Screening for kidney disease in vascular patients: SCreening for Occult REnal Disease (SCORED) experience

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Abstract

Background. SCreening for Occult REnal Disease (SCORED) is a novel screening guideline recently developed to identify individuals with a high likelihood of having prevalent chronic kidney disease (CKD). This simple scoring system, developed from general US representative samples and independently validated, was shown to outperform current clinical practice guidelines. Recently, CKD screening in individuals with cardiovascular disease (CVD) has been emphasized. We therefore evaluated the SCORED model in CVD patients in order to better understand the implications of CKD screening in this population.

Methods. Two clinical trials that enrolled patients with heart attack (N = 2481) or stroke (N = 3680) were combined to create our sample. The performance of the SCORED guideline was evaluated by standard diagnostic measures. Correlations among various risk scores and their predictive abilities for recurrent CVD were ascertained.

Results. For heart attack and stroke patients, respectively, the SCORED guideline yielded sensitivity of 94 and 97%, specificity of 27 and 11%, positive predictive value of 32 and 30%, negative predictive value of 93 and 89%, with AUC of 0.75 and 0.68. SCORED was strongly correlated with other risk scores and exhibited a similar performance in the prediction of recurrent CVD.

Conclusions. The higher risk of CKD in CVD patients with high SCORED values is demonstrated. This simple education and screening tool may help promote awareness of CKD in CVD patients, in addition to general populations, and assess the CKD risk and its relationship with recurrent CVD.

Keywords: CKD; CVD; ENRICHD; VISP

Introduction

Cardiovascular disease (CVD) and chronic kidney disease (CKD) are each major public health problems that share risk factors and present in similar populations [1,2]. Yet, awareness for potential CKD by healthcare professionals and lay persons remains low among at-risk populations, including those with CVD. Indeed, a joint science advisory
board from the American Heart Association (AHA) and the National Kidney Foundation (NKF) recently recommended screening for decreased kidney function among patients with known CVD [3]. Identifying individuals with CKD in this population may provide an opportunity to adopt measures that slow the progression of kidney disease and prevent subsequent CVD.

We recently developed a user-friendly tool to systematically identify individuals with a high likelihood of having CKD, SCreening for Occult REnal Disease (SCORED) [4]. This algorithm identified nine demographic and medical variables and provided a simple scoring system. SCORED has been validated in the general population, community samples and clinical settings; the screening tool also performed favourably compared to the NKF’s Kidney Early Evaluation Program (KEEP) guidelines [4–6].

We now seek to test SCORED in a population with known underlying CVD. Our goals are 2-fold: first, we intend to evaluate test characteristics of SCORED in diverse CVD patients. Second, we would like to assess correlation of SCORED with other algorithms suitable for CVD and to compare their abilities for secondary CVD prediction.

Methods

Study population

We used the data collected from two recent multi-centre, cardiovascular clinical trials, Enhancing Recovery in Coronary Heart Disease (ENRICHD) and Vitamin Intervention for Stroke Prevention (VISP), in our investigation.

ENRICHD is a randomized controlled trial (RCT), sponsored by the National Heart, Lung, and Blood Institute, that tested a hypothesis that a new psychosocial intervention, devised to decrease depression and to increase social support, further improves a composite endpoint of ‘death and nonfatal reinfarction’ after acute myocardial infarction (MI) [7]. Over 3000 participants were screened at 73 hospitals affiliated to eight academic sites in the United States, and 2481 were randomized into cognitive behaviour therapy or usual cardiology care. The trial was conducted from 1996 to 2001 with an average follow-up of 29 months.

VISP, sponsored by the National Institute of Neurological Disorders and Stroke, is an RCT undertaken to study the effectiveness of homocysteine-lowering therapy for recurrent vascular events in patients with non-disabling stroke [8]. VISP aimed to determine whether high doses of folic acid, vitamin B6 and vitamin B12, given to lower total homocysteine levels, further reduce the risk of recurrent stroke over a 2-year period compared with low doses of these vitamins. A total of 3680 adults with non-disabling cerebral infarction participated in this study at 56 hospitals or medical centres across the USA, Canada and Scotland in 1996–2003.

Measurements

The SCORED risk factors, along with additional demographic characteristics, personal health conditions and clinical information at randomization of participants from ENRICHD and VISP, were used to evaluate three screening rules: SCORED, ‘CVD risk factors only’ and KEEP (Table 2). Table 3 presents logistic regression analyses with the SCORED risk factors as predictors of CKD. Most of the risk factors were statistically significant, and the age effect was monotone.

Results

A total of 2145 participants from ENRICHD and 3640 participants from VISP were included for analyses after excluding participants with missing data in key variables. Participants from VISP were, on average, 5 years older than participants from ENRICHD. ENRICHD had more female and minority participants. Notably, the mean eGFR (75 mL/min/1.73 m²) and the prevalence of CKD (27–28%) were similar between the two studies (see Table 1).

