Chelonian Conservation And Biology

Vol. 17No.2 (2022) | https://www.acgpublishing.com/ | ISSN - 1071-8443

DOI:doi.org/10.18011/2022.04(1) 892-903

COMPREHENSIVE REVIEW OF SEX DIFFERENCES IN CARDIOVASCULAR PHARMACOLOGY

Ali Mana Hutailan Almuhmidhi
aalmuhmidhi@moh.gov.sa
Ministry of Health, Saudi Arabia

Hussain Mahdi Hassan ALYAMI
halyami120@moh.gov.sa
Ministry of Health, Saudi Arabia

Salem Saleh Hamad Al Falakah
SALFalakah@moh.gov.sa
Ministry of Health, Saudi Arabia

Sheikha Saleh Hassan
salbleh@moh.gov.sa
Ministry of Health, Saudi Arabia

Mohammd Ahmad Ali Alzogly
Malzogly@moh.gov.sa
Ministry of Health, Saudi Arabia

Saad Saud Hamad Alyami
salyami42@moh.gov.sa
Ministry of Health, Saudi Arabia

Sultan Nasser Mahdi Almuhri
Snalmuhri@moh.gov.sa
Ministry of Health, Saudi Arabia

Hussein Mohammed FahidAlsogor
halsogor@moh.gov.sa
Ministry of Health, Saudi Arabia

Abstract

Cardiovascular pharmacologics, sex differences, and the following topics—pharmacokinetics, pharmacodynamics, and clinical outcome—play significant roles in this review. It deals with the importance of considering sex-related differences in cardiovascular drugs and thus highlights the

ıian Conservation and BiologyarelicensedunderaCreativeCommonsAttribution-lLicenseBasedonaworkathttps://www.acgpublishing.com/

notion of customized therapeutic strategies to improve treatment outcomes holistically. A review was conducted, and central findings from recent studies emphasizing sex hormones, genetic factors, and physiological status's role in drug responses were discussed. Moreover, it illuminates the effects of sex gaps in activity, security, and the unfavourable results of medications. This review provides excellent insight into sex-based variations in cardiovascular pharmacology, which advance the scientific knowledge of sex-specific medicine and thus aid in personalized medicine development.

Keywords: sex differences, cardiovascular pharmacology, pharmacokinetics, pharmacodynamics, and personalized medicine.

Introduction

The significance of cardiovascular diseases (CVD) is immense; presently, they manifest as the most significant cause of death globally. However, the picture becomes far more complicated due to differences observed in the frequency of diseases from male to female, the pathophysiology that serves as a possible basis for the disease, and the responses to the treatment that may vary from one to another. Despite progress in cardiac pharmacotherapy that has continued to challenge women, sex-based variations in pharmacotherapy raise such questions as whether the use of under-researched female sex could affect drug response (Zhao et. al 2020). It is crucial to know these, and it does not rest until the best corresponding treatments are discovered and used to achieve a better patient result. In this regard, the very complex interplay between sex and drug outcomes seems to hold promise for an individualized approach to treatment, which would address the particular needs of both men and women. By being aware of and taking measures to alleviate these differences, health practitioners will work towards equality and individualized cardiovascular care, diminishing the burden of CVDs on global health.

Significance of Sex Differences in Cardiovascular Pharmacology

Data that has been accumulating in recent times asserts undoubtedly the fact that sex difference is a rock-solid base over which the efficacy, safety, and toxicity of cardiovascular drugs take place. Understanding and acknowledging the significance of these differences ‘differences may be the basis for treatment and better patient outcomes. This review embraces an account of pharmacology and cardiovascular systems, focusing on the manifold relationship between gender and type of drug, in which the molecular and clinical aspects are examined in detail (Mauvais-Jarvis et. al 2021)...

Objectives of the Review

This review will attempt to provide a detailed depiction of sex differences in cardiovascular pharmacology, including across the pharmacokinetic and pharmacodynamic domains. Through the process of shining the light on how and why sex steroid hormones have different effects belonging to one sex compared to another, we will get to the core of what makes the body's

response sexually specific. Secondly, the study aims to dissect the nature of those disparities and their relationships with the therapeutic process, the safety of medicine choices, and the incidence of side effects.

