

GenCAD final report

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Written by
GenCAD Consortium

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Colophon

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Executive summary

The GenCAD project aimed to improve the understanding and awareness of sex and gender differences in chronic diseases, using coronary artery disease as an example to highlight differences between women and men in prevention and treatment of coronary artery disease in European countries. It considered existing knowledge on sex and gender differences in coronary artery disease, and the inclusion of sex and gender related aspects in databases and in policies of Member States. It also conducted a study on the awareness of health care professionals and the general population and used this knowledge to develop factsheets on sex and gender in coronary artery disease to improve knowledge and awareness in Europe. Communicating facts and factsheets at two conferences, in the internet and by other ways of dissemination will help closing the gaps between sex and gender knowledge and translation to the medical practitioners, policy makers and the general public in an exemplary field.

GenCAD contributed to the development of a methodological approach as well as to the improvement of knowledge and awareness in the field of sex and gender related health in the European Member States. Therefore, GenCAD provides an approach that could be transferred to other disciplines and diseases and could be used as a template for future studies in other chronic diseases.

GenCAD first assembled in a state of the art study the existing knowledge on sex and gender differences in coronary artery disease, based on the published literature from all over the world. It searched published literature in the areas of prevention and health promotion, epidemiology, disease mechanisms, clinical symptoms and diagnosis, management, as well as outcomes of coronary artery disease. 878 articles were reviewed in detail. Significant sex and gender differences that need consideration were found in all fields described above. For example, diabetes and smoking have a greater weight as risk factors in women than in men. Other gender-related risk factors include: mental health, socioeconomic status, autoimmune and inflammatory diseases,

and disturbances of sex hormones and of sexual function. More sex and gender related differences were found in diagnosis and disease mechanisms, as well as in treatment and outcomes. The most important differences were assembled in factsheets.

A database analysis in existing European sociodemographic and medical databases aimed to test to which degree European databases are suited to analyse sex and gender differences in coronary artery disease. GenCAD therefore analysed these databases from EU Member States for coronary artery disease morbidity and mortality, connected the data to known risk factors such as smoking, diabetes, hypertension, hyperlipidaemia, alcohol use, and socioeconomic parameters and checked the data for their sensitivity to assess sex and gender differences. It was found, that most databases have a limited sensitivity for these analyses. Reasons may be that they have a rather low cut-off point for age at inclusion, and variables are not always broken down to sex. Sex and gender related covariates, like pregnancy complications, hormonal status, number of children, and sexual function are frequently not included in the databases. Experts agreed that they were willing to study gender-related effects, but not enough data is collected in many studies due to limited resources.

To obtain an overview on gender in EU health policies, a policy analysis examined the current political climate of existing policies on gender and coronary artery disease by contacting governmental healthcare departments, national medical and public health societies, funding agencies and active researchers. Overall, 273 policies and guidelines were identified across the 28 EU Member States that made specific reference to gender, either as part of their national gender equality legislation or in relation to cardiovascular disease, but few specific recommendations were found. Thus, the overall conclusions from this analysis are that for all EU Member States there is a policy environment that ensures gender equality and sex discrimination is prohibited; and that there is a growing body of recommendations from leading health organisations supporting more gender sensitive and gender aware

health care. At the level of detailed policy documents and guidelines guiding practice for cardiovascular disease however, there is a high reliance on the European Society of Cardiology guidelines, making their role in ensuring gender sensitive care very important.

To assess the need for information on sex and gender differences in cardiovascular disease, an awareness study was undertaken with two surveys - one for the general public and another for healthcare professionals. The general public awareness study in 6 EU languages in selected sample countries revealed continuing important deficits in knowledge and awareness on gender aspects in risk factors, disease manifestations, needs for action and information on disease outcomes. The survey in health care professionals in all European countries also showed important deficits in knowledge on sex and gender specific disease manifestations, diagnostic and therapeutic approaches. More gender sensitive information campaigns for physicians and the general public are necessary and the internet emerges as leading medium.

Based on the sex and gender differences identified in the bibliographic study, factsheets were developed for both health care professionals and the general public, integrating feedback from consortium partners and GenCAD extended networks. They were validated with groups of experts for general agreement and finalized in discussions with DG Health and Food Safety.

To communicate and discuss findings, two conferences were organized at 1st March 2017 and 11th October 2017 in Brussels. Two representatives from policy makers, medical communities or patient representatives from all Member States were included, as well as a number of experts.

For dissemination of the project results in a sustainable manner, we have developed a homepage hosted by DG Health and Food Safety where the main results are published. The main site is in English, additional materials like factsheets, and executive project summary are available in all EU official languages. Furthermore, the factsheets and project results have and will be

announced and communicated at homepages of the partners and different medical societies, Association of Schools of Public Health in the European Region, European Heart Net, Standing Committee of European Doctors, International Society for Gender Medicine, German Society for Gender-related Medicine, Italian Society of Gender Health and Medicine, The Austrian Society of Gender-Specific Medicine, Canadian Institutes of Health Research, The Pharmaceutical Group of the European Union, and Centre for Cardiovascular Research, Charité Berlin (Table 10). They have also been presented and discussed at major European congresses: EUPHA 2015, International Society for Gender Medicine 2015, Organization for the Study of Sex Differences 2016, European Congress for Internal Medicine 2017, EUPHA 2017, Europeans student conference 2017 and 2018, Organization for the Study of Sex Differences 2017, World Health summit 2017 and 2018, Europrevent 2018, International Society for Gender Medicine 2019; Gender summit 2017 and 2018, and will be presented at many others.

We also communicated the project in lay media during the project period, and will continue after the project period. All partners contributed to reach their specific target audiences, such as healthcare professionals, general public, users associated to health and wellness, patient safety and preventive healthcare. Furthermore, we used social media platforms, e.g. Facebook, Twitter and YouTube to reach our target audiences. Target audiences included healthcare, health and wellness personnel, health organizations and non-governmental organisations. Altogether more than 150,000 people were reached.

