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Review

Sex-Based Gaps in the Prescription of Cardio-Nephroprotective Medications in CKD

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Abstract

Chronic kidney disease (CKD) is a major global health burden associated with substantially increased risks of morbidity and mortality. Cardiovascular disease remains the leading cause of death across all stages of CKD. Over the past decades, several pharmacologic therapies—including renin–angiotensin system inhibitors, sodium–glucose cotransporter-2 inhibitors, mineralocorticoid receptor antagonists, glucagon-like peptide-1 receptor agonists, and lipid-lowering agents—have demonstrated substantial cardio-nephroprotective benefits and are recommended in international guidelines. However, real-world implementation of these therapies remains incomplete, and emerging evidence highlights important sex-based disparities in prescribing patterns. Although CKD is more prevalent in women worldwide, women with CKD are consistently less likely than men to receive guideline-directed cardioprotective and nephroprotective medications. This treatment gap spans both traditional therapies, such as angiotensin-converting enzyme inhibitors and statins, and newer agents with proven outcome benefits. Women are less likely to initiate treatment, less likely to receive high-intensity or target doses, and less likely to achieve recommended blood pressure and lipid goals. Importantly, the presence of CKD attenuates the usual female survival advantage, and the relative excess cardiovascular risk associated with CKD may be particularly pronounced in women. The under-prescription of cardio-renal therapies in women with CKD reflects a complex interplay of factors. These include older age at presentation, higher reported rates of adverse drug reactions, concerns regarding tolerability and safety in advanced kidney disease, therapeutic inertia, underestimation of cardiovascular risk, and persistent underrepresentation of women in clinical trials. Biological differences in pharmacokinetics and pharmacodynamics, as well as structural and system-level barriers, further contribute to inequities in care. Addressing these disparities requires improved risk recognition, sex-informed prescribing practices, enhanced representation of women in clinical research, and implementation strategies that incorporate sex-disaggregated performance metrics. Reducing treatment gaps is essential to improving cardiovascular and renal outcomes and to achieving equitable, precision-based care for women with CKD.

Keywords: under-prescription; women; cardiovascular disease; mortality

1. Introduction

Chronic kidney disease (CKD) affects nearly 800 million people worldwide and is strongly associated with premature mortality, largely driven by cardiovascular disease (CVD). Individuals with CKD face a markedly elevated risk of heart failure, atherosclerotic events, and cardiovascular death across all stages of kidney dysfunction. In recent years, several pharmacological therapies—including renin–angiotensin system inhibitors, sodium–glucose cotransporter-2 inhibitors (SGLT2i), nonsteroidal mineralocorticoid receptor antagonists, and glucagon-like peptide-1 receptor agonists(GLP1RA)—have demonstrated substantial cardio-renal protective effects and are now recommended in international guidelines [1]. However, real-world implementation of these therapies remains incomplete [2].

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Sex disparities represent a critical but under-recognized dimension of CKD care. Although CKD is more prevalent in women globally, women experience differences in disease recognition, risk assessment, referral patterns, and therapeutic management [3]. Importantly, the cardiovascular risk associated with CKD appears to attenuate the usual female survival advantage, and in some settings women with CKD experience a relatively greater excess (compared to men) cardiovascular risk compared with sex-matched individuals in the general population [4].

Emerging evidence consistently shows that women with CKD are less likely than men to receive guideline-directed cardioprotective and nephroprotective medications across multiple drug classes and clinical settings. These disparities likely reflect a complex interaction of biological factors, higher reported adverse drug reactions, therapeutic inertia, concerns regarding tolerability and safety, older age at presentation, and persistent gaps in sex-specific evidence from clinical trials. This review aims to summarize current evidence on sex disparities in the prescription of cardioprotective and nephroprotective therapies among women with and without CKD, explore the underlying mechanisms contributing to underuse, and highlight clinical and research priorities to improve equitable cardio-renal care and outcomes.

