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Chronic kidney disease as a predictor of clinical risk in the elderly

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1 Introduction

Facing the needs of an increasingly ageing population is rapidly becoming a major public health issue in western countries.[1,2] Chronic kidney disease (CKD), whose current prevalence is estimated around 10%–15% in the general population, with considerably higher figures in at-risk groups, is widely known to increase with age.[3] In the elderly, renal impairment is often concomitant or secondary to several other systemic disorders such as hypertension, atherosclerosis, diabetes and cardiovascular (CV) diseases. As accurate clinical risk assessment is a prerequisite for devising effective preventive and therapeutic strategies, identifying and enhancing the presence of renal abnormalities is an important step to effectively deal with the frail patient with comorbidities.

Glomerular filtration rate (GFR) and albuminuria, the two main components of CKD, have been shown to be independent and strong predictors of CV morbidity and mortality and all-cause mortality in the general population as well as in the elderly.[3]

We will briefly review data from the literature supporting the role of renal parameters as practical, low cost and efficient tools for a comprehensive risk assessment in the elderly and will argue in favor of a wider use of these tests in different clinical settings from general practice to specialized hospital centres.

2 The kidney as a sensor of cardiovascular risk

Several studies demonstrated that CKD is a risk factor for CV and all-cause mortality across a variety of different conditions.[3] Furthermore, low GFR and albuminuria have been shown to be predictors of cardio-renal morbidity and mortality independently of each other and other CV risk factors.[4]

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The CKD prognosis consortium has recently published a series of seminal papers on this topic. In an elegant meta-analysis, Hallan, *et al*.[5] reported that a slight reduction in GFR and the presence of albuminuria are both related to an increased risk of end stage renal disease as well as of mortality with a similar trend independently of age. The relationship of renal abnormalities with relative and absolute risk differs across different age classes. In fact, younger subjects showed higher relative risk as compared to older patients who, as expected, had higher absolute and attributable risk. In the elderly, a diminished relative mortality risk was found to be associated with GFR reduction and other traditional CV risks factors, such as hypertension, hypercholesterolemia and obesity, possibly because of the high competitive risk from several comorbidities. However, the absolute risk of both mortality and end stage renal disease (ESRD) remained significantly related directly to the degree of albuminuria and inversely to GFR values across several age classes (Figure 1A).

In view of the well known progressive reduction of GFR values with age,[6] it has been argued that mild reduction in renal function may be a relatively unspecific clinical indicator of renal damage. Nonetheless, the study by Hallan, *et al*.[5] clearly indicates that, although the incidence of events is related to the severity of renal impairment, a significant rise of mortality risk begins at GFR values around 60 mL/min per 1.73 m^2, and this holds true even at age 75 years or older, supporting the current definition of CKD. This is particularly true when renal dysfunction is looked at as a proxy for future CV and general mortality. Accordingly, in a recently published clinical study, in a large cohort of elderly in-patients recruited from a network of internal medicine and geriatric hospital units across Italy, the degree of GFR reduction was found to be related to in-hospital mortality, while GFR values at hospital discharge were shown to be strong predictors of short-term mortality.[7]

Another recent meta-analysis showed that declines in GFR smaller than a doubling of serum creatinine concentra-