Exploring Pharmacokinetic Variations

As the map indicates, pharmacokinetics indicates how drugs navigate the body, covering absorption, distribution, metabolism, and excretion (ADME). Of paramount importance are the sex differences that play a pivotal role in the pharmacokinetic processes that shape therapeutic outcomes through blood concentration and bioavailability. Eminent pieces of scientific data suggest that these disparities are dictated by unavoidable differences between individuals, like how their bodies are composed, the activity of body enzymes, and the level of different hormone fluctuations (Mauvais-Jarvis et. al 2021).

A substantial part of metabolic rates and drug distribution compositions could be significantly influenced by the fat percentage, average muscle mass, and body size differences that are characteristically seen among the male and female groups of humans. The activity of enzymes also influences the ongoing metabolism of drugs. It is mainly mediated by CYP enzymes, which then govern the rate of pharmacokinetic profile of drugs and eventually the rate at which drugs are metabolized and cleared from the body. Besides, the change in reproductive hormones across the menstrual cycle or after menopause affects time-variant drug metabolism and clearance rate, which adds complexity to the pharmacokinetic response. Clinicians can monitor, especially the differences generated by the course of medication, and select treatments to bring them as close as possible to positive treatment outcomes for women and male patients (Ferretti et. al 2020).

Deciphering Pharmacodynamic Disparities

Pharmacodynamics, the alteration brought about by drugs in the body, goes deeper into the system of receptors' interactions, signal paths, and physiological responses. In ladies, differences in pharmacokinetics are determined by hormone level variability, and in men, they result from differences in the structure and expression of receptors. In addition, distinct organ functionalities are other determinants of sex-specific variability. Such nuances carefully compose the sphere of different drug reaction profiles in men and women, making more detailed studies of therapeutic choices imperative.

Hormonal disturbances in which there is an excess or deficiency of estrogen, progesterone, and testosterone can create pivotal differences in responding to drugs by altering receptor expression and signal transduction pathways (Raparelli et. al 2020). The endocrine system's production of various hormones in all genders and phases of our lives in the human body becomes a Besides, there are also differences in receptor expression profiles between males and females, due to which the kinetic and dynamic variations in drug responses concerning sex are discrepancies that defer the drug binding affinity and cellular responses. Differences in the distribution of the receptors between organs and the course of the remedy's action are the reasons why the reactions

to the effect of a medicine are different in men and women. Also, clinicians can recognize these pharmacodynamic differences, comprehend sex-specific responses, and alter treatment approaches to address sex disparities through particular interventions, implying that medicinal results for both sexes remain optimized.

Clinical Implications of Sex Differences

Clinical practice is affected by sex differences in cardiovascular pharmacology, necessitating tailor-made methods for choosing medication, ensuring proper drug intake, and being observant of adverse events. The acquisition of knowledge relating to sex-specific pharmacodynamic peculiarities makes it possible for clinicians to shape up their patients' treatment programs to maximize effect on the one hand and minimize risk on the other. Also, there is a solid need to be more vigilant when it comes to sex-related adverse reactions to be able to further care for the excellent health of our patients and enable them to have personalized cardiovascular care (Raparelli et. al 2020).

Thus, exploring the complicated interplay between sex and cardiovascular pharmacology makes it apparent that women's differences must be respected in the therapy logic. Deconstructing the differences in biomarker behaviour between men and women provides us with the road to a healthcare strategy that helps patients with their problems. Beyond that, we are given an opportunity to scrutinize gender- and sex-specific interventions in the prevailing clinical settings, an action that brought about the era where precision cardiovascular care is commonplace and goes beyond general treatment. However, this journey through the complicated topography of medicine to accommodate the gender- and sex-differentiated adjustments in cardiovascular pharmacology led to the emergence of

Pharmacokinetic Differences

Pharmacokinetics, the underlying pillar of pharmacology, is the detailed mechanism of action of drugs within the human body, and it explains how, once administered, they get metabolized in the body. The term ADME (intake, distribution, metabolism, and expelling) is often applied by scientists to drug use, absorption, distribution, metabolism, and elimination. These changes in the difference-making pharmacokinetic processes of the sexes have a great impact on drug treatment, which is separated or mixed not just by the concentration and rate of drug absorption but also by the gender factor of drug prescription. The multi-faceted process of these differentials (because of multiple physical quantifiers, enzyme activities, and sex hormones) generates the discrepancy.

