Clinically silent myocardial infarctions in the CKD community

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Burden of clinically silent myocardial infarction in patients with kidney disease

Patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) are at a greater risk for incident myocardial infarction and death from coronary heart disease (CHD) compared with the general population [1]. The presence of CKD may accelerate the formation of vulnerable plaques, increase the frequency of plaque disruption and may increase thrombogenicity of the blood, making patients with CKD at high risk for myocardial infarction and mortality. Once diagnosed with CHD, patients with CKD have a greater incidence of recurrent cardiovascular events and mortality [2].

Research has suggested that CHD is unique in patients with CKD and ESRD compared with the general population with early onset, more rapid progression, atypical symptoms and higher rates of death. Although it is estimated that ~13% of patients with CKD have suffered an acute myocardial infarction [3], it is likely that many patients with CKD have clinically silent CHD, which may have serious clinical implications on long-term cardiovascular morbidity and mortality.

In a provocative study in this issue of NDT, Rizk et al. examine the prevalence and long-term impact of unrecognized myocardial infarctions among patients with CKD. In this large study of 18,864 patients with and without CKD enrolled in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort, 12-lead ECGs were used to identify the presence of Q-wave abnormalities [4]. Recognized myocardial infarction was defined as the concurrence of self-reported myocardial infarction as well as Q-wave abnormalities on ECG, whereas unrecognized myocardial infarction was defined as the presence of diagnostic Q-wave abnormalities without self-report. The investigators report that, in patients with eGFR <30 mL/min/1.73 m², the prevalence of unrecognized myocardial infarction was 13% compared with 4% in those without CKD [4]. The presence of macroalbuminuria was associated with a 10% risk of unrecognized myocardial infarction compared with 4% in patients without albuminuria. After 4 years of follow-up, the investigators found that among patients with CKD, the risk of death was similar in those with unrecognized versus recognized myocardial infarctions [4]. These compelling results suggest that unrecognized myocardial infarction appears to be more common in patients with CKD; and notably, unrecognized myocardial infarction conveys a similar negative prognosis compared with a clinically recognized myocardial infarction.

This study makes an important contribution in being one of the first to define the burden of clinically silent myocardial infarctions in the CKD community. Several limitations of this study must be noted. The study cohort was primarily African-American (by design) so results may not be generalizable to other populations. This was a cohort that oversampled from the ‘stroke belt’ so participants likely had a higher prevalence of risk factors for stroke and thus CHD. The authors chose to utilize Q-wave abnormalities on baseline ECGs and self-report to define myocardial infarctions. However, in a cohort of patients sampled to study stroke, there may be issues with self-report of disease. Additionally, the significance of Q-wave abnormalities in representing prior myocardial infarction remains unknown in patients with CKD as patients with kidney disease are vulnerable to factors such as electrolytes abnormalities and fluid shifts, that may alter ECGs transiently. An alternative and perhaps more powerful strategy is to examine changes in markers of myocardial injury.
Kidney disease is critical, contributing to the development of CHD in patients with CHD. Therefore, better understanding of the pathogenesis high risk for atypical presentations or clinically silent studies reveal that patients with kidney disease may be at the burden of asymptomatic CHD in CKD patients, ST elevations (versus 35.9% of non-dialysis patients) dialysis patients) and only 19.1% of dialysis patients had patients presented with chest pain (versus 68.3% of non-
tion, the investigators found that only 44.4% of dialysis among patients hospitalized for acute myocardial infarc-
tional Registry of Myocardial Infarction (NRMI 2) Study, United States Renal Data System (USRDS)/Third Na-
dermulations such as chest pain, shoulder pain or arm pain [11]. These likely to report symptoms typical of myocardial infarction, patients with and without CKD presenting with myocardial infarctions found that patients with CKD were less likely to report symptoms typical of myocardial infarction, such as chest pain, shoulder pain or arm pain [11]. These studies reveal that patients with kidney disease may be at high risk for atypical presentations or clinically silent CHD. Therefore, better understanding of the pathogenesis contributing to the development of CHD in patients with kidney disease is critical.

