Renal dysfunction and ischemic heart disease mortality in a hypertensive population

Susan M. Hailpern, Hillel W. Cohen and Michael H. Alderman

Objective **While recent studies indicate that renal dysfunction may be predictive of all-cause mortality and cardiovascular disease (CVD) outcomes in hypertensive individuals, there has been little attention to the specific association of ischemic heart disease (IHD) mortality and renal function. This study examines the relationship between IHD mortality and baseline glomerular filtration rate (GFR) (estimated by the Cockcroft and Gault formula) among treated hypertensive subjects.**

Design **A prospective cohort study of participants in a worksite-based antihypertensive treatment program in New York City (1981–1999).**

Patients **We studied 9929 subjects who had at least 6 months follow-up (mean 9.6 years) with a baseline serum creatinine.**

Main outcome measures **IHD death outcomes ($n = 343$) ascertained from the National Death Index.**

Results **Multivariate Cox proportional hazard models were constructed adjusting for known cardiovascular risk factors. Mean GFR of the cohort was 91.6 ml/min per 1.73 m^2. Those with lower GFR were more likely to be older, female, White, report a history of cardiovascular disease, have higher cholesterol and blood urea nitrogen values, and lower hemoglobin and body mass index than those with highest GFR. After adjustment for known cardiovascular risk factors, the risk of IHD death increased progressively as the GFR decreased. Hazard ratio for IHD mortality for each 10-unit reduction of estimated GFR below the normal threshold of ≥ 90 ml/min per 1.73 m^2 was 1.33 (95% confidence interval 1.17, 1.50; $P < 0.001$).**

Conclusions **The results of this study suggest an independent inverse association between estimated GFR and IHD mortality among treated hypertensive individuals. *J Hypertens* 23:1809–1816 © 2005 Lippincott Williams & Wilkins.**

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Introduction

Recent studies have indicated that renal dysfunction may be predictive of all-cause mortality and cardiovascular disease (CVD) outcomes [1–15]. Several of these studies have examined the association of renal dysfunction and CVD outcomes among treated hypertensive patients [11–13, 16,17]. A small number of studies have examined the prognostic importance of renal dysfunction on ischemic heart disease (IHD). Most of these studies have focused on specific groups, such as those with chronic renal failure [18], those ≥ 55 years of age with vascular disease [14], survivors of acute myocardial infarction [19], and middle-aged men [20]. Only one of these studies, the Hypertension Optimal Treatment (HOT) Study (mean follow-up 3.8 years), measured IHD events (morbid and mortal) among a primarily White hypertensive cohort. The HOT study found no significant association between baseline renal insufficiency (estimated creatinine clearance < 60 ml/min per 1.73 m^2) and myocardial infarction (MI) events (morbid and mortal) [12].

We could find no previous study that examined the prognostic significance of renal dysfunction exclusively on IHD mortality among a multi-ethnic hypertensive cohort. Therefore, the aim of this observational cohort study was to examine the association of glomerular filtration rate (GFR), estimated by the Cockcroft and Gault formula, with IHD mortality, as the primary outcome, among Black, White and Hispanic participants in a treated hypertensive population.

Methods

Study design and participants

This study examined the experiences of individuals who entered the Worksite Hypertension Control Program (Worksite) between 1981 and 1999 [21–28]. Worksite was a union-sponsored, ethnically diverse, occupationally based hypertension treatment program in New York City. Subjects were eligible for the program if they had an untreated systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg. Eligibility criteria

changed after 1992 to include an untreated systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, following recommendations of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V) [29]. Detailed methods have been published using data collected from the Worksite study in numerous studies [21–28].

Worksite participants ($n = 9939$) ≥ 18 years of age at entry with baseline serum creatinine (SCr) and at least 6 months of follow-up constituted the study cohort.

Outcome measures and follow-up

Death outcomes were ascertained from the National Death Index (NDI) [30] using the International Classification of Disease 9th revision (ICD-9). The primary outcome measure was IHD mortality (ICD-9 codes 410–414.9). Secondary outcomes were all CVD deaths (ICD-9 codes 390–459), stroke (ICD-9 codes 430–438), non-CVD, and all-cause mortality [31]. Follow-up time was calculated from date of entry to date of death due to any cause, or December 31, 2000 for those without a recorded death (the last date for which NDI records were available).

