



Sex Differences Across the Cardiorenal Continuum: Implications for Hypertension, CKD, and Kidney Replacement Therapy

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AT THE 63rd European Renal Association (ERA) Congress, held in Glasgow, UK, from 3rd–6th June 2026, the session ‘Open Your Mind to Sex Differences in Hypertension, Diabetes and Chronic Kidney Disease’ explored how biological sex influences blood pressure regulation, cardiovascular disease, and kidney replacement therapy (KRT) across the spectrum of chronic kidney disease (CKD). Chaired by Juan F. Navarro-González, University Hospital Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain; and Giuseppe Grandaliano, Università Cattolica del Sacro Cuore, Rome, Italy, the symposium highlighted emerging mechanistic insights alongside growing evidence that sex-specific differences remain insufficiently recognised in current clinical practice and research.

SEX DIFFERENCES IN BLOOD PRESSURE REGULATION

Opening the session, Thenral Socrates, University Hospital Basel, Switzerland, described sex differences in blood pressure regulation as fundamental biological processes driven by interactions between sex chromosomes, sex hormones, the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system, immune pathways, and kidney-specific mechanisms.

Blood Pressure Across the Lifespan

Longitudinal cohort data demonstrate distinct blood pressure trajectories in men and women. Premenopausal women generally have lower blood pressure than age-matched men, but blood pressure begins to rise more steeply from the third decade of life.¹ Following menopause, hypertension becomes more prevalent in women than men, affecting approximately 75% of women over 60 years of age. Importantly, women also appear to develop cardiovascular disease at lower blood

pressure thresholds than men, suggesting equivalent blood pressure values may confer different cardiovascular risk between the sexes.¹



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Renal and Hormonal Mechanisms

Socrates highlighted several kidney-specific mechanisms underlying these observations. For example, women exhibit sex-specific regulation of renal sodium transporters, contributing to greater salt sensitivity, particularly after menopause. Oestrogen also modulates the RAAS through multiple pathways, exhibiting a protective effect before menopause, with loss of oestrogen protection leading to increased RAAS activation, endothelial dysfunction, arterial stiffness, and sympathetic nervous system activation.

Emerging pathways, including G protein-coupled oestrogen receptors, Klotho signalling, epigenetic regulation, and renal olfactory receptors, may further contribute to sex-specific blood pressure regulation and represent promising targets for future investigation.

One particularly striking physiological finding was that women aged 20–39 years have substantially higher aldosterone concentrations and lower renin levels than men despite lower blood pressure, resulting in a physiologically higher aldosterone-to-renin ratio. Women also exhibit a greater aldosterone response to angiotensin II.² Socrates suggested these findings may ultimately require sex-specific diagnostic thresholds when investigating disorders such as primary hyperaldosteronism in younger women.

