant system with a patent left internal mammary artery to left anterior descending graft (Figure 1c) and saphaneous vein graft to distal obtuse marginal 1 graft (Figure 1d). Progression of disease in his native coronary arteries was significant with a new total occlusion of the right coronary artery, progression to total occlusion in previously noted obtuse marginal and left anterior descending artery lesions, and a new, ostial left circumflex lesions. No interventions were performed.

With therapy, his troponins and creatinine kinase-MB gradually trended down (Figure 2) and he was discharged 8 days after admission. There was no change in his medications as compared to before his admission.

DISCUSSION

This patient with ESRD on hemodialysis presented with ACS and subsequently underwent cardiac catheterization 5 days after presentation. This patient's presentation raises several important issues with regard to the secondary prevention and acute management of ACS in ESRD patients: first, the increasing burden of CAD in dialysis patients and the challenges associated in its accurate diagnosis; second, the frequent underutilization of standard management/preventive measures for CAD in ESRD patients; and lastly, the appropriate management of ACS and relevance of consensus guidelines aimed at the general population for the treatment of ACS in patients with ESRD.

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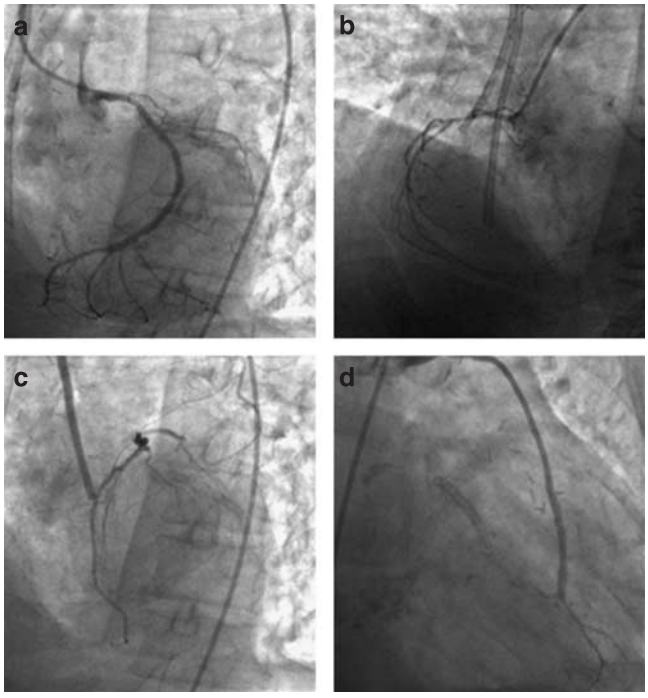

Figure 1 | Images of cardiac catheterization of the index patient. Cardiac catheterization showing grossly normal (**a**) left coronary and (**b**) right coronary and a (**c**) patent left internal mammary artery to left anterior descending graft and (**d**) saphaneous vein graft to obtuse marginal 1 graft.

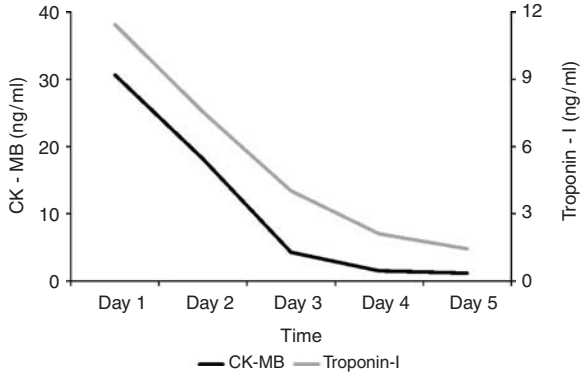

Figure 2 | Trends in serum troponin-I and creatinine kinase-MB during hospital stay.