Statistical analysis

Baseline GFR was estimated using the Cockcroft and Gault formula that uses sex, age, weight, and SCr [32]. Estimated GFR was categorized into four groups: < 45.0 ml/min per 1.73 m^2, 45–59.9 ml/min per 1.73 m^2, 60–74.9 ml/min per 1.73 m^2, and ≥ 75 ml/min per 1.73 m^2, incorporating the guidelines of the National Kidney Foundation [10,33]. Estimated GFR was also dichotomized at 60 ml/min per 1.73 m^2, the currently accepted threshold for moderate renal dysfunction (MRD) [10,33].

Demographic and clinical characteristics and IHD mortality were compared between both GFR and MRD groups. Characteristics between those with MRD and GFR groups were compared using two sample *t*-tests, one-way analysis of variance, and χ^2 tests for continuous and categorical variables, respectively. Age- and sex-adjusted mortality rates/1000 person years and 95% confidence intervals (CI) were calculated to compare IHD death rates between MRD and GFR categories.

To evaluate the independent effect of the estimated GFR on IHD mortality, Cox proportional hazard models were constructed for dichotomous MRD, estimated GFR in four categories, and for estimated GFR as a continuous variable. Models included baseline systolic blood pressure, total cholesterol, and body mass index (BMI) as continuous variables, and impaired fasting glucose [serum glucose ≥ 6.105 mmol/l (≥ 110 mg/dl)], age (dichotomized at the mean], sex, ethnicity (White versus non-White), treatment for hypertension at time of study entry, history of any cardiovascular disease (CVD), a diagnosis of left ventricular hypertrophy (LVH) based on the baseline electrocardiogram (EKG), current smoker, and MRD as dichotomous variables. Hazard ratios (HR) and 95% CI were estimated from Cox models with GFR as a continuous variable, with ≥ 60 ml/min per 1.73 m^2 as the reference for MRD, and > 90 ml/min per 1.73 m^2 as the reference for categorical GFR.

To assess for potential heterogeneity, separate adjusted Cox models were constructed for race and sex. To assess the impact of advanced age and length of follow-up on the association between GFR and IHD mortality, separate Cox models were constructed for those between the ages of 50 and 80 years for 5 and 20 years of follow-up. Separate adjusted Cox proportional hazard models were also constructed for CVD, stroke, and all-cause mortality.

Sensitivity analyses were performed after excluding those at highest risk for IHD mortality (diabetes or fasting serum glucose > 6.993 mmol/l (> 126 mg/dl), history of CVD, and history of LVH) and restricting follow-up time to ≤ 5 years.

Stata/SE 8.2 for Windows 98/95/NT by Stata Corporation running on Windows XP was used in the analysis of these data [34]. All statistical tests used a two-tailed α of 0.05.

Results

The baseline estimated GFR was normally distributed with a mean ($\pm$ SD) GFR of 91.6 ± 27.54 ml/min per 1.73 m^2. During the mean follow-up period of 9.6 years (range 0.5–20), 1084 (10.9%) subjects died. Of these, 343 (31.2%) deaths were attributable to IHD, 511 deaths were attributable to CVD, and 62 to stroke.

Mean in-treatment systolic blood pressure was 135.4 ± 15.8 mmHg; mean diastolic in-treatment diastolic blood pressure was 84.4 ± 9.7 mmHg. Table 1 summarizes the baseline characteristics of the 9939 treated hypertensive subjects stratified by GFR category and MRD. Subjects with the lowest GFR at baseline ($n = 156$) were more likely to be older, female, White and have a higher prevalence of CVD, smoking, diabetes, LVH, antihypertensive medication at entry. Those with the lowest GFR also had higher systolic blood pressure, cholesterol and blood urea nitrogen values, and a lower hemoglobin and BMI when compared to those with a GFR > 75 ml/min per 1.73 m^2. Subjects with MRD ($n = 876$), compared to those with normal renal function, showed similar differences.

