

Cardiovascular and Chronic Kidney Diseases: Impact of Sex and Gender, Compounding Underdiagnosis, Atypical Presentations, Undertreatment, and Underrepresentation

February is
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By Manisha Singh

The fact that chronic kidney disease (CKD) and cardiovascular diseases (CVDs) are closely related would not surprise any healthcare professional. Of note, the data show that the primary cause of death resulting from CKD is a cardiovascular event and also that CKD is one of the important risk factors for CVD.

We have established data that CKD awareness and research are lagging despite the significant impact of this disease on patients and the healthcare system. CVD, traditionally thought to be a “male” problem, is actually the main killer of older people of both sexes universally. In fact, each year CVD is the cause of more deaths in older women than in older men (7.4 million women over 60 years of age compared with 6.3 million men in 2004). In addition, CVDs are thought of as diseases of affluence, whereas in reality, cardiovascular mortality rates for older women are more than twice as high in low-income and middle-income countries as in high-income countries. In addition, women are less likely to seek medical help and therefore may not receive timely and appropriate care.

To make matters even more concerning is the lack of attention to sex and gender differences in the focus of research. This article attempts to assess the impact of sex and gender in both diseases and to highlight areas of gaps in research. We attempt to highlight sex and gender awareness and its relevance to designing appropriate trials, and to bring attention to strategies for increasing the inclusion of women as research participants going forward.

following words: “For transgender people, their own internal gender identity does not match the sex they were assigned at birth. Most people have a gender identity of man or woman (or boy or girl). For some people, their gender identity does not fit neatly into one of those two choices (nonbinary and/or genderqueer). Unlike gender expression, gender identity is not visible to others.” In 2016, about 1.4 million people identified as transgender in the United States.

Gender exposes the person to unique aspects of healthcare, especially disparities and biases that have an impact on access to care. This makes understanding this aspect of a person’s life extremely important for healthcare professionals. The most vulnerable in this group, transgender people, like women, remain severely underrepresented in research. Aside from patient and provider biases from and against healthcare, the healthcare aspects also include the results of gender change surgeries, the effects of hormonal change, delayed diagnosis, and a physicians’ discomfort regarding appropriate treatment strategies, not to mention communication blocks (e.g., how to refer to a transgender person) even from the most well-meaning physician. About 80% of the physicians in a survey at Johns Hopkins thought that patients would not want to talk about their sexual orientation, whereas only 10% of patients said they would refuse to answer that question. In this context, competence in transgender issues is important in the training of a physician. In the realm of CKD and CVD, the transgender group is high risk.

Diagnostics are affected because the reference ranges of all laboratory values are based on biologic sex, whereas there are significant gender-specific changes that happen when a transgender person is receiving therapy. In 2018, at the 70th

cular risk factors, although there was no increase in mortality.

The diagnosis of CKD and ascertaining its risk factors present unique challenges, as mentioned above, because estimated GFR and creatinine measurements change on the basis of sex and generation of creatinine, which is muscle mass dependent. With overlap of the CVD risk factors, there are additional concerns. This patient subgroup has higher risks for recurrent acute kidney injury from obstructions (post-operative complication of urethral strictures), urinary tract infections, depression resulting from genetic body image changes, and poor access to unbiased care.

Conversely, in some cases providers are unable to move past gender identity and blame that for many of these patients’ unrelated health concerns.

Unfortunately, and not unexpectedly, few data are available that focus on gender research, and all the studies identified appear to be using sex and gender as interchangeable entities, limiting our review to binary gender difference. From here onward, the discussion is focused on binary sex difference.

Presentation, treatment, and outcomes

In patients with CKD and in women, “oligosymptomatic” presentation of acute coronary syndrome (ACS) is common. About 44% of patients with CKD grade 3a or higher experience acute MI, presenting with the typical symptoms of chest, arm, shoulder, or neck pain, compared with 72% of patients with normal kidneys. Most patients with CKD present with fatigue and dyspnea. When that is compared with the traditional presentation of women with ACS, major confounding and a potential for missed diagnosis exist. Women commonly present with unstable angina. ACS presentations are broad (atypical): fatigue; dyspnea; pain in the neck, jaw, or back; nocturnal dyspnea; nausea; indigestion; cough; palpitations; dizziness. Women also tend to have more Q wave abnormalities and to be about 10 years older at presentation.

Another concerning piece of data is that women are less likely to be referred for angiography and are less likely to receive fibrinolytic therapy, percutaneous coronary intervention, or coronary artery bypass surgery. The diagnosis of silent ACS, although it was present in a similar number of cases (27% in men, 26% in women) was significantly delayed in women because approximately one half lacked identifiable symptoms and the other half had atypical symptoms that were not recognized by either the patients or their physicians. Women also have higher in-hospital and long-term mortality after MI.

Impact

Population and epidemiology studies reveal that the primary all-cause mortality for women is a cardiovascular event. The World Heart Federation reports that heart attacks claim the lives of 3.3 million women yearly; another 3.2 million women die of stroke, and 2.1 million women die of other CVDs. Diagnostic delays are common, especially because the presenting symptoms in women may be quite different from those in men. Women smokers have a higher risk than men smokers, and the same pattern is seen with weight, lipid profile, and diabetes prognosis. Women are also less likely to seek medical care, especially those living in rural areas, compounding the impact of disparities on access to healthcare.

