Therapeutic implications of the gender-specific aspects of cardiovascular disease

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Abstract | The manifestations of cardiovascular diseases differ between men and women, as do outcomes after therapeutic interventions. It is important that those involved in drug discovery and development, as well as disease treatment, are aware of these differences because such variations are likely to have an increasing role in therapeutic decisions in the future. Here, I review gender differences in the most frequent cardiovascular diseases and their underlying sex-dependent molecular pathophysiology, and discuss gender-specific effects of current cardiovascular drugs and the implications for novel strategies for drug development.

QT interval
The QT interval represents the time for electrical activation and inactivation of the ventricles, the pumping chambers of the heart. Prolongation of the QT interval can result in potentially lethal arrhythmias (some of which are known as torsades de pointes).

Angina
A narrowing of the coronary arteries, frequently as a result of arteriosclerosis, that leads to the chest pains known as angina pectoris.

Echocardiography
The use of ultrasound to image structural and functional abnormalities of the heart.

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Cardiovascular diseases (CVDs) affect women and men differently, and variation exists between the sexes in the age at which CVDs become manifest and the probability of survival[1–16] (TABLE 1). Typically, women develop CVDs 10–20 years later than men, but, if present at a younger age, these diseases have a more malign clinical course in women. Diabetes and hypertension have a relatively greater role as risk factors in women compared with men, and the clinical manifestations of heart failure as well as treatment responses also differ between the sexes.

It is important that those involved in disease treatment, and drug discovery and development, are aware of these differences. Physicians need to understand gender differences in the pathophysiology and pharmacology of CVD to provide optimal treatment. Basic researchers must recognize the significance of sex differences to the pathophysiology of their animal models and cell-culture systems. Finally, regulatory authorities and those responsible for drug development programmes need to realize that women are not just 'small men', and should be aware of how gender affects drug pharmacokinetics and pharmacodynamics — the gender-specific effects of which should therefore be considered as part of strategies for drug discovery, development and application.

With these needs in mind, this review first discusses gender differences in the clinical manifestations of the most frequent CVDs. Next, I consider sex-dependent pathophysiology, including the role of sex hormones and their receptors. Finally, gender-specific effects of current cardiovascular drugs, such as digitalis, inhibitors of the renin–angiotensin system, QT-interval-prolonging drugs and aspirin, are analysed, and potential gender-specific effects of new drugs are discussed. The implications of these three gender-specific aspects of CVD are then brought together in a discussion of gender-sensitive strategies for drug development.

Gender-related differences in clinical syndromes

Coronary artery disease and myocardial infarction. Gender-related differences are found in a large spectrum of CVDs[17–33] (TABLE 2). Gender differences in the clinical presentation of CVD are of particular relevance, because they can contribute to a delay in the diagnosis of CVD in women. For example, women present less frequently with typical exercise angina, and the sensitivity and specificity of the most frequently used test — the exercise electrocardiogram (ECG) — is lower in women than it is in men[17,34]. The increased rate of false-positives observed when testing women is partially attributable to the lower likelihood that coronary artery disease (CAD) is present, and false-negative results can, for example, result from the general lower physical fitness of women and a consequent failure to achieve maximal individual exercise levels. By contrast, echocardiography and imaging techniques, preferentially combined with pharmacological stress, are equally sensitive in women and men, and are therefore particularly recommended for diagnosing CAD in women[17]. Coronary angiography is labelled the 'gold standard' for diagnosis, but in a number of women with typical chest pain no coronary artery stenoses are found at cardiac catheterization, although deficits in myocardial energy metabolism can be documented by magnetic

Table 1 | **Gender differences in the epidemiology of CV syndromes**

Syndrome	Gender difference(s)	Specific features	Refs
Myocardial infarction	Age-dependent prevalence	Develops 15 years later in women	7
	Risk factors	Diabetes and hypertension are a greater risk in women	8–11
Hypertension	Age-dependent prevalence	Steep increase in prevalence after menopause	12–14
Heart failure	Lethality	Lower in women	15
	Risk factors	Diabetes and hypertension are more important in women	15
Sudden death	Prevalence	More frequent in men	16

CV, cardiovascular.

resonance spectroscopy[35]. In this subgroup, microvascular disease has been discussed as an underlying defect in energy metabolism. In addition to these physiological differences, less aggressive diagnosis and treatment still impair the clinical course of CVD in women[36].

The clinical features of myocardial infarction vary between women and men. So-called typical left-sided chest pain occurs less frequently in women with acute myocardial infarction, whereas respiratory and abdominal symptoms, and acute nausea or vomiting, are more frequent. This often leads to a misinterpretation of myocardial infarction as gastrointestinal disease, which can delay diagnosis and contribute to the higher lethality of acute myocardial infarction in women. In-hospital mortality of myocardial infarction is higher in women and is highest in younger women — that is, women 45–60 years of age[18]. Women have more bleeding complications than men after percutaneous coronary interventions, and a higher restenosis rate (adjusted for the different balloon sizes used for the sexes) has been reported in some, but not all, studies[19]. However, long-term outcome, survival and freedom from major cardiovascular events for women seem to be comparable to those of men.

Short-term post-operative mortality is greater in women than in men[21,22], and, in common with myocardial infarction, the greatest differences in early post-operative mortality are found in the youngest age groups (TABLE 2). This difference is hard to explain because women undergoing coronary bypass surgery frequently have better cardiac function, a lower number of diseased vessels, fewer previous infarctions and fewer previous coronary interventions than men. Although it has been proposed that body size, which correlates with coronary artery size, has a significant effect on the difference in post-operative mortality observed, this would not explain the finding that the worst outcomes occur in the youngest women[21,22]. Women also have a higher rate of complications and re-admissions in the first year after surgery[37]. Some as-yet-unknown genetic or clinical risk factors could contribute to this.

Myocardial hypertrophy and heart failure. Myocardial hypertrophy occurs in a number of heart diseases and is a negative prognostic sign by itself. Interestingly, women are better protected against the development of myocardial hypertrophy than men. For example, in women and men with clinical aortic stenosis, better preservation of myocardial function in the presence of pressure overload is observed in women than in men[26]. However, even though myocardial hypertrophy develops later in women than it does in men at a given haemodynamic load, once established it is more malign in women[27].

The better preservation of myocardial function under stress and during ageing might contribute to the relatively higher prevalence of diastolic heart failure (with normal systolic function) in women. Heart failure is a disease of old-age in women and men[15]. However, elderly women with heart failure are more frequently characterized by isolated diastolic dysfunction[28]. This is in agreement with findings at the molecular and cellular levels showing that hypertrophy, apoptosis and fibrosis in the ageing heart are less pronounced in women. Women with heart failure are better protected against apoptotic death signals and show a later onset of cardiac decompensation than men (reviewed in REF. 5).

Brain natriuretic peptide (BNP) is an important diagnostic and prognostic marker for diastolic heart failure and systolic heart failure. However, sex differences should be taken into account when intepreting BNP levels, because normal BNP levels are higher in women than in men. However, BNP levels rise, paradoxically, to a lesser degree in women than in men with heart failure, even in cases of comparable functional impairment (reviewed in REF. 5).

The prevalence of hypertrophic cardiomyopathy is higher in men than in women even though it is mainly an autosomal dominant disease, and the disease-causing genes should be inherited equally by females and males[23]. Sex-specific modifier genes or mechanisms might explain this phenomenon (see below). By contrast, the incidence of stress-induced cardiomyopathies is nine times higher in women than it is in men[24]. In particular, the rare stress-induced Tako-tsubo cardiomyopathy occurs predominantly in women[25].

