The Incidence and Prevalence of CVD in CKD (NKF-DOQI CKD Stages 1–4)

Incidence

Only one prospective study has determined the incidence of CVD in a non-ESRD cohort without CVD at baseline. Jungers et al. [3] followed 147 patients for 10 years and found an incidence of CVD events (myocardial infarction, ischemic stroke) of 41% in men and 19% in women. The incidence of myocardial infarction was three times higher in men with CKD than in the general male population in all age groups. The same was true for women until age 65 years, after which the difference became less marked. The mean GFR was 31 ml/min at the time of the events. In a prospective cohort of non-ESRD patients that included CHF as part of its CVD outcomes, Levin et al. [4] found, in a patient subset, that 7.4% with no previous CVD developed new cardiac disease. This is consistent with a recent population study of approximately 16,000 patients (ARIC study) where the incidence of de novo cardiovascular events was 4.8% (8.3 events/1,000 person-years) if the patient was in stage 2 CKD and 9.3% (16.8/1,000 person years) if in stage 3–4 CKD [5].

In a study of 6,223 people in the Framingham study, 18% of men and 20% of women with renal impairment already had CVD [6]. The incidence rate of cardiovascular events (CAD, CHF, ischemic stroke) was 21.3/1,000 patient-years for men and 25.6/1,000 patient-years for women with stage 3 CKD. This contrasts with 18.5 and 11.0 per 1,000 patient-years in men and women, respectively, with a lower serum creatinine (SCr).

In a Canadian cohort of pre-ESRD patients with known baseline CVD, who were followed for a median of 23 months, 35% developed a new event, worsening CVD, or were hospitalized for cardiac disease [4]. In the ARIC study, the incidence of recurrent events over a mean duration of 6.2 years was 20.4% (38.1 events/1,000 person years; stage 2 CKD) and 28.4% (60.8/1,000 person years; stage 3–4 CKD) [5].

Prevalence

The Framingham Heart Study found the prevalence of CVD in people with renal impairment (SCr 136–265 μmol/l in men and 120–265 μmol/l in women) to be 64% higher compared with individuals with lower SCr values [6]. A recent population-based study of 1.12 million people found a prevalence in patients with GFR <60 ml/min (CKD stage 3 or less) of 14.9% with CAD, 6.8% CBVD, 5.0% PVD and 7.1% with CHF [2]. In a Canadian multicenter prospective cohort of 313 pre-ESRD patients, the prevalence of all CVD was 38% [4]. The prevalence of LVH has been found to increase with a decline in renal function. Indeed, large population-based studies consistently find a high prevalence of CVD [7]. Conversely, in a study of 14,527 people with known CAD (diagnosed myocardial infarction) 33.6% had stage 3 or greater CKD [8].

Incidence and Prevalence of CVD in ESRD

Incidence

The incidence of CVD in the ESRD population is strikingly high. Over a 2.2-year follow-up, a USA prospective study (Wave2 substudy of the DMMS) of 4,204 patients initiating dialysis during 1996 and 1997 found the incidence of acute coronary syndromes, CHF, stroke, and PVD to be 10.2, 13.6, 2.2, and 14%, respectively [9]. Even amongst renal transplant recipients, the incidence of CVD is 3–4 times that observed in age-matched controls [10].

Prevalence

The prevalence of CHF, CAD and stroke is 1.8-, 3.2-, and 4.6-fold greater than its incidence in people with ESRD [9]. Of patients initiating dialysis, only 15% had normal left-ventricular (LV) structure and function by echocardiography [11]. Foley et al. [11] have documented a prevalence of LVH of 74% in this population – almost 2-fold greater than the 38% prevalence found in a study of pre-ESRD patients [7]. From large databases of patients with ESRD, the prevalence of CAD, CHF, CBVD, and PVD are 36, 39, 13, and 22%, respectively [12]. The large discrepancy between the incidence of CVD and its prevalence in this population suggests that we can intervene to delay or prevent CVD. The challenge is to identify the truly significant risk factors that play a role in the development of CVD, in order to determine and apply appropriate interventions.

