Diplomarbeit

Gender related differences of selected diseases concerning prevalence, pathophysiology, diagnosis, therapy and outcome

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Graz, am 31. 10. 2017 **Simone Stoisser eh**

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Zusammenfassung

Einleitung: Frauen sind unterrepräsentiert in klinischen Studien und nur in wenigen Tierstudien werden weibliche Tiere verwendet. Das führt dazu, dass Frauen häufig Medikamente verschrieben bekommen, die nur an Männern getestet wurden und deshalb häufiger an Nebenwirkungen leiden. Das Ziel dieser Diplomarbeit war es die Unterschiede ausgewählter Erkrankungen zwischen Frauen und Männern in Bezug auf Prävalenz, Diagnostik, Pathophysiologie,Therapie und Outcome zu diskutieren.

Methoden: Die Methode dieser Diplomarbeit war eine Literaturrecherche. Pubmed und Google Schoolar wurden verwendet, um die neuesten und relevanten Artikel zu den ausgewählten Erkrankungen zu finden.

Ergebnisse: Frauen mit kardiovaskulären Erkrankungen erscheinen für gewöhnlich später und sind bei Diagnose oft älter als Männer. Das weibliche Herz sowie die Gefäße sind kleiner und steifer. Östrogen hat eine wichtige Schutzfunktion in prämenopausalen Frauen. Frauen werden später diagnostiziert, behandelt und wenn sie behandelt werden, dann weniger aggressiv. 2011 wurden von der American Heart Association Guidelines zur Prävention von kardiovaskulären Erkrankungen in Frauen publiziert.

Im Gegensatz dazu sind Männer, welche an Osteoporose leiden, unterdiagnostiziert und erhalten weniger Behandlungen. Guidelines von mehreren Organisationen zur Behandlung von Osteoporose in Männern sind jedoch vorhanden.

Diabetes mellitus hat eine ähnliche Prävalenz in beiden Geschlechtern. Östrogen schützt Frauen und Androgene schützen Männer - beide Hormone erhöhen die Insulin Sensitivität. Gestationsdiabetes steht in enger Verbindung mit Komplikationen in der Schwangerschaft sowie der Weiterentwicklung in Richtung Diabetes Mellitus Typ II.

Nur 1% der Brustkrebspatienten sind Männer. Mutationen in den Genen sind bei Männern und Frauen unterschiedlich. Eine Mastektomie wird häufiger bei Männern angewandt, brusterhaltende Operationen häufiger bei Frauen. Für Männer ist die Erkrankung häufig auch eine große psychologische Last.

Diskussion: Frauen erleben verschiedene Schwierigkeiten in kardiovaskulären Erkrankungen. Sie kommen später in Notfallambulanzen and erhalten weniger

häufig und weniger aggressive Therapien. Das Hauptsymptom bei Frauen sind untypische Angina pectoris Beschwerden. Obwohl Männer, die an Osteoporose leiden unterdiagnostiziert sind gibt es doch von mehreren Organisationen spezifische Guidelines für die Behandlung von Männern. Brustkrebs betrifft nur sehr wenige Männer und die Behandlung stützt sich vor allem auf die Therapie von Frauen mit Brustkrebs.

Schlussfolgerung: Unterschiede zwischen Frauen und Männern konnten in allen der ausgewählten Erkrankungen aufgezeigt werden. Fortschritte konnten in den letzten Jahren durch den Einschluss von Frauen in klinischen Studien und die Anwendung von präklinischen Studien an weiblichen Tieren erreicht werden. In Zeiten der „personalisierten Medizin“ würden wir zweifelsfrei von genderspezifischen Studien und Guidelines für die optimale Therapie von Frauen und Männern profitieren.

Abstract

Introduction: In preclinical and clinical trials women are underrepresented and animal studies are often performed only on male animals. This leads to treatment in women with drugs mostly tested on men and therefore may lead even to more adverse drug reactions in females. This diploma thesis aims to discuss selected common diseases regarding differences between the sexes concerning prevalence, pathophysiology, diagnosis, treatment and outcome.

Methods: The method was a literature research. The discussed diseases were carefully chosen to report both differences regarding the female and the male population. PubMed and GoogleScholar were searched for relevant and recent articles. The library of the Medical University of Graz and the library of the Karl-Franzens University were also used.

Results: Concerning cardiovascular diseases (CVD), women are usually older at presentation. They have stiffer and smaller hearts and vessels than men. Symptoms differ significantly from those seen in males. Estrogen has protective effects in premenopausal women. Primary reperfusion therapy is performed less in women and treatment in females is less aggressively in general. In 2011 the American Heart Association updated prevention guidelines for CVD in women.

Men suffering from osteoporosis are usually underdiagnosed and undertreated. There are treatment guidelines for men available from several organizations.

Diabetes mellitus is a major health burden. The prevalence is similar in both sexes. Estrogen protects women and androgens protect men and both increase insulin sensitivity. Gestational diabetes is associated with adverse pregnancy outcomes and a high risk of progression into type 2 Diabetes Mellitus.

Only 1% of breast cancer patients are male. Mutated genes in males differ from those in females. Men receive less breast-conserving therapy and mastectomy is performed more often in males. Additionally, men often face substantial psychological burdens.

Discussion: Women face several disadvantages in CVD. They present later and with different symptoms than men with the most common symptom of atypical angina. They are diagnosed later and receive treatment later and less aggressively. To date no specific guideline for treatment of women with CVD are available. No differences exist concerning diabetes mellitus. Men are undertreated

in osteoporosis but several guidelines for the treatment of men exist. Breast cancer affects men only rarely and treatment is based mostly on treatment for women.

Conclusion: In the chosen frequent diseases, sex differences for both the female and male population exist. With the inclusion of women into clinical trials and drug testing on female animals, treatment options for women have improved. In the era of „personalized medicine“ we would doubtlessly benefit from gender specific research and guidelines to allow optimal treatment for women and men

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Abbreviations

ACEI:	Angiotensin-converting-enzyme inhibitor
ACS:	Acute coronary syndrome
AF:	Atrial fibrillation
AHA:	American Heart Association
AMI:	Acute myocardial infarction
AV-node:	Atrioventricular node
AT1:	Angiotensin type 1
BNP:	B-type natriuretic peptide
CABG:	Coronary artery bypass grafting
CAD:	Coronary artery disease
CHD:	Coronary heart disease
CK-MB:	Creatin kinase-MB
CRP:	C-reactive protein
CVDs:	Cardiovascular diseases
DM:	Diabetes mellitus
E2:	Estradiol
ECG:	Electrocardiogram
EF:	Ejection fraction
ER:	Estrogen receptor
FDA:	Food and Drug Administration
FSH:	Follicle-stimulating hormone
GPER:	G-protein coupled estrogen receptor
HDL:	High density lipoprotein
HETE:	Hydroxyeicosatetraenoic acid
HF:	Heart failure
LDL:	Low density lipoprotein
LV:	Left ventricle
LVEF:	Left ventricular ejection fraction
MI:	Myocardial infarction
mV:	milli Volt
NADPH:	Nicotinamide adenine dinucleotide phosphate

NIH:	National Institute of Health
NT-proBNP:	N-terminal pro-BNP
NYHA:	New York Heart Association
NO:	Nitric oxide, nitrogen monoxide
P:	Progesterone
PCI:	Percutaneous coronary intervention
PGE:	Prostaglandin
PGI:	Prostacycline
RAS:	Renin-Angiotensin System
RAAS:	Renin-Angiotensin-Aldosterone System
STEMI:	ST-elevation myocardial infarction
TTC:	Takotsubo cardiomyopathy

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Introduction

A need of change?

We are living in a world covered in diversity: different areas, races, sexes, traditions, believes – different people.
Medicine as we know it today, is not as aware of that as it may need to be, to treat women and men of all kinds of races in respect of their, sometimes, diverse needs. Modern medicine treats people based on trials mostly performed on one half of world's population – men. Modern pharmaceutical industry produces drugs mostly tested on male animals and white Caucasian men. Minorities are often underrepresented in clinical trials and women develop more adverse drug reactions than men do (1–4).

Women face multiple difficulties in medical fields, participating in clinical trials, animal studies and in the matter of diversity and outcome of some specific diseases. To raise awareness is the first aim of this diploma thesis.
The second aim is to high-light the diversity of specific diseases in the matter of sex differences to encourage researchers, physicians and all staff working in medical fields to increase their awareness and to adapt clinical trials and treatments for better representation and possibly outcomes of all sexes.

Definition of sex and gender

According to the World Health Organization, the term „sex" is defined as: „the biological characteristics that define humans as female or male." (5), and the term „gender" is defined as: „Used to describe the characteristics of women and men that are socially constructed. People are born female or male, but learn to be girls and boys who grow into women and men. This learned behaviour makes up gender identity and determines gender roles." (6)
In several studies sex is referred to chromosomes, male and female anatomy and endocrine system and therefore seen as biology of humans whereas the term gender relates to the behaviours and roles as well as expressions and identity of

women and men based on social constructs that changes over time as well as over regions and stages of life. It influences how girls, boys, women, men and gender diverse people feel about themselves and others, how they interact within social norms and expectations and how they deal with certain challenges (7–9).

The effect of gender inequalities on a woman in the 21st century

Gender is described as an institutionalized system of social practices in which social relations of inequalities occur based on the difference of men and women. It includes cultural beliefs of how women and men are expected to behave.
The sociocognitive process of sex categorization means identifying a person as female or male and links social relational contexts and gender beliefs. Unconsciously and automatically everyone is sex categorized by others. This activates gender stereotypes immediately (men are more instrumental and self-determined, women more communal) (8).

In the 21st century in many countries women are still seen as less competent than men regarding instrumental rationality but better at less valued (communal) tasks and nicer in general. This affects all parts of life as it is institutionalized in government policy, media or normative images of the family and one is treated by others according to the hegemonic gender beliefs.
A product produced by a man is evaluated as better than if produced by a female. This effect is even stronger when it is a product of a male dominated domain (e.g.: engineering). A product of a female dominated domain weakly favors women (8).

Important consequences for gender inequalities are found in work or educational settings, particularly in hierarchical dimensions (e.g.: interviews in the hiring process or decision making in staff meetings). The essence of gender hierarchy survived industrialization, movement of women into paid labor force and originally male dominated occupations (e.g. medicine). It assumes that men have more authority and status than women and implies that men are more powerful.
The „glass ceiling problem“ discribes the fact that in almost all sectors women are often midlevel managers but rarely reach the highest authority positions. Women receive resistance and hostility more often when acting as a manager with

directive authority than men do. As in our society the manager role is linked to men this biases women's competence and legitimacy in the manager role (8).

