



KDIGO Controversies Conference Cardiovascular Disease in CKD: What is it and what can we do about it?

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Breakout Group #1: Coronary Artery Disease and Myocardial Infarction

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Epidemiology

Since 1974 when Armando Lindner first reported the high incidence of cardiovascular disease in an early cohort of maintenance hemodialysis patients and hypothesized that atherosclerosis was accelerated in End Stage Renal Disease (ESRD)[1], it has become increasingly clear that chronic kidney disease (CKD) is associated with markedly elevated risks of developing and dying from cardiovascular disease (CVD) [2-6]. Although all forms of CVD are common, coronary artery disease is a particularly noteworthy issue in the CKD population. This presumably reflects the higher prevalence of traditional cardiac risk factors – hypertension, diabetes, and hypercholesterolemia – as well as other potential risk factors – increased arterial stiffness, anemia, increased calcium uptake, abnormalities in bone mineral metabolism, and proteinuria – among patients with CKD. Recent studies have confirmed an unequivocal increase in the incidence and severity of obstructive coronary disease as GFR declines[7]. Chronic kidney disease also tends to be associated with more severe coronary artery disease in which the vessels tend to be calcified and exhibit a diffuse multivessel pattern of disease [5, 8].

CKD, in addition to being a risk factor for CAD, portends a worse prognosis for patients with cardiovascular disease.[9-12] The risks of both initial myocardial infarction (MI) as well as the risks of recurrent MI after an initial presentation with acute coronary syndrome appears to be inversely associated with the level of renal function and rise dramatically as glomerular filtration rate (GFR) declines to <15 mL/min/1.73m² [2, 3]. MI is not only more common in the CKD population, but it is also more likely to be fatal among patients with reduced GFR with a nearly 4-fold increase in the risk of CV death during follow-up as GFR declines from >75 to to <45 mL/min/1.73 m² [2]. Similarly, among patients with ESRD, in-hospital mortality following admission for MI is 26% while CV mortality exceeds 40% during the year after discharge[13]. In fact, the risk of mortality which is often associated with cardiovascular disease far exceeds the risk of renal replacement therapy. [14-16]

Although one recent study suggested that the increased risk of CV death in ESRD is primarily a reflection of the increase in all-cause mortality rates in this population [17], the majority of studies suggest that CKD is a strong and independent risk factor for the development of atherosclerosis and acute coronary syndromes [2, 3, 11, 18-20]. The nature of this high risk remains incompletely understood. Standard CV risk factors such as advanced age, diabetes, hypertension and hyperlipidemia are common in patients with CKD, but they do not appear to fully explain the high incidence of CV events in this population[21-23].

Furthermore, the association between several standard CV risk factors and CV outcomes is attenuated or even reversed at the most advanced stages of CKD[24].

These observations suggest the hypothesis that novel risk factors play a particularly important etiologic role in the development of atherosclerosis in individuals with CKD. The role of these non-traditional CV risk factors have been recently reviewed [19]. Although multiple candidate factors have been identified, inflammation and oxidative stress appear to be particularly important. Both factors have been linked to the pathogenesis of plaque formation and plaque rupture[25], and multiple inflammatory markers such as high C-reactive protein (CRP), high white blood cell count and low albumin are known to be abnormal in advanced CKD and associated with worse CV outcomes [26-29].

Diagnosis

The manifestations of CAD among patients with CKD are highly variable. In the vast majority of patients, CAD may remain occult for years if not decades, detected when noninvasive (stress ECHO, stress nuclear, CT coronary angiography) studies or coronary angiography is performed. As with other forms of cardiovascular disease, early detection of coronary artery plaque permits risk factor modification and the institution of pharmacotherapies for secondary risk reduction. Screening for CAD among asymptomatic patients with CKD remains a controversial issue for two primary reasons. First, the indicators utilized for screening in patients have been extrapolated from cohorts in whom CKD was not prevalent. The KDOQI[30] guidelines currently recommend stress testing for dialysis patients in the following circumstances: (1) kidney transplant waitlist patients with diabetes, a high Framingham risk score, known unrevascularized CAD or CAD with percutaneous intervention prior to one year ago, (2) selected dialysis patients with a high risk of an adverse cardiovascular event but are not kidney transplant candidates, (3) complete revascularization with coronary artery bypass surgery that occurred at least three years ago, (4) incomplete coronary revascularization with coronary artery bypass surgery that occurred at least one year ago, (5) left ventricular systolic ejection fraction less than 40 percent, and (5) change in symptoms related to ischemic heart disease or change in clinical status.

The second challenge in the screening of chronic kidney disease relates to the lower sensitivity, specificity, and accuracy of noninvasive studies in these patients.[31] SPECT radionuclide myocardial perfusion imaging with both adenosine and exercise has been utilized for risk stratification in patients with CKD, and the presence of either scar or ischemia is strongly predictive of cardiac death across the range of renal dysfunction.[32] The annual cardiac death rate for CKD patients (estimated globular filtration rate <60 ml/min/1.73 m²) with a normal test, scar, and ischemia were 2.7%, 5.3%, and 11%, respectively. The corresponding rates among patients without CKD were 0.8%, 2.5%, and 4.5%, respectively. Other studies have confirmed the prognostic value of a positive myocardial perfusion imaging study. [33-35] Sensitivity and specificity for exercise and pharmacologic myocardial perfusion imaging range 70%-85% and 75%-80%, respectively. Technical limitations include the inability of the patient to exercise (estimated to be as high as 30% of ESRD population) and false positive studies due to an increase in attenuation artifacts caused by left ventricular hypertrophy.

