Note: This is a two-article spread with a shared commentary. Please scroll down for the second article.

ETIOLOGY

Reduced glomerular filtration rate was associated with increased death, cardiovascular events, and hospitalization

Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. **Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization.** N Engl J Med. 2004;351:1296-305.

QUESTION

What is the relation of the severity of renal impairment to the risk for all-cause mortality, cardiovascular (CV) events, and hospitalization?

METHODS

Design: Cohort study with 2.84-year follow-up.

Setting: The Kaiser Permanente of Northern California health care system, San Francisco Bay area.

Patients: 1 120 295 patients who were ≥ 20 years of age (mean age 52 y, 55% women) and had ≥ 1 outpatient measurement of serum creatinine levels between January 1, 1996, and December 31, 2000. Exclusion criteria were kidney transplantation or maintenance dialysis.

Risk factors: The Modification of Diet and Renal Disease (MDRD) equation was used to estimate baseline glomerular filtration rate (GFR). The Kaiser Permanente regional laboratory serum creatinine measurement was calibrated with the laboratory used to derive the MDRD equation. GFR was divided into 5 categories (< 15, 15 to 29, 30 to 44, 45 to 59, and ≥ 60 mL/min per 1.73 m^2 of body surface). Other risk factors were age, sex, race or ethnicity, and comorbid illnesses (including coronary disease, stroke or transient ischemic attack, heart failure, peripheral arterial disease, diabetes mellitus, hypertension, dyslipidemia, lung or liver disease, cancer, and dementia).

Outcomes: All-cause mortality, CV events (hospitalization for coronary disease, heart failure, stroke, or peripheral arterial disease), and hospitalization.

MAIN RESULTS

Risk for all-cause mortality, CV events, and hospitalizations increased with decreasing estimated GFRs (Table). The adjusted risk for all-cause mortality ranged from a 17% increase with an estimated GFR 45 to 59 mL/min per 1.73 m^2 to 600% with a GFR < 15 mL/min per 1.73 m^2. The presence of proteinuria was also an independent predictor of all-cause mortality (adjusted hazard ratio [HR] 1.3, 95% CI 1.3 to 1.4), CV events (HR 1.3, CI 1.2 to 1.3), and hospitalization (HR 1.4, CI 1.4 to 1.4).

CONCLUSION

Reduced estimated glomerular filtration rate was associated with increased risk for all-cause mortality, cardiovascular events, and hospitalization.

Source of funding: National Institute for Diabetes, Digestive, and Kidney Diseases.

For correspondence: Dr. A.S. Go, Kaiser Permanente of Northern California, Oakland, CA, USA. E-mail alan.s.go@kp.org.

Association of estimated glomerular filtration rate (GFR) with risk for death, cardiovascular events, and hospitalization*

Outcomes	Adjusted hazard ratio (95% CI)†			
	GFR < 15 mL/min per 1.73 m^2	GFR 15 to 29 mL/min per 1.73 m^2	GFR 30 to 44 mL/min per 1.73 m^2	GFR 45 to 59 mL/min per 1.73 m^2
All-cause mortality	5.9 (5.4 to 6.5)	3.2 (3.1 to 3.4)	1.8 (1.7 to 1.9)	1.2 (1.1 to 1.2)
Any cardiovascular event	3.4 (3.1 to 3.8)	2.8 (2.6 to 2.9)	2.0 (1.9 to 2.1)	1.4 (1.4 to 1.5)
Any hospitalization	3.1 (3.0 to 3.3)	2.1 (2.0 to 2.2)	1.5 (1.5 to 1.5)	1.1 (1.1 to 1.1)

*Patients with GFR ≥ 60 mL/min per 1.73 m^2 were the reference group. CI defined in Glossary.

†Adjusted for age sex, income, education, dialysis, coronary disease, heart failure, stroke or transient ischemic attack, hypertension, dyslipidemia, cancer, serum albumin level ≤ 3.5 g/dL, dementia, cirrhosis or liver disease, lung disease, proteinuria, and previous hospitalizations.

COMMENTARY

Patients with renal insufficiency are easily identifiable, using equations that estimate GFR based on serum creatinine. In recent years, numerous studies have suggested that patients with estimated lower GFR have a higher incidence of future CV events and mortality than those with normal GFR. The large, well-done studies by Go and Anavekar and their colleagues confirm this both in the general population and in patients presenting with acute MI. For example, in the study by Go and colleagues, the age-standardized rate of death per 100 person-years in the general population was 14.1 when the estimated GFR was < 15 mL/min per 1.73 m^2 and was 11.4, 4.8, and 1.1 when the estimated GFR was 15 to 29, 30 to 44, and 45 to 59 mL/min per 1.73 m^2, respectively. Similar trends were also present for CV and hospitalization outcomes. These findings in large numbers of patients, throughout an entire range of GFRs, highlight the clinical and public health importance of this condition.

How can practitioners prevent future morbidity and mortality in these patients? It is evident that patients with moderate reductions of GFR (GFR 30 to 59 mL/min per 1.73 m^2) benefit from established CV protective interventions, such as statins and angiotensin-converting enzyme inhibitors (1, 2). Given their high incidence of future CV events, patients with low GFR may derive an even greater benefit in absolute terms than does the general population. Thus, the importance of using such medications in these patients cannot be overemphasized, and observed deficiencies in health care must be remedied (3). Unfortunately, a number of clinical trials testing CV protective interventions deliberately excluded patients with more marked reductions in GFR. In addition, a recent large trial showed that hemodialysis patients were unresponsive to the benefits of statins (4). Thus, whether patients with GFR < 30 have a similar response to CV agents proven beneficial in the general population remains to be clarified.