Prediction of prevalent CKD

In ENRICHD, sensitivity, specificity, PPV and NPV of the SCORED guideline were estimated to be 94%, 27%, 32% and 93%, respectively. By this rule, 78% of ENRICHD participants were defined to be at high risk for CKD. The application to VISP provided sensitivity of 97%, specificity of 11%, PPV of 30% and NPV of 89%, while 91% of VISP participants were defined to be at high risk. The rule based on the absence versus the presence of CVD risk factors generally yielded reduced test characteristics, although SCORED yielded low specificity. As an additional comparison, we used NHANES data from generally healthy individuals to evaluate three screening rules: SCORED, ‘CVD risk factors only’ and KEEP (Table 2). Table 3 presents logistic regression analyses with the SCORED risk factors as predictors of CKD.
Endpoint-related information

bKEEP was not evaluated in ENRICHD and VISP because data on a majority of risk factors in KEEP were not collected. Raw data in a... high-density lipoprotein cholesterol and other lipids were not measured in secondary CVD prediction.

As expected, Jaffe scores demonstrated the best model fits (with dramatically lower AIC/BIC) as those were developed from ENRICHD. Notably, impaired renal function (i.e. creatinine ≥ 1.3) had the largest risk ratio in Jaffe models [14]. For recurrent stroke, SCORED and SPI II showed similar AUC and AIC/BIC. Overall, SCORED, which is a CKD screening/prediction model, appeared to perform well in secondary CVD prediction.

Discussion

In this paper, we evaluated the SCORED algorithm in RCT participants that represent a diverse, multi-ethnic CVD patient population. Compared to healthy individuals that we tested in previous publications, greater numbers of individuals were identified with elevated risk by SCORED. Specificity was decreased and PPV was increased, while high sensitivity and NPV and moderate to high AUC values were maintained.

In the general population, the SCORED model was designed to identify individuals with undiagnosed CKD who could be referred for further laboratory evaluation and follow-up tests. We expect that the vast majority of CVD...
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Table 3. SCORED model fitted to ENRICHD (N = 2145) and VISP (N = 3640) studies

<table>
<thead>
<tr>
<th>SCORED risk factor</th>
<th>ENRICHD (AUC = 0.75)</th>
<th>VISP (AUC = 0.68)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>P-value</td>
</tr>
<tr>
<td></td>
<td>(95% confidence interval)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>1.4 (0.98–2.1)</td>
<td>0.067</td>
</tr>
<tr>
<td>60–69</td>
<td>3.0 (2.1–4.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥70</td>
<td>5.5 (3.8–7.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>1.5 (1.2–1.9)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Anaemiaa</td>
<td>Not available</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.7 (1.3–2.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.4 (2.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>Not estimableb</td>
<td></td>
</tr>
<tr>
<td>History of heart failure</td>
<td>2.2 (1.7–3.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.2 (0.9–1.5)</td>
<td>0.32</td>
</tr>
<tr>
<td>(circulation problem in legs)c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria (protein detected in urine)</td>
<td>Not available</td>
<td></td>
</tr>
</tbody>
</table>

aAnaemia being treated. bNot estimable because all participants had this condition, i.e., score = 1. cHistory information (e.g. claudication). AUC = area under the receiver-operating-characteristic curve.

patients will have serum chemistry values performed by their primary care physicians and/or cardiologists/ neurologists. We therefore envision the SCORED screening tool serving purposes other than merely identifying CKD.

First, SCORED was designed as a simple checklist for patients to learn about their risk for kidney disease. While a cardiologist may be aware that his/her patient has underlying renal disease, that information may not be routinely communicated to a patient during a typical clinic visit or phone conversation; alternatively, the cardiologist may appropriately assume that the primary care physician has already discussed the concomitant renal disease with the patient. Continued late referral has been reported in not only primary care settings but also in high-risk patients [20–25]. The SCORED tool is patient-friendly and easy to use; many high-risk patients may not know what their creatinine is (or what this measurement means) yet will be able to complete and understand their SCORED testing. SCORED can empower CVD patients to introduce the subject of CKD with their care providers and motivate themselves to be screened (e.g. based on their self-assessment using Figure 1 in this paper).

Second, SCORED can re-emphasize the importance of early kidney disease to cardiologists, neurologists and primary care physicians who may not consider small elevations in creatinine to be significant markers of kidney disease. As eGFRs are appearing more routinely in laboratory reports, this phenomenon of under-appreciating creatinine values should dissipate [20], but SCORED would provide another way to highlight to care providers that, in certain populations, even early deteriorations in renal function require heightened surveillance and, often, concomitant care by a nephrologist. In general, these duties are managed best by nephrologists.

There are some limitations to our investigation. Firstly, the diagnosis of CKD was based on only one determination of eGFR. More than one measurement over time is recommended for accurate clinical diagnosis capturing the ‘chronicity’ definition [10,26]. This is, unfortunately, a common problem in many epidemiologic studies, RCTs, and even some clinical settings. Also, eGFR derived from the MDRD formula might not be optimal, although its utility is regarded as, realistically, the current best definition for CKD [3,27–30]. Secondly, some variables included in
Tients were classified at high risk for CKD by SCORED.

It would be reasonable to encourage the use of SCORED as a simple but useful screening and educational tool. For Framingham risk score, refer to [13]. Framingham score cannot be written as a simple numerical expression.

We used the original primary endpoints of ENRICHD and VISP. Not all risk scores presented in Table 4 were included in this analysis due to highly missing covariates for some risk scores. Note that smaller AIC and BIC indicate a better model fit. AUC were computed from logistic regression and AIC/BIC were computed from Cox regression. AIC = Akaike information criteria; AUC = area under the receiver-operating-characteristic curve; BIC = Bayesian information criteria.

**Conflict of interest statement.** None declared.

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