Stress echocardiography has also been extensively evaluated in the CKD population. Stress echocardiography has an intermediate sensitivity (75% - 84%) and specificity (71% - 91%) to identify a coronary artery stenosis > 70%.[36, 37] Although, a positive stress ECHO study is an independent predictor for cardiovascular outcomes [38-41], CKD patients often have comorbidity that prohibits an exercise protocol. Conversely, pharmacologic stress ECHO is fraught with challenges, in part due to the high prevalence of left ventricular hypertrophy that can reduce specificity [42, 43]. Additional studies have challenged the role of stress echocardiography citing not only a poor sensitivity / specificity for identifying coronary artery disease, but more importantly, an unacceptable number of subsequent cardiovascular events among patients with a negative study [39, 44]. Concerns over stress

echocardiography in the risk stratification of CKD patients led to renal disease not being included in the most recent Appropriateness Criteria for Stress Echocardiography' recommendations [45].

In patients with more advanced coronary artery plaque, the presentation may be in the form of an acute coronary syndrome – unstable angina, non ST elevation myocardial infarction, or ST elevation myocardial infarction. However, the classic triad of ischemic symptoms, elevated cardiac biomarkers, and electrocardiographic changes does not always apply to CKD patients. Patients with chronic kidney disease, like the elderly, may have a more advanced form of coronary artery disease (left main coronary artery involvement or multivessel disease) and may not manifest typical chest pain. Rather, these patients may present with dyspnea or exertional fatigue secondary to heart failure [46]. The electrocardiograms may show left ventricular hypertrophy with a strain pattern secondary to long-standing hypertension and this may mask underlying ST depression diagnostic of coronary ischemia. Cardiac biomarkers – both creatine kinase MB isoform and troponin I – may be elevated among chronic kidney disease and dialysis in the absence of true myocardial necrosis and may reflect apoptosis or small vessel disease[47]. The reduced specificity of the cardiac biomarkers frequently results in the triaging of chronic kidney disease patients to either noninvasive or invasive cardiovascular stress testing.

Treatment

The treatment of coronary artery disease in the chronic kidney disease population involves a two-pronged approach – standard pharmacotherapies and the appropriate use of coronary revascularization. While the aggressive application of standard cardiovascular therapies in this high-risk population might decrease cardiovascular risk, their use is paradoxically lower in patients with CKD than in patients with preserved renal function. The low utilization of medical therapies such as β -blockers, renin-angiotensin axis blockers, statins and aspirin has been observed in patients with moderate to advanced CKD[48-50]. The selective underutilization of potentially life-saving cardiovascular therapies in a population at high risk of cardiovascular death has been referred to as “renalism”[51], and it is tempting to simply advocate increased use of standard therapies as a means of decreasing cardiovascular morbidity in the CKD population. However, it is not clear that more widespread use is indicated. The relationship of typical risk factors with cardiovascular outcomes is markedly different in patients with and without CKD[18, 52, 53], and the routine exclusion of patients with CKD from the majority of clinical trials testing CVD therapies[54, 55] engenders significant reservations about the relevance of the existing standard of care in the general population to the treatment of patients with CKD. In fact, several randomized clinical trials have recently provided firm evidence of the unique nature of CAD in patients with CKD and are consistent with an altered response to standard therapies in patients with advanced CKD[56-58]. The negative results in the 4D and AURORA trials, large randomized clinical trials comparing statins with placebo in chronic hemodialysis patients[58, 59], for example, stand in sharp contrast to the almost universally beneficial effects of statins in other populations[60-63].

The decision to proceed with a conservative strategy with medical therapy versus a more aggressive strategy incorporating coronary revascularization requires consideration of the patient's symptoms, the amount of myocardium at risk, the presence and severity of impaired left ventricular function (reduced ejection fraction), and the severity of coronary artery disease. When coronary revascularization is warranted, the decision to proceed with PCI versus CABG can be a challenging one. Evidence based guidelines recommend PCI in patients with single or two vessel CAD and recommend CABG among patients with multivessel CAD, particularly when there is depressed left ventricular function or diabetes present.[64, 65] Interestingly, while CKD poses similar, if not greater, risks than diabetes, there are no recommendations for this subgroup of patients. There are no randomized clinical trials to date comparing coronary revascularization strategies among CKD patients. Whether the results of the aforementioned trials can be generalized to patients with chronic kidney disease is a point of contention. Subgroup analyses of CKD patients from randomized clinical trials are relatively small and do not reflect contemporary practice [66, 67]. In the ARTS-1 trial, the only randomized trial that reported out results

among CKD patients, there was no significant difference in the primary endpoint (death, MI, stroke) between the PCI and CABG arms in 290 patients with CrCl < 60 mL/min [67]. The revascularization rate, however, was markedly lower in the CABG arm (RR 0.28, 95% CI: 0.14 – 0.54) at 3 years. While recent clinical trials have not excluded patients with impaired renal function, they have not openly solicited for this high risk subgroup of patients.

