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Role of renal function in cardiovascular risk assessment: A retrospective cohort study in a population with low incidence of coronary heart disease

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ABSTRACT

Background. Early-stage chronic kidney disease (CKD), a marker of cardiovascular risk, is susceptible to therapeutic intervention but need further study in populations with low incidence of coronary heart disease (CHD). Incorporating glomerular filtration rate (GFR) could improve cardiovascular risk prediction in these patients.

Objective. To determine if decreased GFR is associated with increased risk of cardiovascular morbidity and all-cause mortality and to analyse GFR effect on cardiovascular risk prediction in a population with low CHD incidence.

Methods. Retrospective, observational, population-based study of 1,081,865 adults (35–74 years old). Main exposure variable: GFR. Outcomes: CHD, cerebrovascular disease, cardiovascular diseases, all-cause mortality. Association between GFR categories of CKD (G1–G5) and outcomes was tested with Cox survival models. G1 was defined as the reference category. Predictive value of GFR was evaluated by integrated discrimination improvement (IDI) and net reclassification improvement (NRI) indices.

Results. Beginning at stage-3a CKD, increased risk was observed for coronary (HR 1.27 (95%CI 1.14–1.43)), cerebrovascular (HR 1.19 (95%CI 1.06–1.34)), cardiovascular (HR 1.23 (95%CI 1.13–1.34)) and all-cause mortality risk (HR 1.17 (95%CI 1.07–1.27)). GFR did not increase discrimination and reclassification indices significantly for any outcome.

Conclusion. In general population with low CHD incidence and stage-3 CKD, impaired GFR was associated with increased risk of all cardiovascular diseases studied and all-cause mortality, but adding GFR values did not improve cardiovascular risk calculation. Despite a four-fold higher rate of CHD incidence at GFR G3a compared to G1, this represents moderate cardiovascular risk in our context.

1. Introduction

Cardiovascular diseases are the leading cause of mortality and morbidity worldwide. They account for 30% of global mortality and are expected to remain the leading cause of death in coming years (World Health Organization, 2011) (Mathers & Loncar, 2006). Although southern Europe has one of the lowest cardiovascular mortality and morbidity rates in the European Union (Nichols et al., 2012), these diseases constitute one of the main morbidity impacts, being the second leading cause of expected years of life lost and the first cause of hospitalization (INE, 2014) (Gènova-Maleras et al., 2011). Therefore, prevention of cardiovascular diseases remains a priority of health policies and biomedical research in this population.

Currently, one of the main disease prevention strategies is to intervene in the high-risk healthy population. Treating cardiovascular risk factors decreases the risk of cardiovascular diseases (Graham et al., 2007). Although risk functions are used to identify those individuals at higher risk, the functions are not sufficiently accurate (Marrugat et al.,

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2007). Therefore, it is necessary to improve the predictive ability of risk functions by considering new risk factors.

Recently, several studies have shown that impaired renal function, even at very early stages, is independently associated with the occurrence of cardiovascular events (Go et al., 2004) (Brugts et al., 2005) (Meisinger et al., 2006) (Van Biesen et al., 2007) (Di Angelantonio et al., 2007) (Astor et al., 2008) (Cirillo et al., 2008) (Matsushita et al., 2010b). Thus, current clinical practice guidelines recommend maximizing cardiovascular prevention in patients with chronic kidney disease (CKD) at all stages (Group KDIGO (KDIGO) CW, 2013) (Bover-Sanjuán et al., 2014) (Rabar et al., 2014 Jan). Moreover, recent research has suggested that markers of CKD would help to improve the prediction of cardiovascular events in addition to traditional cardiovascular risk factors in populations with high cardiovascular risk (Di Angelantonio et al., 2010) (Shara et al., 2011) (Smink et al., 2012). Nonetheless, studies on the role of impaired renal function as a cardiovascular risk are mainly carried out in populations with high incidence of CHD. In this study, we aimed to examine the potential capacity of CKD, as defined by glomerular filtration rate (GFR), to improve the prediction of cardiovascular events and all-cause mortality in a general population with low incidence of CHD (Marrugat et al., 2011).

