Blood Pressure Is a Major Risk Factor for Renal Death
An Analysis of 560 352 Participants From the Asia-Pacific Region

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Abstract—Chronic kidney disease is a major worldwide public health problem that causes substantial morbidity and mortality. Studies from the Asia-Pacific region have reported some of the highest chronic kidney disease prevalence rates in the world, but access to dialysis is limited in many countries, making it imperative to identify high-risk individuals. We performed a participant-level data overview of prospective studies conducted in the Asia-Pacific region to quantify the magnitude and direction of the associations between putative risk factors and renal death. Age- and sex-adjusted Cox proportional hazards models were applied to pooled data from 35 studies to calculate hazard ratios (95% CIs) for renal death associated with a standardized change in risk factors. Among 560 352 participants followed for a median of 6.8 years, a total of 420 renal deaths were observed. Continuous and positive associations among systolic blood pressure, diastolic blood pressure, fasting blood glucose, and total cholesterol levels with renal death were observed, as well as a continuous but inverse association with high-density lipoprotein cholesterol. Systolic blood pressure was the strongest risk factor for renal death with each SD increase in systolic blood pressure (19 mm Hg) associated with >80% higher risk (hazard ratio: 1.84; 95% CI: 1.60 to 2.12). Neither cigarette smoking nor excess weight was related to the risk of renal death ($P \geq 0.10$). The results were similar for cohorts in Asia and Australia. These results suggest that primary prevention strategies for renal disease should focus on individuals with elevated blood pressure, diabetes mellitus, and dyslipidemia. (Hypertension. 2009;54:509-515.)

Key Words: risk factors | renal mortality | hypertension | diabetes mellitus | impaired fasting glucose

The increasing incidence of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) represents a major worldwide public health problem. The National Health and Nutrition Evaluation Survey 1999–2004 in the United States estimated that ≈13% of US adults are affected by CKD and that this proportion is continuing to rise. Elsewhere, survey data from Australia, Europe, Thailand, China, and Japan indicate the prevalence of CKD in the general population to be in the range of 6% to 20%. Individuals with CKD have a reduced life expectancy, and those with ESKD on hemodialysis have mortality rates that are increased 20-fold compared with age- and sex-matched individuals with normal kidney function.

The number of patients initiating renal-replacement therapy is also increasing in most countries, placing a substantial burden on healthcare systems. Developed countries in Asia have some of the highest rates of ESKD in the world, whereas less-developed countries are already unable to meet the rising demand for dialysis treatment. There are >600 million people living in developing countries with no provision for renal replacement therapy, resulting in tens of thousands of deaths annually from ESKD.

The increasing incidence of CKD has been suggested to be driven by 2 main factors: an aging global population and the worldwide epidemic of type 2 diabetes mellitus. Several reports from cohort studies in the United States and Japan have also identified possible risk factors for the development and progression of kidney disease, including suboptimal levels of blood pressure, lipids, and body weight, as well as cigarette smoking. However, quantification of the effects of putative risk factors for renal death has been difficult to achieve, at least partially because of underreporting of renal deaths.

The high incidence and prevalence of kidney disease in the Asia-Pacific region has been identified as a major public health issue by the International Society of Nephrology, the...
Asian Pacific Society of Nephrology, and other groups.  To address this challenge, the Asian Forum of CKD Initiative (APFCKDI) was established in 2007, with the investigation of risk factors for kidney disease in the region as a major priority. Hence, the aim of the current study was to determine risk factors for renal death using data from >560,000 individuals from the Asia-Pacific region and, by doing so, to highlight possible future targets for intervention.

Methods

Participating Studies

The design of the Asia Pacific Cohort Studies Collaboration (APCSC), an overview of prospective observational studies, has been described elsewhere. In brief, studies based in the Asia-Pacific region with a prospective design and ≥5000 person-years of follow-up were eligible for participation. Studies were excluded if participants were selected on the basis of the presence of any disease or risk factor. Studies were classified as Asian if based in China, Hong Kong, Japan, South Korea, Singapore, or Taiwan or from Australia for cohorts in that country. Studies participating in APCSC were eligible for this analysis if data on renal death was available.

