Original Article

Chronic Kidney Disease Increases Cardiovascular Mortality in 80-Year-Old Subjects in Japan

Shuntaro KAGIYAMA[1),2)], Kiyoshi MATSUMURA[2)], Toshihiro ANSAI[3)], Inho SOH[3)], Yutaka TAKATA[1)], Shuji AWANO[3)], Kazuo SONOKI[1)], Akihiro YOSHIDA[3)], Tadamichi TAKEHARA[3)], and Mitsuo IIDA[2)]

Chronic kidney disease (CKD) is one of the greatest risk factors for cardiovascular disease (CVD). The contribution of CKD to CVD mortality is not well understood in very elderly patients. Our study examined whether CKD might be a risk factor for total and CVD mortality in very elderly Japanese individuals. A total of 621 participants were enrolled, all of whom were 80 years old. The subjects were divided on the basis of the presence (CKD(+) group, *n*=280) or absence (CKD(–) group, *n*=341) of CKD. CKD was defined by as an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2. The eGFR of the CKD(+) and CKD(–) groups was 49.7±8.5 and 70.9±9.5 mL/min/1.73 m^2, respectively. During the 4-year study period, 87 individuals died, and 25 of those deaths were due to CVD. A Cox multivariate regression analysis revealed no association between total mortality and CKD (relative risk [RR] 1.17, confidence interval [CI] 0.75–1.82, *p*=0.50). However, the CVD mortality was significantly increased in the CKD(+) group (RR 4.60, CI 1.69–12.52, *p*=0.003). CKD significantly increased the CVD mortality in subjects who were not taking antihypertensive medication (RR 5.15, CI 1.04–25.50, *p*=0.04). Our results suggest that CKD increases the risk of CVD mortality in very elderly individuals. It is not only important to prevent progression toward CKD in patients who do not suffer from CKD, but also critical to manage the risk factors for CVD in patients with CKD, despite their advanced age. (*Hypertens Res* 2008; 31: 2053–2058)

***Key Words*: chronic kidney disease, mortality, elderly**

Introduction

The National Kidney Foundation Task Force on Cardiovascular Disease in Chronic Renal Disease has reported that not only end-stage renal disease (ESRD) but also mild to moderate decreased renal function are risk factors for cardiovascular diseases (CVD). The organization also recommended that care should be taken to prevent patients with chronic kidney disease (CKD) from developing CVD (*1*). As the glomerular filtration ratio (GFR), a representative marker of renal function, gradually decreases with age at a rate of about – 1.0 mL/min/1.73 m^2/year (*2*), the prevalence of CKD is naturally substantially higher in elderly individuals. Furthermore, ethnicity affects the GFR, and the prevalence of CKD varies across different populations. The risk of CKD and CVD mortality should ideally be evaluated in different countries and for different age groups (*3*). Recently, a Modification of Diet in Renal Disease (MDRD) equation for the estimated GFR (eGFR) that includes a Japanese correction coefficient was reported from data contributed by over 500,000 individuals in the general Japanese population (*4*). Japan is rapidly becoming an aged society, and the very elderly (those aged 80 years or over) now represent about 3.4% of the population (*5*); how-

From the [1)]Division of General Internal Medicine and [3)]Community Oral Health Science, Department of Health Promotion, Science of Health Improvement, Kyushu Dental College, Kitakyushu, Japan; and [2)]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

Address for Reprints: Yutaka Takata, M.D., Ph.D., Division of General Internal Medicine, Department of Health Promotion, Science of Health Improvement, Kyushu Dental College, 2–6–1 Manazuru, Kokurakita-ku, Kitakyushu 803–8580, Japan. E-mail: yutaka@kyu-dent.ac.jp

Received July 9, 2008; Accepted in revised form September 28, 2008.