Problems of mothers at the workplace

Mothers face additional specific disadvantages at work. Mothers are seen as less self-determined and much more communal as the stereotype of a mother is a more extreme version of the stereotype of a woman. C. Ridgeway and S. Correll write that those cultural beliefs bias expectations for a women's ability at the workplace. Especially today's idea of the ideal worker in combination with the expectation that a mother is always there for her child creates special pressure for women. Even adding the fact of having a child in woman's CV reduces her anticipated competence, reduced the suitability for hiring and promotion and the wage she is offered (while being a father has no effect on men) (8).

Health inequalities

Inequalities occur between races, levels of socioeconomic status and levels of education. Women have higher morbidity rates and a poorer quality of life although they live longer than men. They suffer from more chronic diseases and have a greater likelihood of functional limitations. Lower socio-economic standards and greater stress exposure due to family and work arrangements may contribute to these facts (9).

The combination of gender and race-ethnicity lead to a greater racial-ethnic inequality in health among women than men. Moreover, interaction of race and education exists, resulting in a greater education-health difference among whites than blacks. So being black or Mexican American and female appears to result in poor health. In later stages of life health advantages due to higher levels of education or income erode and racial-ethnic gaps in self-rated health declines (9).

Women in medicine

Although progress has been made, female medical doctors still experience disadvantages in developing a solid medical carrier.

Women are common in midlevel manager roles along work life (8), but still rarely reach top academic positions such as full professor, hospital/department leaders or editorial board members. A recent work from Amrein et al. analysed the editorial board members of 60 top ranked journals. Only 15.9% of editors-in chief were women. The highest percentage of women as editors was found in Medicine, General and Internal, and the lowest in Critical Care. (10)

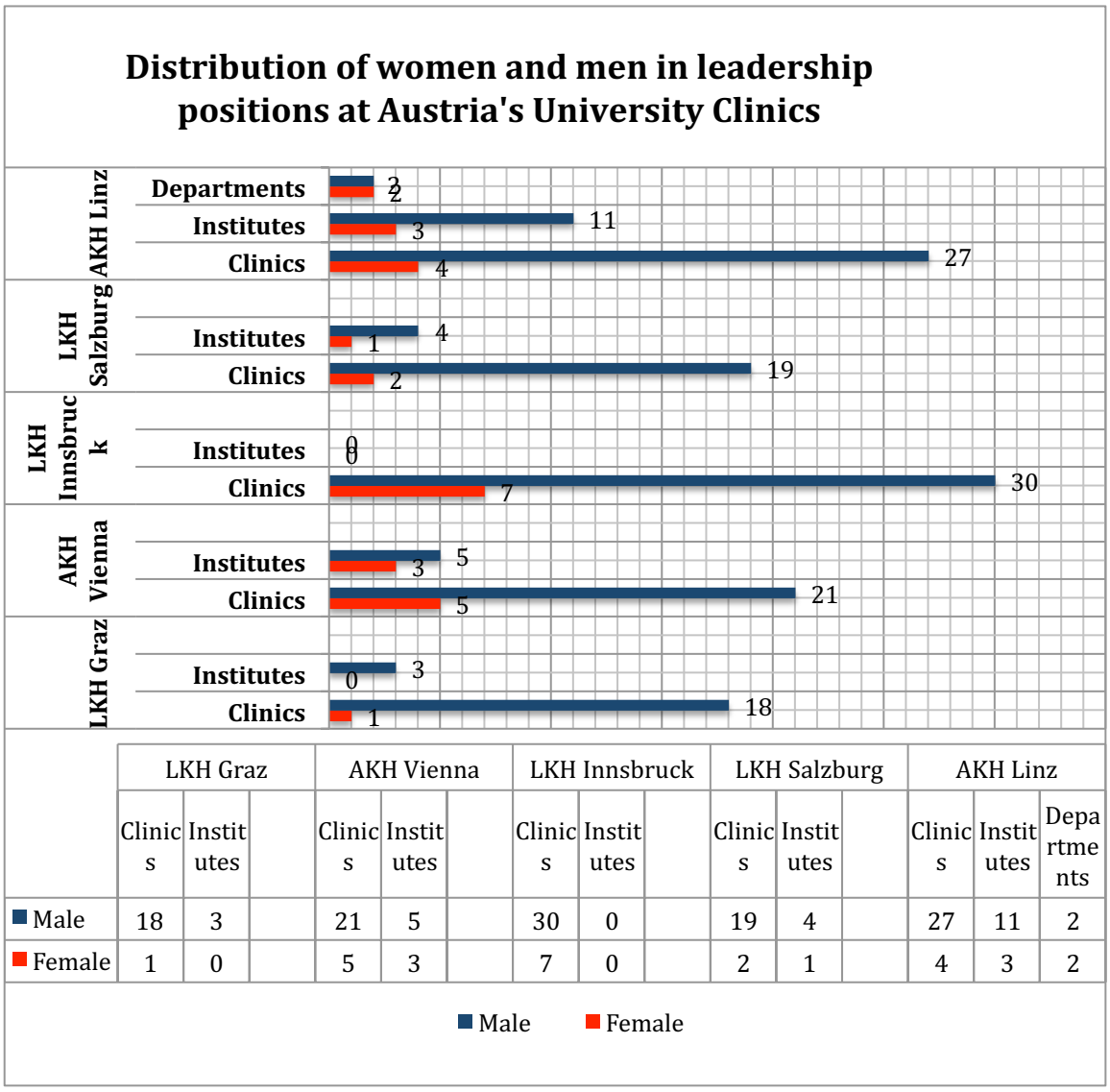
An important opportunity of establishing an academic carrier are medical conferences, were ideas are shared and successful projects can start. Because of different reasons, women are often underrepresented as speakers at conferences, particularly in the subspecialities of Emergency Medicine or Critical Care. (11)

Women are less likely to win prestigious scientific awards. For example from 1901 – 2016 only 12 (5.7%) women (out of 211) won the Nobel Prize in physiology or medicine (12).

Women are also underrepresented as first and senior authors of research articles in medical journals. However, the numbers of female senior authors in 6 prominent journals increased from 4% in 1970 to 19% in 2014 and the numbers of female first authors increased from 6% in 1970 to 29% in 2004. (13,14)

Additionally the paper „Nepotism and sexism in peer-review“ showed that being a woman leads to a 2.5 times higher need of numbers of publications than men are expected to produce. (15)

The chart below shows the distribution of women and men in leadership positions at Austrias University Hospitals (16–20).



	LKH Graz			AKH Vienna			LKH Innsbruck			LKH Salzburg			AKH Linz		
	Clinics	Institutes		Clinics	Institutes		Clinics	Institutes		Clinics	Institutes		Clinics	Institutes	Departments
Male	18	3		21	5		30	0		19	4		27	11	2
Female	1	0		5	3		7	0		2	1		4	3	2

Figure 1.: Distribution of women and men in leadership positions at Austria's University Clinics (16–20)

At the University Hospital of Graz (State Hospital) only 1 out of 19 (4.5%) of leadership positions is held by a women (Clinics and Departments). At the University Hospital of Vienna (General Hospital) women as leaders make up 11.5%, at the State Hospital of Innsbruck women in leadership positions make up 18.9%, at the State Hospital of Salzburg 11.5% and at the General Hospital of Linz only 18.4% of chief positions are held by women.

Gender in clinical and preclinical trials

For the advancement in medicine, research is essential - from animal studies to humans. Preclinical research in many cases mostly relies on male cells and male animals (21).

For many years women have been excluded from clinical trials. Some progress has been made in the last decades, but there is still gender bias existing at all stages of research:

- Women are often underrepresented as trial participants although 55% of medical admissions in the United Kingdom and 47% in the United States are women (22,23).
- Women face challenges during their medical carreer, i.e. they receive less research funding than men. The reason for this are not entirely understood, but fewer applications for research funding by women have been suggested. However, even when they apply, women usually receive smaller rewards (15,22,24,25). Additionally, studies show variable chances of research fundings for women, sometimes 7% lower than men. (26,27).

  Women tend to achieve fewer independent funding awards, are less likely to apply for competitive grants and receive significantly less start-up support (28–30).
- Women don’t benefit from research as much as their male counterparts. Evidence shows that unaddressed gender differences in research lead to inaccurate conclusions. This influences the effectiveness of treatment (22,31).

History of progress of female participation at clinical trials:

1950	Thalidomide was developed for pregnant women as a treatment for morning-sickness. A few thousand children died, even more were born with serious birth defects because of the unknown toxic effects to the unborn. With the in vitro testing on pregnant animals, this tragedy may have been avoided.
1977	The FDA (Food and Drug Administration) banned premenopausal women from Phase 1 and early Phase 2 research except testing for drugs against a life-threatening illness.
1986	The National Institute of Health (NIH) supports the inclusion of women in NIH supported clinical trials.
1990	Establishing the Office of Research on Women's Health
1993	NIH mandates the inclusion of women in clinical trials. The FDA removes the prohibition of premenopausal women.
May 2014	NIH plans the consideration of female cells, cell lines, tissue and animals in preclinical research.
25th January 2016	The consideration of female cells and animals is required for researchers as policy.
2009	Similar policy of Canadian Institute on Health Research. Researchers are required to explain the inclusion or exclusion of both sexes in their trials.
2012	9 different agencies across Europe are funded by the European Commission to report and improve gender/sex based analysis and equality in research.

Table 1: History of involvement of women in clinical trials (10,11,22–26).

Existing sex bias in research

In 2001, it was reported that the FDA removed eight out of ten drugs from the market because of greater health risks to women than to men (21).
For example, 21 years after the release of zolpidem in 1992, the dosing guidelines for females were changed from the FDA in the year 2013. Due to sex-related clearance rates, the same dose caused greater health risks in women compared to men (21,35).
Another example is flibanserin (Addy^{TM}). It is used in females for enhancing libido. Although it is used in women, the preclinical testings almost exclusively used male animals and at pharmacokinetic testing, 28 participants out of 38 were males. When testing the interaction of alcohol and flibanserin, out of 25 participants only two were women (21).