Abbreviations

EACPR	European Association of Cardiovascular Prevention and Rehabilitation
ECG	Electrocardiogram
ESC	European Society of Cardiology
EU	European Union
EUPHA	European Union Public Health Association
GIM	Gender in Medicine Institute - Charité Universitaetsmedizin Berlin
UN	United Nations
WHO	World Health Organisation
WP	Work package

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1. Overview

1.1. Background and objectives

Until recently, the importance of taking gender differences into account has been underestimated in medical practice. However, in the last 10 years cardiovascular diseases were quoted as a key example to illustrate gender-related mechanisms. Men and women with coronary artery disease may exhibit different risk factors, symptoms and clinical manifestations and require different treatment or prevention strategies. This tender focused on coronary artery disease as a model for any chronic disease and aimed at increasing knowledge and awareness of sex and gender-related mechanisms and strategic approaches to prevention, diagnosis, and treatment. While coronary artery disease is an area where gender knowledge is growing, there is still a gap in implementation and in public awareness of this knowledge and GenCAD wants to close this gap.

Gender medicine and use of the terms sex and gender in this report

Sex and gender are relevant to human beings. As widely accepted, gender describes the sociocultural dimension of being a man or a woman. Gender may function at the level of gender norms, gender identity, gender relations and institutional gender and is used to describe socio-cultural factors shaping behaviours and attitudes. Sex is visible from the sexual organs and determines inclusion in birth registries as male or female or in rare cases of gonadal abnormalities, as of undeterminable sex or intersex. For the greater part of human beings, the two classifications according to sex and gender identity are in agreement.

In the medical field, in health and disease, most phenomena are determined by both, by sex and gender related aspects: there are biological substrates like genes, hormones etc. that differ in women and men and there are health behaviours that are influenced by gender norms; the two influences can hardly be separated.

For example, gender-related (health) behaviour / lifestyle is connected with stress hormones and these interact with sex hormones and body reactions

(function of coronary arteries, for example), that differ in women and men. It would be desirable to make a clear distinction between sex and gender related aspects, because these may offer separate ways for intervention. However, in most cases, they are difficult to separate and both approaches are needed for prevention and therapy in cardiovascular diseases.

In the tender, we have used the term "sex" to refer to purely biological conditions; and the term gender was meant to include both the biological and sociocultural condition.

In this report, we will switch to a more developed use of the terms. "Sex" still refers to purely biological conditions. If we refer to phenomena that are predominantly determined by sociocultural aspects, we will refer to them as "gender". If the biological and sociocultural component are believed to be equally strong we will use the term "sex and gender aspects".

Background

Historically, heart diseases have been considered as mainly a problem of men. However, recent evidence supports the view that women and men may often differ in symptoms, and the onset of disease occurs at different ages. Therefore, diagnosis and prevention has to be targeted in a different way for women and men. Also, treatments – especially pharmacological interventions – may work differently in women and men, as pharmacokinetics and pharmacodynamics differ. In recent years, several European research studies have been carried out and several European consensus documents are available that underscore these differences, including the "Red Alert for Women's Hearts" produced by the European Society of Cardiology, the European Guidelines on cardiovascular disease, prevention in clinical practice (version 2012)[1], and policy briefs with information such as "women and cardiovascular disease in the EU developed by the European Institute of Women's Health and in the European project EUGENMED (<http://eugenmed.eu/>). Nevertheless, their impact on clinical practice was low and targeted treatments for women and men are not implemented in heart diseases.

Coronary artery disease is one of the most frequent heart diseases in the European population. In fact, it is the single most common cause of death in Europe, accounting for 1,8 million each year. It is estimated that 22% of women and 20% of men die from the disease.[2] In total, more women are affected but it is still considered a men's disease, mainly for historical reasons and since women get the disease in later periods of their life. Even though coronary artery disease differs significantly in women and men throughout Europe, in age distribution, prevention, clinical manifestation, response to therapies and outcomes, the existing evidence regarding sex and gender related aspects in coronary artery disease is sometimes incomplete or conflicting and the existing findings are frequently not convincingly presented to the medical community and to the general public. In particular, the interaction of biological differences between women and men and the sociocultural determinants of health are not sufficiently understood nor addressed.

In addition, the awareness and perception of heart disease in women and men differs, and this influences their interaction with health care systems. Determining factors are, health literacy, socioeconomic conditions, regional traditions and personal attitudes of both doctors and patients that interact in a complex manner. Scientific studies in different countries show that the general population underestimates the relevance of cardiovascular disease. This is especially prominent in women. In addition, the population frequently has misconceptions and false ideas about risk factors, symptoms, and other aspects of cardiovascular disease. In addition, the sources of information that people use may not be reliable. There is some evidence that people do not get enough information, or adequate information, from their doctors.

Scientific literature on awareness of cardiovascular disease among health professionals is very limited. Also, some demographic factors, and factors associated with work settings, medical specialties, or country, may play a significant role. Because cardiovascular disease has traditionally been thought of as a disease of men, cardiovascular disease severity and prevalence in

women have been underestimated; specific gender biases are visible, such as attributing the same risk factors, symptoms, clinical presentations, etc. to women and men without scientific evidence in both sexes, or providing less or inadequate treatment to women.

Objectives

The overall aim of the GenCAD project was to raise knowledge and awareness of differences between women and men in prevention, diagnosis, and treatment of coronary artery disease, where coronary artery disease was used as an example for other chronic diseases. The project was considered as a pilot effort to define an approach to sex and gender in health that could be replicated for other chronic conditions than coronary artery disease.

The coverage of EU Member States should be broad and balanced, with the aim to involve all EU Member States. Based on the overall objective described above, we developed 5 more specific objectives:

- **The first specific** objective of the project was the analysis of existing knowledge about sex and gender differences in coronary artery disease risk factors, disease mechanisms, clinical manifestations, treatment, access to health care, management and outcomes and to assess sex and gender specific approaches to coronary artery disease and coronary artery disease prevention in the Member States.

For this purpose, we planned a state-of-the-art study on sex and gender-related manifestations of coronary artery disease and treatments and on gender implications on health determinants and risk factors. This included a) extensive bibliographic research in different medical literature databases, b) the analysis of existing sociodemographic and medical databases on the inclusion of sex and gender and c) analysis of Member State policies on gender and health, with a focus on cardiovascular disease.