2. Sex Disparities in the Epidemiology of CVD

Cardiovascular disease is the leading cause of death for women globally, responsible for approximately 30–35% of all female deaths—exceeding mortality for all cancers combined [5]. While substantial advancements have been made in understanding and managing CVD, a growing body of evidence indicates persistent and clinically significant disparities across sexes in its epidemiology, diagnosis, and treatment. CVD mortality is rising specially in younger women (<55 years), with women facing higher rates of death following a first heart attack than men [6]. These disparities are not merely reflections of biological differences, but often stem from a complex interplay of physiological, social, and systemic factors that result in unequal access to optimal care and suboptimal outcomes for a significant portion of the population, particularly women.

Epidemiological data consistently highlights distinct patterns of CVD presentation between sexes. For instance, ischemia with No Obstructive Coronary Arteries (INOCA) and Myocardial Infarction with No Obstructive Coronary Arteries (MINOCA) are markedly more prevalent in women, often leading to worse long-term outcomes, including increased risks of future cardiac events and reduced quality of life [7,8]. Similarly, heart failure with preserved ejection fraction presents a pronounced female prevalence, exhibiting a 2:1 female-to-male ratio [9].

Beyond epidemiological differences, significant disparities are observed in the diagnostic pathways for CVD. Women frequently experience diagnostic delays due to atypical symptom presentation and diagnostic criteria that have historically been normed on male cohorts [10]. For example, while chest pain remains a primary symptom for both sexes during Acute Coronary Syndrome, women are more likely to present with additional non-chest pain symptoms or without chest pain entirely, often leading to delayed recognition and intervention [11]. Women are offered fewer diagnostic tests, such as coronary angiography, and are less frequently referred for specialist CVD care [12].

Moreover, disparities extend profoundly into the treatment and management of CVD. Studies demonstrate that women are less likely to receive guideline-directed invasive management for Acute Myocardial Infarction, like percutaneous coronary intervention [10]. These disparities contribute to worse in-hospital outcomes for women, including higher rates of major adverse cardiovascular and cerebrovascular events, all-cause mortality, and stroke, even after accounting for comorbidities. Furthermore, post-diagnosis, women with established coronary heart disease often achieve fewer secondary prevention targets for lipids and glucose compared to men, despite sometimes exhibiting better blood pressure control [13]. These cumulative gaps in epidemiology, diagnosis, and treatment highlight a systemic deficiency in current cardiovascular care, urge for sex-specific diagnostic protocols and enhanced clinician vigilance to prevent misdiagnosis and improve timely intervention [14].

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3. Sex and Prescription Patterns in Patients with CVD

Sex differences in the use of cardioprotective therapies are consistently observed across the CVD care continuum, from primary prevention to long-term secondary prevention. Women receive fewer guideline-recommended treatments than men, despite comparable or higher cardiovascular risk. These differences reflect the combined influence of patient, clinician, and health system level factors (Figure 1). Awareness of cardiovascular risk among women remains incomplete. Although it increased from 30% in 1997 to 54% in 2009 [15], underestimation of personal risk limits engagement with pharmacological prevention and prioritize non-evidence-based strategies such as fish oil or vitamins. At the clinician level, women are more frequently classified as lower risk despite similar absolute risk [16]. Contributing factors include limited training in sex-specific risk assessment, under recognition of differences in disease presentation, implicit bias, and reliance on risk prediction tools derived largely from male populations. System-level factors include suboptimal performance of traditional risk models in younger women and the persistent underrepresentation of women in cardiovascular clinical trials, which limits the sex-specific evidence base [17].

