Impact of Elevated Cystatin C Level on Cardiovascular Disease Risk in Predominantly High Cardiovascular Risk Populations
A Meta-Analysis

Meng Lee, MD; Jeffrey L. Saver, MD; Wen-Hung Huang, MD; Jessica Chow, MPH; Kuo-Hsuan Chang, MD; Bruce Ovbiagele, MD, MSc

Background—Chronic kidney disease is a growing public health problem that carries substantial risk for cardiovascular disease (CVD). Single studies have differentially examined the role of cystatin C, a novel renal index, with varying cut-point use. We undertook a meta-analysis of prospective studies to properly assess the link between cystatin C (dichotomized and continuous) versus CVD.

Methods and Results—Systematic literature search for studies reporting a multivariate-adjusted estimate, represented as relative risk (RR) with 95% confidence interval (CI), of the association between cystatin C and subsequent risk of (1) any CVD event and (2) specific CVD events. Data were collated from 14 studies, with 13 high cardiovascular risk population cohorts and 1 general population cohort, involving 22,509 subjects with 2,321 CVD events, 7,41 coronary heart disease events, and 828 stroke events. Highest cystatin C category versus lowest was associated with greater risk of CVD (RR, 2.62; 95% CI, 2.05 to 3.37; \( P < 0.001 \)), coronary heart disease (RR, 1.72; 95% CI, 1.27 to 2.34; \( P < 0.001 \)), and stroke (RR, 1.83; 95% CI, 1.12 to 3.00; \( P = 0.02 \)) after adjustment for established cardiovascular risk factors. Each standard deviation rise in cystatin C concentration boosted CVD risk (RR, 1.34; 95% CI, 1.18 to 1.51; \( P < 0.001 \)). Highest cystatin C category was also independently linked to greater risk of all-cause mortality and heart failure.

Conclusions—The meta-analysis, mostly derived from high cardiovascular populations, showed that cystatin C is strongly and independently associated with subsequent CVD risk. Further investigation is warranted to clarify whether measurement of cystatin C can usefully enhance CVD stratification beyond established predictors already in clinical use. (Circ Cardiovasc Qual Outcomes. 2010;3:675-683.)

Key Words: cystatin C ■ cardiovascular diseases ■ coronary artery disease ■ stroke ■ meta-analyses ■ risk factors

Chronic kidney disease is a worldwide health problem that carries a substantial risk for cardiovascular morbidity and death.1-3 Serum creatinine concentrations or creatinine-based estimating equations have served as the primary tool for evaluation of kidney function in clinical practice and in epidemiological research studies. However, the widely used and expert recommended creatinine-based Modification of Diet in Renal Disease study formula for estimating glomerular filtration rate (GFR) still has substantial inaccuracy when applied to healthy persons and older individuals.4

Recently, the use of serum creatinine–based formulas to assess renal function has been challenged by novel markers, particularly cystatin C, which may be a more reliable index of renal function.5,6 Cystatin C is a small serine protease inhibitor that is secreted from almost all active functional cells in the body. At a molecular weight of 13 kDa, the protein is freely filtered by the renal glomerulus and then metabolized by the proximal tubule.6,7 Mounting data suggest that cystatin C is superior to serum creatinine or creatinine-based estimating equations for prediction of cardiovascular events among elderly persons8 and among persons with known coronary heart disease (CHD).9 However, no systematic review has been conducted to evaluate the totality of available evidence regarding a link between cystatin C and subsequent risk of (1) any cardiovascular disease (CVD) event or (2) specific cardiovascular events including major coronary events or strokes. We therefore undertook a meta-analysis of cohort studies to qualitatively and
quantitatively assess the association between cystatin C and risk of CVD.

WHAT IS KNOWN

- Chronic kidney disease is a worldwide health problem that carries a substantial risk for cardiovascular morbidity and death.

- The use of serum creatinine–based formulas to assess renal function has been challenged by novel markers, particularly cystatin C, which may be a more reliable index of renal function. However, little is known about the qualitative and quantitative impact of cystatin C on cardiovascular risk using the totality of published data.

WHAT THE STUDY ADDS

- This meta-analysis, derived mostly from populations at high cardiovascular risk, showed that cystatin C is strongly and independently associated with future cardiovascular events.