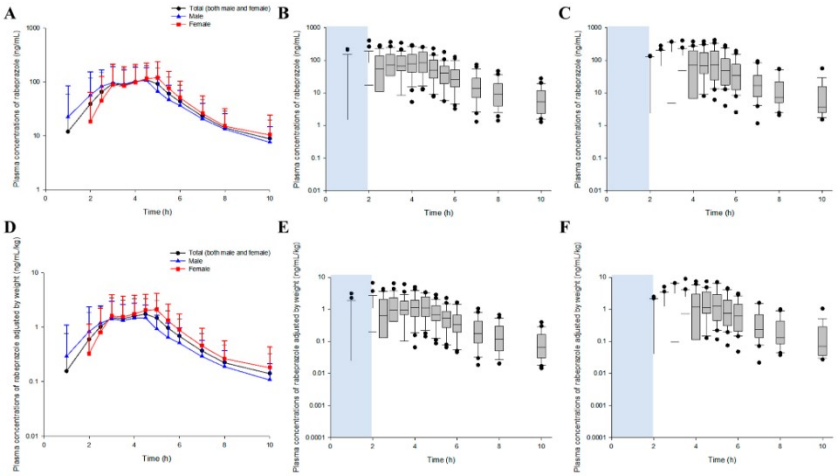
The organic way that sex-related pharmacokinetics differ is through body composition. The female sex hierarchy exhibits different body compositions with respect to fat percentages, muscle size, and general body size, and this might affect drug distribution rates and metabolism. To illustrate this, lipophilic medications with contrasting distribution could be a problem in overweight or obese individuals who have different body compositions as compared to lean

people, giving uneven therapeutic effects. Moreover, either inhibition or lack of enzyme activity, especially for the CYP superfamily, also has an effect on the pharmacokinetic profiles of women. In the aftermath of CYP enzyme expression and activity, genetic differences could lead to the administration of medicine with definite metabolism speed in some cases (Sylvester et. al 2022). Hence, such differences might have different consequences for drug accumulations in the body, leading to contrasting therapeutic outcomes.Other than that, the hormonal changes occurring across the menstrual cycle or as a result of menopause can provide temporal variability in the drug metabolism and clearance rate, which adds to the already existing problem of maintaining constant levels of the drug. In summary, these several factors collectively emphasize the complex nature of sex differences in pharmacokinetics, implying that comprehensive and tailored approaches are needed for the dosing and management of therapeutics to achieve complete treatment potential for both men and women.

Table 1: Summary of Pharmacokinetic Differences between Sexes

Parameter	**Male Response**	**Female Response**
Absorption	Higher gastric emptying rate	Slower gastric emptying rate
Distribution	Higher volume of distribution	Lower volume of distribution
Metabolism	Higher CYP enzyme activity	Lower CYP enzyme activity
Excretion	Higher renal clearance	Lower renal clearance

Figure 1: Comparison of Pharmacokinetic Profiles between Males and Females



(Sylvester et. al 2022).

Figure 1. *Plasma concentration profiles before (**A**–**C**) and after (**D**–**F**) body weight normalization between genders (**B**, **E**: male; **C**, **F**: female) following oral administration of rabeprazole 10 mg enteric-coated tablets. In graphs (**A**, **D**), observations are presented as mean and standard deviation as dots and upward vertical bars, respectively. (**B**,**C**,**E**,**F**) represent boxplots of plasma concentration values after rabeprazole exposure by time point, and the blue*

shading in the graph represents the initial absorption phase area from 0 to 2 h after exposure (established to check absorption differences between genders after exposure)(Sylvester et. al 2022).