Cardiac arrhythmia. The control of heart rate and cardiac rhythm differs in women and men. Women have a higher resting heart rate than men, a shorter sinus node recovery time and stronger modulation of heart-rate variability, probably reflecting greater parasympathetic influences[29]. Women also have longer rate-corrected QT intervals than men and manifest greater lengthening of the QT interval as heart rate slows[30]. At prolonged QT intervals, women are more susceptible to the development of 'torsade des pointes', a rare ventricular tachycardia, which is frequently self-limiting but that can also degenerate into lethal ventricular fibrillation[29–31].

Mutations in cardiac ion channels cause the familial long-QT syndromes (LQT). Patients with LQT1 and LQT2 forms of this syndrome, who have mutations in the genes encoding potassium ion channels, have a higher risk for lifetime cardiac events than patients with the LQT3 form, who have mutated sodium ion channels[33]. During childhood, the risk of cardiac events is higher in LQT1 males than in LQT1 females, but seems equal in males and females with LQT2 and LQT3. During adulthood, however, women with the LQT1 and

Cardiac catheterization
A procedure in which a catheter is introduced into the heart and contrast material is injected to visualize the right and left ventricles, as well as the coronary arteries.

Myocardial hypertrophy
Physiological (pregnancy, training) or pathological growth of the myocardium. Pathological myocardial hypertrophy is a major risk factor for heart failure.

Diastolic heart failure
A condition in which the heart contracts normally, but the ventricle does not distend correctly and so filling of the heart is impaired.

Systolic heart failure
A condition in which inadequate contraction of the heart leads to reduced cardiac output.

Autosomal dominant
A mode of inheritance that requires that the mutation of a single gene be present on either of the paternally and maternally derived alleles for the clinical phenotype to be expressed.

Table 2 | **Gender-specific clinical features of CVD and their risk factors**

Feature	Gender differences	Refs
Symptoms of MI and chronic CAD	Less so-called 'typical angina' in women	7
Sensitivity and specificity of exercise ECG	Lower in women	17
Lethality of acute MI	Higher in women	18
Outcome after percutaneous coronary interventions	More bleeding in women	19
Bleeding complications with thrombolysis	More frequent in women	20
Early outcome after coronary artery bypass surgery	Higher lethality in women	21,22
Interaction between diabetes and CAD	Stronger in women	8
CMP	HCM more frequent in men; stress-induced CMP more frequent in women	23–25
Left-ventricular hypertrophy	Occurs later but contributes greater risk in women	26,27
Manifestation of heart failure	Less systolic dysfunction in women, more diastolic dysfunction	28
ECG and arrhythmia	Longer QT intervals, higher event rate in LQTS, more torsades de pointes tachycardias in women	29–33

CAD, coronary artery disease; CMP, cardiomyopathies; CVD, cardiovascular disease; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome; MI, myocardial infarction.

LQT2 syndromes have a higher risk of cardiac events than men[32,33]. The relatively lower event rate in male adults with LQT1 and LQT2 syndromes is believed to be partially due to the shortening of the QT interval by testosterone. As no gender differences are found in adults with LQT3, it is likely that male (and/or female) sexual hormones modulate the function of the potassium but not the sodium channels[33] (see REF. 33 for a discussion of the contribution of different densities of ion channels in male and female hearts).

Prolongation of the QT interval can also be caused by drugs that have the potential to block the cardiac voltage-gated potassium channels (discussed later) and is more frequent in women[38]. The risk varies during the menstrual cycle[39] and is affected by progesterone and oestrogen.

Gender-specific risk factors: diabetes and hypertension. The recently published INTERHEART study revealed that just five risk factors (smoking, lipids, hypertension, diabetes and obesity) account for about 80% of the population-attributable risk for acute myocardial infarction in a worldwide investigation[11]. Of these, diabetes and hypertension were stronger risk factors in women than in men[8–10,14]. The interaction between diabetes and atherogenic mechanisms and cardiovascular risk in women has been related to sexual hormones but is not yet completely understood. However, it has been shown that protective sex differences in endothelial function, in nitric oxide (NO) production and in the antithrombotic profile in women are abrogated by diabetes[40]. A major protective role for female sexual hormones in the interplay between insulin and atherosclerosis is suggested by the increased risk of young women with polycystic ovarian syndrome (characterized by low oestrogen and relatively high testosterone serum levels) for atherosclerosis and diabetes[10,41–43].

Hypertension contributes to the population-attributable risk of myocardial infarction and to the greater risk of heart failure in women than in men[11,14]. This finding is at least partially a result of the greater prevalence of hypertension in the women who are older than their male counterparts in most studies: hypertension is less common in pre-menopausal women than in men of the same age[13], but its prevalence increases more steeply after the menopause. The greater rate of hypertension in post-menopausal women has been linked to loss of inhibition of the renin–angiotensin system by oestrogens, to alterations in renal sodium handling and to obesity. Post-menopausally sustained hypertension is frequently preceded by hypertension, eclampsia or preeclampsia during pregnancy[44].

Obesity is a major risk factor for hypertension, diabetes and CVD in both women and men. Obesity presents a major and gender-specific health problem because of its dramatic increase in younger women (for a review, see REF. 6). The population-attributable risk of obesity is better assessed by the waist-to-hip ratio than by body mass index (BMI)[11] because of the negative biological functions of visceral fat. Visceral obesity induces hypertension by different sex-dependent mechanisms, such as neurohormonal activation, an increase in intra-abdominal pressure, and glomerular and tubular effects. Pre-menopausal women generally develop peripheral adiposity, with predominantly gluteal fat accumulation[45]. After the menopause, concentrations of lipoproteins, as well as body fat distribution, shift to a more male pattern, to android obesity, which is linked to increased cardiovascular morbidity and risk for type 2 diabetes. Visceral fat and subcutaneous fat differ in the distribution of adrenergic and oestrogen receptors, and in the production of free fatty acids and inflammatory mediators, which contribute to the development of hepatic insulin resistance[46]. A lower percentage of visceral fat might be one of the primary metabolic features that underlie the reduced risk of CVD in pre-menopausal women[45]. Accumulation of visceral abdominal fat is accelerated by the menopause and is associated with the above-mentioned increase in blood pressure, as well as with insulin resistance and increased cardiovascular risk.

Psychosocial risk factors and depression. Psychosocial risk factors have a similar yet underestimated role in women and men for a first myocardial infarction[11]. However, gender-specific effects have been reported after myocardial infarction and in the role of depression in cardiovascular syndromes (for example, the outcome after coronary bypass surgery). Depression is an independent predictor of cardiac events and mortality after cardiovascular surgery, and has a greater role in women than it does in men. Most studies agree that depression is more frequently present in women than in men undergoing cardiovascular surgery[47]. Furthermore, the higher frequency of post-operative depression is likely to contribute to the more frequent hospital re-admissions and slower functional recovery of women[47,48].

Population-attributable risk
The percentage of risk that can be attributed to a given risk factor in a population.

Android obesity
Obesity typically seen in males, which is characterized by visceral fat accumulation.