**Unique pathogenesis as a possible explanation for clinically silent CHD in patients with kidney disease**

The pathology of CHD differs in the presence of CKD and it is possible that this unique pathogenesis contributes to clinically silent CHD. Patients with CKD are vulnerable to accelerated arterial calcification with severe intimal-medial calcification [12] as well as atherosclerotic plaque formation. These parallel processes likely have distinct as well as shared risk factors, which are prevalent among patients with CKD, thus driving accelerated (and perhaps silent) CHD and mortality. Patients with kidney disease have a high prevalence of traditional risk factors such as older age, poorly controlled blood pressure and hyperlipidemia. In particular, the high prevalence of dia-

**Strategies to diagnose clinically silent CHD in patients with kidney disease**

A possible approach to identify patients with CKD at risk for clinically silent CHD is to aggressively test for CHD, even in the absence of symptoms. However, our ability to diagnose CHD in patients with CKD remains limited.
Tools such as the Framingham score have poor accuracy in predicting incident CHD in patients with CKD [23]. Biomarkers such as cardiac troponin measurements may have limited prognostic value as levels may be dependent on renal clearance [24]. Cardiac non-invasive diagnostic tests also have had limited prognostic use in patients with CKD. Exercise electrocardiography is limited by lack of specificity of the ST-segment response and by the inability of many CKD patients to reach a diagnostic exercise threshold [25]. The accuracy of pharmacological perfusion imaging is low in patients with CKD [25]. Stress echocardiography also demonstrates poor accuracy in CKD patients who often have the elevated left ventricular mass and small left ventricular cavity size [26]. Measurement of coronary artery calcium by computed tomography has yielded conflicting data in patients with kidney disease [27–29]. Use of contrast agents (due to concerns of contrast-induced acute kidney injury or other complications) limit the use of computed tomography coronary angiography and magnetic resonance imaging.

Universal screening for CHD in patients with CKD and ESRD is controversial as the benefits must be balanced against the costs and possible side effects. Currently, there are several gaps in knowledge that pose a significant barrier in implementing universal screening tests including: (i) lack of effective CHD diagnostic tests designed for patients with kidney disease, (ii) insufficient evidence that CHD diagnostic testing predicts outcomes (iii) inadequate understanding of the burden of asymptomatic CHD in patients with CKD and (iv) the absence of cost-effective analyses of implementing universal CHD screening. Future studies in these areas may help guide recommendations on early diagnosis of CHD in patients with CKD and ESRD, thereby leading to opportunities for treatment and intervention.

Primary treatment to prevent the development of clinically silent CHD in patients with kidney disease

Primary treatment for CHD may have significant clinical impact in reducing the burden of clinically silent CHD in patients with CKD. In the past, there has been a dearth of randomized controlled trials to test primary cardiovascular treatment strategies in CKD and ESRD. Recently, the placebo-controlled Study of Heart and Renal Protection (SHARP) trial found that simvastatin plus ezetimibe reduced the incidence of major atherosclerotic events in a wide range of patients with advanced CKD [30]. This trial made great strides toward implementing evidence-based practices to prevent CHD in patients with CKD; however, further trials are urgently needed. For example, only one randomized trial of aspirin has included patients with CKD. Although this analysis found that patients with CKD receiving aspirin had a 45% lower risk of death [31], aspirin use still is limited in patients with CKD due to concerns of bleeding. Trials studying the short- and long-term impact of cardiovascular medications, targeted to reduce the burden of traditional as well as novel cardiovascular risk factors, are needed to potentially reduce the burden of clinically silent CHD in patients with kidney disease.

Clinical impact of clinically silent CHD in patients with kidney disease

Clinically silent CHD may lead to delay in the receipt of medical treatment and interventions for CHD, thus contributing to future complications such as recurrent CHD, other cardiovascular complications and death. Rizk et al. [4] noted that the mortality rates were similar among CKD patients with recognized versus unrecognized myocardial infarction. This is in contrast to some studies in the general population that have found that risk associated with clinically silent CHD is greater than recognized CHD [7, 8]. Future longitudinal studies are needed to expand on these results in patients with CKD and ESRD; it is quite possible that clinically silent myocardial infarctions have a larger scope of morbidity and mortality in patients with kidney disease than we are currently able to appreciate (Figure 1). For example, we recently reported that among patients with CKD, there was a strong, graded association between reduced estimated glomerular filtration rate and presenting with acute myocardial infarction versus stable exertional angina [32], suggesting that CKD is an independent predictor of more severe incident CHD; perhaps due to a high burden of clinically silent CHD prior to initial clinical presentation in patients with kidney disease. Silent coronary death may also be responsible for the development of heart failure in patients with kidney disease. Sudden cardiac death is now the leading subset of cardiovascular disease in patients with kidney disease [33] and it is possible that clinically silent CHD is a significant contributor to this burden of disease. In males from the general population, clinically silent myocardial infarctions have been strongly associated with incident stroke and dementia [34, 35]; thus silent CHD may represent an important causal link between kidney disease and neurological disease. Therefore, identification and treatment of patients with CKD and ESRD with clinically silent CHD may have tremendous public health implications in reducing short- and long-term morbidity and mortality.