Observational data, has consistently highlighted an increased risk of operative complications in individuals with CKD [68-76]. In contemporary cohorts, the incidence of operative death after bypass surgery ranges between 9-12.2% for chronic dialysis patients, and is 3 to 7-fold higher in patients with advanced CKD (chronic dialysis or stage 4 CKD) than in patients without CKD [70, 77, 78]. Given the already high background mortality rate, this level of operative risk suggests that PCI may be a preferential strategy in individuals with CKD. Nevertheless, while demonstrating increased hazards among CKD patients, observational analyses have not demonstrated the superiority of either PCI or CABG. Herzog studied dialysis patients undergoing a 1st revascularization between 1995 and 1998 and found that in-hospital mortality was lower with PCI (4.1% vs. 8.6%) but that 2-year survival was better with CABG (56.4% vs. 48.4%)[79]. Similarly, a study of all patients in New York undergoing PCI or CABG between 1993 and 1998, demonstrated that in ESRD, CABG was associated with a relative reduction in the risk of death of 71% compared with PCI[80]. CABG did not confer a survival benefit in pre-dialysis patients with creatinine >2.5 mg/dL (RR 0.86, P=0.50)[80] in this series, but another retrospective study suggested overall mortality is lower with CABG than PCI in advanced CKD patients regardless of the need for dialysis[81]. Available studies thus provide conflicting evidence on the relative merits of PCI and CABG in the CKD population, and may also be confounded by the selective referral of the fittest CKD patients to CABG with shunting of sicker patients to PCI or medical therapy. Differential use of medications in patients receiving the most aggressive therapy (CABG) and those receiving PCI may be an additional factor underlying the beneficial effect of CABG observed in several studies. Furthermore, these studies preceded the approval of drug eluting stents (DES) which have markedly decreased the incidence of post-PCI restenosis and the need for repeat revascularization[82], and they may provide limited insight on the relative merits of PCI and CABG in the DES era. In summary, available evidence provides limited insights into the relative merits of percutaneous vs. surgical revascularization in individuals with CKD.

What Can Be Done

While the interplay between CKD and CAD has received increased attention in the past decade, there remains a large void of knowledge. From the epidemiologic perspective, we must assess the scope of the problem. Estimates of the incidence and prevalence of CAD and CKD, as well as the intersection of these two populations, are presumably low given the latent history of both disease processes. Greater attention needs to be focused on the pathophysiology of CAD among patients with progressive renal decline. Specifically, a better understanding of endothelial dysfunction and the composition of lipid-laden plaque must be ascertained. Similarly, we need to recognize the role of the inflammatory markers and cellular adhesion molecules in the development and rupture of coronary plaque in patients with chronic kidney disease. In regard to the diagnostic dilemma, we need to identify those patients with CKD who require screening for CAD. We also need to determine whether newer imaging modalities – coronary CT angiography and cardiac MR stress imaging – have increased sensitivity / specificity in the identification of coronary artery disease. In regard to pharmacologic therapy, aspirin, statins, and ACE inhibitors / angiotensin receptor blockers are likely to remain the standard of care. The use of these agents should likely be expanded whereas the role of lower target LDLs or the increased utilization of newer anti-platelet therapies in this cohort needs further study. Additional clinical trials will also be required to determine whether CAD in CKD patients is less stable and whether the standard ACC/AHA guidelines for coronary revascularization can be equally applied in this high risk cohort. Finally, randomized clinical trials comparing percutaneous coronary revascularization to coronary artery bypass surgery

(similar to SYNTAX and BARI trials) are required for chronic kidney patients with either left main or multivessel coronary artery disease.

Research Recommendations

- Epidemiologic studies including cohorts with CKD (Stage III-V) studies, to better understand the pathophysiology, traditional / novel risk factors, and outcomes
- Physiologic/Pilot studies to determine efficacy of potential interventions on above risk markers (preferably those that appear to be good surrogates)—followed by large-scale clinical trials of most promising outcome measures
- Validation studies of traditional noninvasive stress tests (exercise / pharmacologic, stress nuclear and ECHO) and newer imaging modalities (coronary CT angiography and cardiac magnetic resonance imaging) using coronary angiography with fractional flow reserve as the gold standard
- Pooled (ie individual patient meta-analysis) analysis of trials of standard interventions for cardiovascular therapy in order to understand efficacy in the limited number of enrolled patients with advanced CKD
- Adequately powered clinical trials evaluating targets and agents for the control of blood pressure, diabetes, and lipid management in patients with advanced chronic kidney disease
- Randomized clinical trials comparing PCI vs. CABG and medical vs. interventional therapies in both advanced CKD and hemodialysis patients with multivessel CAD and / or left main coronary artery disease

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Breakout Group #2: Atrial Fibrillation and Stroke in CKD

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Stroke in ESRD patients

Stroke is more common in ESRD patients than in age-matched people without ESRD. Based on a study of strokes prompting hospitalization from two large databases, the relative risk of stroke in ESRD patients was estimated as 5-10 times that of the age-matched general population. (Seliger SL et al. 2003a) Considering all available data, the overall stroke rate in ESRD patients averages about 4% per year - about 8 times higher than that of non-ESRD patients of similar age and about 2-4 times higher after accounting for the frequent ESRD co-morbidities of diabetes and hypertension.

The best descriptive data about stroke in hemodialysis patients come from the prospective CHOICE Study, involving 1041 incident dialysis patients (74% receiving hemodialysis). (Sozio SM et al. 2009) The observed stroke rate was about 4.2% per year. Most (87%) strokes were ischemic. Independent predictors of higher stroke risk were age and diabetes mellitus. African-American race (surprisingly) was associated with a lower stroke risk, while in another study African-American hemodialysis patients with a history of vascular disease had lower stroke rates than whites, but not those without clinical vascular disease. (Seliger SL et al. 2003b) Similar to another report, about one-third of strokes had onset during or shortly after hemodialysis treatment. (Toyoda K et al. 2005, Sozio SM et al. 2009) The mortality rate of stroke was nearly three times higher (35%) than that typical of non-ESRD patients suffering stroke. The high case fatality rate is supported by results of three randomized trials in which 43% (Fellstrom BC et al. 2009), 38% (Wanner C et al. 2005), and 36% (Boaz M et al. 2000) of all strokes were fatal, and this high rate applied to the subset of ischemic strokes. Less likely, the higher case fatality rate could hypothetically reflect systematic under-detection of minor strokes in ESRD patients. Less is known about stroke rates in ESRD patients undergoing chronic peritoneal dialysis, but available data support similar stroke rates. (Sozio SM et al. 2009, Toyoda K et al. 2004)