2. Materials and methods

2.1. Study design

2.1.1. Retrospective cohort study

2.1.1.1. Data source. Data were obtained from the Information System for the Development of Research in Primary Care (SIDIAP). This clinical database contains the anonymized, longitudinal medical records of nearly five million patients, comprising around 80% of the Catalan and 10.2% of the Spanish populations (Bolíbar et al., 2012). The records contain demographic information, clinical diagnoses (International Classification of Diseases 10th revision [ICD-10]), referral and hospital discharge information (International Classification of Diseases 9th revision [ICD-9]), laboratory tests and treatments (drug prescriptions and drugs invoiced at the community pharmacy). General practitioners follow regulated protocols on data recording, and are assessed for its completeness and continuity: the records qualified as "up to standard" for biomedical research are called SIDIAP^{Q} (García-Gil et al., 2011) and were used in the present study. The quality of SIDIAP data has been previously documented, and the database has been widely used to study the epidemiology of a number of health outcomes (Ramos et al., 2012) (Prieto-Alhambra et al., 2014) (Vinagre et al., 2012) (Simó et al., 2013) (Violán et al., 2013). This study received its approval from the research ethics committee of IDIAP Jordi Gol.

2.2. Participants

In total, 1,081,865 people aged 35 to 74 years without previous history of cardiovascular disease, defined as myocardial infarction (MI), angina pectoris, stroke, transient ischemic attack (TIA), or peripheral arterial disease (PAD), and who were registered with a primary health care centre providing data to SIDIAP^{Q} between January 2008 and December 2013, were eligible for inclusion in this study.

2.2.1. Follow-up and outcomes

The six-year study period was January 2008 to December 2013. The follow-up period was defined from January 2009 to 2013. For individuals with a creatinine measurement, we used the first record as an index date; without creatinine data, January 2009 was the index date. Baseline period was defined as 1-year before the index date.

Patients were censored at the earliest date of the diagnosis of interest, at transfer out of the primary health care centre or at the study end date (31 December, 2013). Time to first event was considered for all analyses.

Vascular diseases were identified in follow-up from relevant SIDIAP^{Q} codes in the patients' clinical files, both primary care and hospital discharge records. The cardiovascular codes have been previously validated in SIDIAP (Ramos et al., 2012).

The primary outcomes were *coronary heart disease*, a composite of myocardial infarction (MI) and angina; *cerebrovascular disease*, consisting of stroke and transient ischemic attack (TIA); *cardiovascular diseases*, a composite of MI, angina, stroke and TIA; and finally, *all-cause mortality*.

The presence of vascular disease was defined according to the following criteria:

- Coronary heart disease: MI (ICD-10 codes: I21-I23 and subcategories; ICD-9 code: 410) and angina (ICD-10 codes: I20 and subcategories; ICD-9: 411.1, 413); and
- Cerebrovascular disease: stroke (ICD-10 codes: I61-I64 and subcategories; ICD-9: 433, except for non-occlusive disease, so 433.00, 433.10, 433.20, 433.30, 433.80, 433.82, 433.90, 434.00, 434.10, 434.11, 434.90) and TIA (ICD-10 codes: G45-G46; ICD-9 code: 435).

2.2.2. Main exposure

- Standardized creatinine was used for CKD-Epidemiology Collaboration (CKD-EPI) calculations, according to "Kidney disease: Improving global outcomes" (KDIGO) guidelines (Group KDIGO (KDIGO) CW, 2013) (mg/dl).
  - o Glomerular filtration rate (GFR) was calculated by CKD-EPI equation (Levey et al., 2009).
  - o GFR categories in CKD were defined by the KDIGO guideline (Group KDIGO (KDIGO) CW, 2013):
    - G1 ≥ 90 ml/min/1.73 m^2
    - G2 60–89 ml/min/1.73 m^2
    - G3a 45–59 ml/min/1.73 m^2
    - G3b 30–44 ml/min/1.73 m^2
    - G4 15–29 ml/min/1.73 m^2
    - G5 < 15 ml/min/1.73 m^2.

2.2.3. Covariates

A set of variables were defined a priori and obtained from SIDIAP^{Q} at baseline:

- Age
- Sex
- Hypertension (yes/no) or record of antihypertensive drug invoicing
- Dyslipidaemia (yes/no)
- Smoking (yes/no)
- Obesity (yes/no) defined as BMI > 30 kg/m^2
- Diabetes (yes/no) or record of antidiabetic drug invoicing
- Systolic blood pressure (SBP) (mm Hg)
- Diastolic blood pressure (DBP) (mm Hg)
- Laboratory tests: fasting glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides
- Body mass index (BMI) (kg/m^2)
- Drug use: antihypertensive agents, antidiabetic agents, or statins and other lipid-lowering drugs
- Ten-year CHD risk, estimated using the Framingham function adapted and validated in the Spanish population by the REGICOR study (Marrugat et al., 2007).

2.3. Statistical analysis

Categorical variables are presented as percentages and continuous variables as mean (standard deviation) and 95% confidence intervals (95%CI) were calculated when required.