Methods

Data Sources and Searches

The search strategy was conducted according to the recommendations of the Meta-analysis of Observational Studies in Epidemiology.10 We performed a systematic search of PUBMED (1966 to May 2010), EMBASE (1947 to May 2010), and the Cochrane Library using the search strategy: “cystatin C” crossed with “cardiovascular disease” or “myocardial ischemia” or “ischemic heart disease” or “coronary heart disease” or “angina” or “stroke” or “cerebrovascular disease” or “cerebrovascular attack” or “cerebral infarct” or “intracranial hemorrhage.” We also searched abstracts in all American Heart Association (AHA)-sponsored meetings, from January 2003 to February, 2009, via the AHA Abstract Archive Tool (http://www.ahainternational.org). The search strategy was conducted according to the recommendations of the Meta-analysis of Observational Studies in Epidemiology.10 We performed a systematic search of PUBMED (1966 to May 2010), EMBASE (1947 to May 2010), and the Cochrane Library using the search strategy: “cystatin C” crossed with “cardiovascular disease” or “myocardial ischemia” or “ischemic heart disease” or “coronary heart disease” or “angina” or “stroke” or “cerebrovascular disease” or “cerebrovascular attack” or “cerebral infarct” or “intracranial hemorrhage.” We also searched abstracts in all American Heart Association (AHA)-sponsored meetings, from January 2003 to February, 2009, via the AHA Abstract Archive Tool (http://www.abstractsonline.com/arch/home.aspx?lookupkey=12345). We restricted the search to human studies. There were no language restrictions. Further information was retrieved through a manual search of references from recent reviews and relevant published original studies.

Study Selection

Studies were selected if they met the following entry criteria: (1) subjects were prospectively followed within a cohort study or clinical trial; (2) cystatin C measured at baseline; (3) reported CVD, CHD, and/or stroke events as outcomes; (4) follow-up duration of at least 1 year; (5) reported quantitative estimates of the multivariate-adjusted relative risk (RR) and 95% confidence interval (CI) for at least 1 of the outcomes associated with baseline cystatin C. Studies were excluded if (1) the study design was cross-sectional or case-control studies; (2) the majority of participants had end-stage renal disease (dialysis or GFR <15 mL/min/1.73 m²)11 or kidney transplant; (3) they only reported unadjusted or age-and sex-adjusted RR; (4) they did not report 95% CI; or (5) data were duplicative. For studies that reported several multivariable-adjusted RRs, we extracted the effect estimate that was most fully adjusted for potential confounders. Cystatin C was not always measured at baseline study entry, and so in certain situations it was assessed retrospectively on baseline frozen blood samples (eg, Cardiovascular Health study).8

Data Extraction and Quality Assessment

Data were extracted using a standardized extraction form and all data from eligible studies were extracted independently by 2 investigators (M.L. and W.H.H.). Discrepancies were resolved by discussion with a third investigator (B.O.) and by referencing the original report. We assessed the quality of all manuscripts that met the selection criteria. Quality assessment was based on guidelines developed by the United States Preventive Task Force as well as the modified checklist used in previous studies.12–14 We assessed the following 8 characteristics: (1) prospective study design; (2) maintenance of comparable groups; (3) appropriate and adequate adjustment of potential confounders (ie, at least 5 of 7 Framingham cardiovascular risk factors); (4) documented loss of follow-up rate; (5) outcomes assessed blinded to exposure status; (6) appropriate and clear definition of exposures (cystatin C) and outcomes (CVD, CHD, and stroke); (7) temporality (cystatin C measured at baseline, not at time of outcomes assessment); and (8) follow-up of at least 1 year. Studies were graded as good quality if they met 6 to 8 criteria; fair if they met 3 to 5; and poor if they met less than 3 criteria.

Data Synthesis and Analysis

There is currently no widely standardized cystatin C measurement, but the nephelometric or turbidimetric methods are most frequently used.15 In a study on 120 samples containing between 0.5 and 9 mg/L by the nephelometric method,16 the 2 methods correlated excellently (r=0.97), although when each was calibrated with the calibrator provided by the manufacturer, the turbidimetric method produced far higher values. Conversely, when a common calibrator was used, the slope of the Passing-Bablok line was not significantly different from 1. Various studies reported different segmentation strategies for grouping patients by cystatin C level, including dichotomous, tertiles, quartiles, or quintiles, or treated cystatin C level as a continuous variable and reported increase in risk for a given unit of increase in cystatin C level. To provide clinically relevant and easily interpretable results, our primary outcomes of interest were the association of CVD, CHD, and stroke risk and cystatin C categorical level, based on the comparison of the highest category of cystatin C versus lowest. We also analyzed cystatin C level as a continuous variable to evaluate the CVD risk, based on per standard deviation cystatin C increase. Our secondary outcomes of interest were risk of all-cause mortality and incident heart failure, based on the comparison of highest cystatin C category versus lowest.