Epidemiology/burden of CAD in ESRD patients

In 2004, the 1-year mortality for patients with ESRD was 22.54%.[1] However, the survival after the occurrence of an MI decreases markedly. During the year after MI, mortality rises to nearly 60%,[2] and approaches 75% at 2 years.[2] Conversely, less than 10% of dialysis-dependant patients survive 5 years post MI.[2]

Myocardial infarction and cardiovascular disease are frequent complications in patients on chronic dialysis. Cardiovascular disease is the leading cause of death among dialysis patients, accounting for approximately 40% of all deaths;[3] Of this 40%, approximately 17% is attributable to ACS.[1] Among patients initiating dialysis, the incidence of ACS and congestive heart failure during a follow up of 2.2 years were 10.2 and 13.6%, respectively.[4] From large databases of patients with ESRD, the prevalence of CAD and congestive heart failure are 36 and 39%, respectively.[5] This high rate of cardiovascular complications is at least partially due to extensive cardiovascular disease in patients both when they initiate dialysis and subsequently.[6] Foley *et al.*[7] and others have documented a prevalence of left ventricular hypertrophy of 74% in this population—almost two-fold greater than the 38% prevalence found in a study of pre-ESRD patients. Conversely, in a series of consecutive incident dialysis patients who underwent cardiac catheterization, more than 60% of patients had significant CAD (defined as more than 75% narrowing of a major coronary artery), with an average of 3.3 lesions per patient.[8]

In summary, patients maintained on chronic dialysis have a high burden of atherosclerotic coronary disease that is associated with an excessively high risk of developing MI and congestive heart failure. Most importantly, it must be appreciated that the risk of cardiovascular death in the dialysis population as a whole is several times higher than other high-risk populations such as patients without renal disease admitted with an MI complicated by congestive heart failure.[5,9] Thus, it may be reasonable to consider dialysis-dependant ESRD as a coronary heart disease equivalent and to consider aggressive use of anti-ischemic and anti-atherosclerotic therapies in all patients on dialysis.

Whether the dialysis procedure itself imposes further ischemia is controversial. Some have suggested that hypoxia during dialysis, rapid fluid and/or solute shifts, and hemodynamic changes may contribute. However, trial data to date has been very limited.

Challenges in accurate diagnosis of CAD in ESRD patients

The management of CAD in patients with chronic kidney disease (CKD) is more challenging than in patients with normal kidney function. This is partly because of the limited predictive value of the traditional triad of symptoms, EKG findings, and cardiac biomarkers in diagnosing ACS in dialysis patients.

Although chest pain is considered to be the cardinal manifestation of coronary ischemia, patients with both predialysis CKD[10] and ESRD[11] present with chest pain as their chief complaint much less frequently than patients with normal renal function. In fact, fewer than 50% of dialysis patients with MI present with chest pain, which likely explains why MI is infrequently suspected on admission.[11] Reasons for the different presentations of ischemia are not well understood but may be related to associated diabetic or uremic neuropathy. Diagnosis of ischemia is further complicated by the fact that other symptoms of ischemia, such as dyspnea on exertion, fatigue, and hypotension, are common in dialysis patients and may be attributed to dialysis-related

factors such anemia, volume overload, acidosis, non-compliance with fluid intake or dialysis or to ultra-filtration during dialysis.

An additional problem in diagnosing ACS is that the primary tests used to diagnose ACS perform poorly in patients with dialysis-dependant CKD. Cardiac enzyme (CK, creatinine kinase-MB and troponin) elevations have been observed on routine testing in dialysis patients without clinical evidence of acute ischemia.[12] In a study by Ooi *et al.*, approximately 29% of patients without overt acute coronary disease had an elevated level of troponin T.[13] Furthermore, only about 11% of patients had concentrations less than 0.01 μg/l (that is, as typically observed in a nonuremic population). Several other studies have also reported false-positive elevations in troponin T levels in ESRD patients without ACS.[14,15] Furthermore, one-, two-, and three-year cumulative mortality rates were increased for patients who had elevated troponin T levels as compared with those who had normal/undetectable levels.[16] The 2-year mortality rate for those with cTnT <0.01 ($n=132$) was 8.4 versus 26% for those with minor increases (cTnT $\geqslant 0.01$ but <0.04 μg/l; $n=214$); 39% with moderate increases (cTnT $\geqslant 0.04$ but <0.1 μg/l; $n=239$); and 47% with larger increases (cTnT $\geqslant 0.1$ μg/l; $n=148$).