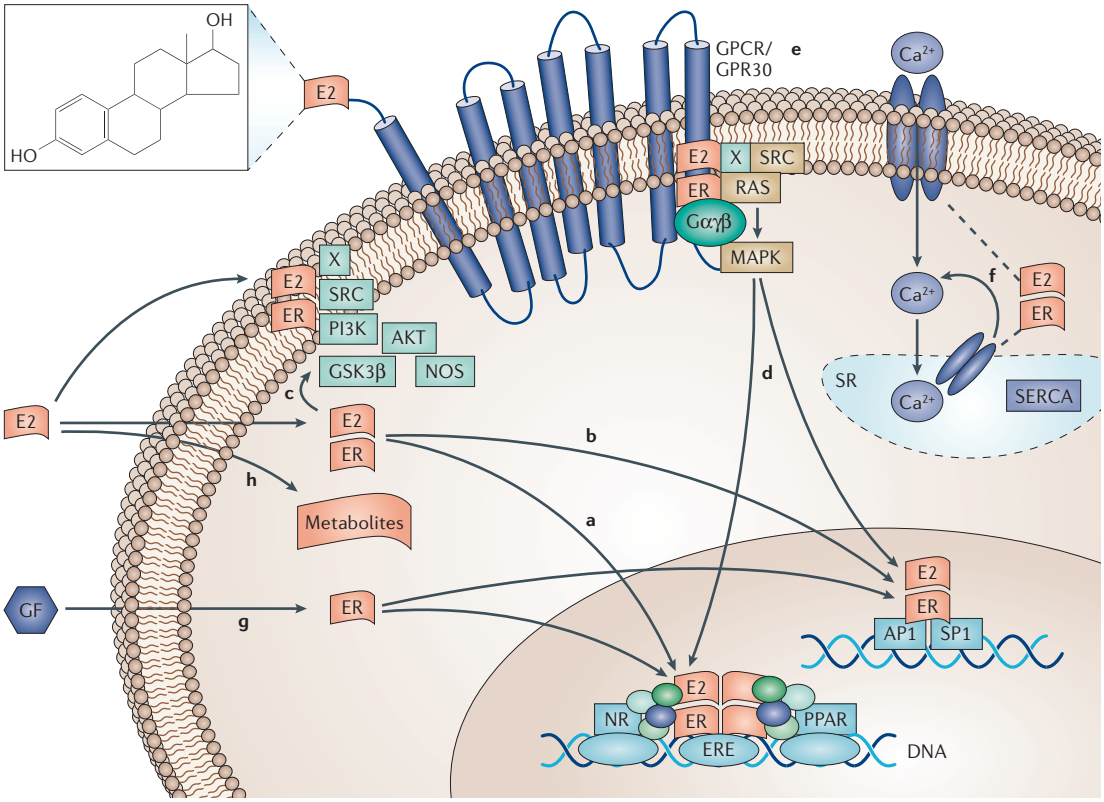

Figure 1 | **Multiple signalling pathways of oestrogen in cardiovascular cells.** Oestrogen (E2) can activate a cytosolic protein-bound oestrogen receptor (ER) that then shuttles into the nucleus and activates gene transcription (**a**). DNA binding can occur in the form of homo- or heterodimers. Several cofactors, which are partially shared with other nuclear receptors (NRs) such as peroxisome proliferator-activated receptors (PPARs), are required for the activation of gene transcription[56,116]. ERs can also control gene transcription by modulating the activity of other transcription factors[53,55] (**b**). In addition, oestrogen can induce membrane association of an ER (**c**), which subsequently stimulates SRC, phosphatidylinositol 3-kinase (PI3K), AKT and glycogen synthase kinase-β (GSK3β), which, in turn, leads to activation of nitric oxide synthase (NOS) and subsequent production of nitric oxide. Membrane association is facilitated by adaptor proteins (X), such as caveolin. Some of these functions of ERα can also be accomplished by the 46-kDa isoform of ERα[74]. ERα also interacts with the mitogen-activated protein kinase (MAPK) pathway[72] (**d**). This pathway involves SRC, RAS and RAF, and is probably facilitated by small adaptor and scaffold proteins; it could involve other membrane receptors[73] (**e**). The G-protein-coupled receptor GPR30 has been suggested as a new ER and is believed to signal via MAPKs[57]. Oestrogen can also modulate calcium influx at the L-type calcium channel or calcium handling at the sarcoplasmatic reticulum (**f**). Growth factors (GF) can activate ERs in a ligand-independent manner[59,60] (**g**). In addition, oestrogen can exert its effects via receptor-independent mechanisms (**h**), via metabolites of oestradiol, particularly catechol-oestradiols and methoxy-oestradiols[58]. ERE, oestrogen-responsive elements; SERCA, sarcoendoplasmic reticulum Ca^{2+} ATPase.

The large number of significant differences in cardiovascular syndromes and risk factors in women and men cannot be considered exhaustively here. Instead, as the molecular basis of gender-specific differences is not completely understood, only the pathophysiological and cellular mechanisms are discussed in the next section.

Gender-specific molecular mechanisms

Sex hormones and their receptors in the cardiovascular system. Receptors for oestrogen, progesterone and androgens (ERs, PRs and ARs, respectively) are candidates to mediate sex-specific effects in the cardiovascular system (FIG. 1; BOX 1). The two known ERs — ERα and ERβ — have been described in the human and rodent heart[2,49–51]. Although a recent report contests the presence of ERs in rodent myocardium[52], the majority of reports agree on the presence and functionality of ERs in mouse, rat and human hearts[49–51] (FIG. 2). Expression of sex hormone receptors are regulated in CVD, underscoring their potential functional relevance. Reduced expression of ERs in atherosclerotic human coronary arteries is a topic of discussion, as is the significant upregulation of ERα and ERβ in human heart hypertrophy[50,51] (for a review, see REF. 5).

ER, AR and PR act by a number of different mechanisms[2,49,53] (FIG. 1). They are transcription factors and bind as hetero- or homodimers to hormone-responsive DNA elements where they initiate the transcription of hormone-sensitive genes such as NO synthases[54] (reviewed in REF. 55). They also modulate the activity of

Box 1 | **Gender differences in CVD: molecular mechanisms**

Effects of oestrogen, progestins and androgens in the cardiovascular system:

- Nitric oxide modulation: antihypertrophic, anti-apoptotic mechanisms and vasodilation
- Vascular function, composition, gene expression: adhesion molecules, vascular endothelial growth factor, and others
- Myocardial gene expression: atrial natriuretic peptide, connexins, extracellular-matrix-related genes, and others
- Myocardial signalling, related to growth and metabolism: phosphatidylinositol 3-kinase and protein kinase B/AKT
- Modulation of cardiac ion channels, calcium handling and β-adrenoreceptors
- Modulation of the renin–angiotensin and endothelin systems
- Effects on fibrinolysis and lipid profile

Effects of cardiovascular genes located on the X-chromosome:

- Gene-dose effects if X-inactivation remains incomplete
- Better compensation for heterozygous gene variants in women

Interference of autosomal gene polymorphisms with sex-specific pathways:

- Effect of peroxisome proliferator-activated receptor-α polymorphism on human left-ventricular hypertrophy only in males[110]

CVD, cardiovascular disease.

other transcription factors. Ligand-bound ERs assemble a large number of essential cofactors that modify DNA structure and histone proteins in the nucleosome. These co-activators and co-repressors are shared with other nuclear receptors, such as thyroid hormone receptors, peroxisome proliferator-activated receptors (PPARs) and glucocorticoid receptors. Competition for cofactors can modulate the activity of the respective pathways in a cell-specific manner[56].