Surprisingly, studies often fail to report the sex of animals and cells used in their trials (36).
In their review from 2014 Yoon et al. pointed out that from surgical research they examined, 22% did not report wether the used animals were female or male. Of those who did, 80% used only male animals. 17% used only females and both sexes were used only by 3% of the authors of those papers. Sex-based results (differences due to sex found or not found) were reported by only 1% of these studies (37).
Another review from 2016 from Phillips S. and Hamberg K. also showed that sex/gender often remain hidden from interpretation in clinical trials (7).
Efforts for increasing women's representation in cardiovascular trials have been moderately successful as the enrolment of women exceeded the prevalence of coronary artery disease (mostly because of single sex trials). In mixed-sex trials the enrolement of women and the prevalence of the disease were equivalent (38).

Arguments used against female participation in clinical trials

Often it is argued that female inclusion is very complicated due to menstrual cycle or fluctuating sex hormones. Equal use of female animals is seen as resource consuming. Identifying the sex of cell lines may be challenging. Another argument is unnecessary duplication of data which may lead to a decrease in progress.

Money, time and space would increase. To report sex-related differences is even seen as an obstruction of innovation by some researchers (21,39,40).

Potential improvements for modern health care

Using female animals, tissue or cells would narrow the lack of research by only using males and adverse drug reactions in women or birth defects in babies could possibly be avoided.The inclusion of females in early stages of research would improve the health of girls and women as researchers would understand the underlying mechanisms and differences of diseases of both sexes. By using female cells and animals, possible new treatments for women may be detected.
It is important to report sex/gender findings even in case of negative findings. Also, sex should always be part of trials as a biological variable. Publishing companies could define guidelines for articles to include sex/gender in their publication (21).

For improving our knowledge about diseases, the possible treatment and outcome, we need preclinical and clinical research. But we need FULL evidence based medicine. Full in the matter of all kind of sexes, for improving health care for everyone. It is absolutely necessary to include female cells, animals, women, transgender persons and minorities into trials. Otherwise we continue practicing a medicine with a lack of knowledge and therefore may harm our patients and ourselves.

Materials and Methods

The method of this diploma thesis was a literature research. The diseases, which are discussed in this diploma thesis related to the topic „gender differences“ were carefully chosen, as I wanted to report not only gender differences regarding women but also regarding the male population. To edit the most representative diseases regarding gender differences, cardiovascular diseases and diabetes were chosen to reflect a female underrepresentation and osteoporosis and breast cancer to reflect the male population

PubMed was searched for relevant and recent articles via the Medical University Graz library server. Unfortunately not all articles where available, so not every relevant article could be involved in this diploma thesis in its full content.

Furthermore, GoogleScholar was used to extend the amount of literature and relevant articles found in the PubMed database.

Additionally, if papers were not available, it was tried to contact the authors to make the articles available but that succeeded only rarely and in most cases unfortunately there was no reply from the authors.

In addition, the medical library of the Medical University of Graz as well as the library of the Karl-Franzens University of Graz was used.

Results

1. Cardiovascular Diseases

1.1 Coronary Artery Disease (CAD), Coronary Heart Disease (CHD), Acute Coronary Syndrome (ACS)

In Austria in the year 2016 cardiovascular diseases (CVDs) are still the leading cause of death for 37% of men (mean age 79.9 years) and 45% of women (mean age 86.6 years), exceeding the rates for cancer, other diseases and deaths caused by trauma (41). In the United States most people die from CVDs with a high rate of myocardial infarctions in women. (42)

Although much information about sex differences in CVDs has been available in research, modern textbooks like the „Herold“ or the „Oxford American Handbook of Emergency Medicine“ mention those aspects rarely.

The aim of this part of my Diploma Thesis is to highlight differences and similarities between anatomic, pathophysiologic, diagnostic and therapeutic aspects in female and male patients.

Prevalence and Risk factors

Women are usually older than men when they first experience an acute cardiac event with a delay of approximately 20 years. CHD prevalence is higher in men until the age of 75. Although protective estrogen effects decline after menopause, the throughout-life prevalence for myocardial infarction remains lower in women (43,44).

More frequent risk factors in women are hypertention, renal impairment and diabetes mellitus as well as increasing levels of total cholesterol and LDL (low densitiy lipoprotein) after menopause (HDL does not change significantly) (44,45).

Women’s risk of myocardial metabolism impairment caused by impaired glucose, obesity and diabetes is greater compared to men (43,44,46).

Anatomy

Female hearts differ in size and shape from their male counterparts. A women's heart is smaller and stiffer and its coronary arteries (and vessels in general) are usually smaller too (47,48).

Periprocedural complications such as coronary dissection phenomena, complications at the puncture site and exaggerated leukocyte-platelet interactions are increased in women (44).

Female vessels are not only smaller, the extent of atherosclerosis and endothelial and smooth muscle dysfunction is also greater than in males. Endothelial dysfunction, caused by hypertension, diabetes mellitus and hypercholesterolemia, factors more prevalent in females, can lead to a higher rate of angina during exercise stress tests in spite of normal coronary angiograms (44).

Symptoms

The most common symptom at CHD onset in women is angina pectoris of which ca. 30% is typical and ca. 70% is atypical angina. Both, typical and atypical angina tend to be more severe in women. Syndrome X describes angina symptoms in combination with a normal coronary angiogram and is more prevalent in women as well (43,44,46).

Women with acute myocardial infarction (MI) present more often with atypical symptoms such as nausea, vomiting, dyspnoea, and/or pain in the abdomen, neck and/or shoulder (43,49).

Concerning HF (heart failure), women more often suffer from HF with preserved LVEF (left ventricular ejection fraction). In one study the most common symptom in men and women was dyspnoea. In one review the authors wrote that women, who were referred for transplantation, had a lower exercise tolerance, poorer kidney and pulmonary function and were more often NYHA (New York Heart Association) class III-IV in comparison with men at the same age or EF (ejection fraction). Women also reported higher pain severity and sleep difficulties as well as a worse quality of life after beeing diagnosed with HF (48,50).

Concerning AF (atrial fibrillation), women have a lower prevalence, maybe due to a smaller left atrium and therefore less reentry circuits. Despite this, AF has a closer association to thromboembolic events in women (48).
Women also have a higher incidence of hypertensive heart disease, more diastolic dysfunction and a steeper pressure-volume relationship and therefore a higher incidence of congestive heart failure, despite better left ventricular function (47,51,52).

The role of estrogen

It is still unclear how sex steroid hormones exactly influence cardiac and vascular pathophysiology. What is known is, that these hormones may control blood pressure and vascular tone. NO (nitric oxide, nitrogen monoxide) is responsible for vasodilatation. As estrogen regulates NO synthases and induces NO genes, women have a higher availability of nitrogen monoxide in their body. Fluctuating estrogen levels during menstrual cycle, pregnancy or estradiol replacement affect vasodilatation and blood pressure additionally. It also affects the prostanoids PGE_2 (Prostaglandin E) and PGI_2 (Prostacyclin), inhibits endothelin-1 and reduces the basal tone of microvessels, resulting in a relaxing effect of the vessels.
The arterial wall response to injury is improved by the hormone. As it supports re-endothelialization and inhibits smooth muscle cell proliferation and matrix deposition, estrogen prevents from artherosclerosis. Additionally, estrogen promotes coronary and peripheral endothelial function and decreases systemic vascular resistance which result in the prevention of coronary artery spasm.
The effects are modulated by the estrogen receptors ERα and ERβ that are both expressed in the smooth muscle and vascular endothelial cells. ERα seems to be responsible for the protective effects against vascular injury and atherosclerosis whereas ERβ is enhanced in the vascular wall of women suffering from ischaemic heart disease.
Nonetheless, Collins et al. showed that when women got coronary estradiol infusions, the hormone improved the coronary blood flow and endothelial function, but this effect was not seen in male patients.
There are known sex differences in cardiac function due to the regulation of female and male sex steroids of the myocardial calcium handling and additionally

female smooth muscle and vascular endothelial cells can carry more receptors to bind estrogen. ERβ is expressed in myocardial cells for regulating NO synthases. Estrogen induces genes responsible for cardiac conduction (I_{sk}, HK2 = potassium channels) and connexion. In animal studies with female mice, estrogen prolonged AV nodal conduction as well as the right ventricular effective refractory period.
The hepatic lipoprotein metabolism is also mediated by estrogen.
Moreover it is known that the risk of venous thrombosis is increased by estrogen as sex hormones regulate genes responsible for hemostasis as well.
Nevertheless, at the time of menopause women do not experience a sudden rise in the prevalence of cardiovascular diseases (44,47,48,53,54).

Diagnosis

Most important is an accurate history with respect to womens different signs and symptoms in comparison to men as mentioned above.
The most common objective procedure for testing myocardial ischemia is an exercise ECG (electrocardiogram). However, in women, ECGs have a low specificity and sensitivity (70% and 60%) and increased false-positive results. Reasons are artefacts because of breasts, hormonal influences, smaller coronary arteries, microvascular disease, fewer coronary artery lesions, vascular spasms, smaller LV (left ventricle) size, single vessel disease or inappropriate release of catecholamines (44).
Due to the European Society of Cardiology, for the diagnosis of STEMI (ST-elevation myocardial infarction) in women, an ST-elevation of more than 0,15 mm in V2-3 (men more than 0,3 mm over 40 years old or 0,25 mV when under the age of 40) and more than 0,1 mm in all other leads of a normal ECG is necessary (55).
However, more men experience a Q-wave and/or STEMI than women younger than 75 years (56).
There is a notable difference concerning cardiac biomarkers between the sexes as in female ACS patients C-reactive protein (CRP) and brain natriuretic peptide are more likely to be elevated. In contrast, in men troponin levels and creatine kinase-MB (CK-MB) are elevated more commonly (47,57).

Treatment

Evidence show that women are presenting later at hospitals after symptom onset longer than males. In particular, women younger than 65 years had similar delay as men, 66-74 year-old women had a longer prehospital delay and after the age of 75 the prehospital delay was greater in men according to Nguyen et al. (44,56).
One reason for women's delay might be their older age, as people tend to delay in seeking medical care in older age. Secondly, women experience more „atypical" symptoms of MI and also healthcare providers may be not aware of these or do not evaluate them correctly (Yentl Syndrome) (44,58).
Women tend to receive fewer primary reperfusion therapies and are diagnosed and treated less aggressively (47,59). Women are less likely to undergo coronary thrombolysis, coronary angiography, coronary angioplasty and coronary artery bypass grafting (CABG) although some studies report that women with advanced CAD receive PCI as often as men (44,47,49).
Concerning medical treatment, women are less likely to receive class I recommendations for medical therapy. Evidence show that 14-25% fewer women receive ACE inhibitors, angiotensin receptor blockers, aspirin, beta-blockers, dual platelet inhibition and statins as secondary prevention drugs (60).