The comparison of the pharmacokinetic profiles between males and females in the diagram shows the significant differences between these processes in drug absorption, distribution, metabolism, and elimination (ADME) between the genders. A graphical representation generally depicts a separate plot or chart of males and females with PH curves, including drug concentration-time profiles, absorption rates, and elimination rates (Sylvester et. al 2022)...

The graph may show distinct patterns of drug absorption kinetics: male and female peak plasma concentration and time to reach the maximum may vary. Moreover, it will identify discourse imbalances with the drug volumes, which will differ due to body composition and tissue perfusion rate diversity. In addition, the graph could display the variance in drug metabolism price in the manner of various enzymatic activity levels or differences in clearance rate between sexes.

This pictorial depiction can provide the desirable trend in pharmacokinetic profiles observed between males and females, helping to understand the sex-specific variations in drug disposition and elimination. That means it is an invaluable instrument for clinicians and researchers to define gender-related drug responses and proliferation. This fine-tunes the development of individual patient dosing regimens and treatments (Xia et. al 2020).

Pharmacodynamic Differences

Pharmacodynamics, a field concerned with how drugs operate in the body, investigates the complicated mechanisms that constitute drug action, including receptor interactions, cellular signalling cascades, and physiological outcomes. "Sex specificity in pharmacokinetics rests on varieties of pathways finally contributing to drug therapies, efficacy, safety, and other outcomes." The creation of such differences often depends on the disparities in the amount of hormones, expression of receptors, and organ purposes between males and females.

The significant characteristic in the production of sex differences in pharmacodynamics is the hormonal landscape. The sex hormones, such as estrogen, progesterone, and testosterone, are the key modulators of drug responses by affecting receptor production, degradation, and downstream signalling pathways. For instance, estrogen can induce a gene that helps enhance the presence of specific drug receptors so that drug efficacy and sensitivity are higher in females than males. In contrast, testosterone might show the opposite influence on receptor expression and signalling routes in women and men. In addition, hormone fluctuations that occur around any life stage, especially puberty, pregnancy, and menopause, bring about temporal changes in responsiveness and drug sensitivity. Hence, care is needed in treatment choices for each stage of life (Xia et. al 2020).

Furthermore, disparities in receptor expression and distribution between males and females cause females to respond differently to drugs in various ways. For multiple drugs, their receptors may have different expression levels or perform unique functions in different sexes, resulting in different receptor-drug associations or downstream cellular responses. The sex-specific alterations in the locations and functions of receptors and their structure further improve the sex differences in drug responses, as shown by some examples in cardiovascular drug metabolic profiles. By mediating this complex system of interplays, sex differences in pharmacodynamics are shown in their multifaceted nature, and the importance of taking into account sex-related aspects in drug development and clinical practice is emphasized to create the best therapeutic outcomes for both sexes of patients.

Figure 2: The Principles of Pharmacodynamic Differences between Genders and Sexes

Bioavailability by oral route	Gastrointestinal emptying time	↑ in women
	Drug transporter such as P-gp	No sex differences
Distribution volume	Gut enzymes	
	AD	↑ in women
	CYP3A4	No sex differences
	Water soluble drugs	↑ in men
	Lipophilic drugs	↑ in women
Protein binding	Albumin	No sex differences
	α_1 acid glycoprotein	↑ in men

AD: alcohol dehydrogenase; P-gp: P-glycoprotein.

(Boscaro et. al 2020).

A schematic diagram showing the relationships between the pharmacodynamic differences caused by sex is used as a visual aid to expose the complex interplay of the factors that play a crucial role in the drug response. Generally, functional hormones, receptor expression patterns, signal transduction pathways, and upstream, downstream, and cross-talk mediators that influence sex-specific pharmacokinetic disparity are represented by this diagram. For instance, hormone-related information like estrogen, progesterone, and testosterone are represented to underline their functions in receptors' expression and signal routes. Receptor site dispersion and activity are examples of how differential involving males and females lead to efficiency in drug-receptor engagement and drug-receptor and cellular reactions.