The EKG may be difficult to interpret due to the frequent presence of left ventricular hypertrophy and pathologic Q waves at baseline as well the presence of ST depression in many patients without clinically evident myocardial ischemia during routine hemodialysis sessions.[17] Furthermore, ST elevation, the most striking electrical sign of ischemia in patients with an MI, is 50% less frequent in those on dialysis versus the nondialysis population. Difficulty in interpreting the EKG may also compromise the utility of exercise stress testing as a tool for the diagnosis of coronary ischemia. The presence of baseline EKG abnormalities along with an inability to reach target heart rate in exercise electrocardiographic testing lowers the sensitivity and specificity of these modalities in CKD patients.[18] Although there is data that suggest a lower accuracy for CAD detection in dialysis patients using stress nuclear or echocardiographic imaging techniques, compared with the general population,[19] echocardiographic and nuclear imaging-based stress testing do appear to perform relatively well as prognostic tools and have at least moderate sensitivity for the detection of advanced obstructive CAD in dialysis patients.[18,20] Combined dipyridamole and exercise thallium imaging may provide increased accuracy in hemodialysis patients. The sensitivity, specificity, positive and negative predictive values, and overall accuracy of thallium imaging were 92, 89, 71, 98, and 90%, respectively.[20] Currently, the 'Kidney Disease Outcomes Quality Initiative' guidelines suggest that dobutamine echocardiography is preferred to vasodilator-induced stress nuclear scintigraphy in diagnosing obstructive CAD in the dialysis population,[21] although this data should be reevaluated periodically as nuclear and echocardiographic techniques continue to be refined.

With advances in technology, newer modalities may ultimately emerge as alternative tools for the detection of CAD in dialysis patients. Contrast enhanced cardiac magnetic resonance imaging allows for very sensitive detection of focal myocardial necrosis or fibrosis,[22] and both cardiac magnetic resonance imaging and computed tomography angiography may also allow for noninvasive detection of obstructive coronary disease. However, neither computed tomography angiography nor cardiac magnetic resonance imaging have emerged as standard clinical tools. Indeed, at the present time, the risk of nephrogenic fibrosing dermopathy[23] is a significant limitation to the use of cardiac magnetic resonance imaging in CKD patients.

This cluster of atypical symptoms and the lack of data to guide the ideal diagnostic approach in dialysis patients make the detection of CAD very challenging in this patient population. Clinical acumen and the maintenance of a high-index of suspicion for the presence of coronary disease remain critical tools for clinicians taking care of patients with ESRD.

Inadequate secondary prevention of CAD in ESRD patients

There is growing concern that CKD patients receive inadequate preventive care for CAD. Although the guidelines promulgated by Kidney Disease Outcomes Quality Initiative[21] and 'American Heart Association'/'American College of Cardiology'[24] recommend the use of aspirin, statins, beta-blockers, angiotensin-converting enzyme inhibitors, and early coronary interventions in patients with ACS, patients with CKD are less likely than non-CKD patients to receive these therapies.[9,25–27] Winkelmayer *et al.*[28] studied the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, and statins in dialysis patients with MI and reported that only 49, 45, and 29% of patients received these agents within the first 90 days following discharge with an MI. Similar results were reported by Berger *et al.*[25] with the use of aspirin, beta-blockers, and angiotensin-converting enzyme inhibitors. These authors also suggested that secondary preventive measures were associated with lower 30-day mortality in this patient population (50, 40, and 48% relative reduction and 20.7, 13.6, and 16.1% absolute reductions in mortality, respectively). The use of glycoprotein IIb/IIIa receptor antagonists was also lower in patients as the renal function declined, despite a mortality-protective benefit after adjustment for degree of renal dysfunction.[29] However, as the renal function deteriorated, the risk of bleeding increased. CKD patients also undergo coronary angiography less frequently as compared with non-CKD patients despite the fact that angiography appears to be associated with lower mortality in CKD patients.[26,30,31] Similarly, elderly patients with Stage 3 or higher CKD undergo coronary angiography after MI less frequently than patients with mild or no CKD.[32]