Age–sex-adjusted rates of IHD mortality increase substantially with decreasing estimated GFR. Mortality rates for MRD were 6.21/1000 person–years (CI: 4.02, 8.40)

Table 1 Baseline characteristics by glomerular filtration rate (GFR)[a]

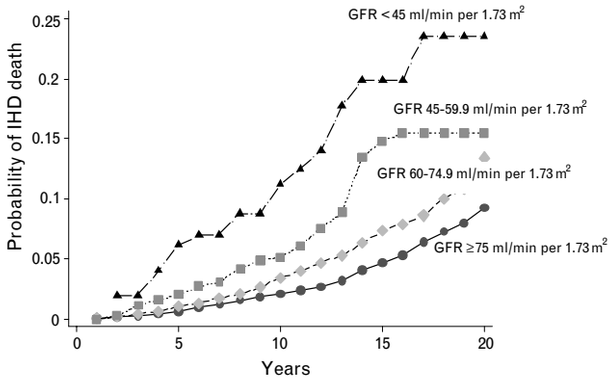
Variable	GFR category ml/min per 1.73 m^{2b}				MRD[c]	
	≥ 1.252 (≥ 75) $n = 7131$	1.002–1.251 (60–74.9) $n = 1932$	0.751–1.001 (45–59.9) $n = 720$	< 0.751 (< 45) $n = 156$	*P* value	*P* value
Male %	65.2 (4647)	56.4 (1090)	48.6 (350)	51.9 (81)	< 0.001	0.013
Age	50.1 ± 8.7	57.0 ± 7.3	60.8 ± 8.4	64.6 ± 10.1	< 0.001	< 0.001
White %	31.6 (2251)	28.0 (541)	34.0 (245)	35.3 (55)	0.004	0.036
History of cardiovascular disease %	9.5 (676)	12.5 (242)	14.3 (103)	14.1 (22)	< 0.001	< 0.001
Smoker %	20.4 (1454)	18.4 (356)	19.6 (141)	19.9 (31)	0.292	0.812
Glucose mmol/l (mg/dl)	5.81 ± 1.05 (104.8 ± 35.2)	5.78 ± 0.24 (104.5 ± 4.3)	5.94 ± 2.34 (107.0 ± 42.2)	5.83 ± 0.17 (105.0 ± 3.0)	< 0.001	0.176
Diabetes %	7.8 (554)	7.7 (149)	7.8 (56)	9.00 (14)	0.995	0.805
Left ventricular hypertrophy %	10.7 (762)	13.6 (263)	16.5 (119)	21.8 (34)	< 0.001	< 0.001
Hypertension treatment at entry %	42.7 (3047)	51.0 (984)	60.7 (437)	64.1 (100)	< 0.001	< 0.001
Cholesterol mmol/l (mg/dl)	5.71 ± 1.13 (220.6 ± 43.5)	5.93 ± 1.16 (229.2 ± 44.8)	6.05 ± 1.18 (233.7 ± 45.7)	6.17 ± 1.45 (238.4 ± 56.1)	< 0.001	< 0.001
Body mass index (kg/m^2)	29.8 ± 4.6	26.4 ± 3.3	25.0 ± 3.4	24.4 ± 3.3	< 0.001	< 0.001
Systolic blood pressure mmHg	149.1 ± 19.4	153.6 ± 21.7	154.9 ± 23.5	158.2 ± 27.0	< 0.001	< 0.001
Baseline GFR ml/min per 1.73 m^2	102.8 ± 24.0	68.4 ± 4.2	54.3 ± 4.1	37.8 ± 6.5	< 0.001	< 0.001
BUN μmol/l (mg/dl)	5.28 ± 1.43 (14.8 ± 4.0)	5.85 ± 1.57 (16.4 ± 4.4)	6.50 ± 2.00 (18.2 ± 5.6)	9.24 ± 4.32 (25.9 ± 12.1)	< 0.001	< 0.001
Hemoglobin g/dl (g/l)	146.2 ± 1444 (14.6 ± 1.4)	144.8 ± 14.1 (14.5 ± 1.4)	141.8 ± 13.79 (14.2 ± 1.4)	137.89 ± 15.82 (13.8 ± 1.6)	0.101	< 0.001

[a]Categorical variables presented as percentages (n) with *P* values calculated by Chi-square for glomerular filtration rate < 60 ml/min per 1.73 m^2 relative to glomerular filtration rate ≥ 60 ml/min per 1.73 m^2. Continuous variables presented as mean $\pm$ standard deviation, with *P* values calculated by one-way analysis of variance between glomerular filtration rate < 60 ml/min per 1.73 m^2 and glomerular filtration rate ≥ 60 ml/min per 1.73 m^2. [b]*n* = Number of subjects. [c]MRD, moderate renal dysfunction; glomerular filtration rate ≥ 60 ml/min per 1.73 m^2 versus < 60 ml/min per 1.73 m^2. BUN, blood urea nitrogen.

and 3.29/1000 person–years (CI: 2.92, 3.65) for the group with normal renal function.