- **The second** objective was to assess awareness among health professionals and the general public in all member states. For this purpose we planned a needs assessment of the topic, including surveys on

awareness of the population and health professionals and assessment of activities of sex and gender research in coronary artery disease in Europe.

- **The third objective** was to generate factsheets on sex and gender aspects in coronary artery disease addressed to both experts and to EU citizens, with the aim to support them to identify and address the gender differences regarding coronary artery disease.

These factsheets were planned to be based on the outcomes of the bibliographic studies, the database analysis and the awareness studies. They were to be developed in all EU languages for two target groups: in an easy and understandable laymen-style for general public, and in a more medical language for general practitioners and other health professionals.

- The fourth **objective** was to communicate and disseminate the GenCAD findings and factsheets to a broad target audience, using a preparatory workshop and two international conferences in Brussels, in order to improve the general knowledge and awareness in the EU for Gender aspects in coronary artery disease.
- As a fifth **objective**, a communication plan was created to support internal and external communication, dissemination across the twenty-eight EU Member States, to assure that the different activities, factsheets, conferences, internet activities and conventional media activities were well interrelated
- As a last objective, a management structure was set up involving steering and advisory boards, a risk and contingency plan, to coordinate timely meetings and reports to DG Health and Food Safety.

1.2. Main activities and results

Based on the objectives described above, we developed six work packages of the GenCAD project including different tasks:

- WP 1 State of the art study
- WP 2 Needs assessment
- WP 3 Factsheets
- WP 4 Conferences
- WP 5 Communication plan

- WP 6 Project management

Figure 1: Schematic overview of the GenCAD process

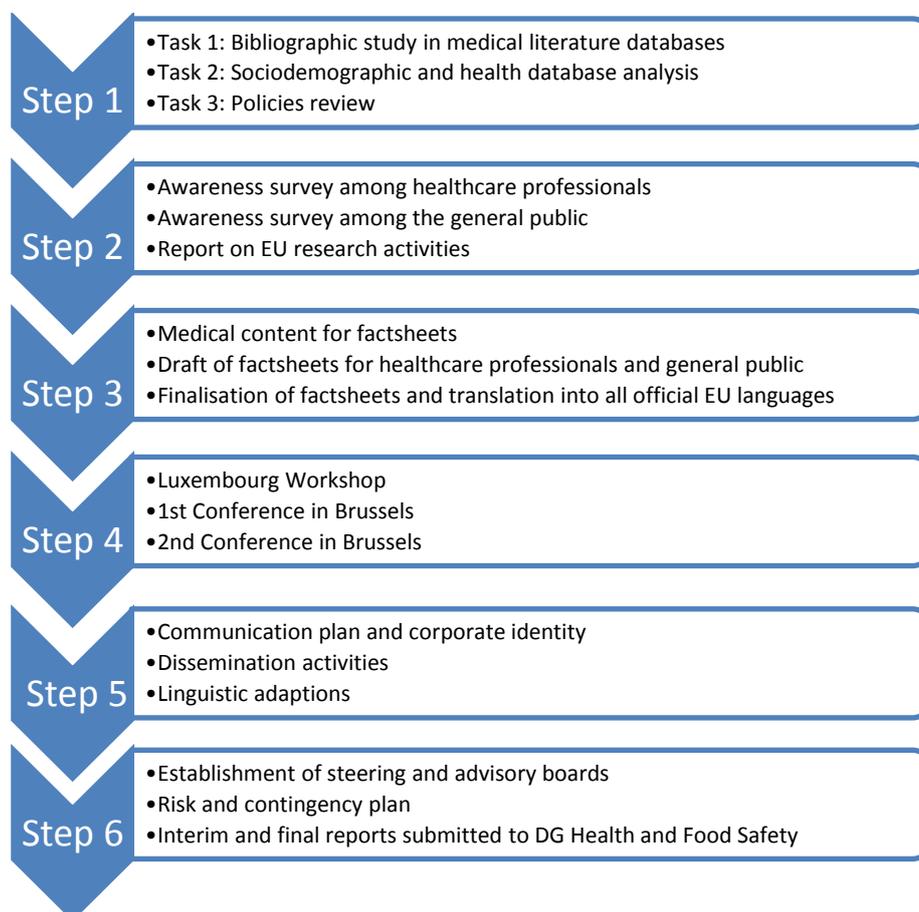


Figure 1: Four steps schematic overview of the GenCAD process

1.2.1. WP 1 State of the art study on gender-related manifestations of coronary artery disease in published literature, sociodemographic and health databases and policies

The first activity/task of work package 1 was to assess existing knowledge about sex and gender differences in coronary artery disease in published literature, thereby creating an extensive and up-to-date review on the topic of coronary artery disease and sex and gender-related mechanisms. References were collected from different literature databases, mainly from the NIH provided database PubMed, the Cochrane library and in the gendermed.db library (<http://gendermeddb.charite.de/>) as explained in the WP below, and

references were manually graded according to their relevance by the Radboud partner. After a review and completion of the findings amongst partners and external experts, the resulting list of references was incorporated into the report (Attachment 1) as well as into the factsheets and surveys.

We found that important gender differences exist in the early onset and progression of atherosclerosis and myocardial ageing. Men develop the classical type of focal, obstructive coronary artery disease earlier in life compared to women, while the latter have a more diffuse pattern of coronary artery disease with relatively more microvascular coronary disease, plaque erosion, and thrombus formation. Sex differences in established and in novel risk factors are emerging. [3-27]

We found that a large number of sex and gender differences in pathophysiology are well known.[26-35] It is also known that prevention strategies have a different weight in women and men.[36-42] Differences in symptoms, in clinical manifestation and diagnosis are frequent and the sensitivity of laboratory and stress tests, and coronary angiography varies among women and men. [33, 43-50] However, most medical and interventional strategies have been developed for the male patient as the gold standard, which is less well suited for women in many ways.[33, 43, 51-56] This concerns dosages of medications, side effects, interactions with other medications, but also bleeding risks during percutaneous coronary intervention and morbidity and mortality after coronary artery bypass graft etc. Evidence for optimal treatment options in coronary microvascular disease is still scarce and in an exploratory phase.

