Atherosclerosis 232 (2014) 289–297

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Association of chronic kidney disease categories defined with different formulae with major adverse events in patients with peripheral vascular disease

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ARTICLE INFO

Article history:
Received 24 September 2013
Received in revised form
1 November 2013
Accepted 1 November 2013
Available online 2 December 2013

Keywords:
Peripheral vascular disease
Chronic kidney disease
Estimated glomerular filtration rate

ABSTRACT

Objective: The aim of this study was to compare the ability of eGFR calculated by modification of diet in renal disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Lund-Malmö formulae in predicting major adverse events in peripheral vascular disease (PVD) patients.
Methods: We prospectively recruited 2137 patients, measured serum creatinine to calculate eGFR using three different formulae and grouped patients into eGFR categories ≥90, 60–89, 45–59, 30–44, 15–29 and <15 ml/min/1.73 m^2. Patients were followed up for a median of 1.3 (inter-quartile range 0.3–3.6) years. The primary outcome was the combined incidence of myocardial infarction, stroke or death. The ability of eGFR categories defined with the different formulae to predict outcome was assessed using the net reclassification index.
Results: 1450 (67.9%), 1515 (70.9%) and 1813 (84.8%) patients had eGFR <90 ml/min/1.73 m^2 according to the CKD-EPI, MDRD and Lund-Malmö formulae, respectively. Using the CKD-EPI formula 276 (12.9%) patients were reclassified to a different eGFR category in comparison to the MDRD formula and the prediction of outcome was improved (net reclassification index 0.106, $p < 0.001$). Using the Lund-Malmö formula 563 (26.3%) patients were reclassified to a different eGFR category in comparison to the MDRD formula and the prediction of outcome was improved (net reclassification index 0.108, $p < 0.001$). Classification using the CKD-EPI and Lund-Malmö formulae was equally effective at predicting outcome (net reclassification index - 0.002, $p = 0.397$).
Conclusions: eGFR categories determined with the CKD-EPI and Lund-Malmö formulae are equally effective at predicting major adverse events in patients with PVD.

1. Introduction

The prevalence of chronic kidney disease (CKD) is estimated to be >10% and increasing [1]. The prevalence of CKD is particularly high in some patients groups, such as patients with cardiovascular disease [2]. Peripheral vascular diseases (PVD) are a group of conditions affecting the vessels outside the heart [3–6]. CKD is a risk factor for PVD development and CKD patients with PVD have an increased incidence of major cardiovascular events [7,8]. There is current controversy over how CKD is best defined with a large number of different ways to estimate kidney function by calculating estimated glomerular filtrate rate (eGFR) being available [9,10]. A number of previous studies have associated CKD with major adverse events in patients with PVD [11–20]. In these studies a number of different equations have been used to calculate eGFR, including the Chronic Kidney Disease-Epidemiology Collaboration group (CKD-EPI) and the modification of diet in renal disease (MDRD) formulae [11–20]. Recently eGFR calculated using the Lund-Malmö formula has been suggested as being more accurate in some patients groups [21]. There are a number of possible reasons to suspect that the most appropriate formula to assess eGFR in PVD patients might be different from healthy individuals. The prevalence of CKD is high amongst PVD patients and eGFR formulae vary in their ability to estimate severe renal function impairment

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http://dx.doi.org/10.1016/j.atherosclerosis.2013.11.034

[1,2,9,10]. Furthermore, the aetiology of CKD in PVD is more likely to be related to renovascular disease which may also influence the most appropriate formula to use [1,2,9,10]. Currently it is not clear which formula best predicts major adverse events in patients with PVD. The primary aim of this study was to assess which of three formulae used to calculate eGFR best predicted major adverse events in patients with PVD.

2. Methods

2.1. Study design

This study was designed as an on-going prospective cohort investigation of patients with PVD aimed at assessing risk predictors of PVD presence and outcome commencing in 2002, as previously described [22]. Since the comparative ability of different eGFR formulae to predict major adverse events in PVD patients had not been previously examined sample size calculations were not straight forward and no formal calculation was performed [11–20]. Monte-Carlo simulations suggest that a multivariate regression model is powered sufficiently when 10 outcome events per degree of freedom of the predictor variables are observed [23]. We estimated that the combined incidence of myocardial infarction, stroke or death at one year would be approximately 10% and planned to adjust for 11 variables (age, male sex, hypertension, diabetes, smoking, coronary heart disease (CHD), presenting complaint, statin prescription, aspirin prescription, angiotensin converting enzyme (ACE) inhibitor prescription and angiotensin receptor blocker (ARB) prescription) in our regression model. Based on these estimates we felt that a sample size of over 2000 patients would be well powered to examine the association of eGFR categories with major adverse events.