Cox proportional hazards models were used to estimate the risk of declining GFR on IHD mortality. After adjusting for known risk factors for IHD mortality, decreasing GFR was associated with increasing risk of IHD mortality (Fig. 1). Hazard ratios ranged from a 41% increase in risk with an estimated GFR of 60–74.9 ml/min per 1.73 m^2 to nearly a three-fold increase in risk with an estimated GFR of < 45 ml/min per 1.73 m^2 (Fig. 2). MRD was also positively associated with IHD mortality (HR = 2.03; CI: 1.47, 2.80). In a Cox proportional hazards model with GFR as a continuous variable, the hazard ratio for a 10-unit reduction in estimated GFR below the normal threshold of ≥ 90 ml/min per 1.73 m^2 was associated with a hazard ratio 1.33 (95% CI 1.17, 1.50; $P < 0.001$) for IHD mortality.

Fig. 1

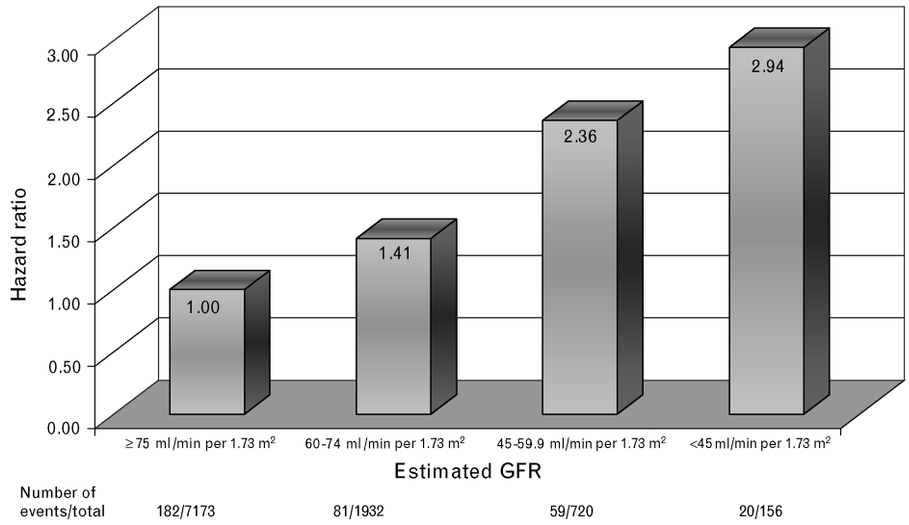


Kaplan–Meier estimates of probability of ischemic heart disease (IHD) death. GFR, glomerular filtration rate.

Subgroup analyses by sex, adjusting for all the above-mentioned covariates, found a significant association between estimated GFR and IHD mortality among men (HR 2.37; CI 1.65, 3.40; $P < 0.001$), but not for women (HR 1.20; CI 0.60, 2.43; $P = 0.602$). However, this may be due in part to the small number of events (1.4%) among female subjects (54 events/3771 women) and a consequent lack of statistical power. Subgroup analysis by race found a statistically significant association for Whites (HR 2.55; CI 1.64, 3.95; $P < 0.001$). Among Black and Hispanics the point estimates between GFR and IHD were of slightly smaller magnitude than that of Whites (Black HR 1.50; CI 0.80, 2.80; $P = 0.195$; Hispanic HR 1.59; CI 0.69, 3.66; $P = 0.273$) and were not statistically significant. Among subjects of other ethnicities, point estimates between GFR and IHD were slightly higher than that of Whites (other HR 3.17; CI 0.15, 67.15; $P = 0.458$), and not statistically significant. These non-significant findings are most likely due to small number of events among Blacks (96 events/2828), Hispanics (64 events/3624), and other ethnicities (six events/395) and subsequent lack of statistical power.