Atrial fibrillation (AF) in ESRD patients

The frequency of AF among hemodialysis patient averages about 15%, but ranges widely (5% to 27%) depending on the mean age of the dialysis cohort, method of detection, and whether patients with self-limited paroxysmal AF during hemodialysis are included. As in non-ESRD patients, advancing age is an independent predictor of AF (US Renal Data Systems 2005; Wizemann V et al. 2010). In the large study international DOPPS cohorts, the frequency of AF was >20% of hemodialysis patients ≥ 65 years old from North America or Europe. (Wizemann V et al. 2010) The prevalence of AF in hemodialysis patients is substantially higher than in patients without ESRD (about 5% of people over age 65 have AF). Most ESRD patients have left ventricular hypertrophy at the time of initiation of dialysis, increasing left atrial filling pressures and predisposing to left atrial enlargement – both risk factors for development of AF. Several investigators have speculated on additional mechanisms underlying this higher prevalence.

From available studies, confounded by small numbers, concurrent antithrombotic treatment, method of stroke detection, uncertain accuracy of classification of AF, it is not possible to accurately estimate the stroke rate in ESRD patients with AF who are not receiving antithrombotic therapy.(Table 1) For example, in the large Fresenius study, strokes were identified only at the time of hospitalization (i.e. probable under-detection), inclusion of patients with TIAs, and nearly half received warfarin.(Chan KS et al. 2009a)

Table 1. Stroke rates in hemodialysis patients with AF

Study (fraction anticoagulated)	% AC'd	N / av fu	Mean age	HTN (%)	DM (%)	Prior stroke (%)	Stroke rate (%/yr)
Lombardia, Italy – 2003 (Genovesi S et al. 2008)	24%	162 / ~2.4 yrs	~73 yrs	~78	~16	~17	~8%/yr+ (n=25)
Jaen, Spain - 1998 (Vazquez E et al. 2000, 2003a)	15%	26 / 2.2 yrs	72 yrs	35	8	NR	7%/yr (n=4)
Fresenius dialysis clinics – 2003 (Chan KS et al. 2009a)	44%	1671 / 1.6 yrs	73yrs	NR	NR	14	5%/yr* (n=102)
Austria 1975-1997 (Wiesholzer M et al 2001)	NR	61 / NR	61 yrs	24	20	10	2%/yr#
Auckland, NZ – 2003 (To ACY et al. 2007)	13%	40 / ~1.5 yrs	64yrs	93	36	20	5%/yr^ (n=3)
Taiwan 2001-2007 (Chou C-Y et al. 2010)	5%	219 / 3.1 yrs	69 yrs	24	36	NR	11%/yr** (n=72)
DOPPS 1996-2004 (Wizemann V et al. 2010)	16%	2011 / 1.4 yrs	NR	NR	NR	NR	3.4%/yr^^ (n=148)

AC'd = anticoagulated; N = number of AF patients, av fu = mean follow-up per patient; NR = not reported; HTN = hypertension; DM = diabetes mellitus; ~ = estimated from available data.

= retrospective ascertainment from 1975-1997.

*Stroke ascertained from hospital discharge coding and included transient ischemic attacks and intracerebral hemorrhage. See table X below for rates according to antithrombotic therapies.

^60% receiving aspirin, 13% receiving warfarin; rates by antithrombotic treatments not provided.

+Total exposure estimated based on mortality rates (50% of patients).

**Ischemic strokes and TIAs (fraction of events that were strokes not provided).

^^Strokes detected at the time of hospitalization or death.

A stroke rate of about 7% per year for all strokes (including intracerebral hemorrhage) is a reasonable estimate based on available data. AF is associated with higher all-cause mortality and cardiovascular mortality in dialysis patients and averages about 25% per year.(Genovesi S et al. 2008; Vazquez E et al. 2000; USRDA 2005; Wizemann V et al. 2010)

There are limited data regarding predictors of stroke in AF patients receiving hemodialysis. Increasing age, heart failure, and systolic blood pressure correlated with stroke risk in one large study, but it was not clear whether these predictors resulted from multivariate analysis.(Chan KE et al. 2009a) In contrast, multivariate analysis of another study reported prior stroke, diabetes mellitus, and advancing age to be independently predictive of hospitalization for stroke, but hypertension and heart failure were

not.(Wizemann V et al. 2010) Both of these studies plus a third reported that the CHADS2 scheme successfully stratified stroke risk in ESRD patient with AF. (Wizemann V et al. 2010; Chou C-Y et al. 2010; Chan KE et al. 2009a)