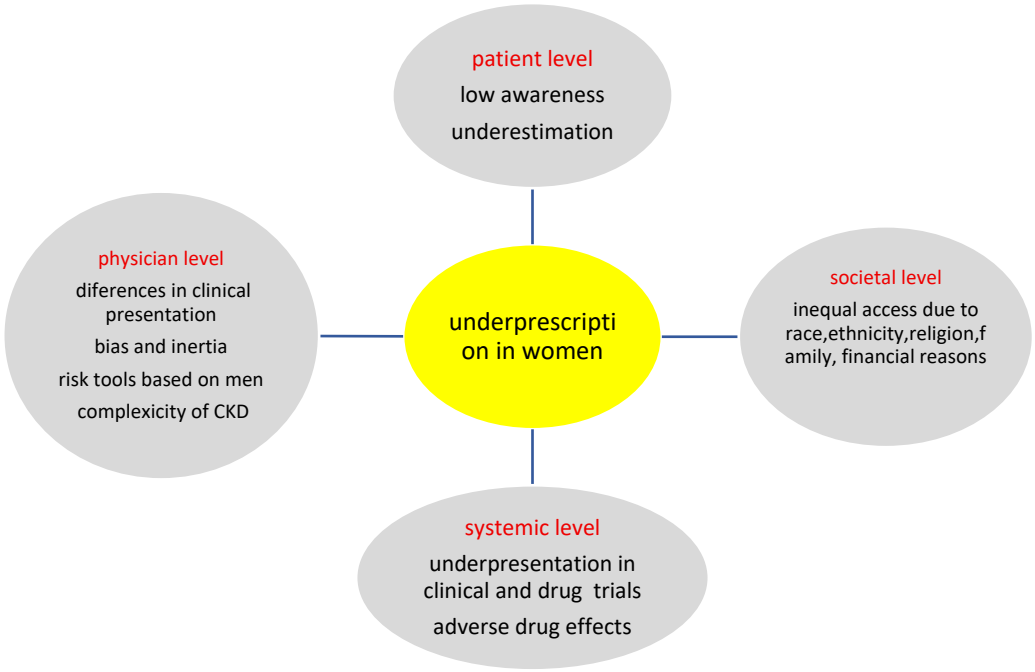

Figure 1. Possible factors φοϱ under-prescription of cardio-nephroprotective medications in women.

3.1. Primary Prevention

Effective primary prevention requires risk identification, treatment initiation, and timely intensification. Sex differences are evident at each step. Women are less likely to receive statins for primary prevention and, when treated, are less likely to receive high-intensity therapy or dose escalation [18,19]. Observational studies show lower treatment rates despite similar or higher lipid levels and a lower likelihood of achieving lipid targets [20]. These disparities persist in high-risk populations, including individuals with diabetes [21].

Overall prescribing rates for antihypertensive therapy are generally similar between sexes. However, women tend to receive lower defined daily doses and are treated more often with beta-blockers and diuretics, whereas men more frequently receive renin–angiotensin system blockers or calcium channel blockers [22,23]. The largest difference in primary prevention is observed for antithrombotic therapy. Women are less likely to receive aspirin when eligible, and lower use persists after adjustment for comorbidity and socioeconomic factors [24]. In atrial fibrillation, women are also less likely to receive anticoagulation despite similar or higher stroke risk [25] (Table 1).

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Table 1. Sex differences in the prescription of major cardioprotective and nephroprotective drug classes in cardiovascular disease and chronic kidney disease (CKD) populations. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; SGLT2i, sodium–glucose cotransporter-2 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonists; CKD, chronic kidney disease; CVD, cardiovascular disease.

A. Cardiovascular disease populations				
Drug Class	**Clinical Setting**	**Men**	**Women**	**Reference**
Statins (guideline intensity)	Coronary artery disease	65.8%	61.6%	26
	Secondary prevention	Non-Hispanic black 19% less likely than white men	Non-hispanic black 25% less likely than white men	27
Aspirin	Secondary prevention	18.2% (events/total participants)	11.9 (events/total participants)	29
Multidrug cardioprotective regimen (antiplatelet + statin +β-blocker +ACEi/ARB)	Secondary prevention	34%	22&	38
SGLT2 inhibitors	Heart failure /Diabetes	19.8%	11.2%	32
	Diabetes and CVD	58.1%	41.4%	34
GLP-1 RAs	Diabetes with CVD risk	59.2%	40.3%	34
B. CKD populations				
Drug Class	**Clinical Setting**	**Men (%)**	**Women (%)**	**Reference**
ACE inhibitors / ARBs	CKD-REIN cohort	79	71	52
SGLT2 inhibitors	Primary care	67.9	56.5	54
	Hert Failure with severe CKD	52.9	34.1	50
	CKD real-world database		42% less likely than men	57
	US Veterans CKD cohort		41% less likely than men	58
GLP-1 RAs	Diabetic CKD	14.9	11.8	59
Oral antidiabetics	CKD-REIN diabetic CKD	26	20	56
Statins	Primary care	Similar	Similar	54

