Chronic kidney disease as independent risk factor for cardiovascular disease

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Chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m², is a broad public health problem. The mean global prevalence of CKD is estimated to be 13.4% [1]. This percentage encompasses the estimated prevalence of diabetes, which is close to 8.2% [1]. Diabetes was considered a coronary artery disease risk equivalent, but subsequent data have not supported this contention. Conversely, CKD is associated with higher all-cause mortality rates compared to previous myocardial infarction [2]. Thus, patients with a coronary heart disease equivalent should have a risk for a coronary event comparable to those with a history of myocardial infarction. Most of the coronary risk in patients with CKD is driven by longstanding exposure to traditional cardiovascular risk factors [3].

Nonetheless, CKD is associated with increased all cause mortality, and remains a well-established, independent risk factor for cardiovascular death, and this is supported by extensive clinical data [2] [4]. Older studies that failed to demonstrate an association between CKD and cardiovascular events were limited by non-uniform definitions of kidney disease, and the inclusion of small number of patients with actual CKD, limiting the statistical power to identify factual associations.

Chronic kidney disease is a highly inflammatory state. Left ventricular hypertrophy, arterial calcifications, and endothelial dysfunction are only part of the main underlying factors that contribute to CKD-mediated cardiovascular disease. Go et al. showed that the risk of death from any cause increased steeply as eGFR diminished, increasing from 17% when eGFR is between 45 - 59, to 343% when eGFR is below 15 [5]. These analyses were adjusted for established risk factors, and derived from a large cohort of 1,120,295 patients. Patients were followed for a median of 2.84 years [5]. Age-standardized rates of death and cardiovascular events also increased considerably when eGFR declined. The adjusted hazard ratio for cardiovascular events was inversely proportional to eGFR: HR=1.4 with eGFR of 45 – 59, HR=2 with eGFR of 30 – 44, HR=2.8 with eGFR of 15 – 29, and HR=3.4 with eGFR below 15. The risk of death was greatest when eGFR fell below 45, and eGFR of 15 – 29 and below 15 were associated with remarkable age-adjusted mortality rates (11.4 and 14.1 per 100 person-years) [5]. A graded inverse association between eGFR and all-cause mortality and cardiovascular mortality in patients with or without hypertension was shown in a meta-analysis of 13 chronic kidney disease cohorts that included more than 38,000 patients [6]. This graded relationship was also demonstrated in a systematic review and meta-analysis of 100 studies, and was independent of age, sex, and other traditional risk factors [1].

With the advent of statins and newer antiplatelet agents as well as extensive investment in research over the last twenty years in management of coronary artery disease, there has been a tremendous decline in incidence rates of acute coronary events among those with diabetes. Gregg et al. showed that there were 95.6 fewer cases of acute myocardial infarction...
per 100,000 persons per year in 2010 compared to 1990 [7]. The decline in the incidence rate of end stage renal disease (ESRD) was much less pronounced (7.9 fewer cases per 10,000). The annual number of cases of ESRD increased by 32,434 cases from 1990 to 2010, whereas the number of acute myocardial infarctions decreased by 4,379 cases. Conversely, the incidence rate of ESRD increased by 65% between 1990 and 2010 in adults without diabetes. This reflects the success that blood pressure control utilizing angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) has had on progression of diabetic kidney disease [7].

The prevalence of CKD increases steadily with age. Note that the average annual loss of GFR among those with no kidney disease or diabetes is about 0.8 ml/min/year; thus, a normal eGFR in an 80-year-old would range between 55 – 65 ml/min/1.73 m2. It has been estimated that 27.9% of CKD patients are older than 70 years of age. The rising prevalence of CKD seem to be mainly due to the aging of the population, as well as to the increased rates of hypertension and diabetes [1].

The dialysis population has grown notably older over the past decade. Forty-eight percent of 5,898 patients started on renal replacement therapy between 2007 and 2011 were 65 years of age or older in a large Southern California health system, per 2015 United States Renal Data System (USRDS) data. The mean age for dialysis initiation was 69 years in 2013 and among US veterans. Incidence rates for new renal replacement therapy starts were 583 per million for veterans aged 55 to 64 years, compared to 1,186 per million for veterans aged 75 years of older, again per a 2015 USRDS report.

Sixty percent of US adults aged 60 or older have hypertension, according to the 1999-2004 NHANES, a 10% increase from the previous NHANES III (1988-1994) [8]. Reduced arterial elasticity is a cardinal feature of aging, affecting the aorta and other large compliance vessels. Subsequent fibrosis ensues, amplifying arterial stiffness, and resulting in the widened pulse pressure typically seen in older hypertensive individuals. Patients over the age of 70 are less able to excrete a salt load and therefore are more likely to be salt sensitive with regard to blood pressure elevations [8].

The prevalence of hypertension increases markedly from stage I CKD (22%) to stage IV CKD (80%). It is inversely correlated to eGFR, and uncontrolled hypertension remains one of the greatest risk factor for progression of CKD into ESRD [6]. Controlling blood pressure in men aged over 70 was consistently harder in clinical trials [7].

Mahmoodi et al. conducted a meta-analysis that included 13 chronic kidney disease cohorts (a total of 17,088 hypertensive patients and 21,072 non-hypertensive individuals). The hazard ratio for ESRD was 4.90 in hypertensive patients with eGFR between 45–74 and proteinuria less than 1.5 grams (compared to 1.99 in non-hypertensive patients). The hazard ratio for progression into ESRD accrued to 8.57 in hypertensive patients with eGFR below 45 and with less than a gram of proteinuria, compared to 5.08 in non-hypertensive patients. The authors also demonstrated that the risk of ESRD significantly increased in patients with CKD regardless of the cause of their kidney dysfunction, whether they had diabetes or not [6]. Major clinical trials in the elderly have shown a substantial reduction in cardiovascular events with the widespread use of antihypertensive medications.

Blood pressure lowering to a routine office measurement between 125 – 130 mm Hg decreased incident cardiovascular disease by 33% per year and total mortality by 32% per year in patients aged 75 or older in the Systolic Blood Pressure Intervention Trial (SPRINT), as well as in people with CKD [9]. Note, the way blood pressure was measured in SPRINT is not typical of office practices and yields much lower values than achieved in routine medical practice, therefore slightly higher BP ranges should be the desired goals [10]. Additionally, elderly patients living in nursing homes, or who have diabetes, stroke, or symptomatic heart failure were excluded from SPRINT, thus, affecting its generalizability.

The consensus of almost all international guidelines is that the systolic blood pressure target be <140 mm Hg up to age 80. Note also that in almost all these trials, including SPRINT, very few individuals had a high pulse pressure (i.e., more than 70 mmHg at baseline). This subgroup of patients tends not to handle lower pressures well and are quite symptomatic. Moreover, the use of ACEi/ARBs in the older people with advanced kidney disease is often not achievable secondary to hyperkalemia, thus limiting the ability to achieve blood pressure goals. The most important time to intervene in this subgroup is early in the CKD staging, by keeping blood pressure values well below 140 mmHg, to slow down CKD progression.

REFERENCES:


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