Measurement of Baseline Variables

Age, sex, and blood pressure at baseline were recorded for every individual. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), triglyceride level (TG), fasting blood glucose (FBG), the presence or absence of diabetes mellitus (self-reported), body mass index (BMI; weight in kilograms divided by the square of the height in meters), and/or self-reported smoking status were also recorded for some individuals. As the studies were initiated, and sometimes recruited, over a long period of time, and developed independently, the methods and instruments used for measuring risk factors and reporting deaths varied both between and within studies.

Outcomes

All of the studies reported deaths by underlying cause. Outcomes were classified according to the Ninth or 10th Revision of the International Classification of Diseases (ICD; N, I, or E prefix denotes ICD-10 coding system and all other coding is ICD-9). ICD-9 outcomes considered to indicate renal deaths in this analysis are diabetes mellitus with renal manifestations (250.4), hypertensive renal disease (403.x), renovascular disease (440.1), Wegener’s granulomatosis (446.4), acute glomerulonephritis (580.x), nephrotic syndrome (581.x), chronic glomerulonephritis (582.x), acute renal failure (584.x), chronic renal failure (585.x), renal failure not otherwise specified (586.x), renal sclerosis (587.x), small kidney unknown cause (589), and unspecified disorders of kidney or ureter (593.9). ICD-10 outcomes included are diabetic renal disease (E1X.2), hypertensive renal disease (I12, I13, I15, and I15.1), diseases of kidney and ureter (N00–29), acute renal failure (N179), end-stage renal disease (N180), chronic renal failure (N189), renal failure not otherwise specified (N19), impaired renal tubular function (N259), and small kidneys (N279). Data regarding the need for dialysis were not available. Sensitivity analyses were performed restricting the outcomes to chronic renal failure and renal failure not otherwise specified.

Statistical Methods

All of the analyses used individual-level participant data. For continuous variables, individuals were classified according to approximately equal fourths, as measured at baseline. For each variable, the hazard ratio (HR) for renal death was calculated using a Cox proportional hazard model with corresponding 95% CIs derived using floating absolute risks, with the reference group being those in the bottom fourth (or top fourth for HDL-c). Log-linearities of the associations with renal death were investigated through analyses by fourths and, where there was a trend, were summarized through the HR (and 95% CI) for a 1-SD increase (decrease for HDL-c). Log transformation of TG values was performed to account for the extreme right skewness of the data. All of the Cox models were stratified by study and sex and adjusted by age.

To determine the association between “usual” level of each continuous variable and renal death, the estimates were adjusted to account for regression dilution bias. Similarly, to determine the association between the usual levels of each variable categorized into quartiles and renal death, the HR estimated for each quartile was plotted against the usual mean in each category rather than against the baseline mean. Information on the availability of repeat measures for each variable is given elsewhere. These repeat measures were used to estimate, for each variable, an attenuation coefficient using a linear mixed-regression model that accounted for the heterogeneity of variance between studies, within-subject correlation, and the varying time intervals between measurements. Regression attenuation coefficients were 1.9 for systolic blood pressure (SBP), 2.1 for diastolic blood pressure (DBP), 1.7 for TC, 1.5 for HDL-c, 1.8 for log-TG, and 1.6 for FBG. Likelihood ratio tests were used to assess the heterogeneity of the effect of each variable on the risk of renal death by subgroups defined by sex and region.

Results

Baseline Data

The 35 studies in the APCSC with data on baseline blood pressure, composed of 560,352 individuals, are summarized in Table 1. Compared with Australia, participants in the Asian cohorts tended to be younger (45 versus 54 years of age) and more likely to be women (47% versus 34%). Participants from the Asian cohorts had lower baseline levels of SBP, BMI, and TC. There was a higher prevalence of diabetes mellitus in the Asian cohorts (7.1% versus 5.4%), although the mean FBG was lower in cohorts from Asia compared with Australia (5.1 versus 5.6 mmol/L).

Outcomes

The median follow-up was 6.1 years in the Asian cohorts and 8.4 years in the Australian cohorts. During follow-up there were 420 renal deaths (Table 2). Most of the renal deaths were coded as chronic renal failure or renal failure without further specification, with a smaller proportion coded as glomerular disease or acute renal failure. Of the reported renal deaths, 64.3% were in Asia and 36.4% occurred among women.