3.2. Secondary Prevention

Among patients with established CVD, women consistently receive less intensive guideline-directed therapy and are less likely to achieve treatment targets. Women with coronary artery disease are less likely to receive high-intensity statins and less likely to achieve LDL cholesterol goals [26]. National data demonstrate women disparities across racial and ethnic groups even after adjustment for clinical and socioeconomic factors [27]. (Table 1).

Aspirin shows the largest sex disparity in secondary prevention. Women are less likely to receive aspirin or other antiplatelet agents [28,29]. Global evidence shows mixed results, but overall patterns favor men, and women are more often treated with clopidogrel rather than more potent P2Y12 inhibitors [30]. Moreover, in secondary prevention populations, women are less likely to receive beta-blockers and ACE inhibitors and more likely to receive diuretics [22]. Similar patterns have been observed internationally, with lower ACE-I/ARB use among women [31].

Sex differences extend to contemporary therapies. Women are less likely to receive SGLT2i [32], mineralocorticoid receptor antagonists [33], and GLP1RAs [34] despite established cardiovascular

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benefit. As optimal secondary prevention requires combination therapy, these differences translate into lower use of comprehensive multidrug regimens. In an Australian cohort, only 22% of women versus 34% of men received a four-drug regimen (antiplatelet + statin + beta-blocker + ACE-I/ARB), indicating women were 35% less likely to receive optimal treatment [35]. In contrast, EUROASPIRE III showed similar prescription rates but poorer risk-factor control among women, suggesting differences in treatment intensity rather than access [36]. Treatment intensity also differs after initiation. Women are less likely to undergo dose escalation and more likely to remain above blood pressure and lipid targets [36]. Following acute cardiovascular events, they are more likely to discontinue therapy within the first year. Across studies, lower target attainment in women reflects a combination of lower treatment intensity, therapeutic inertia, adverse effects, and adherence challenges [21,26,28].

4. Sex Disparities in Epidemiology of CKD

Sex disparities in the epidemiology of CKD are consistent across regions and healthcare systems and have important clinical and public health implications. In 2023, 788 million people aged 20 years and older were estimated to have CKD, up from 378 million in 1990 [37] - more prevalent in women than in men across most geographic areas and socio-demographic strata. In national surveys such as the National Health and Nutrition Examination Survey, women account for approximately 56–59% of individuals with CKD across all stages [38], a pattern that is also reflected in global estimates from the Global Burden of Disease study [39]. This female predominance is observed particularly in earlier CKD stages and in older age groups [39], particularly post menopause.

Paradoxically, despite the higher overall prevalence in women, CKD progression appears to be more rapid in men. Longitudinal cohort studies consistently demonstrate a steeper annual decline in estimated glomerular filtration rate in males, especially among middle-aged and elderly individuals [40,41]. Men are more likely to develop advanced albuminuria and to transition from moderate CKD to kidney failure. In diabetic kidney disease, for example, males more frequently present with moderate-to-severe albuminuria (A2/A3 categories) [42], and similar sex-related differences have been described in hypertensive nephropathy and selected primary and systemic glomerular diseases [43,44]. The sex dimorphism in CKD progression is mainly hormone-mediated, with androgens exacerbating renal injury through pathways like RAAS activation and inflammation, while estrogens provide protective effects by stabilizing RAAS, enhancing antioxidant capacity, and reducing fibrosis [45]. Additionally, sex-specific genes on the X and Y chromosomes influence CKD susceptibility and progression by modulating immune responses, oxidative stress, and fibrosis [45].