[T]here is a scarcity of research in populations with coexisting CKD and CVD, specifically with equitable attention to sex and gender.

Terms

Sex refers to anatomic differentiation, resulting in a binary assignment at birth and leading to physiologic changes and secondary sexual characteristics implying the hormonal and physical changes that happen with biologic maturity. This is commonly a binary system, starting from the chromosomal differences (X and Y) and leading to internal gonadal developments and to external genitalia (male or female at birth). This system can have certain anomalies, leading to assignments of intersex. The impact of sexual differences on individuals with CKD and CVD includes genetic variations, hormonal differences, and the course of diseases affected by these differences, which have a direct impact on reproductive health, including pregnancy and childbirth in women and on erectile dysfunction in men.

Gender, by contrast, refers to the psychological, social, and cultural identity that a person takes up while growing. It can be the role of a man or a woman, and it can also represent a transgender person. The GLAAD (Gay and Lesbian Alliance Against Defamation) website explains these terms with the

Annual Scientific Meeting of the American Association for Clinical Chemistry, scientists presented data showing that 6 months of transgender hormone therapy will produce marked changes in the results of common laboratory tests. This team tracked the comprehensive metabolic panel, complete blood count, and lipid test results for 147 healthy transgender patients using hormone therapy over the course of 5 years and found that red blood cell and creatinine levels underwent the largest shifts when transgender individuals started hormone therapy. These values stabilized after 6 months. In transgender women, platelet counts and low-density lipoprotein levels increased and alkaline phosphatase decreased over years before returning to baseline.

The risk factors for CVD are expected to worsen in transgender persons receiving hormone therapy, including hypertension, diabetes, and hyperlipidemia, along with an increased risk for thromboembolic events. A seminal study in *Circulation* reported that the transgender population, except transgender women, had a higher reported history of myocardial infarction (MI), even after adjustment for cardiovas-

Owing to these factors, women are usually underdiagnosed and undertreated. The risk of dying or of having a significant disability as a result of CVD is also underestimated in women.

In the CKD population, the data show that there are more women in the predialysis CKD cohort. More women volunteer to be kidney donors and primary caregivers to their partners needing care whose chronic conditions require, for example, home dialysis, although their own access to the same services is less. Obesity and diabetes outcomes are also not similar for men and women; positive outcomes favor men. The impact of treatment is also different for women because reproductive health is integral to their care. In addition, complicated pregnancy and childbirth (e.g., intrauterine growth restrictions, small-for-date babies, and prematurity) affect the next generation, regardless of the sex of the baby.

The generalizability of research data to the population requires appropriate sex and gender representation. However, attention to the representation of women remains an area of concern in many trials. Even if women are well represented in numbers, the impact of the sex difference is rarely teased out from the data.

In 2001, the US Food and Drug Administration (FDA) published the results of a retrospective assessment of the drugs withdrawn between 1997 and 2000 as a result of adverse effects. The majority (8 out of 10) were withdrawn because the drugs posed greater health risks to women than to men.

To extrapolate from this, it may not be incorrect to state that women with CKD can be expected to have a very high risk for CVD, stand to be underdiagnosed and undertreated, and are at an exceptionally high risk for ensuing complications.

Research

Studies have consistently shown an increased risk of ischemic heart disease, heart failure, and arrhythmias in patients with CKD. On the other hand, CKD confers a significantly greater risk for poor outcomes in patients with CVD. Despite this association between CKD and CVD, randomized controlled trials investigating CVD have historically excluded

people with preexisting CKD. Of 12,794 studies that appear on clinicaltrials.gov for CVD (studies that were active, recruiting, and not recruiting), only 2712 were focused on CKD, and only 412 were studies on CKD and CVD combined.

The global participation report by the FDA states that globally only 43% of participants in clinical trials are women (the United States leads with 49.1%).

From the 1977 FDA ban of women of childbearing potential from research (which was an attempt to protect the most vulnerable women after the thalidomide disaster) to reversal of the policy in 1993, gender balance has been skewed against women in research participation. This is despite the fact that disease parity exists with worse outlook for women. A review article from the National Institutes of Health Office of Research on Women's Health indicated that women reported inconvenience related to securing transportation, along with the associated cost and time, limiting their ability to participate in clinical research. Women also identified childcare commitments, in addition to transportation, as barriers to participation in multiple research studies. Given the above-stated concerns, a broadening of trial eligibility and attempts to make it easier for women to participate are warranted in the design of new studies.

We conclude that there is a scarcity of research in populations with coexisting CKD and CVD, specifically with equitable attention to sex and gender. These subpopulations have high risks, present atypically, are at high risk for being underdiagnosed and undertreated, and face worse complications. We believe that physicians need deliberate training to diagnose, treat, and recruit for research with intentional inclusion and attention to these populations. ■

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Suggested Reading

1. Sarnak MJ, et al. Chronic kidney disease and coronary artery disease: JACC state-of-the-art review. *J Am Coll*

Cardiol 2019; 74:1823–1838.