Relationship Between Blood Pressure and the Risk of Renal Death

Both SBP and DBP were positively and log-linearly associated with the risk of renal death (Figure 1). In age- and sex-adjusted analyses, a 1-SD increment in SBP (19 mm Hg) was associated with an 84% increase in mortality (HR: 1.84; 95% CI: 1.60 to 2.12; Figure 2). There was no evidence of heterogeneity between Australia and Asia overall (P for heterogeneity=0.46), although there was some variation between countries within Asia (China HR: 1.80, 95% CI: 1.41 to 2.31; Japan HR: 1.79, 95% CI: 1.16 to 2.77; and South Korea HR: 3.59, 95% CI: 2.21 to 5.83). There was some evidence to suggest that the association was stronger among men compared with women (HR: 2.08, 95% CI: 1.74 to 2.50 in men versus HR: 1.54, 95% CI: 1.23 to 1.92 in women; P for heterogeneity=0.04). The relationship persisted after adjustment for the use of BP-lowering medications in the 102,900 participants with such data available, although the
magnitude was slightly reduced (HR: 1.62; 95% CI: 1.28 to 2.05). Sensitivity analyses restricted to participants with deaths attributed to renal failure or chronic renal failure (n=252) showed similar results (HR: 1.94; 95% CI: 1.62 to 2.14). Similar results were also obtained for DBP: a 1-SD increment in DBP (11 mm Hg) was associated with a 57% increase in the risk of renal death (HR: 1.57; 95% CI: 1.32 to 1.87; Figures 1 and 2).

FBG, Diabetes Mellitus and the Risk of Renal Death

Among the 10 studies (227 746 participants; 85 renal deaths) with information on FBG, there was a continuous (P<0.001) and positive association with renal death at FBG levels >4.5 mmol/L (Figure 1). In analyses adjusted for age and sex, a 1-SD increment in FBG (1.42 mmol/L) was associated with a 60% increase in the risk of renal mortality (HR: 1.60;
95% CI: 1.42 to 1.81). There was no evidence of regional (P for heterogeneity = 0.14) or sex differences in the strength of the association (P for heterogeneity = 0.19). Sensitivity analyses restricted to those outcomes classified as renal failure or chronic renal failure (n = 45) showed similar results (HR: 1.56; 95% CI: 1.36 to 1.80).

In the 28 studies (333,388 participants; 301 renal deaths) with information on diabetes mellitus status at study baseline, individuals with a diagnosis of diabetes mellitus had 3 times the risk of renal death compared with those without diabetes mellitus (HR: 3.69; 95% CI: 2.75 to 4.96). As with the FBG analysis, there was no evidence that the association differed by region or by sex (P for heterogeneity = 0.63 for sex interaction and 0.44 for region interaction). There was some variation in the relationship across different countries within Asia (China HR: 8.34, 95% CI: 2.70 to 25.88; Japan HR: 2.22, 95% CI: 0.58 to 8.42; South Korea HR: 5.64, 95% CI: 2.06 to 14.85).

### Cigarette Smoking, BMI, and Risk of Renal Death

Current smoking status was recorded for 526,331 individuals (385 renal deaths) and BMI for 389,777 individuals (349 renal deaths). There was no clear evidence of an association between current cigarette smoking and the risk of renal death.

#### Table 2. Classification of Renal Deaths in APCSC Using ICD-9 and ICD-10

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>ICD Codes</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal failure, chronic renal failure not otherwise specified</td>
<td>585.x, 586.x, N189, N19[1]</td>
<td>252</td>
</tr>
<tr>
<td>Glomerular disease, including diabetic nephropathy</td>
<td>250.4, 446.4, 580.x, 581.1, 581.9, 582.0, 582.8, 582.9, 583.x, 587.x, E1x0.2</td>
<td>69</td>
</tr>
<tr>
<td>Acute renal failure, not otherwise specified</td>
<td>584.x, N179</td>
<td>40</td>
</tr>
<tr>
<td>Hypertensive renal disease, renovascular disease</td>
<td>403.x, 440.1, I12, I13, I15.x</td>
<td>27</td>
</tr>
<tr>
<td>ESKD, small kidneys</td>
<td>589, N180, N279</td>
<td>11</td>
</tr>
<tr>
<td>Tubulointerstitial disease</td>
<td>N12, N259</td>
<td>5</td>
</tr>
<tr>
<td>Unspecified disorders of kidney or ureter</td>
<td>593.9, N00 to N29</td>
<td>1</td>
</tr>
<tr>
<td>Not otherwise specified</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Total renal deaths</td>
<td></td>
<td>420</td>
</tr>
</tbody>
</table>