Table 1. Baseline Characteristics of the Subjects with or without CKD

	CKD(−)	CKD(+)	*p* value
n	341	280	
Sex (male/female)	170/171	80/200	**
BMI (kg/m^2)	22.3±3.1	23.2±3.5	**
Systolic BP (mmHg)	150.2±22.5	150.8±24.2	
Diastolic BP (mmHg)	79.0±12.2	78.8±12.5	
Heart rate (bpm)	69.3±12.2	71.1±11.3	*
Total protein (g/dL)	7.3±0.5	7.4±0.5	*
Total cholesterol (mg/dL)	203.4±37.1	208.5±37.2	
Creatinine (mg/dL)	0.86±0.14	1.15±0.54	**
eGFR (mL/min/1.73 m^2)	70.9±9.5	49.7±8.5	**
Dependent ADL (%)	4.0	5.1	
Smoking (%)	14.3	11.5	
Treatment of hypertension (%)	29.1	44.0	**
History of cardiovascular diseases (%)	21.1	23.9	
Diabetes mellitus (%)	9.1	12.8	

CKD, chronic kidney disease; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration ratio; ADL, activities of daily living. *$p<0.05$, **$p<0.01$.

ever, little is known about the significance of CKD among Japan's older individuals. The 8020 Data Bank Survey, a unique cross-sectional survey conducted in Japan, was originally designed to explore the relationship between the systemic and dental health conditions of very elderly subjects. Our study analyzed the data from this survey to clarify the contribution of CKD to total or cardiovascular mortality in very elderly individuals within the general Japanese population.

Methods

Study Population

This study is part of a community-based cross-sectional survey of the 8020 Data Bank Survey, which was conducted in Japan. The 8020 Data Bank Survey was designed to collect baseline data on the systemic and dental health conditions of 80-year-old subjects and to promote the idea that everyone should still have at least 20 original teeth by the age of 80. All participants were born in 1917 and thus were 80 years old in 1997 when the initial screening was conducted. The data were gathered from nine districts (Buzen City, Munakata City, Yukuhashi City, the Tobata Ward of Kitakyushu City, Kanda Town, Katsuyama Town, Toyotsu Town, Tsuiki Town and Shinyoshitomi Village) in Fukuoka Prefecture, Japan. Across these nine districts, the study identified 1,244 people who were born in 1917. Of these, 697 individuals participated, and 621 completed the physical and blood examinations and were enrolled in the subsequent study. For each individual who died during this observation period, we recorded the date and cause of death using the resident registration cards and official death certificates. The cause of death was classified according to the 10th version of the International Classification of Disease (ICD-10), and there was no loss to follow-up during the 4 years. All participants were ambulatory in their daily life. This study was approved by the Human Ethics Committee of Kyushu Dental College. The details of the study protocol were explained to the subjects, and informed consent was obtained prior to participation.

Data Collection

The examination included completion of a medical questionnaire, which contained questions regarding smoking history and alcohol consumption. The activities of daily living (ADL) status designations were determined by public health nurses who classified the subjects into six groups. Individuals in ADL-1 ($n=529$) were mostly independent in everyday life; they left home on their own and used public transportation or their own vehicles to travel wherever they wished. Those in ADL-2 ($n=67$) were also nearly independent in everyday life, but although they left home on their own, they tended to remain within their local neighborhood. Those in ADL-3 ($n=18$) were almost independent within their homes; they did not stay in bed during the day, but needed assistance to leave home. Those in ADL-4 ($n=4$) were slightly less independent within their homes; these subjects sometimes stayed in bed during the day, left home infrequently, and required assistance when they did go out. Those in ADL-5 ($n=2$) needed some assistance indoors, and although they could walk on their own, they normally stayed in bed during the day. Those in ADL-6 ($n=1$) spent the entire day in bed and needed assistance to eat, change clothes, and use the toilet. This classification was based on the ADL standards provided by the Ministry of Health and Welfare of Japan in 1991. In subse-

Table 2. Hazard Ratio for Total and Cardiovascular Mortality According to the Presence and Absence of CKD