Clinical Implications for Hypertension Management

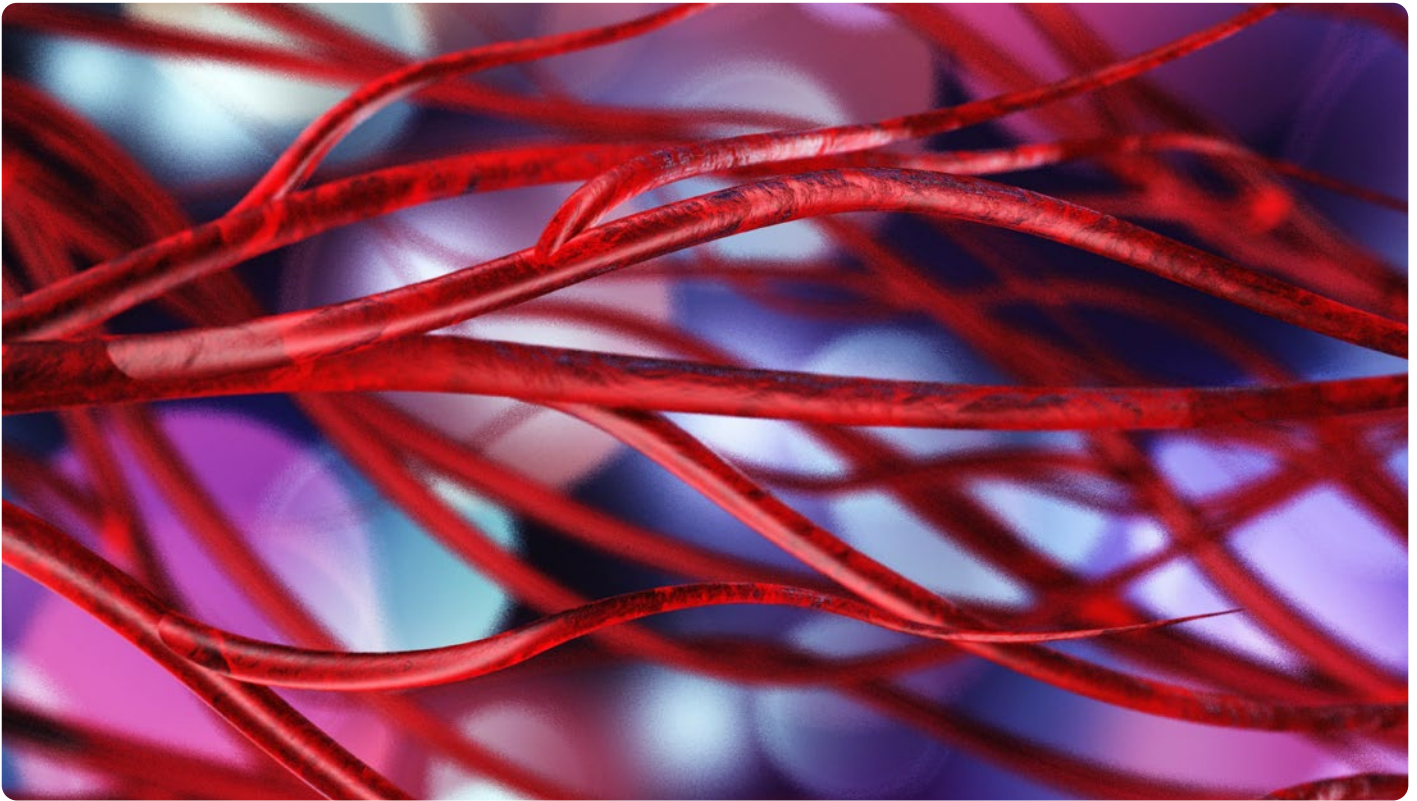
Oestrogen provides broad cardiovascular protection by enhancing endothelial function, increasing nitric oxide bioavailability, modulating the RAAS, and promoting subcutaneous rather than visceral fat deposition. In contrast, androgens

promote vasoconstriction, sympathetic activation, and visceral adiposity. Following menopause, loss of these protective effects contributes to chronic vascular remodelling and renal fibrosis.

These biological differences translate into distinct clinical phenotypes. Women are more likely to develop microvascular disease, heart failure with preserved ejection fraction, and stroke, whereas men more commonly develop obstructive coronary artery disease and heart failure with reduced ejection fraction. Pharmacokinetic differences also influence treatment. Women experience higher rates of angiotensin-converting enzyme (ACE) inhibitor-induced cough, electrolyte disturbances with diuretics, and peripheral oedema with calcium channel blockers, while lower doses of some beta blockers may achieve blood pressure control comparable to that seen with approximately double the dose in men.

Despite these differences, current hypertension guidelines recommend identical blood pressure targets for men and women. Socrates concluded by encouraging greater female representation in clinical trials, alongside studies specifically





designed to evaluate sex-specific therapeutic strategies. She finished by reminding the audience: “We should strive to have future research projects keeping these knowledge gaps in mind.”

CARDIOVASCULAR DISEASE IN CKD

Lucia Del Vecchio, Azienda Socio Sanitaria Territoriale Lariana, Como, Italy, examined how CKD fundamentally alters the established relationship between sex and cardiovascular risk.

Loss of the Female Cardiovascular Advantage

Women in the general population experience lower cardiovascular risk and longer life expectancy than men. However, contemporary registry data indicate that CKD disproportionately increases cardiovascular risk in women. Although women continue to have lower overall mortality than men, the excess risk associated with CKD is consistently greater across all-cause mortality (6.84% in females versus 5.17% in males) and myocardial infarction (5.89% versus 3.81%), as well

as stroke, heart failure, and composite cardiovascular outcomes.³

The impact becomes even more pronounced in advanced kidney disease. Young women receiving dialysis or kidney transplantation lose substantially more years of life expectancy relative to the general population (44.1 years) than men of the same age (37.1 years), highlighting the profound cardiovascular burden associated with kidney failure.⁴

Why Does CKD Affect Women Differently?