Additionally, diagrams may use several organ-specific graphics to distinguish receptor expression and interaction, which, in turn, leads to diverse effects of drugs between men and women. The diagram is a visual demonstration of these processes, and thus, it presents a summarized view of the interaction of diverse elements responsible for pharmacokinetic sexual dimorphisms. It becomes a valuable tool for doctors, researchers, and nurses to investigate sex-

specific pharmacodynamic responses, which can help make customized therapies for cardiovascular diseases and more.

Clinical Implications

Sex differences in cardiovascular pharmacology are something to reckon with in clinical practice; they bring aspects like the selection of drugs and dosing strategies that would affect patient treatment response. Knowing and understanding the purposes behind those differences is paramount to making the most of drug therapy and ensuring the security of any adverse events. Health professionals shall deliberately integrate gender-related concerns, including sex-specific considerations, into prescribing practices to facilitate the proper treatment of patients.

What makes the clinical application of sex differences in cardiovascular pharmacology more critical is the need to personalize the treatment choice concerning patients' characteristics. It is the enormous role of pharmacists to adapt sex-relevant criteria while writing medical prescriptions to different reactions in men and women. This entails considering the extent of PK, PD, and hormonal (H) interaction that is made for efficacy optimization. The development of personal treatment options addressing sex-distinctive responses allows for optimizing treatment outcomes while minimizing chances for clinical failures.

Along the same lines, sex-related differences in cardiovascular pharmacology warrant thoughtful administration of doses to achieve utmost safety. Depending on sex, the differences in the speed of administered medication transformation, clearance, and the number of receptors may appear, and an alarming situation may arise. Thus, the standard dosing regimens need to be adjusted to ensure the drug is effective and well-tolerated by people of both sexes. In general, biochemical differences and physiological processes between sexes are highly variable. Therefore, clinicians should understand this well and be able to adjust the dosages accordingly and ensure that individualized therapies are given to patients with sex-specific considerations.

Furthermore, cardiovascular pharmacology can be tailored according to sex and common side effects that can be visualized and prevented. In so doing, physicians can identify any vulnerabilities or higher risks, especially for women. These make them more proactive moon, or for mishaps and adjust treatment processes suited to the patients. Intensified monitoring for adverse events that may be triggered by gender significantly promotes patient safety, improving complications caused by the treatment (Waheed et. al 2020).

Knowing the pharmacy of both genders and ensuring that the right kind of drug is given to the right patient at the right time is critical for optimizing treatment outcomes and successfully implementing personalized care. Sex-specific factors can help clinicians select treatment plans, determine dose changes, and monitor side effects. This will help the clinician in the foundation of the treatment process, which will also reduce the risk of harm, ultimately improving patient outcomes in men and women with cardiovascular disease (Haider et. al 2020).

Table 2: Clinical Implications of Sex Differences in Cardiovascular Pharmacology

Aspect	Clinical Implication
Drug Selection	Tailored selection based on sex-specific responses
Dosing Strategy	Adjustments to account for pharmacokinetic and pharmacodynamic differences
Adverse Events	Monitoring for sex-specific adverse effects
Treatment Outcomes	Optimization of therapeutic efficacy and safety

Conclusion

Sex differences lead to a profound influence on drug pharmacology, with their power reaching into drug efficacy and treatment outcomes. Individual differences, including their genetic makeup, environmental factors, and prevalent diseases, must be considered while developing personalized medicine that matches individual needs. Incorporation of sex-specific diseases-related factors becomes a compulsion for clinicians and researchers not just in terms of devising treatment strategies but also in designing clinical trials so that the therapy efficiency of all genders, including males and females, can be maximized (Peng et. al 2021).

Through dealing with gender inequalities in cardiovascular pharmacology, we can reap the benefits of tailored drug therapy and ultimately provide better care for the heart organs. By designing treatment strategies to recognize the responding mechanism peculiar to sexual differences, clinicians can provide accurate and successful health care to patients. Additionally, we can effectively leverage sex-specific aspects into the concepts of clinical trial methodologies; such will provide a model that reflects the true-to-life treatment effects in both men and women. Eventually, just recognizing and tackling sex differences in cardiovascular pharmacology would steer into the strive for personalized medicine to achieve the cardiovascular health of all people (Arnold, 2020)...