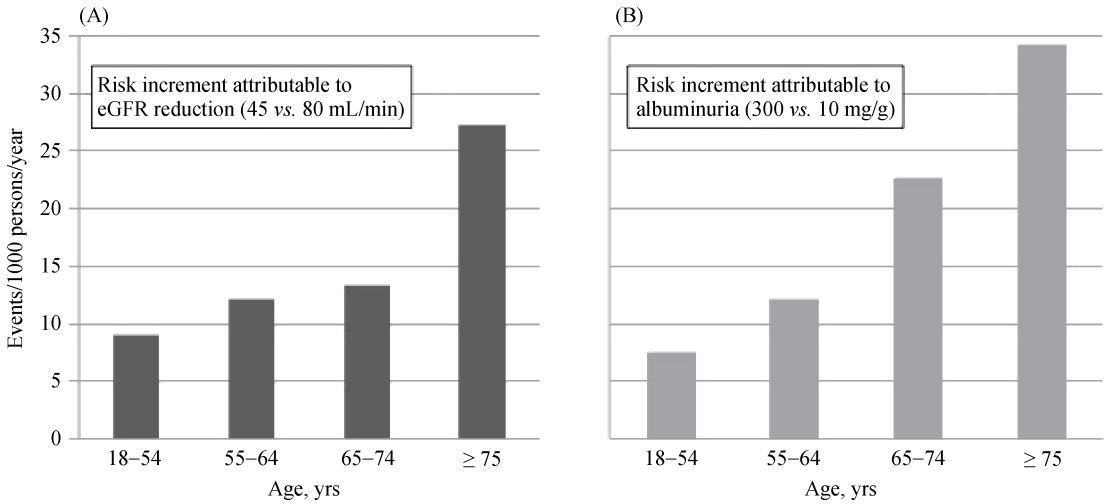

Figure 1. Impact of renal abnormalities on total mortality across different age groups. Increment in mortality rate in patients (A) with reduced GFR (i.e., 45 mL/min) as compared to normal GFR (i.e., 80 mL/min) and (B) with higher albuminuria (i.e., ACR 300 mg/g) as compared to normal albuminuria (i.e., ACR 10 mg/g). ACR: albumin to creatinine ratio; GFR: glomerular filtration rate. Modified from ref. [5].

tion in a relatively short time are not uncommon in the elderly and were strongly and consistently associated with the risk of ESRD and mortality,[8] suggesting that even a 30% reduction in GFR over a two year period may be taken as an alternative end point for CKD progression.

Abnormal urinary albumin excretion is, beside reduction in GFR, another asymptomatic condition which may, or may not accompany renal impairment. Increased albuminuria is generally been associated with more severe hypertension, dyslipidaemia, metabolic syndrome and it is considered a marker of organ damage.[9] Furthermore, albuminuria has been shown to cluster with systemic atherosclerosis and CV organ damage and to predict CV risk, independently of GFR. The predictive power of increased albuminuria also holds across several age classes (Figure 1B) and clinical conditions and has been demonstrated to exceed that of mild GFR reductions. The relationship between albuminuria and mortality risk is rather linear and shows no threshold. Thus, even a slight increase in albuminuria, well within normal limits, may already carry significant unfavourable prognostic value. Furthermore, a very recent meta-analysis has suggested that changes in urine albumin excretion under antihypertensive treatment may parallel similar variations in CV risk and thus provide additional useful information for the management of patients.[10] Measuring on treatment albuminuria to monitor clinical management of high-risk patients is also recommended by international ESH Guidelines in patients with hypertension.[11]

The interrelation between CKD and CV risk is confirmed in different cohorts of older people, such as those with diabetes, and in different clinical settings both out- and in-patient. In the I-DEMAND study, in a large cohort of hypertensive patients attending outpatient clinics of internal medicine, diabetology, nephrology and cardiology, CKD was found to be more prevalent in older patient with a greater burden of CV risk factors, such as impaired fasting glucose and diabetes, uncontrolled blood pressure, hyperuricemia, hypertriglyceridemia and a positive history of CV disease.[12] A greater mortality risk has also been shown to be related to the presence of CKD in hospitalized patients above 65 years both in-hospital and 3 months post-discharge.[7] Furthermore, it has been reported that GFR < 30 mL/min per 1.73 m^2 is related to greater cognitive and functional impairment, higher rate of comorbidities, such as hypertension, diabetes, anaemia, congestive heart failure, ischemic heart disease, stroke and atrial fibrillation, and with inside and outside hospital mortality.[13]

The pathophysiologic rationale for these findings may well reside in the multiple traditional and non traditional metabolic and haemodynamic abnormalities, such as fluid overload, anaemia, mineral bone disease and subclinical inflammation which, albeit often asymptomatic and therefore easily overlooked, follow the development of even mild renal abnormalities.[14]

A wider use of renal function parameters together with non invasive assessment of early vascular organ damage,[15] should improve cardiovascular risk stratification in the elderly and other high risk subgroups.

3 Conclusions

Current demographic trends indicate a progressive increase in population ageing and consequently a growing prevalence of multi-morbid older people especially in western

countries. A global individualized and easy to carry out clinical assessment is a key feature to inform effective therapeutic strategies for this subgroup of frail, high risk patients in a variety of different clinical settings, from general practice to specialist care. Renal function parameters are practical, low-cost tools to evaluate CV and all-cause mortality risk. GFR and albuminuria, the two main components of CKD, are strong and independent predictors of CV morbidity and general mortality in elderly. Looking for renal abnormalities should be part of routine diagnostic evaluation and may lead to improve preventive and therapeutic strategies in these patients.

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