Studies were often limited by the fact that sex disaggregated data were not provided, sex and gender related research questions were not analysed in a prospective manner and state of the art study design and numbers of women included were often too small to draw reliable conclusions. In summary, medical knowledge is not equal for women and men.

The second activity/task of work package 1 was to investigate the sensitivity of European sociodemographic and health databases to record sex and gender related factors in coronary artery disease. We therefore first analysed public

sociodemographic and medical databases for coronary artery disease morbidity and mortality, in EU Member States that were developed by governmental organizations and international health institutions (see Table 2). We then analysed major research databases for coronary artery disease on including sex and gender related data in addition to known risk factors such as smoking, diabetes, hypertension, hyperlipidaemia, prevalence, alcohol use, income gap and checked the data for their sensitivity to analyse sex and gender related effects. Furthermore, we connected with external experts for their opinions on the inclusion of sex and gender in coronary artery disease studies.

We found that a number of sex and gender related variables are included in the the publicly accessible sociodemographic and health databases as well as in major coronary artery research. Analysis of the public databases was hampered by the fact that the age cut-off was low and therefore, age dependency of the different parameters cannot be assessed. Even worse, for some important variables, gender-disaggregated data are not available. Variables like the number of children, miscarriages, hormone therapy, andro- or menopause or true gender variables are incompletely covered in the publicly accessible databases as well as in the research databases. However, in order to conduct a sensitive analysis on the effects of sex and gender on coronary artery disease these sex and gender-related parameters ought to be included in all types of databases.[57]

In summary, gender related variables in European sociodemographic and health databases as well as in research databases are insufficient to analyse the effect of sex and gender on coronary artery disease in a coherent manner. There is a need for better sex and gender disaggregated-data, as well as for increased age cut-offs to obtain a clearer picture of coronary artery disease in women and men across Europe.

The third activity of work package 1 was the assessment of current EU Member State policies and existing preventative approaches in the field of cardiovascular disease by contacting governmental healthcare departments, national medical and public health societies, funding agencies and active

researchers. This involved exploring the policy process environment as well as policy content as we sought to determine the willingness of the EU Member States to embrace a more gender equitable stance on cardiovascular risk and its management. From the analysis, we were able to determine that for all EU Member States there is a policy environment that ensures gender equality; discrimination based on sex is prohibited. There is also a growing body of recommendations from leading health organisations supporting more gender sensitive and gender aware health care. At the level of detailed policy and guidelines guiding practice for coronary artery disease there is a high reliance on the ESC guidelines in many countries but incomplete endorsement of these guidelines in some other countries.

1.2.2. WP 2 Needs assessment

WP 2 assessed awareness of sex and gender related aspects among health professionals and the general public in all member states. For this purpose, we first undertook a needs assessment of the topic, including a survey among health care professionals; the second step was a survey among the general population in different European regions, and the last part was an assessment of ongoing research activities in the area.

1.2.3. WP 3 Factsheets

As one of our main outcomes, the third work package developed factsheets on sex and gender aspects in coronary artery disease that target both experts and EU citizens. These factsheets reflected the results of the state of the art reports. They were drafted and evaluated by participants at the first GenCAD workshop, and further communicated to external experts listed in the Dissemination section. They included both the biological and social factors related to coronary artery disease that impact the risk factors, development, diagnosis, progression, treatment and prevention of coronary artery disease. Two versions were generated, one for health care professionals and one for the general public. Once the factsheets were finalised in English they were translated into all 24 official EU languages and linguistically adapted by native speakers and experts.

1.2.4. WP 4 Conferences

The main goals of work package 4 were 1) to discuss the strategy and first results with experts and with DG Health and Food Safety in the Luxembourg Workshop and 2) to communicate and disseminate the findings of WP 1 and 2 to a broad target audience, in two international conferences to improve the general knowledge and awareness in the EU for sex and gender aspects in coronary artery disease. The preparatory workshop was held in Luxembourg in early 2016, and the conferences were both held in Brussels in 2017. We were able to present and discuss our findings and factsheets to an open audience that agreed to the importance of such endeavours, as well as to the need for factsheets of this nature.

1.2.5. WP 5 Communication and dissemination

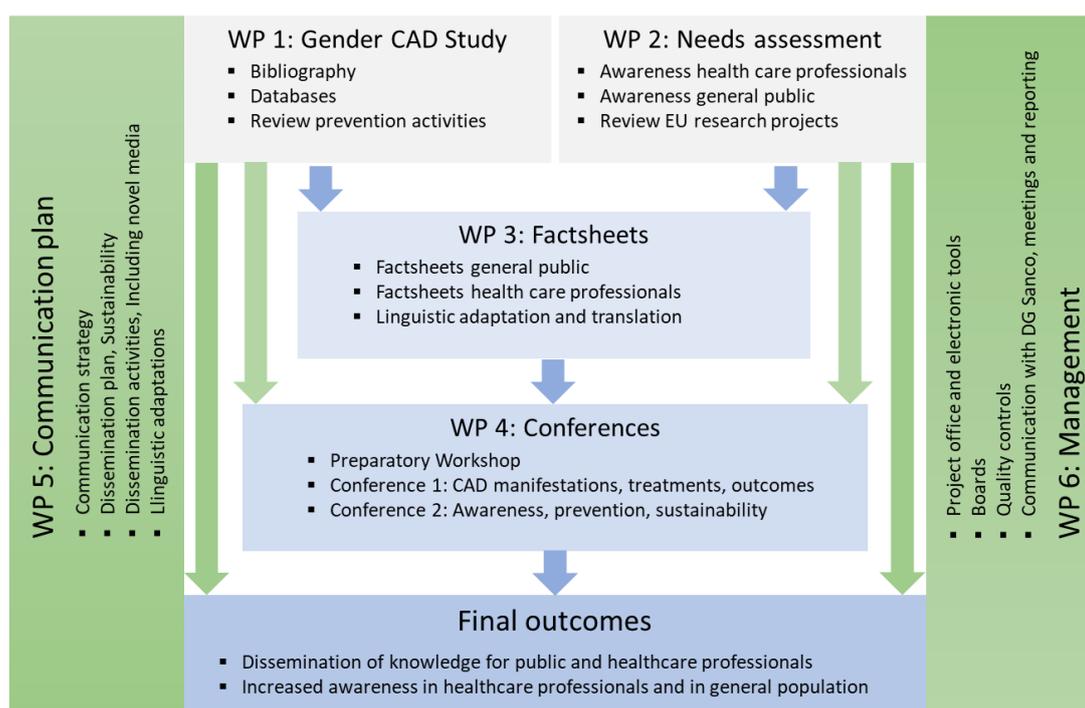
The fifth work package involved communication and dissemination of the results. The first activity aimed at creating a communication plan to support internal and external communication, and to assure that the different activities, factsheets, conferences, internet activities, and conventional media activities were well interrelated. We planned additional symposia at the annual congresses of major societies to disseminate our messages and outline communication with the local cardiovascular disease and prevention societies in Member States. Furthermore, a sustainability plan was developed to ensure that the knowledge and materials generated by the project continue to be circulated to healthcare professionals, patients and EU citizens after the project's end.