Risk Factors for CVD in CKD

Established 'traditional' atherosclerotic risk factors, such as diabetes, hypertension, dyslipidemia, and older age, have been found to be independent predictors of CVD in CKD. In addition, hemodynamic and metabolic factors such as volume overload, anemia, calcium and phosphorus imbalance, chronic inflammation, and a hypercoagulable milieu are unique features of renal insufficiency that may contribute to the risk and pathogenesis of CVD. In renal transplant patients, factors such as source of donation, graft failure, and type of immunosuppressive therapy may play a role.

Several of the traditional risk factors in the general population demonstrate a phenomenon known as 'reverse epidemiology' in the CKD population. For example, obesity and hypertension are established CVD risk factors in the general population, whereas lower body mass index [13] and hypotension [14] have been shown to be risk factors for cardiovascular mortality in ESRD. To date, there has only been one prospective observational study of dialysis patients that controlled for baseline cardiac function [15]. Foley et al. [15]. found that a 10 mm Hg mean blood pressure increase was associated with a 44% higher risk of developing CHF and that patients with chronic CHF or LVH are at higher risk of mortality compared with patients without these cardiac abnormalities.

Outcomes

In 1997, the death rate from CVD (excluding CBVD) was approximately 22 times that from renal disease in the general population [16]. A proportion of 40% of individuals with CKD will have a CVD-related death.

Mortality: Stages 1–4

The proportion of patients that will die due to cardiovascular disease is at least three times greater than that of patients who will die of renal disease. For example, in a randomized, multicenter prevention trial of 347,978 high-risk men with no CVD at baseline (SCr <177 μmol/l) the crude rate of death from CAD was 23 times greater in blacks and 88 times greater in Caucasians than the death rate from renal disease [17]. Individuals with established CVD have 3 times the CVD events and all-cause mortality compared with those without baseline CVD [18].

Mortality: Stage 5

The risk of cardiac events in patients who are dependent on dialysis or a kidney transplant is estimated to be between 3.5 and 50 times higher than in the general population. The annual mortality on dialysis is 20–23%, with cardiovascular causes accounting for 45% of these deaths. Furthermore, the prognosis after acute myocardial infarction is poor. A recent, large population based study demonstrated 1- and 5-year mortality rates to be 59 and 90%, respectively [19]: that is 16–19 times higher compared with the general population. Likewise, transplant patients who develop de novo CAD or CHF have a 1.5–2.0 higher risk of death than nonrenal patients [20]. Mortality after stroke is also increased [21]. For patients who undergo cardiac revascularization, the in-hospital, 30-day and 1 year mortality was worse with greater degrees of renal impairment in a 26,500-patient cohort with a wide range of CKD [22].

Renal Impairment as a Risk Factor for CVD

Is CKD an independent risk factor for CVD or is it simply a marker of underlying atherogenic pathology and CVD? Several large prospective studies have suggested that even mild degrees of renal impairment may be associated with cardiovascular disease and mortality (fig. 1, 2) [8, 23–34]. For example, within a large population-based study (Hoorn) a decrease in glomerular filtration rate of 5 ml/min/1.73 m^2 was associated with a 22% increased risk of cardiovascular death after adjustment for traditional CV risk factors and previous CVD [31]. In a population-based study of 26,500 patients with known CAD awaiting CABG, patients with renal insufficiency (stage 3 or greater) had a greater prevalence of left main disease (23.5%) compared with patients with creatinine clearance >60 ml/min (17.5%) [22]. However, with the high underlying prevalence of CVD and with the knowledge that the severity of general atherosclerosis is highly correlated with the severity of glomerulosclerosis, renal impairment could simply be a surrogate marker for the presence and severity of risk factors and/or underlying arterio- or atherosclerosis.