It is now apparent that sex differences in cardiovascular drug pharmacology should be examined and addressed. Through the inclusion of sex-specific factors into therapeutic methods and research projects, we promote personalized medicine, more effective treatment and the reformation of cardiovascular system care. Developed awareness and experience differences could be overcome by concerted actions, which would lead increase treatment efficiency, improving safety and higher cardiovascular outcomes for every female and male.

Reference

Zhao, M., Woodward, M., Varese, I., Millett, E. R., Klipstein-Grobusch, K., Hyun, K., ...& Peters, S. A. (2020). Sex differences in cardiovascular medication prescription in primary care: a systematic review and meta-analysis. *Journal of the American Heart Association*, *9*(11), e014742.https://www.ahajournals.org/doi/abs/10.1161/JAHA.119.014742

Mauvais-Jarvis, F., Berthold, H. K., Campesi, I., Carrero, J. J., Dhakal, S., Franconi, F., ...& Rubin, J. B. (2021). Sex-and gender-based pharmacological response to drugs. *Pharmacological reviews*, *73*(2), 730-762.https://pharmrev.aspetjournals.org/content/73/2/730.abstract

Medina, D., Mehay, D., & Arnold, A. C. (2020). Sex differences in cardiovascular actions of the renin–angiotensin system. *Clinical Autonomic Research*, *30*(5), 393-408.https://link.springer.com/article/10.1007/s10286-020-00720-2

Raparelli, V., Elharram, M., Moura, C. S., Abrahamowicz, M., Bernatsky, S., Behlouli, H., &Pilote, L. (2020). Sex differences in cardiovascular effectiveness of newer glucose-lowering drugs added to metformin in type 2 diabetes mellitus. *Journal of the American Heart Association*, *9*(1), e012940.https://www.ahajournals.org/doi/abs/10.1161/JAHA.119.012940

Lala, A. N. U. R. A. D. H. A., Tayal, U., Hamo, C. E., Youmans, Q., Al-Khatib, S. M., Bozkurt, B., ... & Gulati, M. (2022). Sex differences in heart failure. *Journal of cardiac failure*, *28*(3), 477-498.https://www.sciencedirect.com/science/article/pii/S1071916421004322

Madla, C. M., Gavins, F. K., Merchant, H. A., Orlu, M., Murdan, S., &Basit, A. W. (2021). Let's talk about sex: Differences in drug therapy in males and females. *Advanced drug delivery reviews*, *175*, 113804.https://www.sciencedirect.com/science/article/pii/S0169409X21001782

Gerdts, E., Sudano, I., Brouwers, S., Borghi, C., Bruno, R. M., Ceconi, C., ...& De Simone, G. (2022). Sex differences in arterial hypertension: a scientific statement from the ESC Council on Hypertension, the European Association of Preventive Cardiology, Association of Cardiovascular Nursing and Allied Professions, the ESC Council for Cardiology Practice, and the ESC Working Group on Cardiovascular Pharmacotherapy. *European Heart Journal*, *43*(46), 4777-4788.https://academic.oup.com/eurheartj/article-abstract/43/46/4777/6711154

Zucker, I., & Prendergast, B. J. (2020). Sex differences in pharmacokinetics predict adverse drug reactions in women. *Biology of sex differences*, *11*, 1-14.https://link.springer.com/article/10.1186/s13293-020-00308-5

Zeng, X., Guo, F., & Ouyang, D. (2020). A review of the pharmacology and toxicology of aucubin. *Fitoterapia*, *140*, 104443.https://www.sciencedirect.com/science/article/pii/S0367326X19317277

de Ritter, R., de Jong, M., Vos, R. C., Van der Kallen, C. J., Sep, S. J., Woodward, M., ... & Peters, S. A. (2020). Sex differences in the risk of vascular disease associated with

diabetes. *Biology of sex Differences*, *11*, 1-11.https://link.springer.com/article/10.1186/s13293-019-0277-z