1.2.6. WP 6 Management

Work package 6 aimed to fulfil the needs of DG Health and Food Safety in a timely and high-quality manner supported by meetings and reports to deliver work of the highest quality. In particular, the management of internal communication, development of a homepage, the installation of a steering board, advisory board, and multi-sectoral expert team, as well as the development of a risk and contingency plan were to be addressed.

The interaction between the WPs is shown in Figure 2 and a more detailed description of all WP is found in the sections 2-7.

Figure 2: Structure of the work



Structure and working plan for the project, interaction between WPs.

1.3. Lessons learnt

All deliverables in this project were reached but some parts required more attention and efforts than others. We learnt some lessons that may be interesting for others, running a similar project and are listing them below:

The bibliographic study required the development of sophisticated search terms for sex and gender to avoid contamination of the retrieved literature with numerous publications that included the word "sex" and only counted the number of women and men included into a study without further sex or gender sensitive analysis. Using the gendermed.db database

(<http://gendermeddb.charite.de/>) was very helpful since it filters titles and abstracts with a textmining programme to identify projects that are really related to sex and gender analysis. This textmining programme was manually and externally validated in more than 30.000 publications and now has a very high standard.

From the state-of-the-art study, we realised that not all potential stakeholders were interested or willing to contribute to the policy analysis. In those countries, where information was missing, we found a desktop search to be valuable in attaining the corresponding documents.

The translation of the factsheets proved somewhat troublesome during the early stages of development. The first drafts of the translated documents did not accurately reflect the original messages even though a very experienced company was chosen following an international tender. We therefore turned to medical experts from our stakeholder list to help transfer the appropriate meaning. This strategy proved beneficial and significantly improved the results.

Conferences were highly dependent on timing and needed preparation a long time ahead. We were able to involve many more EU members of parliament by shifting the location of both conferences to Brussels. As such, we were able to directly interact with those involved in European policymaking.

Keeping the dissemination activities in mind, the use of social media has helped us to reach groups of targeted individuals quicker than other methods. Our target audience included adult women and men with interests in healthcare, health and wellness, health organizations, non-governmental organisations and the general population. We set an arbitrary age limit of 21 years, a limit proposed by the facebook system, to target an adult audience.

1.4. Comparison of countries

Country comparison was not a specific target for this tender, and therefore, we cannot provide valid comparisons that are well based on statistics. Nevertheless, we made some interesting observations and these are listed below, even though they have only descriptive character.

The state-of-the-art study was able to shed some light on the various EU Member States. The database analysis showed a large heterogeneity between European regions in coronary artery disease mortality, socioeconomic and biological risk factors.

From the onset, we assumed that much data in coronary artery disease related factors would be similar for many countries, especially as these were collected for the same type of databases. However, we found that there was an incoherent data collection on an annual basis for many countries or a lack of gender disaggregated data that contributed to the difficulty in comparing regions. A further complication in this matter was the low age cut-off of 65 years for many of the coronary artery disease related factors, which distorts some of the results, because of an increasing average life expectancy in Europe.

Still, the coronary artery disease mortality rate was particularly high in many North-eastern European countries like Latvia, Lithuania, Romania, and Slovakia. The overall discharge rates for ischemic heart disease and stroke show similar regional trends as for coronary artery disease. North-eastern countries (e.g. Lithuania and Bulgaria, Hungary) had the highest rate of ischemic heart disease and stroke discharges and southern countries, like Cyprus and Spain the lowest. However, gender disaggregated data on these parameters were not available, limiting any further analysis.

When comparing EU policies, we found major differences among the 28 EU Member States. From the analysis in WP 1.3. it can be seen that there was a very good level of awareness shown in some countries to the differing risks and needs of men and women. This was reflected in high-level policy documents and guidelines that offered concrete guidance on how services should be adapted to meet the different risks and needs of men and women. However, in other countries a significant lack of documents is recognized. Furthermore, equality and anti-discrimination legislation is well-developed in some countries. Some of the newer members of the European Union are still in the process of developing their equality legislation. For example, Bulgaria has

a National Strategy for Promotion of Gender Equality and a Protection against Discrimination Act, but it does not yet have specific gender equality legislation. The Issue frame analysis demonstrated that there was a strong push within some of the Member States for the recognition of gender as an important factor in both health generally and cardiovascular disease specifically.

Some countries have extensive coverage of the risks women face with regard to their cardiovascular health, such as the 'The Polish Women 50+ Report. Health and its threats'. Medical societies, such as the Italian Society for Cardiovascular Prevention, published a handbook on prevention of myocardial infarction in women; and key non-government organisations, such as the British Heart Foundation developed a Women's Room. There was less information relating to the needs of men and coronary artery disease, with the most notable exceptions being the Danish Men's Health Report and the Irish Men's Health Policy.