The divergence between prevalence and progression is clearly illustrated in kidney replacement therapy (KRT) statistics. Although women constitute most patients with earlier stages of CKD, men are more likely to reach kidney failure and initiate dialysis or undergo transplantation [46,47]. This discrepancy likely reflects a combination of faster disease progression in men and potential gender-related differences in referral patterns, access to specialized care, and treatment decisions. Both in the overall population and across age groups, mortality and the age-standardized DALYs rate of CKD was higher in males compared to females [39]. In some high-income countries, CKD ranks among the leading causes of death in women [48], highlighting its growing public health relevance. However, the relative excess risk compared with sex-matched individuals in the general population may be greater in women, particularly in advanced CKD and during kidney replacement therapy [4]. For instance, in Europe the expectancy remaining years of life for all age groups combined was approximately 66% and 68% shorter for males and females on dialysis, and 46% and 49% shorter for males and females living with a functioning kidney graft when compared to males and females in the general population [49]. These complex and sometimes paradoxical patterns reflect the interplay between biological sex, gender-related determinants, and healthcare system factors, and they emphasize the need for sex-specific analyses in CKD research, prevention strategies, and policy planning.

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5. Under—Prescription of CVD Medications in Women with CKD

While sex disparities in cardiovascular care are well documented in the general population, data on prescribing patterns in patients with CKD remain limited and less well characterized. A multicenter real-world registry of 914 patients with Heart Failure reduced Ejection Fraction found that those with eGFR <30 mL/min/m² received significantly lower proportions of all guideline-recommended medications compared to men: sacubitril-valsartan (30.5% vs. 59.2%), MRAs (31.7% vs. 77.8%), and SGLT2i (34.1% vs. 52.9%) [50]. This disparity spans multiple drug classes—from traditional RAS inhibitors to newer agents like SGLT2i and GLP-1Ras, occurs across diverse clinical settings and represents a major therapeutic gap with profound clinical consequences, particularly in a population where women with CKD face disproportionately higher cardiovascular risk than their male counterparts [4]. In a retrospective cohort analysis with data extracted from TriNetX database of 328,431 individuals, among individuals with CKD the female survival advantage shrinks by approximately 38% compared to what is observed in non-CKD populations [51] (Table 1).

1. Renin-Angiotensin System (RAS) Inhibitors

RAS inhibitors remain fundamental to cardio- nephroprotective therapy across all CKD stages, yet their prescription rates vary significantly by sex and stage of kidney disease, with women consistently being prescribed these agents at lower rates. In the prospective CKD-REIN cohort of 3,011 patients with CKD (eGFR <60 mL/min/1.73m²), women were prescribed RAS inhibitors in 71% of cases compared to 79% in men [52]. Furthermore, women demonstrated higher incidence rates of adverse drug reactions (ADRs) compared to men in the same cohort, so this could be a possible explanation of the lower prescription rates. Beyond that, the consequences of RAS inhibitor discontinuation particularly affect women with advanced CKD. In a prospective analysis of 1,472 patients with eGFR <30 mL/min/1.73m², discontinuation of RAS inhibitors was associated with a 2.13-fold increased risk of major adverse cardiovascular events, with particularly pronounced effects in women [53]. Similarly in a large Australian primary care cohort of over 140.000 patient with CKD, women were 4% less likely to receive ACE or angiotensin receptor blocker, compared to men even after adjustment for clinical and sociodemographic characteristics [54]. In Europe a Swedish observational study of 227,847 patients with CKD demonstrated that women had lower odds of receiving RAS inhibitors at inclusion, disparity that persisted across disease severity [55] .