Subgroup analyses for CVD risk, based on highest cystatin C category versus lowest, were conducted according to baseline population (elderly versus CHD or stroke versus heart failure versus asymptomatic carotid atherosclerosis), location (North America versus Europe versus Asia), mean age (<50 years versus 50–70 years), end point (all CVD versus fatal CVD), follow-up duration (1 to 5 years versus >5 years), CVD events number (∼100 versus <100), baseline estimated GFR interval (eGFR >60 mL/min/1.73 m² versus eGFR <60 mL/min/1.73 m²), cutoff point of the lowest interval (reference) of cystatin C (<0.90 mg/L versus 0.90 to 1.50 mg/L), and cutoff point of the highest interval of cystatin C (0.93 to 1.29 mg/L versus ≥1.30 mg/L). Additional analysis was done to explore the impact of per standard deviation increase in cystatin C on the general and elderly populations.

Data analyses used multivariate-adjusted outcome data (expressed as RRs and 95% CIs). The statistical analysis used the inverse variance approach to combine log RRs and standard errors. We used a random-effects model (DerSimian and Laird method) and explored for sources of inconsistency (I²) and heterogeneity. All reported probability values were 2-sided, with significance set at <0.05. Heterogeneity was assessed by probability values of χ² statistics and I², which describes the percentage of variability in the effect estimates that is due to heterogeneity rather than chance.17,18 We regarded I² of <40% as “heterogeneity might not be important” and more than 75% as “considerable heterogeneity,” based on the suggestion from the Cochrane Handbook for Systematic Review of Interventions.19 Publication bias was estimated visually by funnel plots displaying standard error as the measure of sample size and RR as the measure of treatment effect.20 If publication bias was suggested by the funnel plots, a fixed-effects model would be obtained for the comparison with the random-effects model to clarify the small-study effects.10,21 Thereafter, an analysis excluding small
The systematic literature review identified 53 full articles for detailed assessment, among which 30 were excluded for not having any CVD, CHD, or stroke estimates, 3 for not having appropriate RRs and 95% CIs for at least 1 of the primary outcomes,22–24 and 2 for having follow-up durations <1 year25,26 (Figure 1). Our final primary analysis included 18 articles derived from 14 independent prospective studies.8,9,27–42 Consisting of 22 509 participants. Among the 14 studies, 13 reported CVD outcomes (2321 events),8,9,27,29,31–38,40–42 and 4 reported CHD outcomes (741 events),8,9,31,39 and 4 reported stroke outcomes (828 events).8,9,31,37 The study characteristics are presented in Table 1. Three studies recruited subjects from a elderly population (8816 participants),8,31,38 1 recruited persons from a general population (5067 participants),35 5 recruited persons with CHD or stroke at entry (6701 participants),9,33,34,37,39,42 3 recruited persons with heart failure at entry (932 participants),27,36,40 and 1 recruited persons with asymptomatic carotid atherosclerosis (1004 participants).41 Follow-up duration ranged from 142 to 12.8 years.35 One study included men only,38 whereas others included both men and women. Of the 14 studies, 3 were done in the United States,8,9,31 3 in Sweden,27,35,38 2 in Germany,33,34 1 in The Netherlands,39 1 in Austria,41 1 in Spain,42 2 in Japan,36,40 and 1 in China.35 Overall quality of studies was good (median, 6; range, 4 to 8) on an 8-point scale. Most of the studies included in the meta-analysis used nephelometric assay (Dade Behring, Siemens), whereas 1 study27 used tubidimetric assay. Although most studies used the same assay, the estimate of CVD risk in a study36 was substantially higher than others. The cutoff point in this study was not different from others, but a range of coefficient of variation was not provided, preventing further exploration.36 Overall, 5 of 13 studies that used the nephelometric method provided data on the range of cystatin C levels; among these, the coefficient of variation for cystatin C levels ranged from 2% to 7.7%.