There were 6 countries where there were no apparent policy statements relating to gender and health or coronary artery disease (Belgium, Croatia, Cyprus, Estonia, Lithuania and Slovenia). Some had policies relating to gender and health, but without specific reference to coronary artery disease (Czech Republic, Portugal, Romania, Slovakia).

For the analysis of the Document frame, we looked at the policy guidelines and policies that help develop services directed specifically at sex and gender factors/considerations and cardiovascular disease. The most comprehensive coverage of these was found in Denmark, Germany, the Netherlands and the UK.

Regarding interest in our conferences in the different countries, among stakeholders and experts with interests in coronary artery disease and gender, there were also large country specific differences. Countries with the greatest interest and subsequent representation at the conferences include Germany, Italy, Netherlands, Spain, and the UK.

1.5. Performance indicators

We produced a list of performance indicators that helped identify the progress and the achieved results against the initial objectives. These appear in the

respective sections, i.e. in the conclusion sections of the more detailed WP descriptions in order to compare the achievements with our objectives.

- Number and quality of publications retrieved
- Number of databases analysed
- Cooperation of database holders
- Number of EU Member States reached for policy analysis
- Content analysis for policies performed
- Elaboration and quality of the questionnaires
- Number of people participating in both surveys (General Population: number of questionnaires completed /number of targeted persons contacted by phone)
- Number and representativeness of Member States participating in the surveys
- Finalization and translation of factsheets
- Participation in conferences
- Presentation of GenCAD key strategies, key messages and factsheets at conferences and in press releases
- Interest in factsheets by external organizations
- Reach-out to target populations via the internet
- Timely reporting to DG Health and Food Safety and acceptance of reports
- Building of a steering board, advisory board, and multi-sectoral expert team

1.6. Problems and deviations from the tender

During the inception meeting, the content of the tender was discussed and both parties agreed to some clarifications and changes. In particular, it was clarified that original research was not desired by DG Health and Food Safety, only an analysis of published work.

Some more changes that were set at the inception meeting are listed below:

- Both conference locations were moved to Brussels from Bratislava or Berlin.
- The needs assessment questionnaire was altered, in order to capture the population of family doctors. The questionnaire was translated into 6

languages of our sample survey countries that were chosen for the survey in the general population, countries that are in many aspects representative for the European population regarding cardiovascular disease.

- Given the importance of translation, cultural adaptation and piloting times, both partners agreed that factsheets should be finalized by month 30 and translated by month 34, slightly later than envisioned in the initial tender.
- Only a final report should be produced and not a white paper.

During the project lifetime, some more important changes were agreed among the parties.

- Dates of both conferences were moved further back and adapted in their dates to accommodate the attendance of prominent EU parliament officials.
- Most importantly, the website was moved to DG Health and Food Safety servers and to an area, where different languages can only be used for attachments. This changed the structure of the initially planned website and eliminated the interactive elements planned in the initial tender.

2. State-of-the-art study

A state-of-the-art study with three parts was carried out, including a bibliographic review on sex and gender-related manifestations of coronary artery disease in published literature, presentation of sex and gender aspects in sociodemographic and medical databases and presentation of gender in European policies.

2.1. Bibliography review

2.1.1 Objectives

The first major aim was to assess the existing knowledge on sex and gender differences in coronary artery disease by an extensive bibliographic review. Literature databases were searched, no start time point was set, quotations from all over the world were collected and the endpoint was 31.Dec of 2015.

2.1.2 Methods

We closely followed the strategy described in the tender (p 29, task 1), in the interim report 1. It is also summarized in Fig 3.

We took advantage of our "GenderMedDB" database, (<http://gendermeddb.charite.de/>) which is available to the community as an open access tool.[59] It has been developed since 2008 to identify publications related to sex and gender in specific areas. It has been built using a complex search term for "gender" (combining *male, female, women, men, sex, gender*), combined with several terms for different medical disciplines including "cardiovascular", and searching the whole Pubmed database in the fields of interest (including all years covered in this database). This GenderMedDB database has the advantage that false positive hits obtained with the gender term, i.e. publications that are positive for the gender term only because they mention "women" or "men", "male" or "female" in the abstract (e.g. as number of women and men participating in a study), but do not analyse sex or gender related aspects, are already eliminated. This was done in the first years by individual control of all abstracts, which was supported after 2015 by a text mining programme.

Figure 3: Methods and steps undertaken for the bibliographic review

Step 1 - Define search terms

- Select key terms to search databases, focusing mainly on “women” and “men” or “male” and “female, sex or gender”

Step 2 - Search Databases

- GenderMedDB
- Pubmed
- Cochrane libraries
- ESC guidelines

Step 3 - Select truly gender related publications

- i.e. Eliminate false positives - i.e. publications that are positive in the gender term, only because they mention “women” or “men”, “male” or “female” in the abstract, but do not analyse sex or gender related aspects

Step 4 - Structure results

- Structure results relating to following areas:
 - Prevention and health promotion and public health
 - Epidemiology
 - Pathophysiology
 - Clinical symptoms and diagnosis
 - Management
 - Outcomes