	CKD(+) *vs*. CKD(−)		
	HR	95% CI	*p* value
All-cause mortality			
Unadjusted	1.12	0.74–1.71	0.59
Gender, adjusted	1.28	0.84–1.98	0.26
BMI, adjusted	1.21	0.80–1.85	0.36
Gender and BMI, adjusted	1.37	0.89–2.11	0.15
Gender, BMI, smoking habit, ADL, DM, Hx of CVD adjusted	1.16	0.75–1.80	0.52
Fully adjusted	1.17	0.75–1.82	0.50
Cardiovascular mortality			
Unadjusted	4.57	1.70–12.22	0.001
Gender, adjusted	4.63	1.70–12.60	0.003
BMI, adjusted	4.93	1.83–13.23	0.002
Gender and BMI, adjusted	4.97	1.83–13.51	0.002
Gender, BMI, smoking habit, ADL, DM, Hx of CVD adjusted	4.49	1.65–12.22	0.003
Fully adjusted	4.60	1.69–12.52	0.003

HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; Hx, histories; CVD, cardiovascular diseases; other abbreviations are indicated in Table 1. Gender, BMI, smoking habit, ADL, DM, Hx of CVD, heart rate, systolic blood pressure, total protein are adjusted in the fully adjusted Cox hazard regression analysis.

quent analyses, we regarded those subjects in ADL-1 and ADL-2 as independent and the others as dependent, consistent with the ADL standards. All subjects except those who lived in two cities (Buzen City and Yukuhashi City; 182 subjects) were asked about any medications they were taking. Subjects were considered to have a history of CVD if, during the interview, they reported suffering from cerebrovascular diseases, ischemic heart diseases and arrhythmia. Treatment with antihypertensive medication was assessed on the basis of interview data and by recording the subject's medications list. Diabetes mellitus was recorded if patients claimed to have diabetes, if they presented a prescription for antidiabetic drugs, or if they showed a blood glucose measurement of more than 200 mg/dL. Total protein, total cholesterol, and creatinine concentrations were measured. Estimated GFR was calculated using the simplified prediction derived from the MDRD study modified for Japanese individuals (*4*):

$$\text{eGFR} = 0.881 \times 186 \times 80^{-0.203} \times (\text{serum creatinine})^{-1.154} \times (0.742 \text{ if female}).$$

GFR <60 mL/min/1.73 m^2 was defined as CKD according to the Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease from the Japanese Society of Nephrology. Subjects' height and weight were measured, and their body mass index (BMI) was calculated. BMI was defined as weight (in kg) divided by the square of the height (in m^2). The subjects were kept in a sitting position for at least 10 min in a quiet room, and their sitting blood pressure (BP) was subsequently measured *via* an oscillometric method using an automatic device (BP-103; Nippon Colin, Komaki, Japan). The BP measurements were performed once on each subject in all districts.

Data Analysis

All data are expressed as means±SD. Analyses were conducted using SSPE for Windows, version 15.0J (SPSS, Inc., Chicago, USA). One-way ANOVA or χ^2 tests were used where appropriate to compare groups. The parameters that were used in the other Cox proportional hazards are listed under the tables. The fully adjusted Cox proportional hazards regression model (model 1) was adjusted for gender (male/female), BMI, heart rate, systolic BP, smoking habits (current smoker/noncurrent smoker), ADL (independent/dependent), total protein, diabetes mellitus, and history of CVD. We used model 1 to assess the relative risks in the context of subgroup analysis. p values <0.05 were considered statistically significant.

Results

Table 1 shows the baseline characteristics of each group with or without CKD. The CKD(+) group had more females than the CKD(−) group, and the BMI, heart rate, and total protein in the CKD(+) group were significantly higher than in the CKD(−) group. During the 4-year follow-up period, 87 individuals (46 males and 41 females) died. Of these deaths, 25 were due to CVD (6 heart failure, 5 myocardial infarctions, 4 strokes, 4 aortic aneurysms, 3 ischemic heart diseases, 1 sick sinus syndrome, 1 hypertensive heart disease, and 1 cardiac rapture; 7 males and 18 females), 24 were due to cancer, 16 were due to pneumonia, 7 were due to chronic obstructive lung diseases, 5 were due to accidents such as fire, falling, traffic accidents or suicides, 4 were due to gastric bleeding or hepatic failure, and 3 were due to renal failure. The causes of

Table 3. Hazard Ratio for Cardiovascular Mortality According to the Presence and Absence of CKD by Different Subgroups