Activated ER, AR and PR also interfere with a number of membrane-associated and cytosplasmic signalling pathways[53]. The tyrosine kinase SRC is involved in several early steps and pathways. It supports association of ER with the subunits of phosphatidylinositol 3-kinase (PI3K), which leads to the activation of protein kinase B/AKT and NO (see below). Activation of SRC by ER also activates the mitogen-activated protein kinase (MAPK) pathway, which promotes pro-hypertrophic responses. Fragmented or atypical ER, such as the 46-kDa isoform, might be involved in these pathways[53]. Furthermore, a G-protein-coupled receptor, GPR30, has been suggested to act as an atypical ER in this context[57] and might also exert its effects via receptor-independent mechanisms. Metabolites of oestradiol, particularly catechol-oestradiols and methoxy-oestradiols, have direct effects on vascular cells, and these effects are generally believed to be protective[58]. Catechol-*O*-methyl-transferase (COMT) catalyses the methylation of oestradiol, which can interfere with the methylation of catecholamines by COMT.

Sex differences in cardiac functions in elderly patients with low levels of circulating hormones might also be mediated by ER, as ER can be activated by peptide growth factors in the absence of steroid hormones[59]. Accordingly, transcriptional activity of ER has been found to be independent of plasma oestrogen levels and age[60].

Lessons from oestrogen- and ER-deficient animals. A number of experimental studies have analysed the role of β-oestradiol on infarct size, left-ventricular remodelling and myocardial hypertrophy. Some, but not all, studies suggest that oestrogens reduce infarct size and improve cardiac remodelling. To identify the ER subtype involved, studies were carried out in animals deficient in ER (ER knockouts). More severe ischaemia reperfusion damage has been reported in male ERα-knockout mice than in male wild-type mice, suggesting a protective role of ERα against ischaemia reperfusion damage in males[61]. In female animals, knockout of ERβ increased mortality, and, in a different study[62], knockout of this isoform aggravated markers of heart failure, suggesting a protective role for ERβ in females. By contrast, an effect of ERα on infarct size, overall mortality and left-ventricular remodelling in female ERα-knockout mice was recently excluded[63]. In the same study, ERβ deficiency in female mice resulted in decreased ventricular automaticity after chronic myocardial infarction, which could prevent lethal arrhythmia[63]. These results suggest that the contribution of the ER subtypes differs between the sexes.

There is strong evidence that oestrogen reduces myocardial hypertrophy in female ovariectomized mice with aortic stenosis[64]. Female, but not male, ERβ-knockout animals responded to aortic constriction with a greater degree of hypertrophy than wild-type littermates[65]. On the basis of these data, ERβ might be preponderantly involved in hypertrophic signalling in females.

In summary, the effect of ER subtypes on infarct size and myocardial hypertrophy in genetically modified animal models has yet to be elucidated. Both subtypes of ER might have cardioprotective effects in animal models. How far these are model-specific and how this is in agreement with a yin/yang philosophy of ER actions — the mutual antagonism of ERα and ERβ in selected tissues — remains to be determined in more elaborate organ-specific and conditional knockout animal models and in humans.

Vascular protection by endogenous oestrogens: role of NO. Polymorphisms in the gene that encodes ERα are associated with an increased rate of myocardial infarction in men and in women[66]. Moreover, ERα variants influence the cardiovascular effects of hormone replacement[67]. Men with defects in ERα or in the gene that encodes aromatase, an enzyme that produces oestrogen from testosterone, develop early atherosclerosis[68]. In women and men, oestrogens induce rapid vasodilation, improve endothelial-mediated vasodilation, modulate proliferation or apoptosis of vascular smooth muscle cells (VSMCs) and endothelial cells, and interact with growth and intracellular calcium handling. Endogenous oestrogens also reduce adhesion-molecule expression and increase the synthesis of vascular endothelial growth factor (VEGF), which promotes angiogenesis and stimulates re-endothelialization after injury (for reviews, see REFS 49,53,69).

Oestrogen exerts a number of protective effects on the vasculature via NO, including fast vasodilation, reduction of leukocyte adhesion and inhibition of

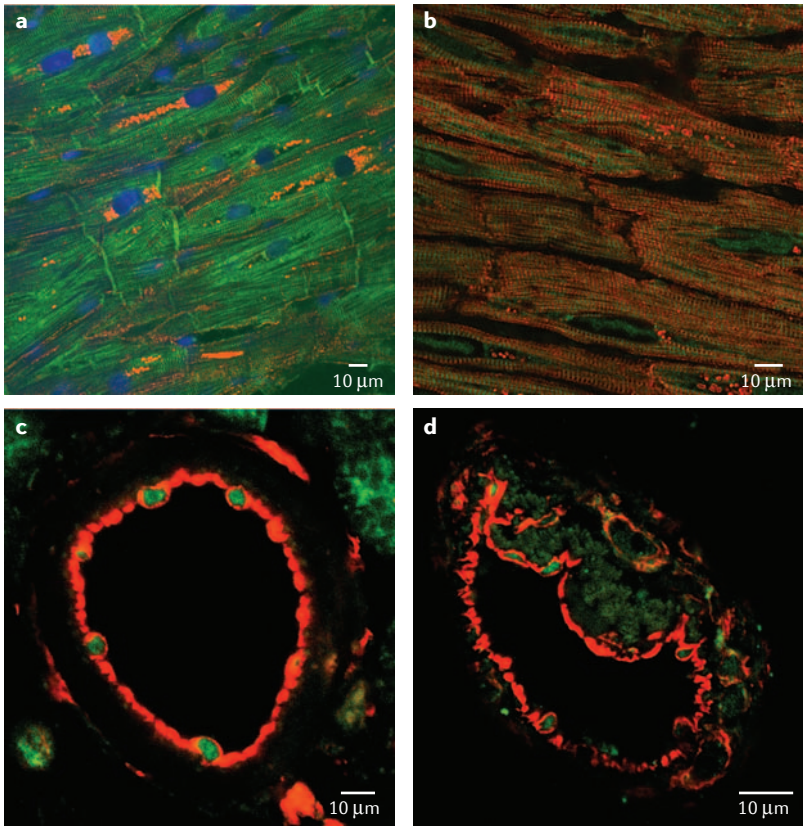

Figure 2 | **Oestrogen receptors are expressed in the human heart. a** | Healthy human female myocardium. Oestrogen receptors (ERs) are stained with fluorescein isothiocyante (FITC) green in the myocardium and coronary arteries. Nuclei are stained with 4′,6-diamidino-2-phenylindole (blue), and lipofuscin produces red signals. The ERs are located in the intercalated discs, at the membranes, in the nuclei and also in the cytoplasm. **b** | Male human heart with dilated cardiomyopathy. ERs are stained with FITC green and troponin-I is stained in red. In the cardiomyopathic heart, the loss of ERs from the intercalated disc is clearly recognizable. **c,d** | Cross-sections through intramyocardial human coronary arteries, with high variability between healthy male subjects. Vimentin is used as a marker of endothelial cells (red) and FITC green for ERα. ERα is seen in the nuclei, in the endothelial cells and in the vascular wall. Fluorescence microscopy carried out as described by Nordmeyer *et al.*[50].