Thrombolysis	In women thrombolytic reperfusion is performed less. They have more bleeding complications and higher short-term mortality rates. Women die twice as often from this intervention (44).
PCI	Women have lower short-term but equal long-term survival rates compared to men. Angioplasty with stents showed equal 3-year survival rates between the sexes but a higher 3-year mortality in women when balloon angioplasty was performed. Significantly higher mortality in women occured only 4 years after PCI (44).
CABG	CABG carries a higher mortality risk for women in general. A 2-fold higher in-hospital mortality occurs after performence in women except very high-risk categories with equal mortality rates of the sexes. The recovery in females is more difficult (44). Some studies showed no differences between the sexes regarding early and late mortality after percutaneous transluminal coronary angioplasty and CABG or long-term mortality after CABG and that the gender difference decreases with the patient's advancing age (61–63).

Postmenopausal hormone therapy	It has many biological effects as it activates coagulation and improves fibrinolysis; on the one hand it has anti-inflammatory effects on the other hand proinflammatory. Effects depend on the age of the women, dosage, route of administration and many more. It definitely increases CRP. There may be a slightly increased risk of CVD (54).

Table 2: Treatment of CVDs and related differences between women and men

Complications

Women experience vascular and bleeding complications (intracranial hemorrhage), heart failure, shock, reinfarction and stroke more often than men. Women tend to cardiac rupture whereas men tend to cardiac arrhythmia-caused death. Females also require red blood cell transfusions more often. More excess dosing of anticoagulants and antiaggregatory drugs are seen in women due to their lower body weight and reduced glomerular filtration rates. Women experience more pulmonary edema and cardiogenic shock. However, if shock has developed, the outcome is independent of sex. After PCI during the hospital stay, women tend to suffer from heart failure more, possibly due to difficulties of tolerating transient ischemic periods during PCI and volume changes in stiffer and smaller female hearts. They also have a greater chance of suffering a reinfarction.
After AMI, women tend to have poorer mental and physical health, have greater probability for depression, return later to work and take part at cardiac rehabilitation programs less frequently (44,49,64).

The following table shows an overview about the female specifics regarding CVD, CHD and ACS:

	Women	Men
Prevalence	Older at first presentation (20years later than men) Throughout life prevalence of MI lower Highest CVD prevalence in black american women older than 20 years ↓ AF prevalence	Until 75 years, higher prevalence of CHD ↑ AF prevalence
Incidence	↑ Hypertensive heart disease ↑ Diastolic dysfunction ↑ Steeper pressure-volume relationship ↑ congestive HF	
Risk factors	Compared to men, women experience higher rates of: Hypertension Renal impairment Diabetes mellitus After menopause: LDL, total cholesterol	
Vascular/cardiac anatomy	Smaller Stiffer Greater extent of artherosclerosis and smooth and endothelial muscle dysfunction ↑ angina during exercise stress test	
Symptoms	Most common angina: 64% atypical, 30% typical ↑ severe angina Syndrome X ↑ pain severety ↑ Sleep difficulties	
Diagnosis	ECG ↓ specifity and sensivity, ↑ false-positive results STEMI: ≥0,15 mV in V_{2-3} ≥ 0,1 mV all other leads	STEMI: ≥0,3 mm over age of 40 and ≥0,25 mV under age of 40 in V_{2-3} ↑ Q-wave and/or STEMI than women under 75 years
Biomarkers	ACS: ↑ CRP and brain natriuretic peptide	↑ Troponin

		↑ CK-MB
Treatment	Presenting later in hospital Diagnosed and treated less aggressively ↓ primary reperfusion therapy ↓ coronary thrombolysis ↓ coronar angiography ↓ coronar angioplasty ↓ CABG ↓ medical treatment	
Thrombolysis	↑ bleeding complications ↑ short-term mortality die twice as often	
PCI	↓ short-term survival equal long-term survival ↑ 3-year mortality after baloon angioplasty equal 3-year mortality after stent ↑ mortality only after 4 years of PCI	
CABG	↑ mortality risk ↑ difficult recovery 2x higher in-hospital mortality Some studies showed no difference in short- and/or long-term mortality	
Complications	cardiac rupture ↑ vascular and bleeding complications ↑ heart failure ↑ shock ↑ reinfarction ↑ stroke ↑ red blood cell transfusion requirement ↑ excess dosing of anticoagulants/antiaggregatory drugs ↑ pulmonary edema ↑ post AMI depression ↓ mental and physical health later return to work ↓ cardiac rehabilitation programs	Cardiac arrhythmias

Table 3: Overview of the differences regarding CVD, CHD and ACS between the sexes.

Prevention

The American Heart Association (AHA) developed guidelines for the prevention of CVD in women, which have been updated in 2011. The following tables and diagrams show the available progress in female medical care regarding CVD (65):

Table 1. Class III Interventions for the Prevention of CVD in Women

Menopausal therapy
Hormone therapy and selective estrogen receptor modulators should not be used for the primary or secondary prevention of CVD
Antioxidant supplements
Antioxidant vitamin supplements (e.g., vitamin E, vitamin C, beta carotene) should not be used for the primary or secondary prevention of CVD
Folic acid*
Folic acid, with or without vitamin B_6 and B_{12} supplementation, should not be used for the primary or secondary prevention of CVD
Aspirin for myocardial infarction in women younger than 65 years
Routine use of aspirin in healthy women younger than 65 years is not recommended to prevent myocardial infarction

NOTE: *Class III interventions are not useful/effective and may be harmful.*

CVD = cardiovascular disease.

**—Folic acid supplementation should be used in the childbearing years to prevent neural tube defects.*

Adapted from Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: A guideline from the American Heart Association. Circulation. *2011;123(11):1245.*

Table 4: „Class III Intervention for the Prevention of CVD in Women“ (65)

Guidelines for the prevention of CVD in women

Cigarette smoking
Women should be advised not to smoke and to avoid environmental tobacco smoke.
Physical activity
Women should be advised to accumulate at least 150 min/wk of moderate exercise, 75 min/wk of vigorous exercise.
Cardiac rehabilitation
A comprehensive CVD risk-reduction regimen such as cardiovascular or stroke rehabilitation or a physician-guided home- or community-based exercise training program should be recommended to women with a recent acute coronary syndrome or coronary revascularization, new-onset or chronic angina, recent cerebrovascular event, peripheral arterial disease *(Class I; Level of Evidence A)* or current/prior symptoms of heart failure and an LVEF ≤35% *(Class I*; *Level of Evidence B)*.
Dietary intake
Women should be advised to consume a diet rich in fruits and vegetables; to choose whole-grain, high-fiber foods; to consume fish, especially oily fish, at least twice a week; to limit intake of saturated fat, cholesterol, alcohol, sodium, and sugar; and avoid *trans*-fatty acids.
Note: Pregnant women should be counseled to avoid eating fish with the potential for the highest level of mercury contamination (eg, shark, swordfish, king mackerel, or tile fish).
Blood pressure: optimal level and lifestyle
An optimal blood pressure of <120/80 mm Hg should be encouraged.
Blood pressure: pharmacotherapy
Pharmacotherapy is indicated when blood pressure is ≥140/90 mm Hg (≥130/80 mm Hg in the setting of chronic kidney disease and diabetes mellitus). Thiazide diuretics should be part of the drug regimen for most patients unless contraindicated. Initial treatment of high-risk women with acute coronary syndrome or MI should be with *β*-blockers and/or ACE inhibitors/ARBs.
Note: ACE inhibitors are contraindicated in pregnancy and ought to be used with caution in women who may become pregnant.
Lipid and lipoprotein levels: optimal levels and lifestyle
LDL-C <100 mg/dL, HDL-C >50 mg/dL, triglycerides <150 mg/dL, and non–HDL-C (total cholesterol minus HDL) <130 mg/dL *(Class I; Level of Evidence B)*.
Lipids: pharmacotherapy for LDL-C lowering, high-risk women
LDL-C–lowering drug therapy is recommended simultaneously with lifestyle therapy in women with CHD to achieve an LDL-C <100 mg/dL. A reduction to <70 mg/dL is reasonable in very-high-risk women
Lipids: pharmacotherapy for LDL-C lowering, other at-risk women
In women >60 y of age and with an estimated CHD risk >10%, statins could be considered if hsCRP is >2 mg/dL after lifestyle modification and no acute inflammatory process is present *(Class IIb; Level of Evidence B)*.

Lipids: pharmacotherapy for low HDL-C or elevated non–HDL-C
Niacin or fibrate therapy can be useful when HDL-C is low (<50 mg/dL) or non–HDL-C is elevated (>130 mg/dL) in high-risk women after LDL-C goal is reached *(Class IIb; Level of Evidence B)*.
Diabetes mellitus
Lifestyle and pharmacotherapy can be useful in women with diabetes mellitus to achieve an HbA1C <7% if this can be accomplished without significant hypoglycemia *(Class IIa; Level of Evidence B)*.
Aspirin: high-risk women
Aspirin therapy (75–325 mg/d) should be used in women with CHD unless contraindicated and is reasonable in women with diabetes mellitus. *(Class I; Level of Evidence A)*. If intolerant of aspirin, use clopidogrel.
Aspirin: atrial fibrillation
Aspirin 75–325 mg should be used in women with chronic or paroxysmal atrial fibrillation with a contraindication to warfarin or at low risk of stroke (<1%/y or CHADS2 score of <2) *(Class I; Level of Evidence A)*.
Warfarin: atrial fibrillation
For women with chronic or paroxysmal atrial fibrillation, warfarin should be used to maintain the INR at 2.0 to 3.0 unless they are considered to be at low risk for stroke (<1%/y or high risk of bleeding) *(Class I; Level of Evidence A*).
Dabigatran: atrial fibrillation
Dabigatran is useful as an alternative to warfarin.
β **-Blockers**
β-Blockers should be used for up to 12 mo *(Class I; Level of Evidence A)* or up to 3 y *(Class I; Level of Evidence B)* in all women after MI or ACS with normal left ventricular function unless contraindicated.
ACE inhibitors/ARBs
ACE inhibitors should be used (unless contraindicated) in women after MI and in those with clinical evidence of heart failure, LVEF ≤40%, or diabetes mellitus *(Class I; Level of Evidence A)*. If intolerant, use ARBs instead.
Note: ACE inhibitors are contraindicated in pregnancy and ought to be used with caution in women who may become pregnant.
Aldosterone blockade
Use of aldosterone blockade (eg, spirololactone) after MI is indicated in women who do not have significant hypotension, renal dysfunction, or hyperkalemia who are already receiving therapeutic ACE inhibitor and *β*-blocker and have LVEF ≤40% with symptomatic heart failure *(Class I; Level of Evidence B)*.