	CKD(+) *vs*. CKD(−)		
	HR	95% CI	*p* value
Gender			
Male (*n*=250)	2.65	0.53–13.23	0.24
Female (*n*=371)	7.18	1.62–31.80	0.009
CVD			
Present (*n*=139)	9.79	1.07–89.69	0.04
Absent (*n*=482)	3.78	1.21–11.87	0.02
Antihypertensive medication			
Present (*n*=156)	1.62	0.28–9.47	0.59
Absent (*n*=283)	5.15	1.04–25.50	0.04
Systolic BP			
≥140 (*n*=414)	4.32	1.33–14.06	0.02
<140 (*n*=207)	9.07	1.01–81.30	0.05

Abbreviations are indicated in Table 1 or 2. Gender, BMI, smoking habit, ADL, DM, Hx of CVD, heart rate, systolic blood pressure, total protein are adjusted in this Cox hazard regression analysis.

death for the other subjects (*n*=3) were unknown. Based on the Cox regression analysis results, the total mortality did not differ between groups (Table 2). In contrast, the relative risk for cardiovascular mortality in the CKD(+) group was significantly higher than that in the CKD(−) group. This significance was not affected by the various adjustments of the Cox hazard regression analysis. Table 3 shows the relative risk for cardiovascular mortality in the different subgroups calculated from the Cox multivariate-adjusted hazard regression analyses. The CKD status was a significant risk factor for cardiovascular death in women but not in men. Although the status of antihypertensive treatment was examined in a limited number of subjects (*n*=439), CKD increased cardiovascular mortality in those subjects who were not taking antihypertensive medication. In contrast, the presence or absence of a previous history of CVD or of high systolic BP (over 140 mmHg) did not affect the risk of CKD or its effects on cardiovascular mortality.

Discussion

Our study demonstrated that CKD in 80-year-old subjects was associated with cardiovascular mortality during a 4-year observation period in a general Japanese population, whereas total mortality was not affected by CKD status.

Cardiovascular morbidity and mortality was increased in subjects with CKD in a general Japanese population (*6*, *7*). In these studies, the subjects with CKD were about 15–20 years older than subjects without CKD. Age is not taken into account in the definition of CKD, and the increasing rate of prevalence of CKD is not linear with aging (*4*). Furthermore, in the Japanese, the cardiovascular mortality rate at 80 years of age is about 3 times that of individuals aged 70 (*4*). In our study, because all subjects were 80 years old and we did not need to correct for patient age, it was clear that the cardiovascular mortality of the subjects with CKD remained significantly higher than that of the subjects without CKD at the age of 80 years.

Although we did not identify an association between CKD and total mortality in our study, several previous studies reported that not only death from cardiovascular causes, but also deaths as a result of total and non-cardiovascular causes was increased in subjects with CKD (*8–11*). We are not able to incontrovertibly explain this discrepancy, but there are several possible explanations. First, the observation period in our study might have been too short or the number of subjects too small to detect such differences. Second, the difference in ethnicity may have affected the results. Iseki suggested that Japan has a higher prevalence of CKD than any other countries on the basis of a comparison between several community-based screening programs (*3*). Stroke is a more common cause of CVD in Japan than coronary heart disease which is contrary to observations in Western countries. The contribution of CKD to total mortality might also be different in Japan.

In our study, CKD was more frequently identified in women than in men, and cardiovascular mortality was increased in women but not in men. Epidemiological studies in Japan, such as the Hisayama study (*6*) or the NIPPON DATA 90 (*7*), have also shown that CKD was more often found in women than in men. The Hisayama study showed that CKD was an independent risk factor for coronary artery disease in men and for ischemic stroke in women. In addition, CKD increased the net occurrence of all cardiovascular diseases (including ischemic stroke and coronary artery disease) only in women (*6*). We did not record data on cardiovascular events, but several previous studies have demonstrated that higher cardiovascular mortality was observed in women after they first exhibited cardiovascular events (*12–14*). Chen *et al*. reported that only women with CKD are at significantly greater risk of coronary artery disease (*15*). They also demonstrated that mild CKD ($45.0 < eGFR < 59.9$) was a significant risk factor for mortality in women but not in men. The pathophysiological reason for this gender difference was not clear, and further studies are needed to clarify these differences in detail.