VSMC proliferation. Modulation of the NO system by oestrogen is a good example of how oestrogen produces physiological effects at different cellular levels and by the stimulation of different pathways in a coordinated manner. First, oestrogen increases NO synthesis by increasing the activity of endothelial NO synthase (eNOS) without affecting its protein expression. This rapid effect is largely mediated via ERα that is located at the plasma membrane of endothelial cells and specifically in the so-called caveoli, which contain a number of signal-transduction molecules. Hormone-activated ER binds the non-receptor tyrosine kinase SRC and the regulatory subunit of PI3K, which leads to the activation of PI3K and protein kinase B/AKT, with subsequent activation of eNOS, which has anti-apoptotic and anti-hypertrophic effects[70,71]. In addition, plasma-membrane ERs stimulate eNOS via G-proteins (heterotrimeric proteins composed of α, β and γ subunits). ERα can, directly or indirectly, interact with the $G\alpha_i$ subunit and the MAPK pathway[72], but also with $G\alpha_q$ and Gβγ. Binding of ER to SRC is a key step in both chains of events and is facilitated by small adaptor and scaffold proteins, such as caveolin or the recently discovered modulator of non-genomic action of ER (MNAR)[73]. These functions of ERα can be accomplished by the regular 66-kDa isoforms, but also by the 46-kDa isoform of ERα[74]. These non-genomic effects of oestrogen on NOS activity are paralleled by the genomic actions of oestrogen — that is, the 'classical' activation of NOS transcription by an oestrogen-responsive element (ERE) in the NOS promoter.

Effects of endogenous oestrogens and ER on myocardial hypertrophy. The observations made in human aortic stenosis of better preservation of cardiac function in women than in men[26], and gender-specific differences in the development of hypertrophy, are supported by animal models. Induction of myocardial hypertrophy and heart failure by mechanical overloading in the rat model showed different phenotypes in the male and female animals, with better preservation of myocardial function in the females. The left-ventricular genomic response was different in male and female hearts[65,75], with part of this protection seeming to be mediated by ERβ[65].

Major differences between male and female hearts were found in hypertrophic signalling (reviewed in REFS 2,5,49). Atrial myocytes from female rats were more sensitive to myofibrillar calcium, whereas male myocytes had a greater response to β-adrenergic stimulation. Older reports describe sex differences in mRNA expression of functional and structural cardiac proteins, and in DNA synthesis. Recently, it was shown that oestrogen antagonizes isolated myocyte hypertrophy via induction of ANP synthesis. In addition to prohypertrophic and profibrotic pathways, metabolism of glucose and fatty acids, and the activity of connexins, are modulated by oestrogen and testosterone[76].

However, fewer data are available on human hearts. In human myocytes, oestrogen stimulates the protein kinase B/AKT pathway[77], which leads to phosphorylation of forkhead-transcription factors and increased NO synthase activity. These mechanisms are generally believed to be anti-apoptotic and cardioprotective. Oestrogen is also involved in the reduction of the activity of a central hypertrophic pathway, the p38MAPK pathway, by stimulation of its inhibitor MAPK phosphatase 1 (MKP1), and controls extracellular-regulated kinase (ERK) phosphorylation[78].

The phosphatase calcineurin is particularly relevant for the development of cardiac hypertrophy. In patients with aortic stenosis, the increase in ERβ was associated with the suppression of this hypertrophic mediator[50]. This is in agreement with cardioprotective effects of ERβ.

The human cardiac noradrenaline transporter has lower activity in women than in men, which might, by some as-yet-unknown mechanisms, contribute to the higher rate of orthostatic intolerance in women[79]. At least, a functional mutation in the norepinephrine transporter (*NET*) gene causes familial orthostatic intolerance. A link between gender differences in myocardial

Table 3 | **CV drugs with gender-specific therapeutic and adverse effects**

Drug	Gender-specific effects	Refs
Angiotensin-converting enzyme inhibitors	Found to be not effective in women in some major studies (possibly as a result of study design) More side effects in women	5,96–98
Digitalis	More deaths reported in women	88,89
Aspirin	Not effective in primary prevention of myocardial infarction in women	105
Diuretics	More frequently used in women	5,86
Statins	More side effects in elderly, low-body-weight patients	142
Beta-blockers	Found to be not effective in women in some major studies (possibly as a result of study design)	91–95
Sotalol and QT-prolonging drugs	More tachycardia in women	31,99–101, 143
Thrombolytic agents and anticoagulants	More side effects in women	20

CV, cardiovascular.

noradrenaline handling and myocardial hypertrophy is suggested by the existence of Tako-tsubo cardiomyopathy in women, which is probably due to sympathetic overstimulation[25] (see earlier).

Oestrogen and the renin–angiotensin system. Cardiovascular protection in pre-menopausal women has been associated with increased inhibition of the endogenous renin–angiotensin system by oestrogens. Endogenous, but not exogenous, oestrogen inhibits angiotensinogen synthesis in the liver and angiotensin AT1 receptor (AT1R) expression in the myocardium, but increases the expression of the supposedly protective AT2R in the ageing myocardium (reviewed in REF. 5) and the kidneys. Exogenous, orally administered oestrogens act differently and can induce hepatic angiotensinogen synthesis.

Progesterones and androgens. PRA and PRB are expressed in the cardiovascular system. PRs can interact partially synergistically/partially antagonistically with oestrogens[53]. In VSMCs, oestrogen and progesterone are antagonistic in regard to AT1R expression[80]. PRs have more frequently been shown to induce hypertrophy and vasoconstriction. Testosterone, which is a precursor for oestrogen biosynthesis, can also mediate cardiac myocyte hypertrophy, but there is ongoing discussion about which of its effects are direct and which are mediated via oestrogen[81–83].

Effects of oestrogens: discrepancy between pathophysiology and clinic. Although a number of beneficial oestrogen- and ER-mediated effects have been described, the latest outcome trials with hormone-replacement therapy (HRT) have made it clear that these pathophysiological effects do not translate into clinical cardiovascular benefit[84,85]. Outcome can be influenced by differences between exogenous and endogenous hormones, first-pass effects in the liver, effects of synthetic progesterones (which must, in most cases, be co-administered with oestrogen), basal hormone status, phyto-oestrogens in the diet and timing of hormone intake, and these factors might have prevented therapeutic benefit from HRT so far. Nevertheless, the manifold interactions of oestrogens and androgens with cellular functions can modify the response to a number of other cardiovascular drugs.

CVDs: gender differences in drug response

Gender-related differences in the clinical effects of major cardiovascular drugs have been observed. Here, I outline these effects and briefly discuss the mechanisms that underlie these differences. The reader is also referred to previous reviews that discuss these issues in heart failure and other CVDs[5,86,87].

Digitalis. In 1997, the Digitalis Investigation Group (DIG) reported the positive results of a randomized trial evaluating the efficiency of digoxin therapy for patients with heart failure (TABLE 3). Thereafter, guidelines strongly endorsed the use of digoxin for these patients. However, in a *post hoc* subgroup analysis, digoxin was associated with a significantly higher risk of death among women taking digoxin compared with those taking placebo, an effect that was not observed in men[88]. Dose-related effects, as well as an interaction with HRT, were discussed as potential explanations for this unanticipated result. Higher serum digoxin concentrations were associated with increased crude all-cause mortality in men[89]. In women, a similar trend was observed, but did not reach significance because the number of women participating in the study was too small. In the absence of definitive evidence, doses should now be used that lead to plasma levels below 0.8 ng per ml. These data reinforce the possibilities of gender-related effects and therefore underscore the need to perform gender-specific analysis and to include sufficient numbers of women in trials[88,89].

Beta-blockers. Gender-specific differences in the pharmacokinetics of beta-blockers lead to greater drug exposure in women[90]. Women have so far been a minority in clinical trials testing beta-blockers, representing 20–30% in the first major trials (reviewed in REFS 5,86). Two major trials, the Metoprolol CR/XL study and the COPERNICUS trial, failed to find a beneficial effect on mortality in women[91,92]. In a detailed gender-specific analysis for the CIBIS II study, women profited significantly from treatment with bisoprolol[93,94], which had a greater unadjusted effect on all-cause mortality in women than in men. Pooling of mortality results from MERIT Heart Failure, CIBIS II and COPERNICUS showed survival benefits in both women and men[95]. The lack of evidence in some large beta-blocker studies is therefore probably due to the under-representation of women in the trials.