Highest cystatin C category versus lowest was associated with greater overall CVD risk (RR, 2.62; 95% CI, 2.05 to 3.37; \( P<0.001 \)), CHD risk (RR, 1.72; 95% CI, 1.27 to 2.34; \( P<0.001 \)), and stroke risk (RR, 1.83; 95% CI, 1.12 to 3.00; \( P=0.02 \)) after adjustment for established cardiovascular risk factors. Each standard deviation rise in cystatin C concentration was associated with increased risk for overall CVD (RR, 1.34; 95% CI, 1.18 to 1.51; \( P<0.001 \)) (Figure 2). The highest cystatin C category was also associated with greater risk of all-cause mortality (RR, 2.22; 95% CI, 1.69 to 2.92; \( P<0.001 \)) and incident heart failure (RR, 2.23; 95% CI, 1.77 to 2.81; \( P<0.001 \)) (Figure 3).

In heterogeneity testing and sensitivity analysis for studies reporting CVD outcomes (highest cystatin C interval versus lowest), significant heterogeneity was present (\( P<0.001, I^2=82\% \)) but exclusion of any single study for the analysis did not alter the overall finding. For studies reporting CHD outcomes (highest cystatin C interval versus lowest), significant heterogeneity was present (\( P=0.001, I^2=73\% \)) but exclusion of any single study for the analysis did not alter overall finding. For studies reporting stroke outcomes (highest level versus lowest), significant heterogeneity was present (\( P<0.001, I^2=89\% \)) and exclusion of the Cardiovascular Health Study8 from the analysis resulted in a rise in relative risk that was not significant (RR, 1.93; 95% CI, 0.55 to 6.84; \( P=0.31 \)). For studies reporting CVD outcomes (per standard deviation increase), significant heterogeneity was present (\( P<0.001, I^2=84\% \)) but exclusion of any single study for the analysis did not alter the overall finding. Asymmetry was noted in CVD and CHD funnel plots (highest category versus lowest) and the underrepresentation of small studies showing neutral or unexpected protective effects suggesting some degree of publication bias (supplement Figure 1). The estimate of CVD risk from fixed-effects model (RR, 2.29; 95% CI, 2.07 to 2.54) was smaller than estimated from the
random-effects model (RR, 2.62; 95% CI, 2.05 to 3.37), which suggested small-study effects. When we excluded small studies (CVD events <100) in our pooled analysis, the CVD risk was still substantial (RR, 2.09; 95% CI, 1.80 to 2.43; P<0.001) and the funnel plot did not suggest gross publication bias (supplement Figure 2).

Potential sources of heterogeneity in the strength of the association between cystatin C (highest category versus lowest) and subsequent risk of CVD were examined by conducting subgroup analyses (Table 2). Significant heterogeneity between pooled analyses were noted for study location (North America [RR, 2.51; 2.13 to 2.95] versus Europe [RR, 2.01; 1.62 to 2.51] versus Asia [RR, 8.00; 1.41 to 45.50], P for heterogeneity among subgroups <0.001), baseline eGFR interval (eGFR >60 mL/min/1.73 m² [RR, 1.90; 1.24 to 2.91] versus eGFR <60 mL/min/1.73 m² [RR, 3.24; 1.72 to 6.08], P for heterogeneity among subgroups, 0.02), CVD event number (≥100 events [RR, 2.09; 1.80 to 2.43] versus <100 events [RR, 5.02; 2.20 to 11.49], P for heterogeneity among subgroups <0.001), and end points (fatal