Del Vecchio outlined several potential contributors, as CKD accelerates hormonal changes, reduces oestrogen signalling, and promotes vascular stiffness, inflammation, anaemia, and exposure to uraemic toxins. Female-specific factors, including hypertensive disorders of pregnancy, gestational diabetes, autoimmune disease, and premature menopause, may further increase cardiovascular risk.

Analysis of the FINE-HEART pooled analysis showed that women with diabetes, heart failure, and CKD carried a greater burden of advanced cardiovascular-kidney-

metabolic syndrome despite receiving fewer evidence-based therapies. Del Vecchio suggested that recognising this mismatch between disease burden and treatment intensity represents an important opportunity to improve care.⁵

“**Women aged 20–39 years have substantially higher aldosterone concentrations and lower renin levels than men despite lower blood pressure**”

Inflammation and Sex-Specific Risk

Women also appear particularly susceptible to microvascular dysfunction, potentially contributing to conditions including myocardial infarction with non-obstructive coronary arteries, heart failure with preserved ejection fraction, stroke, and hypertensive disorders of pregnancy.⁶

Inflammation may represent another important mechanism. Analyses of large population cohorts demonstrated higher inflammatory biomarker levels in women, with female sex conferring an inflammatory burden comparable to established cardiovascular risk factors such as smoking.⁷

Anaemia may also have sex-specific consequences. In the CKD-REIN cohort, both women demonstrated a greater increase in risk of major adverse cardiovascular events (MACE) than men with lower haemoglobin concentrations (≤ 12 g/dL). Interestingly, women were also observed to have a greater MACE risk at higher haemoglobin concentrations (≥ 14 g/dL), representing a U-shape curve, whereas men showed a more linear association, suggesting that both low and high haemoglobin concentrations may increase cardiovascular risk in women.⁸

Encouragingly, recent evidence suggests sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists provide comparable cardiovascular benefit in women and men. However, women remain underrepresented in cardiovascular outcome trials, limiting evidence for several other therapeutic strategies.⁹

SEX DIFFERENCES IN KIDNEY REPLACEMENT THERAPY

Closing the session, Vianda S. Stel, ERA Registry, Amsterdam, the Netherlands, presented data from the ERA Registry examining sex differences across KRT in Europe.



Epidemiology and Access to Care

Approximately 60% of patients commencing KRT are men and 40% are women. Although CKD prevalence is generally higher in women, kidney function declines more rapidly in men, resulting in greater progression to kidney failure and higher KRT incidence.¹⁰

Registry data showed that diabetes remains the leading cause of kidney failure in both sexes, while the burden of KRT continues to increase across Europe, rising more rapidly in men than women.

Within individual countries, however, the distribution of dialysis and kidney transplantation is remarkably similar between the sexes.¹¹ Although more men receive kidney transplants overall because more men progress to kidney failure,¹⁰ Stel noted that barriers to transplant waiting-list access may still exist, particularly for older women.

Outcomes and Ongoing Care Gaps

Five-year survival after dialysis remained below 50% in both sexes, while survival following a first kidney transplant approached 90%, with women retaining only a slight survival advantage.¹⁰

Importantly, registry findings suggest that disparities may begin well before KRT. Population studies from Sweden¹² and Wales¹³ indicate that women are less likely to receive a diagnosis of CKD, undergo

repeat kidney function or albuminuria testing, or be referred to a nephrologist. Such findings suggest that differences in disease progression alone cannot explain observed disparities, highlighting opportunities to improve earlier diagnosis and management.

CONCLUSION

Across all three presentations, a consistent message emerged: biological sex influences every stage of cardiorenal disease, from blood pressure regulation and cardiovascular risk to CKD progression and access to KRT. Yet clinical guidelines, diagnostic thresholds, and many treatment strategies continue to adopt largely uniform approaches.

The speakers emphasised that improving outcomes will require more than simply increasing female representation in clinical trials. A better understanding of sex-specific physiology, more equitable access to diagnosis and treatment, and studies specifically designed to evaluate sex-based therapeutic strategies are needed to translate biological insights into meaningful improvements in patient care.

As precision medicine continues to evolve, recognising sex as a clinically relevant biological variable may represent an important step towards more personalised management of hypertension, cardiovascular disease, and CKD.

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