2.2. Patients

Patients were recruited from in and out-patient vascular services at The Townsville Hospital, The Mater Hospital Townsville and The Royal Brisbane and Women's Hospital. Patients with all types of PVD were considered for inclusion. All patients diagnosed as having any type of PVD by a Royal Australasian College of Surgeons accredited vascular specialist were considered for inclusion into the study. Inclusion criteria for the current study included a diagnosis of PVD, the assessment of serum creatinine to enable the calculation of eGFR and a least one follow-up assessment as an in or outpatient. Ethical approval for the study was granted by the local Institutional Ethics Committees at The Townsville Hospital, The Mater Hospital Townsville, The Royal Brisbane and Women's Hospital and James Cook University. Written informed consent was obtained from participants.

2.3. Definition of presenting complaint

Presenting category was broadly defined into one of seven groups namely venous disease; miscellaneous PVDs (including aortic dissection, reno-vascular hypertension, mesenteric ischaemia and peripheral vascular trauma); asymptomatic carotid stenosis; mild lower limb or upper limb peripheral athero-thrombosis; aneurysm of the aorta or peripheral arteries; symptomatic carotid artery stenosis; and critical lower limb ischaemia, as previously described in detail [22,24–28].

2.4. Definitions and diagnosis of PVD

PVD was defined using the following criteria: a) Venous disease: This was defined according to the CEAP classification [29]. This included telangiectasia or reticular veins (C1); varicose veins of ≥3 mm (C2); oedema (C3); skin changes due to chronic venous disease (C4); healed venous ulcer (C5); and active venous ulcer (C6). All patients underwent venous duplex imaging; b) Miscellaneous PVD problems including aortic dissection, reno-vascular hypertension, mesenteric ischaemia and peripheral vascular trauma were diagnosed based on history, examination and imaging using duplex imaging or computed tomographic angiography; c) Asymptomatic carotid artery stenosis: Defined as the presence of ≥50% stenosis or occlusion of at least one carotid artery identified by carotid duplex but the absence of physician confirmed symptoms of focal transient ischaemic attack, amaurosis fugax or stroke as previously described [24]; d) Mild lower limb or upper limb peripheral athero-thrombosis: This included patients with intermittent claudication, atypical or no symptoms with clinical evidence of lower or upper limb ischaemia but not critical lower limb ischaemia. Limb peripheral athero-thrombosis was confirmed by a vascular specialist by identification of absence of lower or upper limb pulses, ankle brachial pressure index <0.9 and/or significant stenosis (>50%) or occlusion of lower or upper limb arteries on computed tomographic angiography or duplex imaging [25,26]. e) Aneurysm of the aorta or peripheral arteries: Aortic aneurysm was defined as maximum aortic diameter ≥30 mm [25–27]. Iliac artery aneurysm was defined by common or internal iliac artery diameters ≥15 and ≥8 mm, respectively. Femoral artery aneurysm was defined by common femoral or superficial femoral artery diameter of ≥15 mm. Popliteal artery aneurysm was defined as popliteal artery diameter ≥9 mm as previously described [28]; f) Symptomatic carotid artery stenosis: Defined as the presence of ≥50% stenosis or occlusion of at least one carotid artery identified with carotid duplex with the presence of physician confirmed symptoms of focal transient ischaemic attack, amaurosis fugax or stroke as previously described [24]; g) Critical lower limb ischaemia: Rest pain, arterial ulcer or gangrene of the leg due to athero-thrombosis of the lower limb. Peripheral athero-thrombosis was confirmed as detailed above [25,26]. For patients with more than one presenting complaint classification was determined by the complaint which was deemed most severe.

2.5. Definition of other risk factors

Hypertension was defined by a history of high blood pressure or receiving treatment to reduce blood pressure [22,24–28]. Diabetes was defined by a fasting blood glucose concentration ≥7.0 mM, or history of, or treatment for hyperglycaemia [22,24–28]. Smoking status was classified as ever and never smokers [22,24–28]. CHD was defined by a history of myocardial infarction, angina or treatment for coronary artery disease [22,24–28].

2.6. Medications

At the time of recruitment a list of each patient's medications was recorded including whether the participants were prescribed statins, aspirin, ACE inhibitors or ARBs.

2.7. Measurement of serum creatinine and calculation of eGFR

Serum creatinine was measured in a pathology laboratory using a spectrophotometry method in line with established guidelines as previously described [30,31]. eGFR was calculated using the CKD-EPI, MDRD (isotope dilution mass spectrometry aligned) and Lund-Malmö formulae [9,21,32]. All these formulae have been previously described in detail and utilise creatinine, age and gender in their calculations [9,21,32]. The following