### Table 1: Study Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Population</th>
<th>Participant No. (Women, %)</th>
<th>Mean Age, y</th>
<th>Follow-Up, y</th>
<th>Primary End Points, n</th>
<th>Comparison Cystatin C Level, mg/dL</th>
<th>*Adjusted Framingham Risk Factors, n</th>
<th>Other Adjusted Covariate, n</th>
<th>Study Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alehagen et al, 2009</td>
<td>Sweden</td>
<td>Heart failure</td>
<td>464 (48)</td>
<td>73</td>
<td>10</td>
<td>Fatal CVD (113)</td>
<td>Highest quartile (≥1.66) vs lowest (&lt;1.22)</td>
<td>4</td>
<td>6</td>
<td>Good</td>
</tr>
<tr>
<td>Amimoto et al, 2005</td>
<td>Japan</td>
<td>Heart failure</td>
<td>140 (38)</td>
<td>66</td>
<td>1.3</td>
<td>Cardiac death (32)</td>
<td>Per SD</td>
<td>1</td>
<td>3</td>
<td>Fair</td>
</tr>
<tr>
<td>Cardiovascular Health Study, 2005 and 2006</td>
<td>USA</td>
<td>Elderly ages ≥65 y at entry</td>
<td>4637 (58)</td>
<td>75</td>
<td>7.4</td>
<td>Fatal CVD (530), all MI (370), and all stroke (405)</td>
<td>Highest quintile (≥1.29) vs lowest (≥0.89); per SD and high (≥1.0) vs low (&lt;1) in eGFR ≥60 mL/min/1.73 m² persons</td>
<td>4</td>
<td>7</td>
<td>Fair</td>
</tr>
<tr>
<td>Health, Aging, and Body Composition study, 2006 and 2008</td>
<td>USA</td>
<td>Functional elders ages 70–79 y at entry</td>
<td>3044 (51)</td>
<td>74</td>
<td>6</td>
<td>Fatal CVD (242), all CHD (294), and all stroke (163)</td>
<td>High (≥1.19) vs low (&lt;0.84); per SD</td>
<td>6</td>
<td>14</td>
<td>Good</td>
</tr>
<tr>
<td>Heke et al, 2010</td>
<td>Austria</td>
<td>Asymptomatic carotid artery atherosclerosis</td>
<td>1004 (37)</td>
<td>69</td>
<td>3</td>
<td>All CVD (346)</td>
<td>Highest quintile (≥0.96) vs lowest (≤0.5)</td>
<td>4</td>
<td>8</td>
<td>Fair</td>
</tr>
<tr>
<td>Keller et al, 2009</td>
<td>Germany</td>
<td>CHD, eGFR ≥60 mL/min/1.73 m²</td>
<td>1827 (19)</td>
<td>61</td>
<td>3.7</td>
<td>Fatal CVD (66)</td>
<td>Highest quintile (0.91–2.48) vs lowest (0.42–0.70)</td>
<td>4</td>
<td>5</td>
<td>Good</td>
</tr>
<tr>
<td>Koenig et al, 2005</td>
<td>Germany</td>
<td>CHD</td>
<td>1033 (15)</td>
<td>59</td>
<td>2.8</td>
<td>All CVD (71)</td>
<td>Highest quintile (≥1.24) vs lowest (≤0.91)</td>
<td>4</td>
<td>5</td>
<td>Good</td>
</tr>
<tr>
<td>Malmö Diet and Cancer study, 2009</td>
<td>Sweden</td>
<td>General</td>
<td>5067 (60)</td>
<td>58</td>
<td>12.8</td>
<td>All CVD (418)</td>
<td>Per SD</td>
<td>7</td>
<td>2</td>
<td>Good</td>
</tr>
<tr>
<td>Naruse et al, 2009</td>
<td>Japan</td>
<td>Heart failure</td>
<td>328 (38)</td>
<td>73</td>
<td>2.5</td>
<td>Fatal CVD (52)</td>
<td>Highest quartile (≥1.31) vs lowest (≤0.91)</td>
<td>4</td>
<td>5</td>
<td>Good</td>
</tr>
<tr>
<td>Ni et al, 2007</td>
<td>China</td>
<td>Stroke and controls</td>
<td>1187 (59)</td>
<td>61</td>
<td>5</td>
<td>All CVD (57) in stroke cohort, all stroke (260) in stroke + controls cohort</td>
<td>Highest quintile (≥1.42) vs lowest (≤0.87)</td>
<td>2</td>
<td>3</td>
<td>Fair</td>
</tr>
<tr>
<td>Taglieri et al, 2010</td>
<td>Spain</td>
<td>Acute coronary syndrome</td>
<td>525 (26)</td>
<td>66</td>
<td>1</td>
<td>All CVD (157)</td>
<td>Highest 2 quintiles (≥0.93) vs lowest (≤0.81)</td>
<td>NR†</td>
<td>NR†</td>
<td>Fair</td>
</tr>
<tr>
<td>Uppsala Longitudinal Study of Adult Men, 2008</td>
<td>Sweden</td>
<td>Approximately 71-year-old men in a city</td>
<td>1135 (0)</td>
<td>71</td>
<td>10</td>
<td>Fatal CVD (138)</td>
<td>High (≥1.5) vs low (≤1.5); per SD</td>
<td>7</td>
<td>3</td>
<td>Good</td>
</tr>
<tr>
<td>Windhausen et al, 2009</td>
<td>Netherlands</td>
<td>Acute CHD, secondary analysis of a clinical trial</td>
<td>1128 (27)</td>
<td>62</td>
<td>3</td>
<td>All MI (77)</td>
<td>Highest tertile (≥1.01) vs lowest (≤0.86)</td>
<td>4</td>
<td>13</td>
<td>Fair</td>
</tr>
</tbody>
</table>
Figure 2. Risk ratios for A, cardiovascular disease; B, coronary heart disease; and C, stroke associated with highest interval of cystatin C level versus lowest. D, Risk ratio of cardiovascular disease associated with per standard deviation increase of cystatin C level. a, b, and c denote different cystatin C levels within the fifth quintile of the Cardiovascular Health Study.
CVD [RR, 2.98; 2.05 to 4.33] versus all CVD [RR, 2.07; 1.66 to 2.58], P for heterogeneity among subgroups, 0.03). There was no evidence that the strength of the association differed according to baseline population (elderly versus CHD or stroke versus heart failure versus asymptomatic carotid atherosclerosis), mean age (<70 years versus ≥70 years), follow-up duration (1 to 5 years versus >5 years), cutoff point of reference of cystatin C levels, and cutoff point of highest cystatin C interval (1 to 1.3 mg/L versus >1.3 mg/L). However, the impact of per standard deviation increase in cystatin C was larger in the elderly population versus the general population (RR, 1.32; 95% CI, 1.25 to 1.40 versus RR, 1.13; 95% CI, 1.04 to 23; P for heterogeneity among subgroups, 0.003).