Angiotensin-converting enzyme inhibitors. In several multicentre studies, angiotensin-converting enzyme inhibitor (ACEI) data are insufficient to prove a mortality reduction in women. In Consensus I, SAVE and SOVLD, only small percentages of women were included[5,86]. A meta-analysis including 7,105 heart-failure patients

claimed that the effects were comparable in women and men, but detailed data by gender were not included[96]. The apparent lack of evidence in women could reflect the small number of women treated, as was the case in the beta-blocker studies. Later trials, such as AIRE and HOPE, showed a significant benefit of ACEI in women. However, the recent Second Australian National Blood Pressure Study demonstrated a significant reduction in cardiovascular events in men, but not in women, despite similar reductions in blood pressure in both sexes[97]. The side effects of ACEIs (for example, cough) are reported more frequently in women[98]. A number of questions concerning the sex-specific mechanisms of ACEIs therefore remain to be answered.

Diuretic agents. Diuretic drugs are more frequently used in women, despite the fact that they can cause more adverse events in this sex. For example, hyponatraemia and hypokalaemia occur more frequently in women than in men taking diuretics, and both of these electrolyte disturbances have the potential to cause severe arrhythmia[5]. This might suggest the possibility that women will experience more arrhythmia than men because they have longer QT intervals and more long QT-associated rhythm disturbances, and are therefore more vulnerable. However, no such data have so far been reported in large studies.

Anti-arrhythmics. Clinical and experimental studies show that a longer, corrected QT interval at baseline and a greater response to drugs that block inward potassium channels (I_{Kr}), both of which facilitate the emergence of arrhythmia, are associated with women. These results most likely stem from a specific regulation of ionic channel expression (potassium, calcium and so on) by sex steroids, although non-genomic effects might also contribute to the observed side effects. Women are in more danger than men of showing side effects with QT-interval-prolonging drugs[31,99–101]. Drug-induced torsade de pointes is a rare life-threatening adverse drug reaction that is more frequent in women.

Drugs that prolong cardiac repolarization also have the potential to block cardiac voltage-gated potassium channels, particularly the rapid component (I_{Kr}) of the delayed rectifier potassium current (I_K). They include not only anti-arrhythmics but also gastrokinetics, antipsychotics, antihistamines and antibacterials[102]. For those QT-interval-prolonging drugs that were examined specifically for sex-specific differences, women consistently had a higher incidence of QT prolongation and torsades de pointes than men for all of the following drugs: amiodarone, bepridil, disopyramide, quinidine, erythromycin, halofantrine, ibutilide, probucol, sotalol and terfenadine[103].The SWORD trial, which compares D-sotalol with placebo, was terminated early because of increased mortality in the placebo group: women were at a greater risk for excess mortality in this trial[104].

Aspirin. In studies in men older than 50 years of age, aspirin reduces the risk of myocardial infarction by up to 44%[105] but does not significantly affect the risk of stroke. Results from a recent long-term study of aspirin in women contradict these findings. Placebo or aspirin were administered to 39,876 healthy women of 45 years of age and older[105], and then the women were monitored for 10 years for a first major cardiovascular event. The reduction of all cardiovascular events and the effect on myocardial infarction or death from cardiovascular causes were not significant. So far, no definite explanations have been found for these results. Higher aspirin levels in women than in men after equal dosing have been reported, as well as different effects on platelets, but both effects do not explain the results. It has also been shown that the benefit from aspirin is related to the cardiovascular risk in the subgroup studied and that the low risk for CAD in the subgroup of young women might explain the lack of an effect in this group.

Side effects. Overall, women have been reported to be at greater risk than men of experiencing an adverse reaction to medication. In the cardiovascular field, treatment with ACEIs causes a typical form of dry cough more frequently in women than in men[98]. However, a higher rate of side effects is a more general phenomenon in women. In an analysis of 48 cohort studies in Great Britain, Martin and colleagues found a 1.5- to 1.7-fold higher risk for adverse events in women compared with men[106].

Mechanisms: pharmacokinetics. There are several pharmacokinetic differences in the ways in which women and men metabolize drugs. These discrepancies are based on differences in drug absorption or metabolism, and are frequently related to the cytochrome P450 (CYP) system. Women typically have a lower body weight and higher body fat, whereas the activities of some enzymes seem to be higher in men than they are in women, specifically the CYP isoenzymes CYP1A (and, potentially, CYP2E1), the drug efflux transporter P-glycoprotein, and some isoforms of glucuronyltransferases and sulphotransferases. Women are thought to have higher CYP2D6 or CYP3A activities, but data are conflicting. No major gender-specific differences seem to exist for CYP2C9 and CYP2C19. Lower hepatic P-glycoprotein activity in women relative to men increases intrahepatic substrate availability and subsequent clearance of substrates[107–109].

Women in cardiovascular trials. The number of women included in cardiovascular trials has been low in the past, as discussed above for digitalis, beta-blockers and ACEIs. Low numbers of women were also found in the early trials on statins and aspirin (reviewed in REFS 5,86). A low percentage of women in major clinical trials or a lower event rate in the female cohort could explain the higher variability in women and, therefore, the failure to achieve statistical significance.

Several classes of drugs have different effects on men and women, and these effects should be considered when choosing treatments for CVDs. Mechanisms underlying gender-related differences in pharmacology and the possibility of avoiding them in drug development are discussed in the following section.

Hyponatraemia
A deficiency of sodium in the blood.

Hypokalaemia
A deficiency of potassium in the blood.