The data examining whether or not renal impairment is an *independent* risk factor are conflicting. Even when adjustments are made for the severity of the coronary anatomy, the risk of future adverse events remain elevated in patients with renal insufficiency, suggesting that it may be an independent risk factor. A large population-based study (>1.1 million) demonstrated a graded independent increase in hazard of death from any cause, any cardiovascular event (hospitalization for CAD, CHF, CBVD, or PVD) or any hospitalization with progressively declining renal function [35]. This analysis adjusted for multiple covariates, including most traditional cardiovascular risk factors. A prior pooled analysis of four large community-based studies demonstrated that CKD is a risk factor for the composite outcome of all-cause mortality and cardiovascular disease in patients with stage 3 or 4 CKD compared with individuals with a GFR ≥ 60 ml/min [36]. However, renal function was not a risk factor

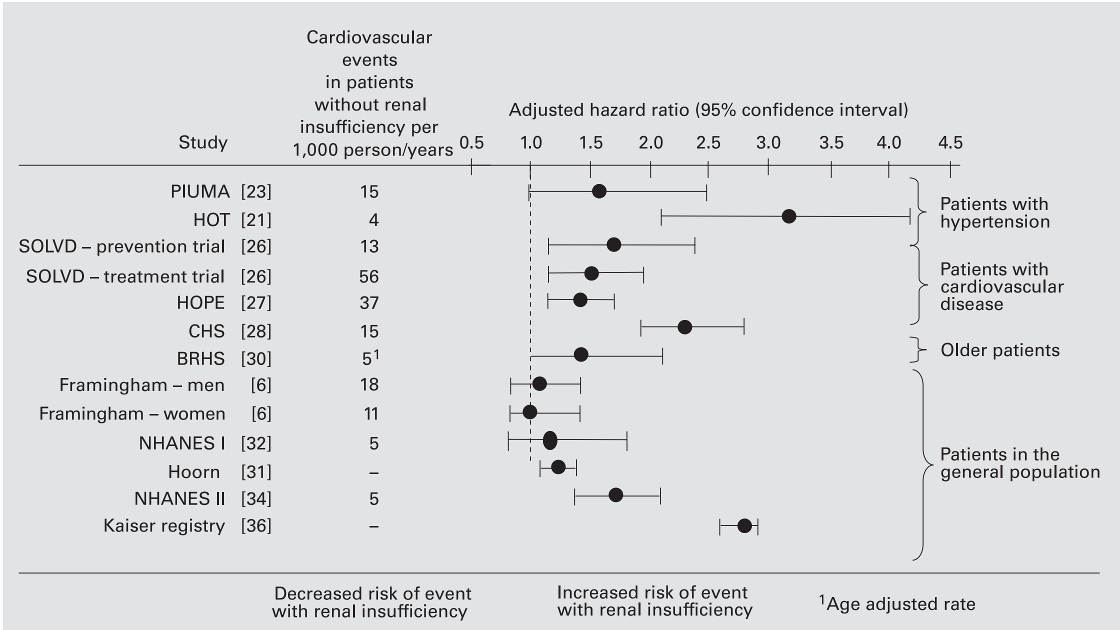

Fig. 1. Graphical presentation of the independent risk of renal insufficiency on cardiovascular events, adjusted for traditional cardiovascular risk factors. Comparing cardiovascular event rates was problematic as different cardiovascular outcomes were reported in studies. Cardiovascular events represent heart failure, myocardial infarction, stroke, associated mortalities or some composite of cardiovascular disease.