#### Figure 1. HRs, with 95% CIs, for renal death for usual levels of SBP (millimeters of mercury), DBP (millimeters of mercury), FBG (millimoles per liter), and BMI (kilograms per meter squared) by fourths (base: lowest fourth).

#### Figure 2. HRs, with 95% CIs, for a 1-SD increment in SBP, FBG, TC, TG, and BMI or a 1 standard decrement in HDL-c and renal death.
Findings from the current study, based on prospective data
information from 343,989 individuals (n = 246 renal deaths) contributed to the analysis for the association between TC and the risk of renal death, whereas for TG and HDL-c there were less data available (93 renal deaths among 74,925 individuals for TG and 79 renal deaths among 60,568 individuals for HDL-c). There was some evidence to suggest that TG was positively associated with mortality risk in the overall analyses, such that a 1-SD increase in TC (1 mmol/L) was associated with a 20% greater risk of renal death (HR: 1.20; 95% CI: 0.99 to 1.46; $P = 0.059$; Figures 2 and 3). This result was stronger when the outcomes considered were restricted to deaths attributed to renal failure or chronic renal failure (56 deaths; HR: 1.46 95% CI: 1.13 to 1.89). There was no significant difference in the strength of the association by region or sex ($P$ for heterogeneity = 0.77 for region interaction and 0.57 for sex interaction). There was limited evidence to support a direct association between TG levels with the risk of renal death (HR: 1.41; 95% CI: 0.93 to 2.12 per SD increment in log TG; $P = 0.10$; Figure 2).

There was a significant inverse association between levels of HDL-c and risk of renal death (Figure 3). When the relationship was examined continuously, a 1-SD decrease in HDL-c corresponded with a 50% increase in the risk of renal death (HR: 1.50; 95% CI: 1.01 to 2.22; Figure 2), with no evidence of regional ($P$ for heterogeneity = 0.16) or sex differences ($P = 0.92$).

**Discussion**

Findings from the current study, based on prospective data from $>$560,000 individuals from the Asia-Pacific region, provide good evidence of direct and continuous associations between both blood pressure and blood glucose and risk of renal death. The magnitude of these associations was such that an SD increment in blood pressure and blood glucose was associated with an $\approx 80\%$ and $60\%$ greater risk of mortality from renal disease, respectively. Similarly, among those individuals with diabetes mellitus at study baseline, the risk of renal death was $>3$ times that compared with unaffected individuals. There was some evidence to suggest that adverse lipid profiles may also predispose individuals to death from renal disease. Raised levels of TC and low levels of HDL-c were both independently associated with increased risk of renal death, although the relationships were less strong than with either blood pressure or blood glucose. Interestingly, there was no evidence in the current study to implicate excess body weight and cigarette smoking, which are both important risk factors for cardiovascular disease, as being associated with renal death.

The high incidence and prevalence of CKD in this region have been identified as major public health issues leading to interest in the delineation of factors associated with kidney disease in the region as a priority. The large size of this study bestows high power to identify factors associated with renal death. Previous attempts to identify risk factors have been hampered by several issues, not the least the large number of renal events required to obtain reliable results and the low rate of reporting kidney disease as a cause of death. A recent study found that, although only 2% of death certificates listed kidney disease as the primary cause of death, it was listed as an associated condition in a further 7% of deaths. As such, $\approx 1$ in 10 death certificates cite kidney disease, a proportion higher than for many major diseases, including diabetes mellitus, lung cancer, breast cancer, and colorectal cancer. This paucity of data has resulted in the substantial underestimation of the importance of kidney disease.