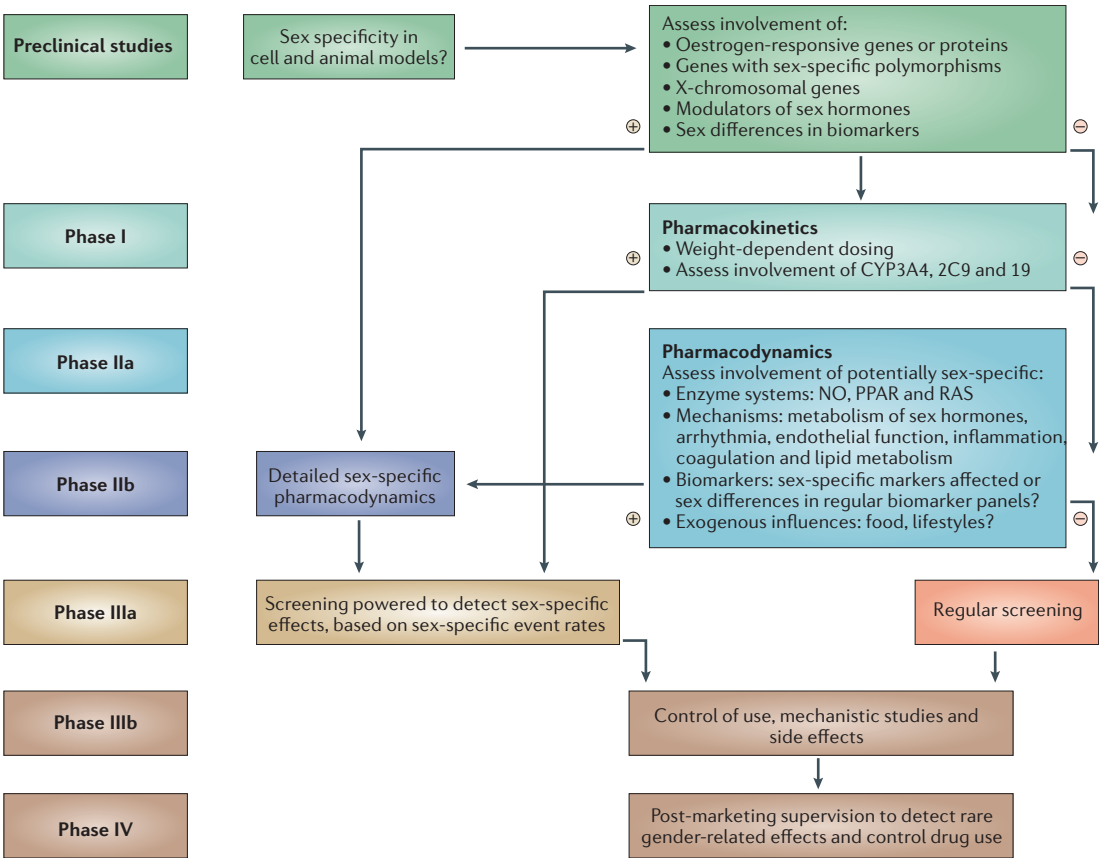

Figure 3 | **Strategies to detect gender-specific effects in drug development.** The flow diagram shows where preclinical, Phase IIa, Phase IIb, Phase III and Phase IV studies most effectively investigate gender differences. Differences can be found at the cellular, molecular and genetic levels. There might be effects on pharmacokinetics and pharmacodynamics and on clinical phenotypes. CYP, cytochrome P450; NO, nitric oxide; PPAR, peroxisome proliferator-activated receptor.

Relevance of gender for drug development

Given the knowledge of the role of gender in CVD and its treatment, a systematic search for gender-related differences in the pharmacodynamics and pharmacokinetics of drugs should be integrated into all phases of drug development, from preclinical studies through Phase I and II testing to large-scale clinical trials (FIG. 3).

In vitro *and non-human* in vivo *studies*. Preclinical studies can yield useful information on whether gender effects are likely to occur with a novel drug (FIG. 3). The likelihood is increased if a drug interferes with the effects of sex hormones, with their metabolism or with sex-hormone-stimulated pathways in a given cell. Oestrogen-sensitive proteins form approximately 2–5% of all proteins in human cardiac myocytes and fibroblasts and can be identified by screening techniques such as two-dimensional gel electrophoresis or chromatin immunoprecipitation (ChIP), which identifies oestrogen-responsive genes. Drugs that interact with gender-specific pathophysiological mechanisms or with effects of genes, which, due to their location on the X- or Y-chromosome, produce different effects in women and men, are candidates for gender-specific effects.

To identify gender-specific pathophysiological pathways, mutations in autosomal genes that lead to gender disparities are helpful (TABLE 4). Polymorphisms in the *PPARα* and *PPARγ* genes, which encode central regulators of lipid and glucose metabolism, and in a related co-activator (PPARγ co-avtivator 1 (PGC1)) that is used by PPARs as well as by ERs, are associated with left-ventricular hypertrophy, hypertension, obesity and leptin synthesis in a gender-specific manner[110–113]. In mice deficient in PPARα, inhibition of fatty-acid oxidation led to severe lipid accumulation, myocardial hypertrophy and death for 100% of male, but only 25% of female, mice[114,115]. PPAR can interfere with sex-specific pathways by induction of target genes and by competing for cofactors with other nuclear receptors, such as ER and oestrogen-related receptors[16,116]. PPARs also inhibit oestrogen and testosterone synthesis in isolated ovarian cells[117]. In addition, sex differences in the pharmacokinetics of pioglitazone (Actos; Takeda) in rats have been described and these differences have been assumed to explain the greater effectiveness of pioglitazone in women than in men in clinical studies[118]. In a small clinical study with troglitazone, correlations between VEGF levels and weight gain were found in female patients with diabetes[119]. It might therefore be suspected that some of the PPAR effects will be sex-dependent. However, in

Table 4 | **Polymorphisms in autosomal genes associated with sex-specific phenotypes in humans**

Polymorphic gene	Gender-specific phenotype	Group affected	Refs
PPARα	Left-ventricular hypertrophy	Men	110
PPARγ	Obesity	Obese women	112
PPARγ	Leptin levels increased	Diabetic women	113
PPARγC1	Hypertension	Diabetic men	111
ACE	Right-ventricular hypertrophy	Men with COLD	121
Lipoprotein lipase	Triglyceride levels, risk for ischaemic heart disease	Women	122
Methionine synthase	Longevity	Men (more protected)	123
Plasminogen activator inhibitor 1	Cardiovascular mortality	Women (higher mortality)	124
Angiotensin receptor type 2	Modulation of left-ventricular hypertrophy in HCM	Women	128
Apolipoprotein E	Depression in Alzheimer's disease	Women	125

ACE, angiotensin-converting enzyme; COLD, chronic obstructive lung disease; HCM, hypertrophic cardiomyopathy; PPAR, peroxisome proliferator-activated receptor.

the only large cardiovascular outcome study with glitazone (Avandia; SmithKline Beecham) and pioglitazone, no sex-specific analysis has been presented so far[120].

Autosomal genes that are associated with cardiovascular phenotypes in a sex-specific manner are related to the renin–angiotensin system, lipid metabolism, homocysteine and folate metabolism — all of which are pathways that are suspected to be gender-specific — and to the phenotypes of blood pressure, longevity, ischaemic heart disease, cardiovascular mortality and depression[121–126].

Genes that are relevant in the cardiovascular system and that are located on the X-chromosome are also candidates for causing gender differences. On the one hand, mutations in these genes or functionally relevant polymorphisms might be better compensated in women, who have two copies of the gene, than in men. On the other hand, about 15% of the X-chromosomal genes are assumed to escape X-inactivation, which could result in higher gene doses in women[127]. The AT2R, located on the X-chromosome, has been shown to modulate left-ventricular hypertrophy in women who have hypertrophic cardiomyopathy, but not in men[128]. In an animal model of vascular injury, the protective effect of valsartan (Diovan; Novartis) was based on an observed greater upregulation of the AT2R in female mice[129].

In an impressive number of recently reviewed transgenic animal models, a more severe cardiovascular phenotype develops in male than in female animals, and the progression of heart failure and death from heart failure occur earlier in the male animals[130,131]. Frequently, the more severe cardiovascular phenotype in male animals or in ovariectomized females can be rescued by the administration of oestrogen[132]. The genes involved in these pathways are also candidates for gender effects.

Choosing the right experimental model to detect gender differences in drug effects is the next challenge. Recently, sex differences have been described in a large number of non-transgenic animal models, of which only a small selection can be presented (TABLE 5). This sample includes common models for infarction, left-ventricular hypertrophy, hypertension and metabolic disorders. These models offer the opportunity to study gender-related differences in animal physiology and drug effects, and to select models that properly reflect target populations. Frequently, gender-related differences become more pronounced with age. Young male animals are probably not helpful for defining side effects and mechanisms associated with antidiabetic medication that occur in older women, but old Zucker diabetic fatty rats show many sex-specific differences that might be relevant to humans[133]. Phytooestrogens in the diet also affect phenotypes in males and females[134]. A systematic search for gender-specific drug effects could include the comparison of a panel of biomarkers covering major pathophysiological pathways in male and female animals.