Future directions

CHD is unique in patients with CKD, with novel pathogenesis, accelerated progression and worse outcomes compared with the general population. However, the cumulative burden of CHD in the CKD community is likely underappreciated largely due to clinically silent CHD, as revealed by the thought-provoking study by Rizk et al. in this issue of NDT. Undoubtedly, diagnosing patients with CKD who have clinically silent CHD is challenging; however, the clinical implications of this unrecognized and untreated pathological process may be much greater than appreciated. Further longitudinal studies using sophisticated tools to identify clinically silent CHD are critical to understand the short- and long-term morbidity and mortality associated with this silent
disease. A translational approach is needed to elucidate the contribution of novel cardiovascular risk factors on the pathogenesis and clinical presentation of CHD. Research to test CKD-specific diagnostic tools for early identification of patients at risk for CHD is crucial. Following the lead of the SHARP trial, further trials to test primary medical therapies to prevent CHD are needed. These research initiatives may enhance our ability to prevent, diagnose and treat CHD. Greater awareness of this burden of silent CHD is needed by clinicians, who in turn, must increase efforts toward primary cardiovascular counseling and management in patients with kidney disease. Future studies may reveal that the burden of clinically silent CHD is greater than we recognize in patients with kidney disease with tremendous clinical impact on morbidity and mortality.

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References

Diagnosis of acute pyelonephritis with recent trends in management

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Renal infection can be regarded as a spectrum of clinical entities progressing from mild acute pyelonephritis (APN) to renal abscesses or emphysematous pyelonephritis. APN is traditionally characterized by bacterial or fungal invasion of the kidney, causing acute interstitial inflammation and tubular cell necrosis (Figure 1). The term chronic pyelonephritis applies to the findings of pelvicaliceal inflammation, fibrosis and deformity of the kidney on histopathologic examination. Previous estimates suggest an incidence of 250,000 episodes per year of APN in the USA with nearly 200,000 requiring admission [1, 2].

In this issue of the journal, Rollino et al. describe a series of 223 patients who presented with clinical evidence of APN to an emergency department during the course of 103 months. Their study sheds light on the inferiority of urine culture and blood culture over imaging modalities in the diagnosis of APN. The group was comprised predominantly of women who had a 9-fold increased risk of developing APN compared with men. This is in contrast to previous studies that reported only a 4-5-fold greater risk in women from a large US database [3].

Rollino’s study focused on imaging modalities as a tool for diagnosis of APN along with treatment and follow-up of patients with APN. All of the patients were treated as inpatients and were considered to have APN clinically diagnosed on the basis of fever, flank pain, leukocytosis and elevated C-reactive protein (CRP). Only 26.9% of the patients were considered to be at high risk at presentation. The diagnosis of pyelonephritis was not based on culture alone as there were positive urine cultures in only 23.5%, blood culture in 15.8% and both blood and urine culture in only 7.6% of patients. Computed tomography (CT) and magnetic resonance imaging (MRI), however, confirmed APN in 92% of the patients. This low culture positivity rate is surprising and may be related to prior antibiotic therapy in the outpatient setting, culture techniques, low virulence bacteria or atypical pathogens. This study also suggests that although imaging can detect a majority of cases, it cannot be used as a gold standard as twelve patients had negative CT results but typical symptoms and positive urine cultures. This highlights the previous recommendation that all patients with symptoms suggestive of APN should have a properly collected mid-stream urine sample and culture for identification of the organism and tailoring of the treatment [4]. Hospitalization as a result of APN is five times more common in women than in men, with 11.7 versus 2.4 hospitalizations per 10,000 cases [3]. Women, however, show a lower mortality rate than men with 7.3 versus 16.5 deaths per 1000 cases [3]. A seasonal variance in incidence with most infections occurring in summer is also seen [5]. Acute uncomplicated infections primarily occur in younger women as shown in the current study by Rollino where 54.4% of patients were <40 years of age.

Among the 23.5% of patients who had a positive urine culture, Escherichia coli was the most common organism (87.5%) followed by Klebsiella (6.3%), Proteus mirabilis (3.2%) Enterococcus faecalis (1.5%), and co-infection of Klebsiella with E. faecalis (1.5%) and blood cultures grew E. coli (90%), Acinetobacter iwoffii (2.5%), P. mirabilis (2.5%), Streptococcus saprophyticus (2.5%) and Staphylococcus hominis (2.5%) in 15.8% of patients. The study by Rollino et al. showed almost a similar microbiological pattern when compared with previous reports with E. coli being the commonest organism [6]. Two special situations in which APN needs prompt intervention need to be mentioned. APN in pregnant women occurs in 1–2% of women increasing the risk of pre-term labor and low-birth weight infants [7]. Prompt diagnosis, hospitalization and intensive treatment are required in pregnant women with