Discussion

Our systematic review of over 22,000 participants from 14 prospective studies found that, compared with individuals with the lowest baseline cystatin C levels, those with the highest levels have a 162% increase in the risk of CVD, 72% increase in the risk of CHD, and 83% increase in the risk of stroke. When cystatin C level was analyzed as a continuous variable, each standard deviation increase was associated with 34% rise in overall CVD risk. Persons in the highest levels of cystatin C had a 122% increase in the elderly population versus the general population (RR, 1.32; 95% CI, 1.25 to 1.40 versus RR, 1.13; 95% CI, 1.04 to 23; P for heterogeneity among subgroups, 0.003).

A major cystatin C study that did not meet the inclusion criteria of the current meta-analysis bears mention because this is the only study that compared cystatin C with measured GFR (not eGFR) for cardiovascular risk prediction. In this non-diabetic chronic kidney disease cohort, the association of cystatin C level with CVD mortality was as strong as that of iothalamate GFR with these outcomes, raising the possibility that cystatin C may not just be a marker of chronic kidney disease but also a CVD risk factor perhaps reflecting proinflammatory and proatherogenic states. Indeed, the potential role of cystatin C beyond just being a chronic kidney disease marker may also provide an explanation for why high cystatin C was associated with a substantial increase in CVD risk among persons with eGFR ≥60 mL/min/1.73 m², who do not meet the conventional definition of chronic kidney disease. Still, there is a possibility that eGFR is not sensitive enough to reflect the real association between mild renal insufficiency and CVD.

We used subgroup analyses to assess the varying influence of several factors on the association between cystatin C and CVD risk. Asians with high cystatin C levels appear to be at higher CVD risk than their European and American counterparts. It has been suggested that hypertension tends to develop in Asians at earlier ages than in other races, and it is conceivable that a longer history of hypertension may cause more profound damage of end organs and vessels, thereby leading to a higher likelihood of vascular events within a given study period. However, the results should be interpreted with caution because the only 2 Asian studies were based on relatively small populations, and there was substantial heterogeneity within these 2 studies.

We observed that the impact of elevated cystatin C was more profound on the risk of fatal CVD versus all CVD,
which probably points to the association of compromised kidney function with risk factors for generally poor clinical outcomes such as oxidative stress, widespread inflammation, electrolyte derangements, procoagulation, and presence of uremic toxins.\textsuperscript{1} The finding of a larger impact of elevated cystatin C in the elderly versus the general population is interesting. It may signify an increasing impact of kidney disease on CVD risk with rising age, as the effect of some classic risk factors (eg, total cholesterol) diminishes. We found that studies with fewer CVD events showed larger risk ratios in terms of CVD risk, which may be partly due to the underrepresentation of small studies showing neutral or unexpected protective effects, as shown in the funnel plots. There were several approaches (eg, fail-safe N) to deal with publication bias issue, but none is generally ideal.\textsuperscript{19} We compared estimates obtained from a fixed-effects model with our random-effects model to assess the issue of a small-study effect.\textsuperscript{19} Although we found the estimate of CVD risk obtained solely from large studies was smaller than the original one, it was still substantial and highly significant. Therefore, the positive association between elevated cystatin C and CVD risk probably is not completely attributable to publication bias.