Chertow *et al.*[26] highlighted the underutilization of coronary angiography by demonstrating that only 25.2% of CKD patients underwent angiography as compared with

46.8% of non-CKD patients and that these differences persisted even among well-suited candidates for angiography. Furthermore, 1-year mortality was 30.2% in CKD patients who underwent angiography as compared with 60.2% in those who did not.[26] Although randomized data are lacking, it appears that the use of coronary angiography is associated with a significant reduction in the risk of death in patients with advanced CKD[26] and that this intervention should be strongly considered in patients with ACS regardless of renal function.

Collectively, these studies are limited by the presence of selection bias, wherein the subjects who received cardioprotective medications and angiography may be a healthier cohort with fewer comorbid conditions compared with the subjects who did not receive such therapy. This may partly explain the reduced survival in the latter group of patients. Furthermore, sample sizes are generally small, raising concerns about generalizibility.

Recommendations

Given the high-risk burden of coronary disease in the dialysis population, it is reasonable to perform screening for cardiovascular disease when initiating chronic dialysis therapy. Kidney Disease Outcomes Quality Initiative guidelines suggest that the work-up should include at least a baseline EKG and an echocardiogram.[21] All dialysis patients with CAD who are not allergic to aspirin should receive aspirin, and the use of beta-blockers, statins, and angiotensin-converting enzyme inhibitors should be considered in patients without contraindications.[21]

When patients present with signs or symptoms suggestive of coronary ischemia, maintenance of a high index of suspicion is important. Interpretation of diagnostic tests should be made in the context of the high prevalence of CAD and ACS in the dialysis population, recognizing that the post-test probability of CAD may remain high despite negative (noninvasive) diagnostic tests.[33] Once ACS is diagnosed, guidelines recommend that the treatment of ACS in dialysis patients should be similar to that of the non-dialysis patient population (summarized in Table 1). Patients should receive aspirin, beta-blockers, statins, thrombolytic therapy, percutaneous coronary intervention, and CABG according to the usual indications.[21] Unfractionated heparin and low molecular weight heparin have been used in patients with unstable angina and ACS. The use of low molecular weight heparin is controversial from the perspective of dosage adjustment, as its clearance is affected by kidney function and because of the difficulty of monitoring factor Xa levels in the outpatient setting. Collet *et al.*[34] reported significantly lower 30-day mortality with the use of low molecular weight heparin compared with unfractionated heparin (4.2 versus 6.2%, $P = 0.0001$). Glycoprotein IIb/IIIa receptor antagonists should also be considered as an adjunctive therapy, with abciximab and tirofiban as preferred agents (no dosing changes for abciximab and dialysis-specific dosing recommendations are available for tirofiban).

Table 1 | Recommendations for management of patients presenting with ACS (adapted from Kidney Disease Outcomes Quality Initiative[21])

Treatment of ACS
Aspirin
Beta-blockers
Statins
ACEI
Thrombolytics
In addition to the above
ST elevation MI—emergent PCI or thrombolytics
Left main or three vessel disease—CABG
Patients with stents—clopidogrel

Furthermore, MI patients with ST-segment elevation should receive acute reperfusion therapy if emergent percutaneous coronary intervention is unavailable.[21] Percutaneous coronary intervention/CABG are appropriate revascularization techniques for symptomatic ischemia, and CABG should be considered in those with three-vessel and/or left main disease.[21] Clopidogrel should be prescribed for all patients with coronary stents and considered in other patients with stable CAD or established atherosclerotic cardiovascular disease.[21]

It must be noted that randomized data supporting these recommendations are not yet available in the dialysis population.[35] In fact, prospective trials of standardized cardiovascular therapies have generally suggested lower efficacy in the dialysis population than the general population.[36,37] Further studies to determine how to optimize treatment of CAD in the dialysis population are badly needed, but the preceding recommendations represent a reasonable approach based on a synthesis of currently available evidence.