2. Glucose lowering treatments

Sex-based differences in glucose-lowering treatment efficacy and safety have important implications for overall management of patients with type 2 diabetes and CKD. The CKD-REIN prospective cohort study indicated that glycemic control, treatment response and hypoglycemic symptoms exhibit sex-specific patterns [56]. Hypoglycemic symptoms were more frequent in women and required closer monitoring with appropriate patient education, particularly in the female population. While overall metformin use was similar between sexes in CKD stage 3, more women than men used insulin at stages IV and V.

Robust evidence supports the use of SGLT2i in patients with CKD for their cardiorenal protective effects including reductions in eGFR decline, albuminuria, and heart failure risk [1]. However, significant gender disparities persist in this population in real world. A retrospective study in Japan, that included 358.134 patients with GFR <60ml/min with or without diabetes with or without established CVD, stated that being a woman was an independent risk factor for lower prescription rates [57] . Even following regulatory approval and guideline endorsement, prescription rates have increased more slowly for women demonstrating a persistent gender gap. Similarly in the US a study conducted among 172.443 Veterans with CKD, diabetes and CVD, women had significantly lower odds to be prescribed with SGLT2 inhibitors compared to men [58].

GLP-1 RAs represent a transformative therapeutic class with compelling evidence for cardio-renal protection in patients with type 2 diabetes and CKD. Yet these agents remain profoundly underutilized globally, with particularly stark sex-based disparities in prescription patterns [34]. In an Italian registry of 139,202 diabetic patients stratified by cardiorenal phenotype, women with

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isolated CKD (without CVD) received GLP-1 RAs in 11.8% of cases compared to 14.9% of men [59]. In the same study GLP-1RA prescriptions were driven more strongly by body mass index and age than CV or renal risk, potentially disadvantaging women wih high CV risk bit lower body mass index.

3. Lipid lowering therapies:

Current KDIGO guidelines recommend a «fire and forget» primary prevention strategy with the prescription of a high intensity statin in the setting of an initial pharmacological approach [1]. Despite these recommendations, real world data are far from being aligned with these guidelines. In the Australian primary care study, no significant difference was found in overall statin use rated between men and women. However, women were less likely to achieve lipid control targets within 18% lower likelihood of reaching LDL targets [54]. Similarly in a Swedish cohort, women with CKD had lower probabilities of receiving guideline- recommended statin at inclusion [55].

In advanced CKD, cardiovascular risk is particularly high, and suboptimal treatment is associated with substantial excess morbidity. Older women with CKD represent a vulnerable subgroup in whom cardio-renal therapies are frequently underutilized or insufficiently optimized. The sex gap in cardiovascular prescribing in CKD is multifactorial. As kidney function declines, therapeutic decisions become more complex, particularly in stages 3–5 CKD, where concerns regarding hyperkalemia, hypotension, drug accumulation, and renal safety may limit initiation or continuation of therapy. Women with CKD also tend to present at older ages than men with comparable disease severity, and clinicians may adopt more conservative prescribing practices in elderly populations. In addition, women are less likely to receive dose escalation to guideline-recommended targets and report higher rates of adverse drug reactions across several cardiovascular drug classes. Importantly, some of these differences may reflect not only clinical complexity but also persistent sex bias in drug development and clinical research, which has limited the generation of robust sex-specific efficacy and safety data.

4. Sex bias in drug trials

The biological reality that “every cell has a sex” is a fundamental principle often ignored in modern drug development and biomedical research. For decades, scientific inquiry has leaned heavily on an androcentric model, predominantly using male subjects to represent the entire human population. This historical bias has created a significant “sex-gap” that stretches from early preclinical animal studies to clinical trials and post-marketing drug surveillance, often resulting in suboptimal therapy and increased health risks for women [60]. This prompted the National Institutes of Health in the United States in 2016 to implement a policy requiring investigators to consider sex as a biological variable [61]. A 10-year follow-up study of sex inclusion across interdisciplinary research identified that there was a significant increase in the number of studies that included both sexes across neuroscience, immunology, endocrinology, general biology, physiology and behavioral physiology [62,63]. Nevertheless, in pharmacology, there was no change in the proportion of studies that included data specifically analyzed by sex.