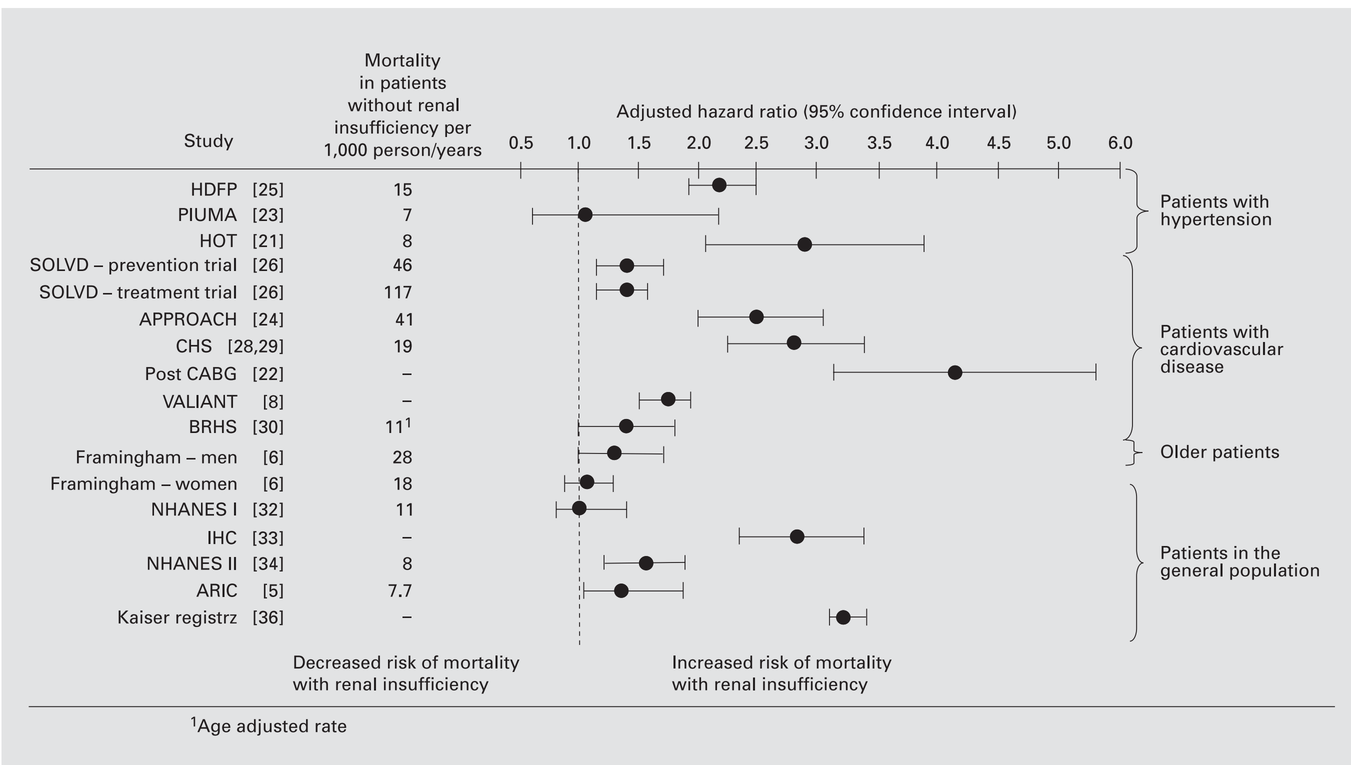

Fig. 2. The independent risk of renal insufficiency on total mortality, adjusted for traditional cardiovascular risk factors.

for CAD or CBVD in their fully adjusted model. In other large population-based studies, including the Framingham and NHANES I studies, any univariate associations with mild or moderate renal insufficiency and cardiovascular or all-cause mortality lost significance when adjustments were made for traditional CVD risk factors [4, 21]. Some of the traditional CVD risk factors are also risk factors associated with a faster GFR decline. Therefore it is difficult to determine whether declining GFR is a risk factor for CVD due to its confounding effect. It is highly likely that there are significant undeclared risk factors that play a role in both CKD and CVD that are not fully accounted for by statistical analysis.

The question of whether CKD is independently associated with an increased risk for CVD, whether CVD causes CKD, or whether some known or unknown factor(s) causes both, will continue to be hotly debated. However, to an extent, CKD is nonreversible. The key focus should be the early detection and prevention of progression of CKD at stages 1 and 2 using established and emerging therapies. Cardiovascular risk factor identification and management may depend on CKD staging. Special focus on non-traditional risk factors in CKD stages 3–5 may be appropriate in addition to traditional risk factor modification initiated in CKD stages 1 and 2. Lastly, there is a need to disseminate information to primary care providers who may be key players in initiating and maintaining the most appropriate management strategies. For those with established CVD and CKD that require intervention, the increased risks must be considered and addressed.

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