We defined CKD as a GFR <60 mL/min/1.73 m^2, which is consistent with the Clinical Practice Guidebook for the Diagnosis and Treatment of Chronic Kidney Disease from the Japanese Society of Nephrology of 1st edition. We also examined the hazard ratio of the GFR as a continuous variable using Cox multivariate-adjusted regression analyses and found a significant inverse association between GFR and cardiovascular mortality. The prevalence of CKD in our study was about 45%, which is almost comparable to that of a previous study reported by Imai *et al*. (*4*). Because over

7,130,000 people are over 80 years old in Japan, our estimate is that at least 3,200,000 subjects suffer from CKD (*5*). Because the rate of developing ESRD for patients with CKD and without proteinuria in Japan is less than 5/1,000 persons every 7 years (*16*), the management of CKD in individuals over 80 should be primarily directed at preventing CVD events. Clinical trials are seldom conducted on therapies to prevent CVD in CKD patients. The Heart Outcomes and Prevention Evaluation (HOPE) study demonstrated that patients with mild renal insufficiency have a higher incidence of cardiovascular events and death and that angiotensin-converting enzyme inhibitor effectively decreases the incidence of these events (*17*). We demonstrated that CKD increased cardiovascular death in subjects who were not taking antihypertensive medication but not in subjects who were on an antihypertensive medication regimen. The systolic BP of patients taking antihypertensive medication was significantly higher than that of patients not taking such drugs (148±24 mmHg *vs*. 155±22 mmHg, $p<0.01$). Those patients taking antihypertensive medication regularly attended a clinic or hospital and may therefore have received more consistent health evaluations. A previous study demonstrated that multidisciplinary care for patients with CKD resulted in reduced mortality (*18*). We did not precisely analyze what types of drugs the subjects were taking, but antihypertensive medication itself may decrease the incidence of cardiovascular death in scenarios other than antihypertensive effects. In larger clinical trials, researchers have suggested that antihypertensive drugs such as an angiotensin-converting enzyme inhibitor or an angiotensin type 1 receptor blocker may prevent progression of CKD and/or decrease cardiovascular mortality in addition to eliciting BP reduction (*17*, *19*, *20*). Concomitantly, our results indicated that preventive medications for CVD should be prescribed for patients with CKD.

The limitations of our study are as follows: first, the study cohort was not large. Second, we did not measure hemoglobin concentration and urinary protein excretion. Anemia is a common symptom in patients with heart failure and increases the morbidity of patients hospitalized with heart failure, as well as their mortality rates (*21*). CKD induces anemia because of a deficiency in erythropoietin, even if the GFR is between 30 and 59 mL/min/1.73 m^2 (*22*). There is still controversy over whether CKD and anemia are independent or dependent risk factors for CVD. The Atherosclerosis Risk in Communities study showed an interaction between anemia and CKD (*23*), but in the Second National Health and Nutrition Examination Survey Mortality Study anemia was not an independent risk factor for coronary heart disease mortality after adjustment for various other risk factors (*24*). Proteinuria and decreased GFR have been reported as independent risk factors for cardiovascular mortality (*25*). Adjustment for proteinuria might significantly increase the relative risk of CKD for cardiovascular death, but the effect might not be that marked, because proteinuria has been reported to affect only about 5% of the general population in Japan (*16*).

Recently, the Hypertension in the Very Elderly Trial (HYVET) demonstrated that antihypertensive medication can greatly decrease cardiovascular events and deaths in patients over 80 years of age (*26*). Large clinical trials must be conducted to identify the effects of antihypertensive medication on the prevention of CVD in elderly subjects with CKD. We note that cardiovascular events, even if not fatal, can significantly worsen ADL. Accordingly, we must provide preventive medical care to decrease cardiovascular morbidity in the elderly.