In patients with GFR < 30 mL/min per 1.73 m^2, is there any role for the treatment of potential novel risk factors that become pronounced with GFR decline? The studies by Go and Anavekar and their colleagues

(continued on page 51)

Renal impairment increased mortality and cardiovascular complications after myocardial infarction

Anavekar NS, McMurray JJ, Velazquez EJ, et al. **Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction.** N Engl J Med. 2004;351:1285-95.

QUESTION

In patients who have had myocardial infarction (MI), what is the relation of the severity of renal impairment to the risk for all-cause and cardiovascular (CV) mortality?

METHODS

Design: Analysis within a randomized (allocation concealed*), blinded (clinicians, patients, and outcome assessors),* controlled trial (Valsartan in Acute Myocardial Infarction Trial [VALIANT] trial).

Setting: {931 centers in 24 countries}†.

Patients: 14 527 patients ≥ 18 years of age (mean age 66 y, 69% men) who had had acute MI within the previous 12 days that was complicated by clinical or radiologic signs of heart failure, left ventricular systolic dysfunction, or both. Patients with serum creatnine levels ≥ 221 µmol/L (2.5 mg/dL) were excluded.

Risk factors: Baseline glomerular filtration rate (GFR) was estimated using the Modification of Diet and Renal Disease equation, which incorporates age, race, sex, and serum creatinine level, and divided into 4 categories (< 45, 45 to 59.9, 60 to 74.9, and ≥ 75 mL/min per 1.73 m^2 of body surface).

Outcomes: All-cause mortality and a composite CV endpoint of CV mortality, congestive heart failure, recurrent MI, resuscitation after cardiac arrest, and stroke.

Main results: Risk for all-cause mortality and the composite CV endpoint increased with decreasing estimated GFRs (Table). For estimated baseline GFR levels < 81.0 mL/min per 1.73 m^2, each 10-unit decrease was associated with a hazard ratio of 1.10 (95% CI 1.08 to 1.12) for death and CV complications.

CONCLUSIONS

In patients who have had a myocardial infarction, the presence of renal disease increased the risk for all-cause and cardiovascular (CV) mortality and complications. Progressive reductions in renal function were associated with increasing mortality and CV complications.

Source of funding: Novartis Phamaceuticals.

For correspondence: Dr. M.A. Pfeffer, Brigham and Women's Hospital, Boston, MA, USA. E-mail mpfeffer@rics.bwh.harvard.edu. ■

*See Glossary.

†**Pfeffer MA, McMurray JJ, Velazquez EJ, et al.** N Engl J Med. 2003;349:1893-906.

Association of estimated glomerular filtration rate (GFR) with risk for death and composite cardiovascular (CV) outcomes‡

Outcomes	Adjusted hazard ratio (95% CI)§		
	GFR < 45 mL/min per 1.73 m^2	GFR 45 to 59.9 mL/min per 1.73 m^2	GFR 60 to 74.9 mL/min per m^2
All-cause mortality	1.70 (1.50 to 1.93)	1.38 (1.24 to 1.54)	1.14 (1.02 to 1.27)
Composite CV endpoint	1.49 (1.35 to 1.65)	1.26 (1.16 to 1.37)	1.10 (1.02 to 1.19)

‡Patients with GFR ≥ 75.0 mL/min per 1.73 m^2 were the reference group. Composite CV endpoint included CV mortality, reinfarction, congestive heart failure, resuscitation after cardiac arrest, and stroke. CI defined in Glossary.

§Variables in adjustment included 70 baseline characteristics.

COMMENTARY

(continued from page 50)

both describe a "dose-dependent," independent association between decrements in GFR and future CV events. The risk in patients with GFR < 30 mL/min per 1.7 $3m^2$ was more than 3-fold that of patients with preserved GFR. These associations persisted after adjustment for established cardiovascular risk factors and other relevant comorbid conditions. Proposed novel mechanisms potentially amenable to therapeutic intervention include elevated calcium-phosphate product, hyperhomocysteinemia, anemia, and inflammation. However, whether low GFR is causally related to CV disease remains controversial. For example, in the study by Anavekar and colleagues, a portion of the independent association between low GFR and future CV events is expected to be noncausal residual confounding from such factors as concomitant renal vascular disease, generalized atherosclerosis, and renal hypoperfusion. Thus, while promising, the potential to reduce the burden of CV disease by treating unique renal pathogenic mechanisms remains uncertain. The CV benefits of erythropoietin and phosphate binders in these patients are the subject of ongoing clinical trials, and their results will inform both patient care and the causality debate.

Amit X. Garg, MD, MA, FRCPC
London Health Sciences Centre
London, Ontario, Canada

References

1. **Tonelli M, Isles C, Curhan GC, et al.** Effect of pravastatin on cardiovascular events in people with chronic kidney disease. Circulation. 2004;110:1557-63.
2. **Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S.** Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med. 2001;134:629-36.
3. **Nissenson AR, Collins AJ, Hurley J, et al.** Opportunities for improving the care of patients with chronic renal insufficiency: current practice patterns. J Am Soc Nephrol. 2001;12:1713-20.
4. **Wanner C, Krane V, Marz W, et al.** Randomized controlled trial on the efficacy and safety of atorvastatin in patients with type 2 diabetes on hemodialysis (4D study): demographic and baseline characteristics. Kidney Blood Press Res. 2004;27:259-66. Epub 2004 Aug 16.