In recent studies, 26% to 44% of ESRD patients with AF have been treated with warfarin. There are no randomized trials assessing the value of warfarin for ESRD patients with AF. A retrospective study of 1671 incident hemodialysis patients with AF in 2003-2004 followed for a mean of 1.6 yrs reported warfarin use to be associated paradoxically with an *increased* stroke risk (HR = 1.9, 95%CI 1.3-2.9).(Chan KE et al. 2009a). Strokes included transient ischemic attacks and brain hemorrhages along with ischemic strokes and were detected from hospital discharge data. Mean INR was 2.3, but time in therapeutic range and other indices of anticoagulation quality were not available. Analysis of AF patients in the large Dialysis Outcomes and Practice Patterns Study (DOPPS) I and II cohorts (1996-2004) also reported warfarin use to be independently associated with increased stroke risk after adjustment for other risk factors.(Wizemann V et al. 2010) The point estimate was statistically significant only for those >75 years (HR 2.2, 95%CI 1.0-4.5).(Wizemann V et al. 2010) Ischemic and hemorrhagic strokes were not distinguished in this study, nor were INR data available. A retrospective study of 41,425 incident hemodialysis patients (not restricted to AF patients) reported a *higher* mortality rate in those given antithrombotic therapies.(Chan KE et al. 2009b)

Experts have lamented the lack of evidence-based stroke prevention strategies in ESRD patients with AF, citing the dangers of extrapolating results of trials that have systematically excluded patients with ESRD. Current treatment recommendations are not evidence-based and have been challenged by recent observational studies (“The effectiveness and safety of warfarin in hemodialysis patients require additional investigation.”(Wizemann V et al. 2010)) While several difficult design issues must be addressed (what should be the control group? double-blinded? target intensity of anticoagulation), a randomized trial of oral anticoagulation in ESRD patients with AF appears feasible and is likely to importantly contribute to stroke prevention in ESRD patients and our broader understanding of the safety of anticoagulation in ESRD patients.

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Breakout Group #3: Congestive heart failure in chronic kidney disease

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Epidemiological aspects

The progression of chronic kidney disease (CKD) is associated with an increased risk for cardiovascular (CV) diseases, including atherosclerosis, arteriosclerosis and cardiomyopathy (i.e., chronic reno-cardiac syndrome or cardio-renal syndrome type 4) [1]. Therefore, clinically CKD is associated with increased prevalence of congestive heart failure (HF), ischemic heart disease, cardiac arrhythmias and cardiac valve disease [2].

Several observational studies have found increasing prevalence of HF associated with declining renal function [3]. However, there is relatively wide heterogeneity in the prevalence of HF in different studies, according to the characteristics of the population studied, the method chosen to estimate glomerular filtration rate (GFR), and the criteria to diagnose HF.

HF is the leading cause of death among the CV events in patients with CKD [4]. Of interest, mortality has been shown to be higher in CKD patients with diastolic HF than in CKD patients with systolic HF [5].

Pathophysiologic and clinical aspects

The progression of CKD is accompanied by progressive left ventricular hypertrophy (LVH) and diastolic dysfunction [6]. Studies in patients with CKD have reported increasing prevalence of LVH along with declining renal function, in such a way that in patients with end-stage renal disease (ESRD) the prevalence of LVH is higher than 70% [7]. In the study by Nardi et al. [8] performed in patients with stage 2-5 CKD a multiple regression analysis confirmed that the association between the progressive loss of renal function and the progressive increase in LV mass was independent by potential confounders. Arterial hypertension and stiffness, and alterations of fluid and electrolyte balance are identified as the major determinants of LVH in CKD [7]. However, beyond hemodynamic factors, other factors, such as an inappropriate activation of the renin-angiotensin-aldosterone system, catalytic iron-dependent oxidative stress, inflammation and stimulation of pro-hypertrophic and profibrogenic factors (i.e., cardiotrophin-1, galectin-3, TGF- β , FGF-23) may have also a relevant role [7]. In more advanced stages of CKD anemia, disturbances of mineral bone metabolism and uremic factors may also contribute to LV growth [7].

LV diastolic dysfunction is very frequent among CKD patients and is associated with risk of HF and with mortality; impairment of diastolic function in patients with CKD may occur very early, even in the absence of LVH [7]. Interstitial and perivascular fibrosis is a frequent finding in heart biopsies and necropsy studies in patients with CKD, namely in those with LVH [9]. Myocardial fibrosis is the result of the unbalance between exaggerated collagen synthesis and unchanged or depressed collagen degradation and can be a major determinant of LV stiffness, increased LV filling pressure, and disturbances in diastolic filling in CKD patients thus predisposing to the development of diastolic dysfunction/failure [10].

Resting LV systolic function is usually normal or even increased in patients with CKD in the absence of ischemic heart disease and/or sustained marked hemodynamic overload with LV dilatation [11]. Uremic factors that diminish myocardial contractility (either interfering with cardiomyocyte calcium handling or stimulating cardiomyocyte apoptosis) may also contribute to depress systolic function [11]. In addition, an association between low triiodothyronine and LV systolic dysfunction has been described in ESRD patients with LVH [12]. Finally, hemodialysis is associated with repetitive hemodynamic instability and subsequent myocardial ischemia, which may be due to coronary microvascular dysfunction and result in prolonged LV systolic dysfunction (myocardial stunning) that confers a dismal prognosis for patients undergoing hemodialysis [13].

Diagnosis

Once HF is suspected because of the presence of the corresponding symptoms and signs on physical examination, several diagnostic tests (i.e., chemistry panel, complete blood count, thyroid function tests, electrocardiogram and chest X ray in two planes) are employed routinely to confirm or rule out the diagnosis of HF in CKD patients as they are in non-CKD patients. However, the use of echocardiography and laboratory tests for the diagnosis of HF in CKD patients requires some specific considerations.