Table 5: Extract of the guidelines for the prevention of CVD in women (65)

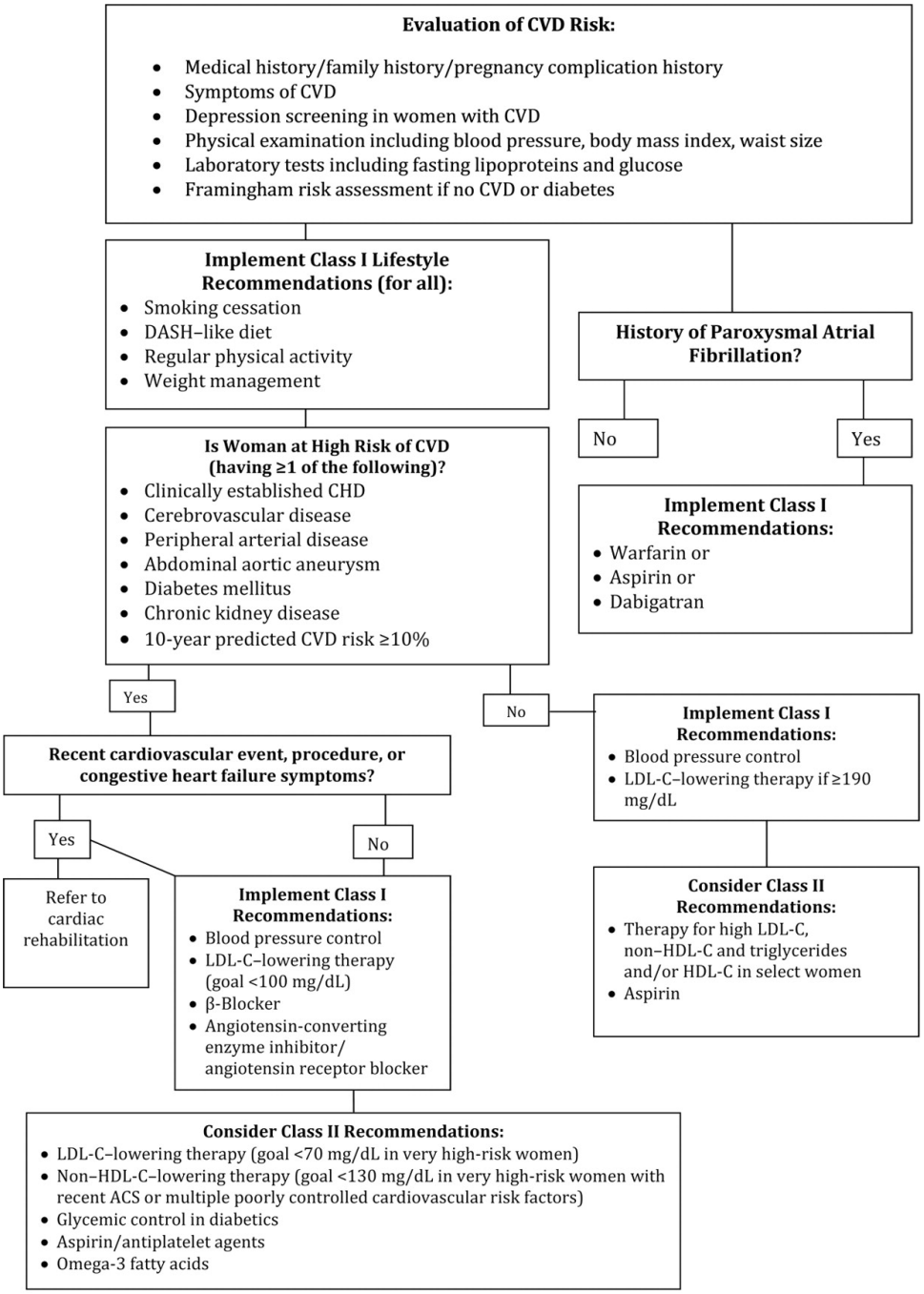


Figure 2: Evaluation of the CVD risk from the 2011 updated AHA guidelines for the prevention of CVD in women (65)

1.2 Takotsubo cardiomyopathy (TTC)

It was first reported in 1991 by Dote et al in Japan and confirmed in the late 1990s in reports from Europe and the United States. Only in 2006 it was approved as an acquired cardiomyopathy by the American Heart Association. The disease was also named stress-related cardiomyopathy, apical ballooning syndrome, ampulla cardiomyopathy or broken heart syndrome (66–69).

Incidence

The majority of TTC patients are women. Of patients presenting with suspected ACS in hospitals, approximately 2% (10% in females) are ultimately diagnosed with TTC. The Minneapolis Heart Institute reported an increase in numbers of TTC patients since 2001, with about 50 cases in 2014 (69).

Classification

Via transthoracic echocardiography and levo-cardiography one can distinguish between different types of the ballooning pattern of the ventricular wall.
The different types are: apical, mid-ventricular, basal and focal. The most common form is the apical one (81.7%) followed by the other types with 14.6% mid-ventricular, 2.2% basal and 1.5% focal type (70).

Clinical Presentation

TTC is a form of acute cardiac failure, mimicking an MI without epicardial coronary artery obstruction. In the majority of patients the left ventrical (LV) obstruction is reversible. TTC commonly affects older, usually postmenopausal women aged between 65 and 70 years (69,71,72).
The most common symptoms in patients with prehospital onset of TTC are chest pain and dyspnoea and often they are treated with aspirin and anticoagulants. Cardiogenic shock or ventricular fibrillation may occur as well (73). With in-hospital onset, typical triggers are procedures (surgeries, tissue biopsies, chemotherapy, endoscopy, etc.) and acute medical conditions like stroke, sepsis or respiratory failure. There are two major triggers for TTC: emotional and physical triggers. However, TTC may also occur spontaneously without any trigger (69,71).

Usually patients suffer from acute reduction of regional LV contractile function and a reduction of EF between 30-35%. Additionally an elevated LV end-diastolic pressure due to an upward shift in the LV diastolic pressure-volume curve can occur. This may result in hemodynamic instability as patients experience hypotension, pulmonary edema and cardiogenic shock (69).

40-50% of TTC patients present with ST- segment elevation in the precordial leads. Left bundle branch block, diffuse T-wave inversion or anterior Q waves are also common. About 2% of TTC patients have normal ECGs. Over several in-hospital days, QT lengthening, as well as progressive T-wave inversion may occur or may be even present on arrival as patients might present late. QT prolongation might result in torsade de pointes in TTC patients (69).

90% of TTC patients develop initial troponin level abnormalities with a peak generally about <1ng/ml, and creatine kinase levels are generally lower than 500 U/l. Compared to ACS patients, TTC patients have generally greater levels of BNP (B-type natriuretic peptide) and NT-proBNP (N-terminal pro-BNP) resulting in a peak after 48h and elevation up to 3 months after onset. These biomarkers are associated with the severity of the disease with lower LV ejection fraction and higher plasma catecholamine levels (69).

Pathophysiology

How TTC develops with its pathophysiological mechanisms is not fully understood. High levels of circulating catecholamines such as in diseases like paraganglioma or pheochromocytoma may be associated with TTC. Additionally, Abraham at al. claims that catecholamines like dobutamine and epinephrine may induce TTC (74–76). One leading explanation suggests that the acute increase of catecholamines combined with cellular calcium overload results in regional microvascular dysfunction and spasm. Therefore this may cause myocardial stunning in TTC patients (70).

Gender differences

Overall TTC seems to affect more women, specifically older and postmenopausal women than men (69,73,77,78). The prevalence of male TTC patients was between 4.4% and 22.8% in several studies (71,77,79,80).
A Japanese study from 2005 examined 368 TTC patients of which 77.2% were female (284 patients). Men were younger than women. Within the chief complaints chest pain and dyspnoea, men had fewer complaints about chest pain than women. Men were more likely to experience TTC from physical stress (50% men compared to 35.6% of women) whereas emotional stress was more common in females. Heart rate, blood pressure and arterial oxygen saturation did not differ between the genders as well as there were no differences in ECG abnormalities between women and men. Biomarkers such as CK on admission and the peak CK level during the hospital stay was significantly higher in males but CRP and white blood cell count did not differ. There was no gender difference found in the matter of performed coronary angiography. There was a gender difference observed within outcome rates as men developed more severe heart failure (Killip Class ≥ III) and were more likely to experience serious ventricular arrhythmias than women (not statistically significant however). Men needed more respiratory support as well as permanent pacemakers or cardioverter-defibrillators. Furthermore, composite cardiac events during hospital stay were more common in men (77).

Role of estrogen

Because the majority of TTC patients are post-menopausal women, researchers believe that sex hormones might play an important role in the pathophysiology of the disease. Brenner at al. studied and compared sex hormones in postmenopausal women presenting with TTC or MI. On admission estradiol (E2) concentrations were higher in TTC patients compared to MI patients. Progesterone (P), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) did not differ between the groups. Progesterone was positively correlated with estradiol and CK inversely with estradiol. Estradiol and progesteron levels were higher in younger patients. Estradiol has been lower in patients with a history of

statin use or dyslipidemia. They did not find a correlation between heart rate, blood pressure or CRP and sex hormones.

At 1 month follow up left ventricular ejection fraction (LVEF) had normalized in all patients. Compared to admission, estradiol and progesterone concentrations declined but gonadotropin levels stayed the same over time. Progesteron levels in TTC patients were lower compared to MI patients at follow up. Estradiol levels tended to be lower in TTC patients at follow up (78).

In an ovariectomized rat model, Ueyama et al. and Akashi et al. showed that reduced levels of estrogen may induce vulnerability to stress, as the rats showed a decrease of stress induced cardiac dysfunction (as well as a rise of heart rate and blood pressure) when estrogen was given (72,81).