In sensitivity analyses, the significant association between declining estimated GFR and IHD mortality was consistent over length of follow-up, but appeared

Fig. 2



Hazard ratios by estimated glomerular filtration rate (GFR).

somewhat more pronounced among those with ≤ 5 years follow-up. Furthermore, the association between GFR and IHD mortality persisted in Cox regression models when the highest risk groups were excluded individually and in combination. The significant association between MRD and IHD mortality persisted in Cox regression models where analysis was restricted to those between the ages of 50 and 80 years for both 5- and 20-year follow-up (HR 2.17; CI 1.55, 3.05; $P < 0.001$ and HR 2.83; CI: 1.43, 5.57; $P = 0.003$, respectively). Cox proportional hazards models excluding those at highest risk for IHD mortality (a fasting blood glucose ≥ 6.993 mmol/l (≥ 126 mg/dl), a history of diabetes, CVD, or LVH) consistently showed a significant association between MRD and IHD mortality (Table 2).

In Cox proportional hazards models adjusting for all previously mentioned covariates, estimated GFR was significantly associated with CVD, stroke, and all-cause mortality (Table 3). No significant association was found between estimated GFR and non-CVD mortality (HR 0.84; CI 0.49, 1.4; $P = 0.520$).

Discussion

The principal finding of this study is that estimated baseline GFR is significantly associated with IHD

Table 2 Adjusted hazard ratios for ischemic heart disease (IHD) death by estimated glomerular filtration rate (GFR)[a]

Model	Hazard ratio for MRD	*P* value
Full model (MRD) ($n = 9939$)	2.03 (1.47, 2.80)	< 0.001
Full model (GFR categories)		
GFR ≥ 75 ml/min per 1.73 m^2 ($n = 7173$)	1.00	
GFR 60–74.9 ml/min per 1.73 m^2 ($n = 1932$)	1.41 (1.04, 1.91)	0.028
GFR 45–59.9 ml/min per 1.73 m^2 ($n = 720$)	2.35 (1.62, 3.44)	< 0.001
GFR < 45 ml/min per 1.73 m^2 ($n = 156$)	2.94 (1.59, 5.47)	0.001
Exclusion of diabetes or fasting serum glucose > 6.99 mmol/l (126 mg/dl) ($n = 9442$)	2.28 (1.59, 3.25)	< 0.001
Exclusion of cardiovascular history ($n = 8896$)	1.82 (1.25, 2.65)	0.002
Exclusion of left ventricular hypertrophy ($n = 8761$)	2.08 (1.45, 2.97)	< 0.001
Exclusion of cardiovascular history and left ventricular hypertrophy ($n = 7853$)	1.90 (1.25, 2.88)	< 0.001
Exclusion of diabetes or fasting serum glucose > 6.99 mmol/l (126 mg/dl), cardiovascular history, and left ventricular hypertrophy ($n = 7473$)	2.25 (1.39, 2.64)	0.001
Follow-up restricted to 10 years	1.57 (1.10, 2.22)	0.012
Follow-up restricted to 5 years	2.67 (1.42, 5.01)	0.002
Males ($n = 6168$)	2.36 (1.65, 3.40)	< 0.001
Females ($n = 3771$)	1.20 (0.60, 2.42)	0.602

[a]Glomerular filtration rate ≥ 60 ml/min per 1.73 m^2 as reference. MRD, moderate renal dysfunction.

Table 3 Adjusted hazard ratios for glomerular filtration rate (GFR) by cause of death