Although current literature and clinical practice have emphasized the usefulness of M-Mode and 2-D echocardiography (including both mitral inflow assessment and tissue Doppler imaging) for the diagnosis of LVH and subclinical LV dysfunction, the prediction of cardiovascular risk, and in the orientation and follow-up of treatment strategies in CKD patients [14], due to cost and availability issues the necessity of an echocardiographic examination in each CKD patient is questionable. Nevertheless, it is a reasonable approach to perform an echocardiogram in each CKD patient with cardiac symptoms, new clinical event, or a treatment likely to affect cardiac function [15]. On the other hand, current guidelines recommend the echocardiogram for all ESRD patients 1-3 months after the start of renal replacement therapy and in intervals of 3 years subsequently, despite the symptoms [16]. Recent data suggest, however, that follow-up with serial studies at closer intervals of 12-18 months seems to add prognostic value [17,18] and should be considered for most patients.

Whereas many studies support the usefulness of B-type natriuretic peptides (BNP and NT-proBNP) in the diagnosis and management of HF patients, the relationship between these peptides, renal function, and the severity of HF is less clear. Patients with CKD have higher levels of BNP and NT-proBNP than age- and gender-matched subjects without reduced renal function, despite similar hemodynamic stimuli [19]. Although these higher levels of NPs have been attributed to reduced renal clearance, there is likely some contribution from other factors including anemia and cachexia [19]. Thus, the BNP cut points for detecting and handling HF may need to be raised when the estimated GFR is less than 60 ml/min [20]. However, it should be noted that the diagnostic accuracy of NPs for HF is reduced in this setting, and NT testing for HF should be discouraged in ESRD patients [20].

A role for the biomarkers of cardiomyocyte damage troponins (cTns) T and I continues to accumulate in HF, particularly their use in risk stratification. However, the clinical significance of increased cTn concentrations in CKD patients with HF is unclear [19]. It is a controversial issue whether decreased renal clearance [21] or additional cardiomyocyte damage [22,23] might contribute to elevated cTnT in CKD patients with HF, and large studies are needed to clarify this topic.

Despite that HF and CKD have a close inter-relationship, the utility of the biomarkers linking deterioration of renal function with cardiac damage has not been adequately studied. For instance, high levels of cystatin C have been shown to be associated with LVH [24] and HF [25] in hypertensive patients. Furthermore, a number of clinical findings support cystatin C as a prognostic factor in HF patients [26]. Of interest, collagen degradation has been reported to be decreased in the failing fibrotic myocardium of mice with an excess of cystatin C [27], thus supporting the hypothesis that cystatin C-mediated inhibition of collagenolytic enzymes such as cathepsins may participate in the development of myocardial fibrosis [28]. Therefore, the possibility that exposure of the heart to high circulating levels of cystatin C due to the reduction of GFR, may result in myocardial fibrosis and LV dysfunction/failure in CKD patients deserves further investigation.

Management

Prevention is at the core of the management of HF in CKD. Prevention relies on modification of usual risk factors of HF and attention to its major underlying cardiac causes, as well as on the reduction in the rate of progression of CKD. Although active treatment of HF in CKD patients is based on the European Society of Cardiology Guidelines for the treatment of HF [29], therapeutic strategies are not evidence-based, as CKD patients are not adequately represented in randomized controlled trials in HF.

Regarding pharmacological treatment of HF in CKD some particular considerations may be of interest [30]. First, HF patients with renal dysfunction often have excessive salt and water retention and require more intensive diuretic treatment than HF patients with normal renal function. In patients with creatinine clearance <30 mL/min, thiazide diuretics are ineffective and loop diuretics are preferred. Aldosterone antagonist should be used with caution in patients with renal dysfunction as they may cause significant hyperkalemia. Second, although there is strong evidence from well-designed randomized clinical trials that treatment strategies using angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) reduce CV morbidity and mortality in HF, there is a paucity of equivalent evidence for patients with CKD [31]. The lack of evidence may explain that repeated studies have shown that only a small proportion of CKD patients with HF are prescribed these drugs [32,33]. Thus, randomized clinical trials of management of HF with the above medications are required in both CKD and dialysis patients. On the other hand, there is no absolute level of creatinine which precludes the prescription of these compounds to avoid the mild deterioration of renal function that is usually associated with its use in HF patients. However, if the serum creatinine level is >250 $\mu\text{mol/L}$ (2.5 mg/dL), specialist supervision is recommended. Third, despite initial controversial data on the efficacy and safety of the use of beta-blockers, more recent data strongly support the use of either bisoprolol [34] or celiprolol [35] in CKD patients with HF. Finally, renal dysfunction is associated with impaired clearance of many drugs (e.g. digoxin). To avoid toxicity, the maintenance dose of such drugs should be reduced and plasma levels monitored.

Besides prescribing adequate medications, the other key management strategies of HF in CKD patients include correcting anaemia and minimizing vascular calcification [30]. Correction of anaemia, aiming for a haemoglobin >10 g/dL has been shown to reduce LVH in CKD patients [36]. In addition, the use of erythropoietin stimulating agents and/or intravenous iron may result in improvements in exercise tolerance and reduction in New York Heart Association functional class of HF but without survival benefit [37,38]. Optimal control of calcium and phosphate concentrations is beneficial to minimize vessel calcification in CKD patients. Therefore, the use of non calcium-containing phosphate binders [39,40], as

well as the adequate restoration of vitamin D availability and the avoidance of an excess of parathyroid hormone are mandatory [41].

In ESRD patients, adequate dialysis must be provided when HF is present [42]. In this regard, beside dietary sodium restriction lower sodium dialysates [43] are essential to reduce interdialytic weight gains, thus lowering ultrafiltration requirements and reducing intradialytic hypotension and repetitive ischaemic stunning to the heart. Finally, it is important to note that high-flow fistulae or grafts may cause significant cardiac shunting leading to pulmonary hypertension and high output HF [44], and that patent arterio-venous fistula in renal transplant patients predispose to HF [45].