CONCLUSION

The prognosis of patients with ESRD is poor, and this stems in part from a high frequency of ACS and a high mortality from ACS among dialysis patients. This high risk is likely multifactorial, representing an interplay of unique pathophysiologic factors. Underdiagnosis and/or inadequate treatment of underlying CAD in these difficult patients, the wide spectrum of 'atypical clinical presentations', performance of diagnostic tests, and underutilization of standard therapies are areas that merit further study in this patient population. Given the high risk of cardiovascular death in this population, we believe aggressive workup and treatment of ischemia have the potential to save lives and are warranted, while we await the availability of randomized data in the dialysis population.

REFERENCES

1. US Renal Data System USRDS 2007 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2007.
2. 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.

3. US Renal Data System USRDS 1998 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 1998.
4. Foley RN, Herzog CA, Collins AJ. Smoking and cardiovascular outcomes in dialysis patients: the United States Renal Data System Wave 2 study. *Kidney Int* 2003; **63**: 1462–1467.
5. Foley RN, Herzog CA, Collins AJ. Blood pressure and long-term mortality in United States hemodialysis patients: USRDS Waves 3 and 4 Study. *Kidney Int* 2002; **62**: 1784–1790.
6. Foley RN, Parfrey PS, Harnett JD *et al.* Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 1995; **47**: 186–192.
7. Levin A, Singer J, Thompson CR *et al.* Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. *Am J Kidney Dis* 1996; **27**: 347–354.
8. Joki N, Hase H, Nakamura R *et al.* Onset of coronary artery disease prior to initiation of haemodialysis in patients with end-stage renal disease. *Nephrol Dial Transplant* 1997; **12**: 718–723.
9. Anavekar NS, McMurray JJ, Velazquez EJ *et al.* Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004; **351**: 1285–1295.
10. Sosnov J, Lessard D, Goldberg RJ *et al.* Differential symptoms of acute myocardial infarction in patients with kidney disease: a community-wide perspective. *Am J Kidney Dis* 2006; **47**: 378–384.
11. Herzog CA, Littrell K, Arko C *et al.* Clinical characteristics of dialysis patients with acute myocardial infarction in the United States: a collaborative project of the United States Renal Data System and the National Registry of Myocardial Infarction. *Circulation* 2007; **116**: 1465–1472.
12. Tun A, Khan IA, Win MT *et al.* Specificity of cardiac troponin I and creatine kinase-MB isoenzyme in asymptomatic long-term hemodialysis patients and effect of hemodialysis on these cardiac markers. *Cardiology* 1998; **90**: 280–285.
13. Ooi DS, House AA. Cardiac troponin T in hemodialyzed patients. *Clin Chem* 1998; **44**: 1410–1416.
14. Apple FS, Sharkey SW, Hoeft P *et al.* Prognostic value of serum cardiac troponin I and T in chronic dialysis patients: a 1-year outcomes analysis. *Am J Kidney Dis* 1997; **29**: 399–403.
15. Li D, Keffer J, Corry K *et al.* Nonspecific elevation of troponin T levels in patients with chronic renal failure. *Clin Biochem* 1995; **28**: 474–477.
16. Apple FS, Murakami MM, Pearce LA *et al.* Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. *Circulation* 2002; **106**: 2941–2945.
17. Zuber M, Steinmann E, Huser B *et al.* Incidence of arrhythmias and myocardial ischaemia during haemodialysis and haemofiltration. *Nephrol Dial Transplant* 1989; **4**: 632–634.
18. Sharma R, Pellerin D, Gaze DC *et al.* Dobutamine stress echocardiography and the resting but not exercise electrocardiograph predict severe coronary artery disease in renal transplant candidates. *Nephrol Dial Transplant* 2005; **20**: 2207–2214.