Estrogen supplementation decreases the exaggerated stress response and influences calcium entry in sarcomere of the epicardium and regulates the effects of epinephrine-release in the presynaptic cardiac sympathetic nerve fibres. So it naturally protects women from adrenergic stress during pregnancy and delivery but women lose this protection after menopause, resulting in a predisposition to TTC (82).

1.3 Hypertension

In the United States, one out of 3 adults suffer from high blood pressure but the prevalence does not differ by gender. Until 45 years old it affects more men, from 65 years on more women and between 45 and 65 years both sexes are equally affected. Women have higher rates of awareness, treatment and control rates of hypertension in all races (83).

Pathophysiology

The exact pathophysiology of hypertension is yet not fully understood. Multiple factors might play a significant role such as the metabolic syndrome, insuline resistance or a genetic component (84). The developement and progression of high blood pressure is associated with the renin-angiotensin-aldosterone system (RAAS), and evidence suggests that female sex hormones have protective effects by modulating this system (85).

Gender differences and the effects of sex steroid hormones

There are three different types of estrogen known with different prevalence within females. In premenopausal women estradiol is most common, ostrone in postmenopausal women and during pregnancy oestriol is produced from the placenta. Additionally three types of estrogen receptors (ERs), ERα, ERβ and GPER-1 (bound in the membrane of the endoplasmatic rediculum), are located within our bodies. ERα and ERβ are present in the vessels and kidneys and GPER-1 in the kidneys as well. ERβ expression is higher in male hearts but ERα is represented equally in men and women. ERα is also found in the brain – in the nuclei of hypothalamic cells in men and premenopausal women but in postmenopausal women it is located in the cytoplasm (86). As premenopausal women have lower blood pressure than age-matched men and blood pressure is higher in postmenopausal females, it is suggested that estrogen plays a significant role in hypertension development (87–89).
Concerning hormone replacement therapy inconsistent evidence exists and shows increased, decreased or no effect on blood pressure. Despite that, there may be no benefits in the matter of cardiovascular events and can even have negative

effects resulting in pulmonary emboli, ischaemic stroke or other cardiac complications (86).

Androgens might contribute to the development of cardiovascular-related diseases as androgen levels are decreased in males with chronic diseases (like hypertension). It was shown that men with low testosterone levels have a greater risk of all-cause mortality of ischaemic heart disease and in older men testosterone levels were negatively associated with systolic blood pressure and increased risk of death (86,90,91).

Sex hormones also influence the RAAS system but the exact mechanism is not fully understood yet. Salt-sensitive hypertension mediated by enhanced activity of RAAS in male rats is one aspect. Another aspect is the possible influence of sex hormones on sodium handling as in premenopausal women blood pressure is salt-resistant whereas it is not in postmenopausal females. Therefore salt-restricted diet has positive effects in postmenopausal women (92–94).

Modulation of blood pressure through endothelin in the kidneys seems to be different between the sexes as vasoconstriction mediated through type A receptors is more common in male animals (attenuation after gonadectomy). Female animals have more type B receptors, therefore more diuresis and natriuresis which results in a protection of high blood pressure (83).

In terms of atherosclerotic processes, women have less inflammation processes, thrombotic plaques are fewer and plaques are more stable (95–97).

Blood pressure is modulated by the sympathetic nervous system as a renal denervation results in a reduction of blood pressure in hypertensive male and female rats but remains elevated. That implicates that the sympathetic nervous system is not gender specific and that there must be more mechanisms responsible for blood pressure regualtion.

Another possible mechanism is the RAAS system. It was shown that ACEI (ACE Inhibitors) reduces blood pressure in both sexes equally. ACEI given intracerebroventricularly reduces the blood pressure in male rats as well.

Blood pressure was more increased by chronic treatment of angiotensin II in male than female rats whereas female rats responded better to ACEI depression. Males on high-salt diet had further increase of blood pressure whereas females had not.

Losartan, an AT1-receptor (angiotensin type 1) antagonist, reduces blood pressure in male rats by blocking RAAS as hypertension in males is mediated by RAAS, whereas in female rats, endothelin-1, RAAS and 20-HETE (hydroxyeicosatetraenoic acid) mediate hypertension.

Superoxide dismutase mimetics and NADPH oxidase inhibitors are oxidative stress inhibitors. Interestingly, they only decrease blood pressure in male hypertensive rats but not in females. Molsidomine (increases oxidative stress) also increases blood pressure only in males. That leads to the assumption that antioxidants might only be effective in males (86).

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As mentioned in the chapters above, estradiol modulates NO and therefore acts as a vasodilator. Estrogens also influence the RAAS system via downregulation of ACE, attenuating angiotensin II synthesis and increasing ACE2 synthesis as well as it down-regulates the AT1 receptors. All of these contribute to an antihypertensive effect (98,99).

Summarized, estrogen increases angiotensinogen, ACE2, AT2 receptor density and endothelial NO synthase while decreasing renin, ACE, AT1 receptor density and NADPH oxidase (Nox1+2) which favours vasodilatation (100).

Androgens, on the other hand, have an influence too as they stimulate sodium absorption in the kidneys which is blocked by AT1-receptor antagonists. In the kidneys, testosterone increases angiotensinogen synthesis. Therefore renin enzyme activity could be enhanced. Androgens also increase endothelin levels. In obese men, testosterone replacement decreases diastolic blood pressure (86).

In summary, testosterone increases renin, ACE and AT1 receptors while downregulating AT2 receptors resulting in favourisation of vasoconstriction (100).

Interestingly, androgen therapy in postmenopausal women was not beneficial and could even increase the risk factors of cardiovascular diseases in women (101).

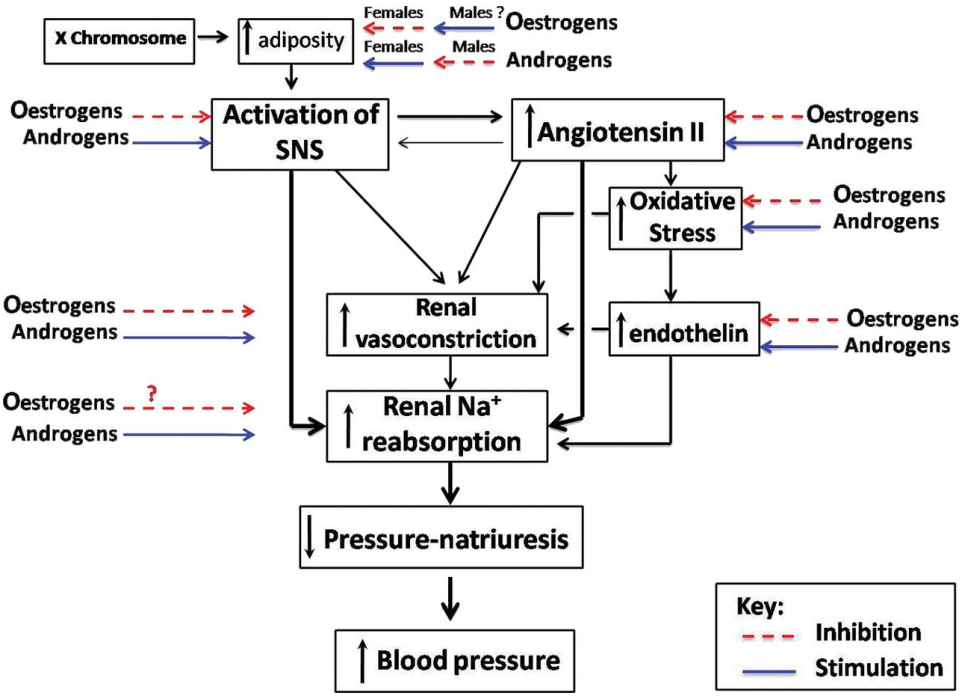

Figure 3: „Potential mechanisms by which oestrogens and androgens may control blood pressure“ (86)

Gender differences besides RAAS

Hypertension affects the heart, resulting in ventricular hypertrophy. 24% of men and 16% of women suffering from hypertension develop left ventricular hypertrophy. Women are more likely to develop concentric hypertrophy whereas men tend to develop eccentric hypertrophy more. Hypertrophy increases with age in women with a prevalence as high as 80% in women in their nineties (83,102).

The number of women with preserved ejection fraction in heart failure is two times higher than in men. Furthermore, older women tend to develop flow-mediated dilatation abnormalities more often than men (83).

Women have a higher prevalence of hypercholesterolemia as well as higher HDL cholesterol levels but mean triglyceride levels are lower. There are no gender differences regarding LDL-cholesterol levels (83).

Renal function decreases faster in males with age but this effect is reversed in postmenopausal and older women. Beneficial effects of estrogen on the kidneys are known as well as higher levels of fibroblast growth factor-23 in women, which is a predictor of renal disease progression. In terms of chronic kidney disease

different data is available as the prevalence was either lower, similar or higher than in men (83).

Some of the risk factors for cardiovascular diseases, such as the metabolic syndrome, develop through inactivity. Women are known to spend less time on physical activities than men and are even more inactive when getting older (83).

In postmenopausal women, blood pressure is higher in peripheral arteries than in central ones, due to arterial stiffening. A study showed additionally, that pulse pressure amplification, known as brachio-carotid pulse pressure ratio, is independently associated with cardiovascular and all-cause mortality and this seems to be stronger in women. This might be the result of estrogen loss after menopause and therefore a decrease in arterial elasticity (83,103).

Pregnancy

It is known that for future hypertension as well as cardiovascular events blood pressure during pregnancy is a significant risk factor. There is a 3 times increased risk for diabetes mellitus, a 4 times greater risk for chronic hypertension and a 2 times increased future risk for stroke and coronary heart disease in pregnant women suffering from preeclampsia (83).

The American Heart Association has mentioned especially pregnancy and the risk and harmful effects of preeclampsia in the case of future hypertension and risks in their new guidelines (65).

Treatment concerning hypertensive women

Women are less likely to receive optimal diagnostic procedures and therapy and significantly fewer tests are performed on women (83).