Sylvester, S. V., Rusu, R., Chan, B., Bellows, M., O'Keefe, C., & Nicholson, S. (2022). Sex differences in sequelae from COVID-19 infection and in long COVID syndrome: a review. *Current Medical Research and Opinion*, *38*(8), 1391-1399.https://www.tandfonline.com/doi/abs/10.1080/03007995.2022.2081454

Ferretti, M. T., Martinkova, J., Biskup, E., Benke, T., Gialdini, G., Nedelska, Z., ...& Schmidt, R. (2020). Sex and gender differences in Alzheimer's disease: current challenges and implications for clinical practice: position paper of the Dementia and Cognitive Disorders Panel of the European Academy of Neurology. *European journal of neurology*, *27*(6), 928-943.https://onlinelibrary.wiley.com/doi/abs/10.1111/ene.14174

Soumya, R. S., Unni, T. G., & Raghu, K. G. (2021). Impact of COVID-19 on the cardiovascular system: a review of available reports. *Cardiovascular drugs and therapy*, *35*, 411-425.https://link.springer.com/article/10.1007/s10557-020-07073-y

Xia, S., Du, X., Guo, L., Du, J., Arnott, C., Lam, C. S., ...& Ma, C. (2020). Sex differences in primary and secondary prevention of cardiovascular disease in China. *Circulation*, *141*(7), 530-539.https://www.ahajournals.org/doi/abs/10.1161/circulationaha.119.043731

Waheed, N., Elias-Smale, S., Malas, W., Maas, A. H., Sedlak, T. L., Tremmel, J., & Mehta, P. K. (2020). Sex differences in non-obstructive coronary artery disease. *Cardiovascular research*, *116*(4), 829-840.https://academic.oup.com/cardiovascres/article-abstract/116/4/829/5709809

Boscaro, C., Trenti, A., Baggio, C., Scapin, C., Trevisi, L., Cignarella, A., &Bolego, C. (2020). Sex differences in the pro-angiogenic response of human endothelial cells: focus on PFKFB3 and FAK activation. *Frontiers in pharmacology*, *11*, 587221.https://www.frontiersin.org/articles/10.3389/fphar.2020.587221/full

Haider, A., Bengs, S., Luu, J., Osto, E., Siller-Matula, J. M., Muka, T., &Gebhard, C. (2020). Sex and gender in cardiovascular medicine: presentation and outcomes of acute coronary syndrome. *European heart journal*, *41*(13), 1328-1336.https://academic.oup.com/eurheartj/article-abstract/41/13/1328/5687217

Peng, M., He, J., Xue, Y., Yang, X., Liu, S., & Gong, Z. (2021). Role of Hypertension on the Severity of COVID-19: A Review. *Journal of cardiovascular pharmacology*, *78*(5), e648-e655.https://journals.lww.com/cardiovascularpharm/fulltext/2021/11000/role_of_hypertension_on_the_severity_of_covid_19_.3.aspx

Arnold, R. H. (2020). COVID-19–does this disease kill due to imbalance of the renin angiotensin system (RAS) caused by genetic and gender differences in the response to viral ACE 2 attack?. *Heart, Lung and Circulation*, *29*(7), 964-972.https://www.sciencedirect.com/science/article/pii/S1443950620301451

Terentes-Printzios, D., Ioakeimidis, N., Rokkas, K., &Vlachopoulos, C. (2022). Interactions between erectile dysfunction, cardiovascular disease and cardiovascular drugs. *Nature Reviews Cardiology*, *19*(1), 59-74.https://www.nature.com/articles/s41569-021-00593-6

Napoli, C., Tritto, I., Benincasa, G., Mansueto, G., &Ambrosio, G. (2020). Cardiovascular involvement during COVID-19 and clinical implications in elderly patients. A review. *Annals of Medicine and Surgery*, *57*, 236-243.https://www.sciencedirect.com/science/article/pii/S2049080120302375