References

1. Levey AS, Beto JA, Coronado BE, *et al*: Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. *Am J Kidney Dis* 1998; **32**: 853–906.
2. Sarnak MJ, Levey AS, Schoolwerth AC, *et al*: Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Hypertension* 2003; **42**: 1050–1065.
3. Iseki K: Chronic kidney disease in Japan. *Intern Med* 2008; **47**: 681–689.
4. Imai E, Horio M, Iseki K, *et al*: Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. *Clin Exp Nephrol* 2007; **11**: 156–163.
5. Public Health Division, Statistics and Information Department, Ministry of Health Labour and Welfare: Online Reporting System of Vital Statistics 2004 (in Japanese).
6. Ninomiya T, Kiyohara Y, Kubo M, *et al*: Chronic kidney disease and cardiovascular disease in a general Japanese population: the Hisayama Study. *Kidney Int* 2005; **68**: 228–236.
7. Nakamura K, Okamura T, Hayakawa T, *et al*: Chronic kidney disease is a risk factor for cardiovascular death in a community-based population in Japan: NIPPON DATA90. *Circ J* 2006; **70**: 954–959.
8. Go AS, Chertow GM, Fan D, *et al*: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351**: 1296–1305.
9. Fried LF, Shlipak MG, Crump C, *et al*: Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. *J Am Coll Cardiol* 2003; **41**: 1364–1372.
10. Fried LF, Katz R, Sarnak MJ, *et al*: Kidney function as a predictor of noncardiovascular mortality. *J Am Soc Nephrol* 2005; **16**: 3728–3735.
11. Weiner DE, Tabatabai S, Tighiouart H, *et al*: Cardiovascular outcomes and all-cause mortality: exploring the interaction between CKD and cardiovascular disease. *Am J Kidney Dis* 2006; **48**: 392–401.
12. Kannel WB, Sorlie P, McNamara PM: Prognosis after initial myocardial infarction: the Framingham study. *Am J Cardiol* 1979; **44**: 53–59.

13. Tofler GH, Stone PH, Muller JE, *et al*: Effects of gender and race on prognosis after myocardial infarction: adverse prognosis for women, particularly black women. *J Am Coll Cardiol* 1987; **9**: 473–482.
14. Maggioni AP, Maseri A, Fresco C, *et al*: Age-related increase in mortality among patients with first myocardial infarctions treated with thrombolysis. The Investigators of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2). *N Engl J Med* 1993; **329**: 1442–1448.
15. Chen R, Kumar S, Timmis A, Feder G, Yaqoob MM, Hemingway H: Comparison of the relation between renal impairment, angiographic coronary artery disease, and long-term mortality in women *versus* men. *Am J Cardiol* 2006; **97**: 630–632.
16. Iseki K, Kinjo K, Iseki C, *et al*: Relationship between predicted creatinine clearance and proteinuria and the risk of developing ESRD in Okinawa, Japan. *Am J Kidney Dis* 2004; **44**: 806–814.
17. Mann JF, Gerstein HC, Pogue J, *et al*: Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Ann Intern Med* 2001; **134**: 629–636.
18. Hemmelgarn BR, Manns BJ, Zhang J, *et al*: Association between multidisciplinary care and survival for elderly patients with chronic kidney disease. *J Am Soc Nephrol* 2007; **18**: 993–999.
19. Lewis EJ, Hunsicker LG, Clarke WR, *et al*: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; **345**: 851–860.
20. Brenner BM, Cooper ME, de Zeeuw D, *et al*, RENAAL Study Investigators: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; **345**: 861–869.
21. Hunt SA: ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 2005; **46**: e1–e82.
22. Astor BC, Muntner P, Levin A, *et al*: Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988–1994). *Arch Intern Med* 2002; **162**: 1401–1408.
23. Abramson JL, Jurkovitz CT, Vaccarino V, *et al*: Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: the ARIC Study. *Kidney Int* 2003; **64**: 610–615.
24. Brown DW, Giles WH, Croft JB: Hematocrit and the risk of coronary heart disease mortality. *Am Heart J* 2001; **142**: 657–663.
25. Hallan S, Astor B, Romundstad S, *et al*: Association of kidney function and albuminuria with cardiovascular mortality in older *vs* younger individuals: the HUNT II Study. *Arch Intern Med* 2007; **167**: 2490–2496.
26. Beckett NS, Peters R, Fletcher AE, *et al*: Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008; **358**: 1887–1898.