Phase I studies. On the basis of the preclinical studies, gender differences in pharmacokinetics and pharmacodynamics should be assessed in Phase I and II trials. As recently reviewed, data from FDA submissions showed that significant gender differences in bioavailability were present in approximately 30% of submitted drugs and differences in exposure reached as much as 50%[20]. Lower weight and distribution volume in women might partially explain these effects. Weight-adjusted regimens are standard for digoxin, unfractionated heparins, antiarrhythmic and thrombolytic drugs, as well as other agents, and should be elaborated for all new drugs. The increased risk of bleeding in older women treated with fixed doses of thrombolytic drugs or glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors emphasizes the importance of weight adjustment[20]. Kidney function — that is, glomerular filtration — is generally better in men than it is in women and is poorest in elderly women, which is only partially explained by the body-weight differences.

Primary drug-metabolizing enzymes in the intestinal villi include CYP450 enzymes (predominantly CYP3A) (see earlier section). Cytochromes are also the major enzymes involved in hepatic drug clearance. CYP1A and CYP3A substrates are cleared differently by women

Table 5 | **Gender differences in commonly used non-transgenic animal models**

Animal model	Intervention	Phenotype with sex difference	Sex difference	Refs
SD rat	Aortic banding	Left-ventricular function, gene expression	More hypertrophy and better function in females	75
SD rat	Aortocaval shunt	Left-ventricular remodelling	Better function in females	144
SD rat	MI (with and without exercise)	Infarct size, remodelling	Smaller MI in females	145
SD rat	MI	Post-infarct remodelling	Better in females	146
SD rat	Angiotensin II	Hypertension	Only in males	147
SHR	Reduction in oxidative stress	Hypertension	Stronger effects of antioxidants in males	148
SHR	No treatment or treatment with angiotensin II	Blood pressure	Higher in males	149
SHR-SP	Omapatrilat, Irbesartan	Hypertrophy, endothelial function, NO-release	Stronger reduction in left-ventricular hypertrophy in males	150
SHHF	Diet	Obesity, NIDDM, CHF	Synergistic effect of male gender and obesity	151
ZDF	High-fat diet	NIDDM and lipoprotein profile	More favourable in females	133
STZ	Streptozotocin-induced diabetes	Cardiac function	Greater left-ventricular dysfunction in females	152
C57Bl6mice	Exercise	Cardiac hypertrophy	Better hypertrophic response in females	153

Gender differences in transgenic animals are reviewed in REFS 130,131. CHF, congestive heart failure; MI, myocardial infarction; NIDDM, non-insulin-dependent diabetes mellitus; NO, nitric oxide; SD, Sprague Dawley; SHHF, spontaneous hypertensive heart failure rats; SHR, spontaneous hypertensive rats; SHR-SP, SHR-stroke prone; STZ, streptozotocin-induced diabetes; ZDF, Zucker diabetic fatty rats.

and men[20,87]. These substrates include cyclosporine, tacrolimus, calcium-channel blockers, such as nifedipine and verapamil, and statins, among numerous others. Other hepatic processes — for example, the activity of COMT, which metabolizes the neurotransmitters noradrenaline, adrenaline, dopamine and L-dopamine, as well as oestrogens — are higher in men, which leads to faster clearance of these drugs in men than in women[135].

Phase II. Phase II should focus on gender-related differences in the specific mechanisms of action of the drug under investigation, and their relation to gender-specific pathways. The important role of NO in women could cause a number of gender-specific effects. NO is involved in vascular protection (see earlier), and in the reduction of myocardial hypertrophy; it contributes to the elimination of free radicals and its loss in women mediates devastating effects in diabetes[40]. If we postulate that women, because of their physiologically higher NO levels, depend to a larger degree on NO than men, then NO-modulating drugs — including NO donors, phosphodiestrase inhibitors, possibly angiotensin receptor blockers and ACEIs, among others — might have a greater effect in women than in men, as does smoking, which destroys NO. Accordingly, destruction of NO by L-NAME (NG-nitro-L-arginine methyl ester) induced a more pronounced blood pressure increase in female than male rats[136]. The interaction of drugs with PPARs and the renin–angiotensin system, and the interaction with sex-specific pathways outlined earlier, should be studied. The interaction of drugs with sex hormones, their metabolism and function should also be tested[117].

Some areas with high potential for gender-related differences have so far been neglected. These include the effects of oestrogen on thrombosis, thrombolysis and fibrinolysis, all of which involve platelets. Platelet function is gender-dependent and even changes during the menstrual cycle[137]. Platelets carry ERβ and AR, but not ERα or PR[138], and testosterone regulates platelet ER and AR expression: coagulation and fibrinolysis are also affected by sex hormones[139]. So far, gender-related differences have been observed during treatment with warfarin, aspirin and the GPIIb/IIIa inhibitors. Drug use and pharmacokinetics might explain some, but not all, of the differences observed.

Panels of biomarkers that cover major CVDs or gender-specific pathways will become helpful in two ways: first, established biomarkers can be screened for differences in male and female animals; and second, a set of known markers that label gender-specific pathways could be introduced. For this purpose the following, among others, could be useful: BNP; C-reactive protein; plasminogen-activator inhibitor (PAI1); and serum amyloid A or osteoprotegerin, both of which are predictors of CVD outcome in women. The metabolic markers adiponectin, leptin and resistin, as well as some cytokines and prostaglandin derivatives, might also prove useful as biomarkers of gender differences. If

suspicions of gender-specific mechanisms are confirmed, they must be targeted more specifically in Phase IIb.

Phase III and post-marketing studies. Depending on whether sex-specific issues are anticipated, Phase III studies can proceed with a regular protocol but should include prespecified gender-specific analysis, or alternatively they can be modified to detect suspected gender-related effects. Strategies should be modified in accordance with the search for an effect in women or men, or in both. When investigating an effect that occurs in both sexes, women and men should be included not only in equal numbers, but also in such proportions that equal numbers of events are likely to occur in both sexes[140]. This might necessitate the inclusion of a larger number of women in some trials for those diseases with a low event rate in women, such as myocardial infarction or acute coronary syndromes.

After Phase III trials and approval of a drug, the final important step is to carefully monitor gender-related differences that have escaped earlier detection because of the limited number of cases studied. In large cohorts and in the general population, gender-specific effects and side effects can be affected by drug use, prescription habits or gender-specific co-medication, including hormone therapy, life-style factors, such as high intake of phytoestrogens or vitamins, or genetic variations that can interact with sex hormones[141]. Inhibitors of 3-hydroxy-3-methylglutaryl-co-enzyme A reductase (HMG CoA reductase) showed their greatest rate of myopathy in older women and this was probably due to the non-consideration of the adaptation of the recommended dose to weight in this subgroup[142]. Improved knowledge of gender-related differences in cardiac electrophysiology will lead to very cautious and ECG-supervised use of QT-prolonging drugs in women. Furthermore, observational studies should be used to detect possible interaction of cardiovascular drugs with hormone therapy in women.

Conclusions

Gender differences in CVDs definitely exist and are very likely to have an increasing role in therapeutic decisions in the near future. This should be supported by gender-specific research on existing drugs and gender-specific strategies in the development of novel agents. Research on oestrogen and testosterone and their receptors has begun, but gender in all its complexity is only starting to be recognized as a scientific category in medicine. We need a comprehensive approach to understand the entity of gender-related differences, including their genetic basis and gene–environment interactions, as well as the pathophysiology of sex hormones through all developmental stages to optimize pharmacological therapy for women and men.

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Competing interests statement
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