19. Herzog CA. How to manage the renal patient with coronary heart disease: the agony and the ecstasy of opinion-based medicine. *J Am Soc Nephrol* 2003; **14**: 2556–2572.
20. Dahan M, Viron BM, Faraggi M *et al.* Diagnostic accuracy and prognostic value of combined dipyridamole-exercise thallium imaging in hemodialysis patients. *Kidney Int* 1998; **54**: 255–262.
21. National Kidney Foundation. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis* 2005; **45**: S1–S154.
22. Wu E, Judd RM, Vargas JD *et al.* Visualisation of presence, location, and transmural extent of healed Q-wave and non-Q-wave myocardial infarction. *Lancet* 2001; **357**: 21–28.
23. Yerram P, Saab G, Karuparthi PR *et al.* Nephrogenic systemic fibrosis: a mysterious disease in patients with renal failure—role of gadolinium-based contrast media in causation and the beneficial—effect of intravenous sodium thiosulfate. *Clin J Am Soc Nephrol* 2007; **2**: 258–263.
24. Braunwald E, Antman EM, Beasley JW *et al.* ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol* 2000; **36**: 970–1062.
25. 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**: 201–208.
26. Chertow GM, Normand SL, McNeil BJ. 'Renalism': inappropriately low rates of coronary angiography in elderly individuals with renal insufficiency. *J Am Soc Nephrol* 2004; **15**: 2462–2468.
27. Winkelmayer WC, Charytan DM, Levin R *et al.* Poor short-term survival and low use of cardiovascular medications in elderly dialysis patients after acute myocardial infarction. *Am J Kidney Dis* 2006; **47**: 301–308.
28. Winkelmayer WC, Charytan DM, Brookhart MA *et al.* Kidney function and use of recommended medications after myocardial infarction in elderly patients. *Clin J Am Soc Nephrol* 2006; **1**: 796–801.
29. Freeman RV, Mehta RH, Al Badr W *et al.* Influence of concurrent renal dysfunction on outcomes of patients with acute coronary syndromes and implications of the use of glycoprotein IIb/IIIa inhibitors. *J Am Coll Cardiol* 2003; **41**: 718–724.
30. Charytan D, Mauri L, Agarwal A *et al.* The use of invasive cardiac procedures after acute myocardial infarction in long-term dialysis patients. *Am Heart J* 2006; **152**: 558–564.
31. Chertow GM, Normand SL, Silva LR *et al.* Survival after acute myocardial infarction in patients with end-stage renal disease: results from the cooperative cardiovascular project. *Am J Kidney Dis* 2000; **35**: 1044–1051.
32. Charytan DM, Setoguchi S, Solomon DH *et al.* Clinical presentation of myocardial infarction contributes to lower use of coronary angiography in patients with chronic kidney disease. *Kidney Int* 2007; **71**: 938–945.
33. Schuijf JD, Poldermans D, Shaw LJ *et al.* Diagnostic and prognostic value of non-invasive imaging in known or suspected coronary artery disease. *Eur J Nucl Med Mol Imaging* 2006; **33**: 93–104.
34. Collet JP, Montalescot G, Agnelli G *et al.* Non-ST-segment elevation acute coronary syndrome in patients with renal dysfunction: benefit of low-molecular-weight heparin alone or with glycoprotein IIb/IIIa inhibitors on outcomes. The Global Registry of Acute Coronary Events. *Eur Heart J* 2005; **26**: 2285–2293.
35. Charytan D, Kuntz RE. The exclusion of patients with chronic kidney disease from clinical trials in coronary artery disease. *Kidney Int* 2006; **70**: 2021–2030.
36. Wanner C, Krane V, Marz W *et al.* Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005; **353**: 238–248.
37. Zannad F, Kessler M, Lehert P *et al.* Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies. *Kidney Int* 2006; **70**: 1318–1324.