In a recent review by Doumas et al. the effects of antihypertensive treatment by gender was summarized. It seems that beta blockers reduce mortality only in men. ACE-inhibitors might not be as effective in women as in men. Calcium antagonists seem to be more beneficial in stroke prevention than ACE-inhibitors in females compared to males but calcium antagonists reduce all-cause mortality only in men. In women, antihypertensive treatment causes frequent adverse effects like dry cough in ACEI two times more often than in men. Females on diuretics suffer more from hypokalemia, hyponatremia and less from gout. Women on beta blockers are

more likely to suffer from sexual dysfunction than men (83).

However, the 2014 guidelines for the management of hypertension only recommend blood pressure treatment relating to age but not to gender (104).

2. Osteoporosis

Osteoporosis is a classical „woman's disease", but men are underdiagnosed and therefore undertreated (105,106). In the year 2010, approximately 5.5 million men in the European Union suffered from osteoporosis (107).
In the United States, one out of four men older than 50 years will develop a fracture caused by osteoporosis. In 2005 there were 2 million osteoporotic fractures of which 25% occured in men. After hip fracture, one third of men die in the first year after the event and one third will fracture again (105).
Interestingly, in the male Asian population the incidence of osteoporosis is half of that found in Caucasian men (108).

Pathophysiology

The development of osteoporosis is gender specific and differs between males and females. Sex hormones as well as physical activity and bone size are important factors that contribute to bone development in early life as well as puberty. Puberty seems to start later in most boys and lasts longer, and men develop longer bones than women and have a longer maturation period. The sex hormone testosterone is responsible for the development of larger skeletons in men. As the hormone estrogen, which reduces bone resorption and conserves bone mass, testosterone reduces bone resorption as well, which may be because of testosterone conversion to estrogen. In some extent, testosterone contributes to enhancing bone tissue formation. While estrogen conserves bone mass testosterone increases bone mass. During their young lives, men will develop higher peak bone mass, greater bone strength and larger bone size and therefore will develop a natural protection from fragility fractures due to extra body weight or physical activity that influences bone development (105,109–111).
With aging, estrogen levels decrease in women rapidly with menopause which is causing a 90% increase of bone resorption but only 45% of bone formation that result in a loss of bone. In males, the decrease is more gradual and the loss of bone strength is less severe. Another difference is, that female bones tend to replace more mineralized bones with less mineralized and additionally lowering trabecular surface, which can increase micodamage on the bones. In men on the other hand, bone formation increases and the bone mineral density declines in a

smaller amount (105).

Types of osteoporosis

One can classify male osteoporosis in a primary and a secondary osteoporosis. Primary is age-related or idiopathic. With increasing age, men (as well as women) are more likely to suffer from loss of bone density so this is seen typically in men older than 70 years. Reasons for idiopathic osteoporosis might be genetic factors.
Secondary osteoporosis may be caused by chronic diseases for example gastrointestinal disorders, COPD, hypogonadism, rheumatoid arthritis, hyperparathyroidism or multiple sclerosis. Other factors, such as alcohol abuse or glucocorticoid excess, can also cause osteoporosis (105).

Risk factors in men

Typical male risk factors include a history of fractures after the age of 50, tricyclic antidepressants, increased age, depressed mood, recent falls and poor neuromuscular function. Nonvertebral fracture risk increases six fold in patients suffering from three or more of these risk factors (105).
Additionally, Drake et al. found in 2012 that the risk of fractures increases significantly in alcohol abusing men, men who smoke, who have a low body mass index or long-term corticosteroid use, who did experience a recent fall or fracture, who are suffering from hypogonadism, stroke or diabetes mellitus (112).

Gender differences in the treatment of osteoporosis

Many societies have developed guidelines for treatment of men with osteoporosis: the Endocrine Society, the National Osteoporosis Foundation (NOF), Osteoporosis Canada or the National Osteoporosis Guideline Group (NOGG). These guidelines mainly recommend treatment, based on the presence of clinical risk factors and the bone mineral density (105).

Osteoporosis treatment guidelines for males:

Organization	Pharmacological treatment recommendations
National Osteoporosis Foundation (NOF)	Treatment recommended for men aged 50 years and older with hip or vertebral fracture (clinical or on imaging); T-score less than −2.5 at femoral neck, total hip, or lumbar spine; T-score between −1.0 and −2.5 at the femoral neck or lumbar spine; and a 10-year probability of a hip fracture ≥3% or a 10-year probability of a major fracture ≥20% based on the US-adapted FRAX.
The Endocrine Society	Recommend treatment in men who had hip or vertebral fracture without major trauma; BMD of spine, femoral neck, or total hip 2.5 SD or more below mean of normal young males; T-score between −1.0 and −2.5 at the femoral neck or lumbar spine plus a 10-year probability of a hip fracture ≥3% or a 10-year probability of a major fracture ≥20% based on FRAX. Treatment is also suggested in men aged 50 years and older receiving long-term glucocorticoid therapy (equivalent to 7.5 mg or greater of prednisone for 3 months) as recommended in the 2010 guidelines of the American Society of Rheumatology.
Osteoporosis Canada	Assess fracture risk using CAROC or Canadian FRAX. Recommend treatment for high-risk men with 10-year fracture risk >20%, prior hip or spine fracture, or multiple prior fractures. In men with moderate fracture risk (10-year risk between 10% and 20%), consider treatment for those with the following risk factors: vertebral fracture identified by imaging, previous wrist fracture in those over the age of 65 years or with T-score less than or equal to −2.5, lumbar spine T-score much smaller than femoral neck T-score, androgen deprivation therapy for prostate cancer, long-term glucocorticoid use, recurrent falls, or other disorders associated with osteoporosis, bone, loss, or fractures.
National Osteoporosis Guideline Group (NOGG)	Assess 10-year osteoporotic fracture probability in men aged 50 years or older using UK FRAX. Treatment thresholds both with and without BMD testing are based on age and fracture probability.

Table 6: Osteoporosis treatment guidelines for men cited from the review: „The clinical epidemiology of male osteoporosis“, from Willson et al. (105).

Nonpharmacologic treatment options for male patients include diet and lifestyle changes, as well as adequate calcium and vitamin D intake, regular weight-

bearing and muscle-strengthening physical activity, stopping smoking, no excess alcohol drinking and fall prevention strategies.
Pharmacological treatment in men includes teriparatide, denosumab, alendronate, risedronate and zoledronic acid. Strontium ranelate is additionally approved in the European Union. Teriparatide, exceptionally, is used for enhancing new bone growth. It has to be mentioned though, that these drugs have mostly been tested on postmenopausal women and studies including men tend to be small.
Evidence showed a reduce of vertebral fracture risk in males by alendronate, risedronate and zoledronic acid and a decrease of incidence of nonvertrebral and hip fractures by risedronate in men. Nevertheless, Willson et al. mention a lack of evidence, concerning the effectiveness of bisphosphonates in osteoporotic men.
Teriparatide is a parathyroid hormone used for glucocorticoid-induced or severe osteoporosis in men which increases the incidence of vertebral fractures but should not be used for more than two years.
Denosumab increases bone mineral density in men as well as strontium ranelate (105).

A recent study from Bor et al. from Hungary evaluated gender inequalities concerning osteoporosis treatment in the Hungarian population. Their results show that men were significantly undertreated and that medication use was higher in females. Men were approximately 10 times less treated with Vitamin D than women, they were significantly undertreated with calcium compounds, males recieved 20 times less treatment with bisphosphonates and no man recieved treatment with ibandronic acid or denosumab between the years 2010 and 2011 (106).
Despite this, several randomized controlled trials showed the equal effectiveness of anti-osteoporotic drugs in both women and men (113–115).

3. Diabetes mellitus type II

Diabetes mellitus (DM) is a major health burden in modern industrialized and developed countries, especially in the United States. In 2012 one out of thirteen American was diagnosed with diabetes of which are 90-95% DM type II. The prevalence seems to be similar in men and women (10.8% females, 11.8% males) (116), but a review from 2016 showed, that globally more men are suffering from diabetes (117). As DM is a cofactor in more than 50% of all deaths (116), it is an important topic to evaluate if there are gender/sex related differences in the matter of pathophysiology or treatment to further improve future medical treatment.

Pathophysiology

Women tend to be more obese after 45 years of age but men are more prone to be overweight when they are younger. Those sex differences are larger in countries with greater gender and income inequality. Due to different development of body shape during puberty, women tend to leg and gluteal adiposity whereas men are more prone to develop central obesity. Furthermore, there is an association of central obesity with cardiometabolic risk factors. As age increases, women tend to an increased waist circumference which appears to be the best predictor for diabetes in elderly British women (117).

The role of sex hormones

Estrogen may protect women against insulin resistance. Oral contraceptives lower estrogen levels as well as insulin sensitivity. Female mice treated with estrogen replacement were protected against hepatic steatosis and showed improved insulin sensitivity. Evidence also shows anti-obesity effects, reduced lipogenesis in the liver but more lipolysis in adipocytes. Males with reduced estrogen production show insulin-resistance and glucose-intolerance. Progesterone, on the other hand, antagonizes those effects as it promotes insulin resistance. The menstrual cycle influences lipid and glucose metabolism of diabetic women (118). Men with decreased androgen levels are prone to develop insulin resistance and diabetes and treatment with testosterone reduces body fat and improves insulin sensitivity.

Women with increased androgen levels, as in polycystic ovary syndrome, are prone to develop insulin resistance and obesity (119).