Step 5 - Evaluate and rank all retained publications

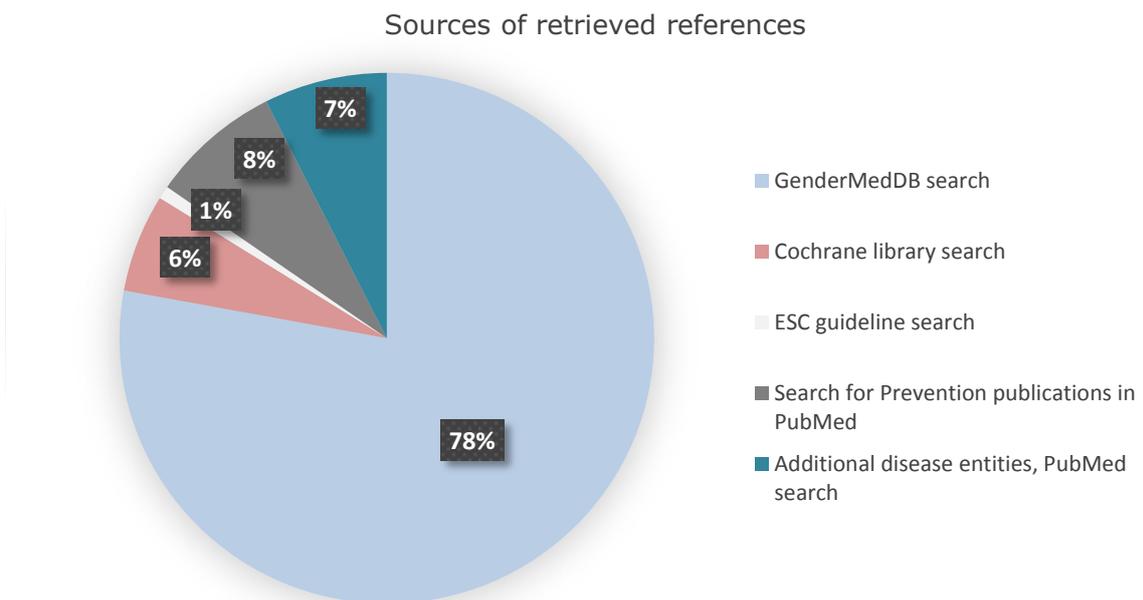
Steps used to identify, search, and analyse publications for bibliographic review

Using this approach, we retrieved 690 articles with a focus on sex and gender in our 9 subspecialties. To check for completeness, additional searches were performed in PubMed to add any articles that could have overlooked in our database with more specific search terms, related to prevention, diagnosis and management of specific and gender-related types of Acute coronary syndromes such as sudden coronary artery dissections and Takotsubo cardiomyopathy yielded > 120 additional relevant publications (case-reports excluded). Another additional search was done on the emerging subject of coronary microvascular disease which are probably more prevalent in women than in men, and with the names of authors that were suggested by external experts, which provided > 30 relevant papers.

In addition to the work with the above-mentioned databases, we also distinctively searched the Cochrane Library for additional publications on coronary artery disease and sex and gender aspects (n=53) and assembled the guidelines on coronary artery disease management or prevention by the European Society of Cardiology. For the latter we included all the guidelines that were in a broad sense linked to the prevention and disease of the coronary arteries, i.e. also the ones on myocardial infarction.

Finally, we checked the publications of the leading authors in the field by name and contacted our experts to identify publications that we might have overlooked.

Figure 4: Sources of retrieved literature



PubMed, GenderMedDB, Cochrane library and ESC guideline databases were used to retrieve references

In order to structure our results, we defined the following six areas:

- I. Prevention and health promotion and public health
- II. Epidemiology
- III. Pathophysiology
- IV. Clinical symptoms and diagnosis

V. Management

VI. Outcomes

After structuring the results, a first ranking was done by partners from the Radboud University Nijmegen Medical Centre (RUMC). Relevant articles were evaluated based on structure, size, publication type and metrics and relevance in the field. Ranking criteria are focusing on the relevance of differences for disease diagnosis and treatment, the soundness and reproducibility of the reported differences and the transferability of any recommendations to all 28 Member States.

The evaluation of the single most relevant papers and their ranking can be found in Attachment 1. Literature was included based on the ranking according to relevance. Our analysis focused on the publications with high (2) and very high relevance, ranked as (2) and (3).

Next, we sent the results to our internal and external networks of experts, received and integrated their comments after extensive discussions with the international experts at the Luxembourg workshop in February 2016. A second ranking was done to determine which of the publications should be included into the factsheets. This ranking was circulated again and adapted to the responses before being included into the draft factsheets presented at the 1st GenCAD conference in Brussels 2017.

In summary, the following activities were taken in the bibliographic study:

- a) Identification of relevant disease entities
- b) Performance of searches in GenderMedDB, PubMed and Cochrane library
- c) Structuring of results
- d) Evaluation of results and first ranking
- e) Summary of most significant and relevant findings
- f) Circulation of findings among partners and external experts for feedback
- g) Incorporation of additional feedback
- h) Second ranking to define content for factsheets

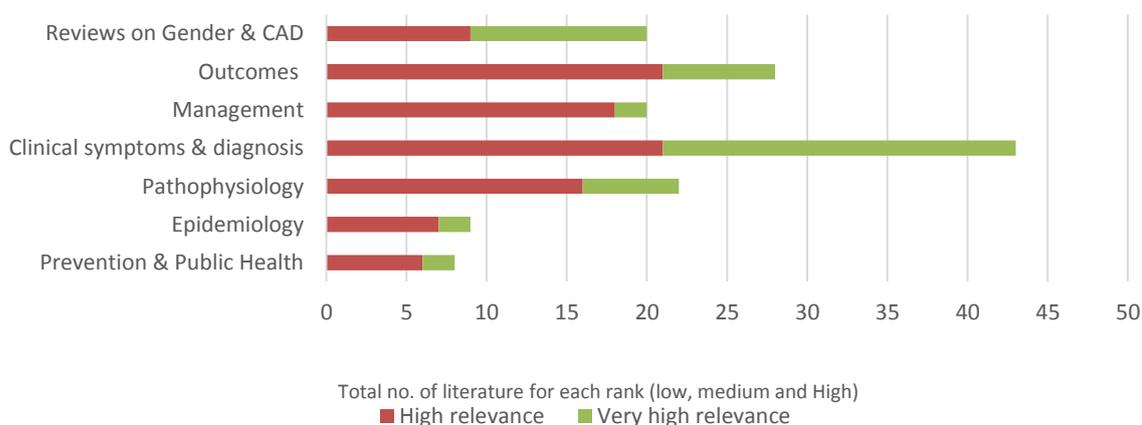
2.1.3 Results

Searching the databases and discussion with our experts for publications from all over the world, we retrieved 878 articles about epidemiology, pathophysiology, clinical manifestations and diagnosis, management and outcomes in coronary artery disease with a true focus on sex and/or gender analysis that were found to be relevant to the review by partner RMC (see Attachment 1). As mentioned in the methods section above, the results of the search are structured into following sub-sections:

- a) Epidemiology
- b) Risk factors and prevention
- c) Pathophysiology
- d) Clinical symptoms and diagnosis
- e) Management
- f) Outcomes

Of the 878 relevant publications retrieved, 120 were considered to be high and very high relevance by partner RMC. Their distribution over the different areas is depicted in Fig 5. If a publication belongs to 2 areas, only the most important is mentioned. The most important findings are described below.