A primary driver of this disparity is the disproportionate use of male animals in preclinical research. A survey of nearly 2,000 animal studies revealed a male bias in eight out of ten biological disciplines, most notably in neuroscience (5.5 males to 1 female) and pharmacology (5 males to 1 female) [62]. This bias persists even though many diseases, such as anxiety, depression, and certain thyroid disorders, are significantly more prevalent in women. Researchers have historically avoided female animals due to the misconception that estrous cycles introduce excessive data variability [64]. By excluding females, researchers fail to identify sex-specific disease mechanisms, leading to animal physiological and pharmacokinetic differences.

Sex-specific differences in pharmacokinetics and pharmacodynamics are well documented. Variations in body composition [65], gastrointestinal physiology, [66], drug metabolism and transporter expression affect absorption, distribution and clearance of medication in women [67,68] - aspirin is a notable example of this [69]. The failure to account for these differences has been

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associated with a 50–75% higher rate of adverse drug reactions (ADRs) and hospitalizations in women compared to men [70,71]. Many drugs are prescribed at the same dose for both sexes, despite known differences in clearance rates. A hallmark example is the sedative zolpidem; for years, women were prescribed the same dose as men, leading to high rates of next-day cognitive impairment until the FDA eventually recommended halving the female dose [72]. Beyond baseline differences, female-specific states—such as the menstrual cycle, pregnancy, and menopause further complicate drug performance. Fluctuations in estradiol and progesterone can manipulate drug efficacy [73], yet pregnant women are often excluded from trials, leaving healthcare providers to guess the risk-benefit ratio of essential treatments.

Bridging the sex gap in therapeutics requires systematic adoption of sex-informed methodologies across the research continuum. Funding bodies and journals should mandate balanced sex inclusion and require sex-disaggregated analyses, including transparent reporting of the sex of cell lines and preclinical models. Advanced tools such as physiologically based pharmacokinetic modeling can help define sex-specific dosing strategies, while artificial intelligence systems must be developed using adequately representative datasets to prevent algorithmic bias. Emerging technologies, including individualized drug manufacturing platforms, may further support tailored dosing approaches. Finally, regulatory agencies should require the submission of sex-specific efficacy and safety data for all new drug applications to ensure equitable evidence generation and therapeutic guidance.

6. Conclusions, and Future Directions

Women with CKD remain systematically undertreated with evidence-based cardioprotective and nephroprotective therapies, including RAS inhibitors, SGLT2i, GLP-1 receptor agonists, and optimized lipid-lowering treatment. This therapeutic gap occurs despite a substantial cardiovascular burden, and the loss of the usual female survival advantage once advanced CKD is present. Under-prescription is multifactorial, reflecting clinical complexity in advanced CKD, higher reported adverse drug reactions, older age at presentation, conservative prescribing practices, and persistent structural and knowledge gaps within healthcare systems. Failure to implement guideline-directed therapy likely contributes to preventable cardiovascular events, faster kidney disease progression, and excess mortality in this population.

Reducing sex disparities in CKD care requires coordinated action at multiple levels. Clinician education and training should emphasize sex-specific cardiovascular risk, differences in pharmacokinetics and tolerability, and the importance of treatment optimization rather than therapeutic avoidance. Routine audit and feedback using sex-disaggregated prescribing and target-achievement metrics may help identify gaps and improve accountability. Greater patient awareness and shared decision-making are also essential to address concerns about adverse effects and improve long-term adherence.

Future research priorities include ensuring adequate representation of women in clinical trials, mandatory sex-specific efficacy and safety analyses, and investigation of optimal dosing strategies tailored to biological differences. Implementation science approaches should evaluate system-level interventions that improve equitable access to cardio-renal therapies across the CKD spectrum. Integrating sex as a biological variable throughout research, guideline development, and clinical practice is essential to advancing precision medicine and achieving equity in cardio-renal outcomes for women with CKD.

Conflicts of Interest: The authors declare no conflicts of interest.

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