Unfortunately, there is limited evidence for the management of acute HF in CKD patients. In this context it is of interest to consider the use of inotropic therapy in patients with worsening renal function secondary to the fall in cardiac output. Although this treatment regimen still needs to be tested (albeit the impediments to randomized studies in this population are obvious), the routine use of inotropes or other adrenergic stimulating agents for acute decompensated HF is not indicated in CKD patients [46]. Other inotropic drugs are being developed, and evaluating their renal effects will be important.

Future directions

Future clinical studies need to evaluate the prevalence of asymptomatic LV dysfunction in CKD, examine the temporal profile/change to both kidney and cardiac function over time and incorporate kidney- and cardiac-specific biomarkers to further establish the mechanistic link of kidney-heart interaction in these patients, namely in conditions of acute HF. Likewise, clinical studies are needed to investigate the incidence of and risk factors for HF in patients with CKD. In addition, future clinical trials and phase IV observational studies need to evaluate the impact and tolerance of CKD patient with HF-specific risk-modifying (i.e. statins) and/or cardio-protective therapies (namely ACEIs and ARBs).

But beyond these general actions, a new paradigm of CKD with HF that places prevention and reversal of LVH and fibrosis as a high priority is needed [47]. This will require novel approaches to management. For instance, recent data suggest that the loop diuretic torasemide, but not furosemide, reduces myocardial fibrosis and ameliorates cardiac function in patients with HF through local mechanisms beyond its effects on the renal excretion of fluid and electrolytes and systemic hemodynamics [48-50]. These results are provocative and warrant controlled interventional trials to provide evidence to fuel the transition from old to new cardiac and renal treatment strategies in CKD patients.

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Breakout Group #4: Sudden Death in Chronic Kidney Disease

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Definition of SCD

The most widely accepted definition of sudden cardiac death (SCD) is the sudden and unexpected death within an hour of symptom onset [1]. The International Classification of Diseases, Tenth Revision further refines this definition by adding that this event must occur out of hospital, in an emergency department, or in an individual reported dead on arrival at a hospital[2]. Whether this definition extends to patients with end-stage kidney disease (ESKD) who spend a disproportionate amount of time in a health-care facility is debatable. In the general population, it is understood that SCD may be due to a variety of catastrophic events and that sustained ventricular tachycardia (VT) and ventricular fibrillation (VF) constitute about half the cases. The distribution of causes in patients with ESKD is unknown.

Epidemiology of SCD in ESKD

SCD is an important cause of death among patients with chronic kidney disease (CKD). In patients with ESKD treated with either hemo- or peritoneal dialysis, the association with SCD is independent and alarming. According to United States Renal Data System (USRDS) registry data, SCD accounts for about 1 of every 4 deaths among both hemodialysis and peritoneal dialysis patients at an annual rate of 6-7% [3, 4]. While cause of death derived from registry data may be prone to misclassification due to lack of a precise definition of SCD, data from randomized clinical trials (HEMO, 4D) and several prospective hemodialysis (CHOICE) and peritoneal dialysis cohorts report similar findings on the relative contribution of sudden death to all-cause mortality (22-26%) among dialysis-maintained ESKD patients[5-8]. Survival following a sudden cardiac arrest among ESKD patients is universally poor, with a 6-month survival between 3-11% [9-12].

Epidemiology in Pre-dialysis CKD

The relationship between less severe stages of CKD and the specific risk of SCD has recently been explored. Secondary analyses of subjects with moderate CKD enrolled in the MADIT-II and COMPANION implantable defibrillator trials have reported an incremental risk of SCD with decreasing baseline glomerular filtration rate (GFR)[13, 14]. Inverse linear relationships between kidney function and SCD risk has also been observed among a large cohort with CKD and significant coronary heart disease[15], postmenopausal women with coronary heart disease[16], and elderly persons without clinically significant cardiac disease[17]. In these studies, the increased risk of SCD associated with CKD could not be accounted for by the degree of measured cardiac or other comorbidities.

Proposed mechanisms of SCD in CKD patients.

The association between ESKD and SCD is multifactorial and complex and likely involves a combination of vulnerable myocardial substrate with superimposed transient triggers. Unfortunately, both are abundant in the dialysis population. Coronary heart disease (CHD) is prevalent among patients with CKD, and produces both structural heart disease (ischemic cardiomyopathy with decreased systolic function) and a source of triggering events (acute myocardial ischemia) from which terminal arrhythmias arise. [18] CHD is the underlying substrate in the vast majority SCD in non-CKD patients,[18] and recognized risk factors for CHD identified in the general population are prevalent among CKD patients.