Differences between women and men in type 2 diabetes related to co-morbidities

Metabolic syndrome	Prevalence is equal in men and women but increasing in young women. Women present with normoglycemia more often than men. Increased waist circumference and abdominal obesity are leading factors for DM in women (116).
Biomarkers	The lower cardiometabolic risk in women may be explained by upregulated adiponectin expression and therefore higher levels of adiponectin and leptin in females. In males, increased levels of plasma leptinlead to an increased diabetes risk (117). Additionally, only in women an association of low 25 (OH) vitamin D3 and type II diabetes was found (120).
Prediabetes	Women are more prone to impaired glucose tolerance, whereas men are more prone to develop impaired fasting glucose (117).
Lifestyle	Overall, women tend to be more inactive than men but tend to eat less meat, more vegetables and fruits but also more sugar (117). Interestingly evidence suggests that moderate alcohol consumption improves insulin sensitivity in females only (121).
Coronary heart disease	Differences have been described in the chapter above. Diabetes specific sex differences include higher rates of atherosclerosis and higher intima media thickness in men with a recent diagnosis of diabetes with a higher plaque rate. In women, diabetes is a greater risk factor for nonfatal CVD than in men. Diabetes influences the positive effect of estrogens leading to impaired endothelial response, inhibition of antiproliferative effects and therefore to the development of atherosclerosis especially in diabetic women (117).
Coagulation	Diabetic women show a higher protrombotic fibrin profile, denser fibrin clots and prolonged fibrinolysis. Men showed an increased atherothrombotic risk (117).
Cardiomyopathy	Female hearts use rather lipids and males rather glucose. Diabetes mellitus often results in nonischemic diabetic cardiomyopathy. Wall thickness and left ventricular mass is greater in women. In younger age, males are more prone to develop heart failure and myocardial dilatation. Women on the other

	hand develop hypertrophic cardiomyopathy, diastolic heart failure and preserved ejection fraction more often than men. Diabetes seems to decrease women's natural protection on progression of cardiomyopathy (117).
Stroke	There is no consistent evidence regarding type II diabetic women and risk of stroke as there are reports suggesting lower, similar or higher risk compared to males with the same age. After the first stroke, diabetic women face more reduced long-term survival (122). Janghorbani et al. reported in their Nurses' Health Study, that in type I diabetic women the incidence of total stroke was 4-fold higher and in type II diabetic women 2-fold higher compared to nondiabetic women (123).
Diabetic foot syndrome	Lower extremity amputations are more frequent performed in men. When men are diagnosed with diabetes at younger age, the risk of amputations is higher (124,125).
Diabetic nephropathy	Progression is faster in males and dialysis therapy is performed more often in men. On the contrary during chronic dialysis treatment, diabetic women are at a higher mortality risk (117).
Sexuality	Both sexes often suffer from reproductive problems and sexual dysfunction. In females this tends to relate more to psychosocial factors and depression whereas in males physiologic factors, metabolic syndrome and cardiorespiratory fitness are important (117).

Table 7: Differences between diabetic women and men related to co-morbidities

Pregnancy and diabetic women

Diabetes can be a major burden for pregnant women. Firstly, women with gestational diabetes carry a 70% higher risk of progression to type II diabetes. Secondly, gestational diabetes is associated with adverse pregnancy outcomes including malformation and higher mortality rates. Interestingly, being pregnant with a male fetus is associated with a higher risk of developing gestational diabetes but being pregnant with a female fetus carries a higher risk of developing type II diabetes (117).

Gestational diabetes together with preeclampsia is a major risk factor for future CVD in women. Additionally, they are more prone to develop hypertension, greater vascular resistance, greater intima-media-thickness or lower cardiac output (116).

4. Breast cancer

Breast cancer is considered widely as a woman's disease. Only up to 1% of all breast cancer patients are male patients (126–130).
In Austria in the year 2014, the incidence of breast cancer was 1.8 out of 100.000 men compared to 118 per 100.000 women. The mortality rate was 32 out of 100.000 women and 0.4 out of 100.000 men (131).

Male specific characterizations of breast cancer

At initial presentation, the great majority of men are already in an advanced tumour stage and therefore are already symptomatic. Men most frequently complain about a painless retroareolar mass. Compared to females, males show more skin and nipple involvement including ulceration, retraction, oozing and bleeding as well as nodal and perineural involvement (130).

In men all histological subtypes of breast cancer are seen but the most common ones are the papillary and the cribriform pattern. The most common subtype is invasive carcinoma of no special type. In men, invasive papillary carcinoma and invasive micropapillary carcinoma are more common compared to women. Less common are the lobular carcinoma and carcinomas with a basal cell phenotype as well as mucinous adenocarcinoma, secretory carcinoma, adenoid cystic carcinoma and apocrine carcinoma (130,132).

Sex differences within intrinisic subtypes of breast cancer

There are 5 different intrinsic types:

1. Luminal A: 50-60% of all patients and most of them are estrogen receptor (ER) positive. It is characterized with low proliferation and has the best prognosis.

2. Luminal B: 10-20% of all patients and as well mostly ER positive. It is characterized with high proliferation. Mamma

carcinomas with BRCA2 mutations are often luminal B tumours.

3. Basal-like: 10-20% of all patients and often ER, progesterone receptor (PR) and HER2 negative („triple-negative“). Mamma carcinomas with BRCA1 mutations are often basal-like tumours. Together with the HER2-enriched subgroup, it shows the worst prognosis.

4. HER2-enriched: 10-15% of all patients and often ER negative. Together with the basal-like subgroup, it shows the worst prognosis.

5. Normal-like: 5-10% of all patients. This subgroup is poorly defined. (128)

Male breast cancer shows a luminal A characterization in 60-98%. Basal-like and HER2 tumours where fewer reported in males (128). Despite this, it has also been reported that lumal B and HER2 phenotypes are increasing in male patients showing the BRCA2 mutation (130). In the matter of receptor expression, ER and PR (progesterone receptor) are more often expressed in males whereas men are less HER2 amplified (half as frequently as women) (130).
Up to 33% of men with breat cancer have a family history of breast and ovarian cancer. 50-92% show BRCAX families which implys an underlying genetic mechanism. A BRCA2 mutation is more frequent in men and is the strongest risk factor with an 80 times higher risk of developing breast cancer. BRCA2 positive tumours in males seem to be more aggressive and show a higher proliferative index (130).

Treatment of male breast cancer

Treatment guidelines for breast cancer in men are mainly based on female therapeutic strategies as there are no male specific guidelines available at this time (129,130,133).

A study in Colorado by Fields at al. analyzed primary invasive male and female breast cancer that occured during the years 1973-2008. They found significant differences in the treatment of male and female breast cancer. Mastectomy was used more often in males compared to females (males: 67.5%, females 38.3%) and fewer rates of breast-conserving surgery was performed in men (9.7% men, 42.6% women). Of men, who were diagnosed with localized disease, only 4.6% received lumpectomy and radiation therapy whereas 70.3% were treated with mastectomy. The amount of men in early-staged breast cancer treated with lumpectomy and radiation therapy was only 6%, leaving 94% receiving only mastectomy. Over the years, men with regional breast cancer received more postmastectomy radiation therapy (though only up to 36.8%) but had grade 3 disease and where younger than females. The authors concluded that postmastectomy radiation treatment is highly underutilized in males (134).
An older review from 2007 from the University of Massachusetts claimed, that tamoxifen is used as adjuvant therapy in ER-positive tumours in male breast cancer patients. Disease free survival and overall survival rates of those patients increased in comparison with those not treated with tamoxifen. In this review, adjuvant chemotherapy is a treatment option for patients younger than 70 years, axillary node involvement and ER negative breast cancer (133).

Outcome of male breast cancer patients

Bender et al. found no difference between the two sexes in the matter of disease-free survival and overall survival rates (127). Other literature also suggests no relevant difference in mortality rates between the sexes (130).

The psychological effect on men suffering from breast cancer

For some men, being diagnosed with breast cancer is a burden as they see it as a women's disease. Many men react with surprise and it was also reported that some of them wish that the disease had another name. They complained about too little information, especially for men and few to no support groups for male breast cancer patients. When confronting friends and relatives with their diagnosis, some experienced disbelief and even reactions of amusement (133,135).

Discussion

All of the described diseases show significant gender differences. In cardiovascular disease, women seem to have important disadvantages. They are older at diagnosis, have more comorbidities and have a worse outcome. Women often present with atypical angina, they present at emergency departments later and receive treatment at a later stage. Women are treated less aggressively and generally get less treatment than men but experience more complications during procedures possibly due to their smaller and stiffer heart and vessels.

Estrogen has many protective effects in premenopausal women as it modulates blood pressure and vasodilatation and therefore prevents women from atherosclerosis and CVDs. Surprisingly, there is no sudden rise in CVD prevalence in menopausal women due to the decline of estrogen levels compared to men. However, the exact pathways of estrogen influence are not fully understood yet.

To date no special guidelines for treatment of CVDs in women are available. Nevertheless, the AHA has published guidelines especially for CVD prevention in women. The majority of takotsubo cardiomyopathy (TTC) patients are postmenopausal women. The pathophysiology is not fully understood but high catecholamine levels and calcium overload appear to play an important role. Differences between the genders occur within TTC triggers as in male patients physical triggers are more common compared to females where emotional triggers are more relevant. Men are also more likely to suffer from additional events as severe heart failure or ventricular arrhythmias and need more medical support e.g. pacemakers.

Below 65, more men suffer from high blood pressure but after the age of 65 this effect is reversed and more women are diagnosed with hypertension. Women undergo less diagnostic procedures and receive less treatment than men. Additionally, research suggests that the various antihypertensive agents act differently in men and women. β-Blockers as well as calcium antagonists might reduce mortality in males only, ACE-Inhibitors seem to be less effective in women but for stroke prevention calcium antagonists seem to be more effective in women

than ACE-Inhibitors.
For diabetes mellitus type II, no specific differences exist and comorbidities such as stroke, coronary heart disease or diabetic complications appear to be equally distributed. However, women may develop gestational diabetes which is associated with a 70% higher chance of progression to type II DM. Gestational diabetes also may lead to adverse pregnancy outcomes.

In osteoporosis, men are less often affected, but are underdiagnosed and undertreated. Several specific treatment guidelines for men are available from several organizations.

Breast cancer is a women's disease as only 1% of patients are male.
Men present later and are mostly at an advanced stage. Men show estrogen receptor and progesterone receptor positivity as well as higher frequency of BRCA2 more often than women. Male patients often suffer from psychological burden and may not get respectful reactions and support from relatives and friends.
Treatment is mainly based on women's treatment. In general, men receive mastectomy more often but fewer breast conserving surgery and fewer radiation therapy. Nevertheless, disease-free survival and overall survival is equal in both sexes.

Conclusion

Many diseases have specific differences between the sexes regarding prevalence and incidence, diagnosis, treatment and prognosis. In this thesis, we aimed to give an overview on gender differences in selected frequent diseases.

Besides, an important problem in the last decades was that female cells and animals and female patients were often excluded or underrepresented in research. This has improved recently with the inclusion of women in clinical trials as well as testing drugs not only in male but also in female animals.

Even in the frequent diseases we chose for this thesis, the awareness of sex-specific differences is often absent or very poor, impairing optimal treatment for men and women. Furthermore, often no gender differences are mentioned in treatment guidelines with exception of prevention guidelines for women in CVD and male osteoporosis.

As we live in an era of rapid evolving „personalized medicine“, we would doubtlessly benefit from gender specific research and guidelines that include gender specific aspects that would allow optimal treatment for men and women.

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