We observed blood pressure and glucose levels to be the strongest predictors of renal death in this population. Although these findings are not unexpected given that hypertension and diabetes mellitus are among the leading causes of ESKD worldwide, limited data are available on the relationship between FBG levels, regardless of diabetes status, and renal death. Analyses from the Framingham Offspring Study showed a positive association between impaired fasting glucose or impaired glucose tolerance and subsequent CKD, although this was no longer significant after adjustment for other vascular risk factors. In the current study, we observed...
a continuous association between FBG and the risk of renal death, suggesting that glucose may be an important aspect of renal risk prediction and is likely to be a useful target for screening and prevention strategies.

Our findings are consistent with a study from Japan where a linear relationship between blood pressure and new-onset ESKD was identified in >100 000 community-based individuals undergoing health examinations, as well as other studies that have identified a strong relationship between blood pressure and the risk of ESKD, even after adjustment for confounding by baseline kidney disease. The demonstration, in a number of randomized trials, that blood pressure and glucose-lowering therapies reduce the progression of CKD and the incidence of ESKD, further underlines the importance of these factors. Because blood pressure and glucose levels can be checked quickly and cheaply, routine measurement of both should be a simple, feasible, and highly cost-effective strategy for identifying patients at increased risk for CKD that is likely to be affordable for developed, as well as developing, countries.

The published literature on a direct association between BMI and renal death is conflicting, with some studies reporting a positive association between BMI and kidney disease, whereas other studies, including the current study, have observed no relationship either before or after adjustment for other risk factors. It is possible that a long duration of exposure is necessary for the relationship to develop. For example, the relationship between BMI and ESKD only became apparent in the Okinawa Study after >10 years of follow-up. Alternatively, other markers of body size, eg, waist:hip ratio, may be better markers of risk than BMI, as has been suggested recently.

The relationship between lipid levels and the development or progression of kidney disease has been an area of intense recent interest. We observed a significant inverse relationship with levels of HDL-c, and there was some suggestion of a weak direct association with levels of TC. These results are consistent with previous reports from the Physician’s Health Study and the Helsinki Heart Study, which identified higher total or low-density lipoprotein cholesterol levels, as well as lower HDL-c levels, as risk factors for progressive kidney disease. Additional support for a potential role for lipids in the progression of kidney disease is provided by posthoc analysis of the Cholesterol and Recurrent Events Study and a recent meta-analysis that have suggested that therapy with statins may slow the decline in kidney function among people with CKD. The Study of Heart and Renal Protection has randomized participants with kidney disease to therapy with either simvastatin and ezetimibe or matching placebo, and ~5 years of follow-up is planned.

The lack of data on baseline kidney function and proteinuria is an important limitation of our study, raising the possibility that some participants in the studies may have had CKD and making it impossible to assume that the relationships that we have observed are causal. This issue of confounding subclinical kidney disease is frequently cited in related studies and is difficult to avoid. Nevertheless, the use of the findings in identifying clinical markers for individuals at high renal risk is unaffected. The effect of underreporting of kidney failure as a cause of death would have been to dilute the observed strength of the relationship between the risk factors studied and death because of kidney disease. This is likely to have been the case in the current study, where, although only 1.7% of all deaths in APCSC were reportedly attributed to renal disease, the true percentage is likely to be several-fold higher. Similarly, the potential for competing mortality risks (eg, cardiovascular causes of death) in someone who would have otherwise died of kidney disease may have resulted in an underestimation of the strength of the relationships. Finally, limited or no detail on drug therapy was available for the majority of participants.

In summary, these findings extend the current understanding in this important area by identifying a clear, continuous association between both blood pressure and FBG and renal disease, with some evidence of similar effects of dyslipidemia in a large, prospective study. The results also provide evidence that risk factors for CKD are likely to be equally important in Asian and Western countries.

Perspectives

Population-wide campaigns targeting both blood pressure and glucose levels offer the potential to significantly reduce renal morbidity and mortality, particularly in developing countries, where treatment availability for ESKD is very limited. Screening for and treating these risk factors is simple, cost-effective, and likely to be highly effective at reducing the risk of death attributed to both kidney and cardiovascular diseases. Public health and community-based programs should be considered to lower the levels of glucose and blood pressure so as to reduce the personal and socioeconomic impacts of these devastating conditions.

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Disclosures

None.

References


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Asia Pacific Cohort Studies Collaboration

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