Mortality outcome	GFR measure	Hazard ratio	*P* value
IHD ($n = 342$)	GFR < 60 ml/min per 1.73 m^2	2.03 (1.47, 2.80)	< 0.001
	Full model (GFR categories)		
	GFR ≥ 75 ml/min per 1.73 m^2	1.00	
	GFR 60–74.9 ml/min per 1.73 m^2	1.41 (1.04, 1.91)	0.028
	GFR 45–59.9 ml/min per 1.73 m^2	2.35 (1.62, 3.44)	< 0.001
	GFR < 45 ml/min per 1.73 m^2	2.94 (1.59, 5.47)	0.001
CVD ($n = 573$)	GFR < 60 ml/min per 1.73 m^2	2.07 (1.62, 2.65)	< 0.001
	Full model (GFR categories)		
	GFR ≥ 75 ml/min per 1.73 m^2	1.00	
	GFR 60–74.9 ml/min per 1.73 m^2	1.40 (1.09, 1.79)	0.008
	GFR 45–59.9 ml/min per 1.73 m^2	2.21 (1.61, 3.01)	< 0.001
	GFR < 45 ml/min per 1.73 m^2	3.65 (2.29, 5.84)	< 0.001
Stroke ($n = 62$)	GFR < 60 ml/min per 1.73 m^2	2.47 (1.20, 5.07)	0.014
	Full model (GFR categories)		
	GFR ≥ 75 ml/min per 1.73 m^2	1.00	
	GFR 60–74.9 ml/min per 1.73 m^2	1.16 (0.56, 2.41)	0.681
	GFR 45–59.9 ml/min per 1.73 m^2	2.03 (0.83, 4.95)	0.119
	GFR < 45 ml/min per 1.73 m^2	7.41 (2.32, 23.68)	0.001
All cause ($n = 1084$)	GFR < 60 ml/min per 1.73 m^2	1.63 (1.40, 2.02)	< 0.001
	Full model (GFR categories)		
	GFR ≥ 75 ml/min per 1.73 m^2	1.00	
	GFR 60–74.9 ml/min per 1.73 m^2	1.26 (1.07, 1.49)	0.007
	GFR 45–59.9 ml/min per 1.73 m^2	1.72 (1.38, 2.14)	< 0.001
	GFR < 045 ml/min per 1.73 m^2	3.00 (2.15, 4.17)	< 0.001

IHD, ischemic heart disease; CVD, cardiovascular disease.

mortality among treated hypertensive subjects, while adjusting for traditional cardiovascular risk factors. Furthermore, this study shows a graded increase in risk as GFR declines. The study finds also that an estimated GFR of < 60 ml/min per 1.73 m^2 in treated hypertensive adults was associated with nearly twice the age–sex-adjusted mortality rates (6.21 per 1000 person–years) as those with GFR ≥ 60 ml/min per 1.73 m^2. The increased risk persisted in models where those at highest risk were excluded, and when follow-up time was restricted to 5 years.

While the statistically significant association was apparent among Whites, subjects who were Black, Hispanic, and those of other ethnicities exhibited a trend towards elevated risk, though with fewer events among these subjects, hazard ratios were not statistically significant. The association found in this study between GFR and CVD, stroke, and all-cause mortality is consistent with what others have reported [17,35].

In general, previous studies have reported similar findings with other endpoints [15,18,19]. Because several of these studies examine the relationship between renal dysfunction and IHD among patients more acutely or chronically ill than in our study, any direct comparison should be made with caution.

The study of Jungers *et al.* [18] found the unadjusted incident rates of morbid and mortal MI events to be 2.5–3.0 times higher among 147 patients with pre-dialysis progressive chronic renal failure (GFR 20–50 ml/min per 1.73 m^2) than among the general French population over a 10-year follow-up. Jungers *et al.* suggest that uremia may be a major risk factor for accelerated atherosclerosis. The degree of renal dysfunction studied by Jungers *et al.* was evident in only 2.9% (291/9939) of our cohort, thereby limiting a direct comparison to our study.

Also consistent with our results, Borch-Johnsen *et al.* [15] reported a relative risk of 2.3 for fatal and non-fatal IHD events among those in the Danish MONICA (Monitoring Trends and Determinants of Cardiovascular Diseases) study with renal impairment (defined as urinary albumin-to-creatinine ratio $>$ 90th percentile) compared to those with normal renal function. Subjects in the Danish MONICA study were not necessarily hypertensive (mean blood pressure 121/72 mmHg). The Borch-Johnsen *et al.* study findings suggest that microalbuminuria is an independent risk factor for IHD, and its presence increases the risk of traditional risk factors.

Data pooled from the TIMI-10, TIMI-14, and InTIME-II trials ($n = 12377$) further support the association between impaired renal function and increased IHD mortality observed in our study. Among patients presenting with acute MI and ST elevation treated with fibrinolysis, Gibson *et al.* [19] reported that moderate MRD was associated with increased mortality after adjusting for traditional risk factors [odds ratio (OR) 1.38; CI 1.10, 1.73; $P = 0.006$].