However, the pathophysiologic paradigm of CHD as the main determinant of SCD risk is problematic among CKD patients. First, several lines of evidence suggest that CHD-related risks are insufficient to

explain the dramatically increased risk of SCD among CKD patients. In pre-dialysis CKD patients, SCD risk associated with diminished GFR cannot be accounted for by severity of CHD, congestive heart failure, the prevalence of diabetes, or decreased use of cardiovascular medications[15]. In clinical trials such as the 4D study, only 9% of deaths were directly attributable to CHD, whereas SCD accounted for 26%[6]. Recognized risk factors such as left ventricular systolic dysfunction are present in only a minority of ESKD patients, whereas diastolic dysfunction due to left ventricular hypertrophy (LVH) is endemic[19, 20]. Secondly, non-cardiac mechanisms may contribute significantly to sudden death in dialysis patients. The degree to which unique dialysis-specific complications such as hyperkalemia, air embolism, exsanguination from vascular access, and other non-cardiac mechanisms contribute to the overall sudden death rate is unknown, and only scant autopsy data is available. A small autopsy study of dialysis patients who suffered SCD found stroke as the most frequent cause of sudden death (25.8%), followed by cardiac disease (19%), and infectious disease (17.2%)[21]. Third, while ischemia-associated VT/VF has been implicated in the majority of SCD in non-uremic patients[22], it is also unclear whether or not the same pattern holds true among ESKD patients given the differences in underlying cardiac disease patterns outlined above. Small retrospective studies of presenting arrhythmias in ESKD patients with SCD report a wide range of ventricular arrhythmias (19%-72%)[10, 22-24]. Unique metabolic derangements and other non-cardiac events occurring in ESKD patients may result in other non-ventricular terminal arrhythmias. Characterization of SCD arrhythmias in hemodialysis patients is important, since non-ventricular arrhythmias would not be expected to respond to traditional resuscitative measures involving defibrillation.[25]

SCD Risk Factors in CKD:

In view of the exponential growth in the number of dialysis patients and their excessive risk of SCD, preventive strategies should be a major public health concern. Any attempt to evaluate the efficacy of preventive strategies for SCD in the CKD population must rely on reasonable risk-stratification data. This is extremely challenging given the fact that SCD is a generic term encompassing widely disparate events whose risk factors can also be expected to vary widely. As discussed above, diminished GFR by itself should be considered a significant risk factor for SCD [13]. ESKD requiring dialysis confers an additional risk, with one study suggesting a doubling of SCD risk between CKD Stage 5 subjects and ESKD dialysis patients.[15] Most studies on specific SCD risk factors have focused on the dialysis population from retrospective and small observational prospective cohorts, and these have been limited by small sample size, inherent limitations in the adjudication of endpoints, and the failure to examine a wide range of candidate variables. An important and consistent observation is that most SCD in hemodialysis patients occur on the first hemodialysis day of week following the long intradialytic period, suggesting that dramatic fluid and electrolyte shifts may be important triggering factors for SCD[23, 26]. Concordantly, exposure to low potassium and calcium dialysate, volume removal on dialysis, and predialysis hyperkalemia and hypokalemia have been associated with an increased risk of intradialytic SCD in several cohorts [7, 10, 27]. Measures of structural heart disease have been variably associated with increased SCD risk, with one small study suggesting that change in left ventricular mass index as the most potent predictor of SCD, while another study failed to find an association between LVH and SCD risk [7, 28]. The high prevalence of LVH in the ESKD population would limit its utility in SCD risk stratification. While an ejection fraction $\leq 35\%$, regardless of etiology, has been shown to identify a subgroup of heart failure patients with a high risk of sudden death due to arrhythmia, even more mild degrees of left ventricular dysfunction may be associated with increased event rates in peritoneal dialysis patients. [8] Other non-invasive cardiac markers including ambient ventricular ectopy, heart rate variability, QT dispersion, baroreflex sensitivity, and T-wave alternans, have not been sufficiently studied in this population to be of clinical utility. Serum biomarkers, particularly cardiac troponin T, have been associated with all-cause mortality and SCD as it serves as a marker for ongoing myocardial ischemia. [8, 29] Other biomarkers associated with SCD among dialysis patients include markers of inflammation (IL-6[7], C-reactive protein[7], and adiponectin[30]) and nutrition (serum albumin[7], pre-dialysis serum creatinine[27]), but these factors have not been validated across cohorts.

Prevention of SCD

The major question facing any risk-stratification study is what to do with the results. Avoidance of rapid fluid and electrolyte shifts and specifically low potassium dialysate in hemodialysis is supported by observational data, but it remains to be seen if frequent or long slow hemodialysis or other modifications to improve the tolerability of the dialysis procedure will prove beneficial in preventing SCD. Otherwise, there appear to be few effective therapies available to prevent SCD in dialysis patients. Beta-adrenergic blockers, a proven therapy in the post-myocardial infarction and heart failure patient, hold promise but have been insufficiently studied [31]. There are no data on prevention of SCD using anti-arrhythmic therapy. Implantable cardioverter-defibrillators (ICD), a highly effective but expensive technology with a proven track record in the heart failure population, have also been inadequately studied. Though dialysis patients currently make up 4% of all ICD implants in the U.S., there is no prospective trial data assessing their utility. The USRDS reports a median survival of only 18 months in dialysis patients receiving an ICD for primary prevention indications, well below that of the non-dialysis ICD recipient[32]. Furthermore, dialysis patients have a 5-fold increase in complications following device implantation, some potentially serious[33, 34].

Future directions:

Clearly, major issues remain. It is apparent that the standard risk factors for SCD derived from the general population may not apply to dialysis patients and that disease specific, large-scale, prospective cohort studies are necessary to better risk-stratify these individuals. These studies should include heterogeneous populations of both peritoneal and hemodialysis patients, employ a full spectrum of available non-invasive risk stratification techniques from cardiac imaging to biomarkers to electrophysiologic assessments, and have carefully adjudicated endpoints. Barriers preventing the linkage of data from registries such as the USRDS and ICD Registries should be removed in order to allow for population-wide cohort and case-control studies. Ultimately, randomized trials assessing the spectrum of interventions, from medical therapies to ICDs, will be necessary. In order to even hope to impact on the alarming SCD rate in CKD patients, we must clearly start from the beginning.

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