2. Maini R, et al. Persistent underrepresentation of kidney disease in randomized controlled trials of cardiovascular disease in the contemporary era. *J Am Soc Nephrol* 2018; 29:2782–2786.
3. Marenzi G, et al. Chronic kidney disease in acute coronary syndromes. *World J Nephrol* 2012; 1:134–145.
4. Sosnov J, et al. Differential symptoms of acute myocardial infarction in patients with kidney disease: A community-wide perspective. *Am J Kidney Dis* 2006; 47:378–384.
5. https://www.who.int/gho/women_and_health/mortality/situation_trends_causes_death/en/
6. Lynch M. Women in clinical research through the years. <https://www.fda.gov/consumers/womens-health-topics/women-clinical-trials>.
7. EUGenMed Cardiovascular Clinical Study Group, et al. Gender in cardiovascular diseases: Impact on clinical manifestations, management, and outcomes. *Eur Heart J* 2016; 37:24–34.
8. Women's health and kidney disease. *Nat Rev Nephrol* 2018; 14:139.
9. <https://www.glaad.org/about>.
10. Streed CG, et al. Cardiovascular disease among transgender adults receiving hormone therapy: A narrative review. *Ann Intern Med* 2017; 167:256–267.
11. Alzahrani T, et al. Cardiovascular disease risk factors and myocardial infarction in the transgender population. *Circ Cardiovasc Qual Outcomes* 2019; 12:e005597.
12. Whitley CT, Greene DN. Transgender man being evaluated for a kidney transplant. *Clin Chem* 2017; 63:1680–1684.
13. Whitley C. <https://thebodyisnotanapology.com/magazine/the-amazing-failing-body-being-a-trans-person-with-kidney-disease-2/>.
14. SoRelle JA, et al. Impact of hormone therapy on laboratory values in transgender patients. *Clin Chem* 2019; 65:170–179.
15. Review of the literature: Primary barriers and facilitators to participation in clinical research. https://orwh.od.nih.gov/sites/orwh/files/docs/orwh_outreach_toolkit_liter-view.pdf.

Coronary Microvascular Dysfunction Is Linked to Cardiovascular Risk in CKD

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In people with chronic kidney disease (CKD), the risk of cardiovascular events is independently related to coronary microvascular dysfunction—and not to estimated glomerular filtration rate (eGFR), according to a study by Navkaranbir S. Bajaj and colleagues in a recent issue of *Circulation*.

The longitudinal study included 352 patients referred for stress myocardial perfusion positron emission tomography (PET) at the authors' hospital from 2006 through 2016. Other evaluations included two-dimensional echocardiography and serum creatinine measurement. Patients with overt obstructive coronary artery disease were excluded from the analysis.

The patients' median age was 55 years; 63% were women and 22% were black. Their median left ventricular ejection fraction was 62% on echocardiography and 59% on PET, and more than 70% had abnormal left ventricular remodeling. CKD was present in 35% of patients, who had a mean eGFR of 41.0 mL/min/1.73 m².

Those patients with stage 3 or higher CKD were more likely to have hypertension and diabetes, and they also had a lower body mass index. On PET, patients with CKD had lower stress myocardial blood

flow (1.7 versus 2.1 mL/min/g) and lower coronary flow reserve (1.5 versus 1.9). The authors considered these findings to represent coronary microvascular dysfunction. Both eGFR and coronary flow reserve were associated with diastolic and systolic echocardiographic indexes, as was the risk of adverse cardiovascular events.

On multivariable analysis, however, coronary flow reserve was independently associated with cardiac mechanics and cardiovascular event risk whereas GFR was not. And on stratified analysis, a severely abnormal coronary flow reserve of less than 1.5 was associated with a 1.61 adjusted hazard ratio for major adverse cardiovascular events.

In this study, coronary microvascular dysfunction was a significant mediator of the associations among eGFR, cardiac mechanics, and cardiovascular events. In fact, in fully adjusted models, coronary microvascular dysfunction accounted for 32% of the relationship between impaired renal function and major adverse cardiovascular events, the authors noted.

Even in the absence of overt coronary artery disease, patients with CKD are at elevated risk of cardiac dysfunction and cardiovascular events. Coronary mi-

crovascular dysfunction might help to explain the impaired cardiac function and increased cardiovascular risk associated with abnormal renal function, according to the authors.

The new study suggests that coronary microvascular dysfunction is associated with cardiovascular risk in CKD patients without overt coronary artery disease and might mediate the effects of eGFR on cardiac function and cardiovascular events.

"The presence of coronary microvascular dysfunction signals the transition from physiological to pathological left ventricular remodeling that increases the risk of heart failure and death in patients with chronic kidney disease," Bajaj and colleagues write.

"[O]ur study raises the possibility that efforts to attenuate microvascular disease could produce benefits on myocardial dysfunction and cardiovascular events," they state. ■

Bajaj NS, et al. Coronary microvascular dysfunction, left ventricular remodeling, and clinical outcomes in patients with chronic kidney impairment. *Circulation* 2020; 141:21–33.