While consistent with studies mentioned above, our findings are, however, at variance with two earlier studies. A sub-analysis of a study of primarily White middle-aged men aged 40–59 years in 24 British towns found no independent association between SCr and risk of major IHD events (morbid or mortal) after adjusting for

traditional cardiac risk factors [20]. Approximately 5% of the cohort was treated for hypertension at study baseline. However, SCr has been shown to be an inaccurate measure of GFR and insensitive to detect mild-to-moderate kidney disease [36]. Furthermore, because of the non-linear association of SCr to GFR (due to variations in age, sex, and race), the accuracy of this measure is limited [10]. While the British study did not find an association between SCr and IHD events, study methodology may have obscured the presence of such an association.

Closer to this study, the Hypertension Optimal Treatment Study (HOT) did not find a significant association between GFR at baseline (estimated by Cockcroft and Gault formula and dichotomized at ≤ 60 ml/min per 1.73 m^2) and adjusted relative risk of MI (morbid and mortal) events [12]. Differences between the HOT study and the present study are worth noting. The HOT study was a multi-center study, consisting primarily of White men and women between the ages of 50 and 80 years, and reported on relatively few (205/18597; 1.1%) morbid and mortal MI events during a mean follow-up time of 3.8 years. In contrast, the ethnically diverse Worksite cohort, consisting of a nearly equal distribution of Blacks, Whites and Hispanics, reported on 342 (3.4%) IHD fatalities. Furthermore, the Worksite cohort was younger that that of the HOT study, with a mean age of 52 (range 22–85 years). In an attempt to achieve a more consistent comparison with the HOT study, when we restricted our analysis of the Worksite cohort to those between the ages of 50 and 80 years, with both 5- and 20-years of follow-up, the significant association between GFR and IHD mortality persisted. Demographic differences and study methodology between these two studies may, in part, account for these disparate findings. Difference in outcomes between our study, which examined IHD mortality exclusively, and those of the HOT study, which examined both morbid and mortal IHD, may be another explanation for the difference in findings. However, a more likely explanation for the dissimilar findings may be insufficient statistical power of the HOT study. The HOT study reports a non-significant adjusted relative risk (RR = 1.46) for morbid and mortal MI, which is similar to the results we have reported here. And, with fewer events, the HOT study may have had insufficient statistical power to detect a significant difference. Furthermore, the statistically significant adjusted relative risk for CVD mortality in the HOT study (RR = 1.80) with a greater number of events was similar to findings reported here.

In our study, there exist a number of possible explanations for the observed association between GFR and IHD mortality: traditional risk factors, biological mechanisms, non-traditional risk factors, and metabolic changes. First, those with lower levels of estimated GFR were more likely to have a history of prior CVD and known risk factors for IHD. However, in multivariate Cox regression models, the risk of IHD mortality was independently associated with reduced GFR. When the analysis was repeated on a low-risk subset, the association between GFR and IHD mortality persisted.

Biological mechanisms for the observed association between GFR and IHD mortality cannot be determined by this study. They are likely multi-factorial. For example, among hypertensive patients an increase in SCr is often attributed to nephrosclerosis, which is characterized by hyalinization of renal arterioles. It has also been reported that among patients with coronary heart disease, renal arteriole hyalinization is more pronounced than in healthy individuals [37]. Renal arteriole hyalinization was also found to be positively correlated with coronary and aortic raised lesions in autopsy studies of asymptomatic young men and women [38]. Hence, the association between IHD mortality and GFR might be explained, in part, by shared traditional risk factors for both IHD and renal dysfunction. However, the observed association remained after statistical adjustment for traditional risk factors, and in models removing those at highest risk. This casts some doubt on the suitability of the shared risk factor explanation.

An increase in non-traditional CVD risk factors, such as homocystine, C-reactive protein, apolipoprotein-B, serum lipoprotein(a), homocystine and plasma fibrinogen, and lower levels of apolipoprotein-A1 [39–41] may also be associated with a decrease in renal function. These non-traditional risk factors have been found to be independent risk factors for coronary heart disease in a number of studies [42–45]. On the other hand, a study of elderly persons, aged ≥ 65 years with chronic kidney disease, found non-traditional risk factors to have less impact on CVD mortality than do traditional CVD risk factors [46]. Another possible explanation for our study findings is that the association between GFR and IHD mortality may reflect unknown risk factors induced by elevated SCr and reduced GFR.