There are concerns about whether novel biomarkers, including cystatin C, can actually provide additive value in the prediction of CVD on top of classic risk factors. Two included studies\textsuperscript{35,38} adjusted all 7 Framingham risk factors (ie, age, sex, systolic blood pressure, diabetes mellitus, high-density lipoprotein cholesterol level, total cholesterol or low-density lipoprotein cholesterol level, and smoking), and pooling data from these 2 studies showed per standard deviation increase in cystatin C was associated with increased risk of cardiovascular disease. Furthermore, 1 study showed that addition of cystatin C to the model with established risk factors showed the trend of improvement of the C statistic for predicting cardiovascular death and that the C statistic in-...
factor, yet has been consistently proven to be an independent predictor of cardiovascular mortality, and cystatin C is a reliable renal index, it may not be unreasonable to consider incorporating cystatin C in cardiovascular risk assessment to further delineate risk.

This study has limitations. First, meta-analyses may be biased if the literature search fails to identify all relevant studies or the selection criteria for including a study are applied in a subjective manner. To minimize these risks, we developed the study protocol a priori and performed thorough searches across different data bases using explicit criteria for study selection, data abstraction, and data analysis. Second, the studies varied with respect to the characteristics of participants and the definitions of CVD, CHD, and stroke in outcome assessment and follow-up duration, and indeed heterogeneity was found by formal analysis. To explore the potential heterogeneity, we did subgroup analyses to identify plausible biological and selection sources of the variation. Third, each study has its own adjustment for variables; therefore some studies adjusted more than others. Because this study was a study-level meta-analysis and not an individual-level meta-analysis, it is impossible for us to apply a uniform adjustment for variables to all studies. Fourth, cystatin C is a novel biomarker, and the best cutoff point is still under debate. Our current meta-analysis does not solve this issue. In general, cystatin C 1.3 mg/L or greater was strongly associated with subsequent CVD risk. However, when cystatin C level was analyzed as a continuous variable, the meta-analysis found a 34% increase of CVD risk in each standard deviation increase (eg, 0.18 mg/L of cystatin C level in the Cardiovascular Health Study28). This implies that CVD risk may increase steadily from very low cystatin C levels. Further studies using more statistically sophisticated methods may be able to more precisely explore the effect of the cutoff values.

In summary, although limited by varying cystatin C cutoff points in different studies, this meta-analysis, mostly derived from high cardiovascular risk populations, which analyzed cystatin C in highest versus lowest category as well as per standard deviation increase, found that cystatin C is strongly and independently associated with subsequent risk of CVD, CHD, and stroke. Further and more detailed investigation is warranted to clarify whether measurement of cystatin C can usefully enhance CVD stratification beyond established predictors already in clinical use.

Acknowledgments

We thank Yueh Lee, MSc, for retrieval of reports.

Sources of Funding

Dr Lee was supported by a grant from Chang Gung Memorial Hospital, Taiwan (CMRPG 660311), Dr Saver was supported by the Specialized Program on Translational Research in Acute Stroke (SPOTRIAS) from the National Institutes of Health, and Dr Ovbiagele was supported by the University of California, Los Angeles–Resource Centers for Minority Aging Research under National Institutes of Health/ National Institutes on Aging grant No. P30-AG021684. The sponsors played no role in the study design, data collection and analysis, or decision to submit the article for publication.

Disclosures

None.

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Circ Cardiovasc Qual Outcomes. 2010;3:675-683; originally published online October 5, 2010;
doi: 10.1161/CIRCOUTCOMES.110.957696
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272
Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7705. Online ISSN: 1941-7713

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**SUPPLEMENTAL MATERIAL**

**Supplementary Figure 1:** Funnel plots for studies included in primary outcomes. (A) Cardiovascular disease, (B) coronary heart disease, and (C) stroke, analyzed with highest interval of cystatin C level versus lowest. (D) Cardiovascular disease analyzed with per standard deviation increase of cystatin C level.
**Supplementary Figure 2:** A funnel plot for large studies (CVD events ≥ 100) in cardiovascular disease outcome