Reduced SCr is also associated with several metabolic changes that enhance the atherogenic process at the systemic level. Oxidative stress, inflammation, and elevated levels of homocystine are all found in the early stages of renal disease [41,47,48]. Finally, the presentation of renal dysfunction may be a manifestation of generalized atherosclerosis at the systemic level of the kidney and may represent the impact of generalized vascular disease on the kidney. Additional research is needed to define the role of these and other factors that increase the risk of IHD mortality in patients with reduced GFR.

Whatever the underlying mechanisms responsible for the observed association between reduced GFR and IHD mortality, recent studies suggest that screening for renal

disease among high-risk groups, such as hypertensives, might improve the health outcomes. One such study demonstrated that stringent blood pressure control and use of angiotensin II neutralizing agents have the potential to stop or slow the progression of renal dysfunction [49]. A subgroup analysis of the GREACE (Greek Atorvastatin and Coronary Heart Disease Evaluation) study found statin treatment to increase creatinine clearance in dyslipidemic patients with CHD, with greatest benefit among those with early renal dysfunction [50]. And in yet another recent report, subjects with mild renal insufficiency from the HOPE (Heart Outcomes Prevention Evaluation) study found those treated with ramipril (an angiotensin-converting enzyme inhibitor) significantly reduced cardiovascular risk despite a moderate elevation in serum creatinine [14].

Study limitations and strengths

Our study has several limitations. This is a self-selected cohort of treated hypertensive subjects. The hypertensive nature of the study cohort places this group at higher risk for cardiovascular events than the general population. Since the entire cohort was hypertensive, it is impossible to say whether the observed associations between GFR and IHD mortality may be limited to the hypertensive nature of the population.

Prescription patterns changed in the Worksite program as standards of practice in the treatment of hypertension changed. Since outcome reporting was by NDI and follow-up time for many subjects extended beyond the time of their participation in Worksite, it is impossible to determine the association between medication and IHD mortality outcomes. Some believe that treatment for hypertension with diuretics may lead to impaired renal function. However, an earlier study reporting on this cohort [51] found no adverse renal effect in 2125 men treated for mild to moderate hypertension over an average of 5 years. None the less, it is possible, although unlikely, that the introduction of new anti-hypertensive medication over time may have had an impact on renal function associated with outcomes.

We did not have a sufficient number of patients with 24-h urine specimens to calculate GFR directly. Consequently we had to rely on the Cockcroft and Gault formula to estimate GFR. The single SCr measurements used may have provided an insensitive marker for GFR. Furthermore, the stability of estimated GFR is unknown in this study. It is not known whether renal dysfunction seen at baseline was transient or chronic. While this may have led to some misclassification of renal status, there is no apparent reason for it to have a differential association with IHD mortality.

Despite the limitations, our study has several strengths. Among these are the long period of follow-up and systematic treatment for hypertension. Another strength of the current study is good in-treatment blood pressure control (systolic 135.4 ± 15.8 mmHg; diastolic 84.4 ± 9.7 mmHg), which is also known to improve renal prognosis. In fact, serum creatinine increased 1.52 mmol/l (0.02 mg/dl) and estimated GRF decreased 5.43 ml/min per 1.73 m^2 from baseline measures. A minimal decline in renal function would be expected to occur over follow-up time with the advancing age of the cohort. Furthermore, our findings are consistent without regard to length of follow-up, though more pronounced among those with ≤ 5 years of follow-up. Exclusion of those at highest risk [diabetes or fasting serum glucose > 6.993 mmol/l (> 126 mg/dl), history of CVD, or LVH)] also had similar point estimates. The overall consistency of our findings adds confidence that the observed association between GFR and IHD mortality is not merely statistical.

Finally, while SCr concentration is not likely to be a reliable estimate of GFR, the Cockcroft and Gault formula that we used has been shown to be more reliable and has reported a correlation coefficient between predicted and mean measured GFR of 0.83 [31].

In summary, we have found that GFR is a strong significant and consistent risk factor for IHD mortality among treated hypertensive subjects. While we cannot determine whether the observed association between GFR and IHD mortality is result of independent causal factors, mediators, shared traditional risk factors, or other risk markers, our findings, together with earlier studies, suggest that in treated hypertensive patients cardiovascular risk may develop even with a modest decrease in renal function, irrespective of cause. Assessment of renal function among hypertensive patients may prove especially useful for risk stratification and early intervention to improve health outcomes.

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