Figure 5: Distribution of top publications from retrieved literature and their ranking



Gender specific ranking of literature under each category 2= high relevance, and 3 = very high relevance.

- a) Epidemiology

Ischemic heart disease develops on average 7-10 years later in women compared to men in most western societies. However, most likely due to unfavourable life-style changes over the past decades, manifestations of ischemic heart disease in younger women are increasing.[34, 60] Acute coronary syndrome, ST-elevation MI (STEMI) or NSTEMI occurs 3-4 times more often in men than women below age 60, but after 75 years women represent the majority of patients. Recently, the number of acute coronary syndrome in relatively younger women has increased in France and Germany. This is importantly related to a deterioration of life-style factors such as smoking and obesity.[34, 60]

b) Risk factors and prevention

Gender differences in cardiovascular risk factor profiles reveal an advantage for women at younger age and a higher cardiovascular risk factor profile at older age. This leads to the misconception that women are at generally at lower risk, which is not. In the totality of women and men, women accumulate as many risk factors as men, but they do this at a higher age. In addition, the less obstructive pattern of coronary artery disease in women further adds to the misperception that coronary artery disease is not that serious in women, resulting in less optimal secondary prevention. Secondary prevention goals are less well often achieved in women than in men.[34, 60]

Important data on gender differences in risk factors and in secondary prevention have been derived from the Euro Heart Survey studies and in primary prevention on many regional cohorts that have also served for gender-based risk estimation in the SCORE project.[21, 61]

This has also led to the conclusion that within Europe low and higher risk areas are present <http://www.escardio.org/Guidelines-&-Education/Practice-tools/CVD-prevention-toolbox/SCORE-Risk-Charts>. However, there is no specification according to sex or gender related to these risk profiles.

The Euroaspire I, II, III surveys have shown that risk factor treatment in Europe has improved over the past 15 years, but that especially younger

women have taken up more smoking habits.[62] From older studies, such as the Copenhagen City Heart Study, it has been known that the relative risk of smoking for having an acute coronary syndrome before the age of 55 is two times higher in women compared to men.[63] In addition, a number of publications contributed knowledge on gender differences in risk factors and we list a few more specific findings.

Premenopausal women have less often hypertension and lower lipid levels than similarly aged men, whereas this reverses at older age.[64] Systolic blood pressure rises more steeply in ageing women compared with men.[65] Hypertension results in a higher prevalence of strokes, left ventricular hypertrophy, and diastolic heart failure (HF) in women than in men.[66] But even moderate or borderline hypertension (<140/90 mmHg) causes more endothelial dysfunction and cardiovascular complications in females than in men.[67]

High lipid levels are an underestimated risk factors in women. Databases show that women with hyperlipidemia are less intensely treated than men, Eugenmed study group, 2016.[68] However, the risk attributed to increased lipid levels is similar in women and men.[69]

Diabetes emerged as a major risk factor that worsens coronary artery disease outcome more in women than in men. In a meta-analysis of 37 prospective cohort studies, the risk increase of fatal ischemic heart disease was 50% higher in women with diabetes compared with men.[7] More comorbidities including obesity and inflammation as well as more unfavourable changes in coagulation and endothelial function may contribute to greater cardio-metabolic risk factor load in diabetic women.[26] Diabetes therefore dilutes the female advantage of better cardiovascular disease health in patients < 60 years and should be treated equally as in men.[51]

Depression and various forms of sustained mental stress (anxiety, anger, marital conflicts, work stress, depression etc.) have been acknowledged as etiological and prognostic risk factors for coronary artery disease.[64] They increase the risk to develop coronary artery disease to similar degree in

women and men. However, the prevalence is significantly higher in women, particularly in younger women and this adds more to worse outcomes. [70, 71]

Concerning men's health cardiovascular disease screening in patients with symptoms of erectile dysfunction can contribute to better prevention measures in men.[72]

Other relevant findings:

- There is increasing evidence that air pollution and noise caused by traffic is associated with the degree of atherosclerosis in both men and women. This needs much more attention in design of infrastructure and environment in urban areas.[73]
- A low birth weight is more associated with a higher cardiovascular disease in women than in men.[38]
- Genetic factors are important in premature cardiovascular disease, and some studies support that this is more often present in men [74], while others found that this accounts more for women.[75]
- Higher prevalence of strokes in younger women compared to men (age 45-54 years). Strokes are often outside the scope of cardiologists, but are potential life threatening cardiovascular disease events and have a high impact on people's lives.[76]
- Peripheral arterial disease is underestimated in women and presents with different clinical characteristics.[12]

Preeclampsia is an emerging cardiovascular disease risk factor in women and has been included in the 2014 AHA prevention guidelines of stroke.[14]

c) Pathophysiology

Acute coronary syndrome, STEMI or NSTEMI without epicardial coronary artery disease or structural heart disease occur more frequently in women than in men. [77] In particular, younger women with acute coronary syndrome may present with open coronary arteries, with plaque erosions with distal embolisation rather than plaque rupture with thrombus formation.[78, 79] Not

unfrequently, angina or acute coronary syndrome in women may be due to coronary microvascular disease, also called microvascular angina.[15, 45] Women have more frequently components of pathological vasoreactivity, such as spasm and endothelial dysfunction.[49, 80] An underdiagnosed cause of acute coronary syndrome is spontaneous coronary artery dissection, which occurs predominantly in women, mostly between 45-60 years of age, preferentially in pregnancy or in the immediate postpartum period and may be caused by hormonal changes.[81] Estimated 8 % of acute coronary syndrome in women but less than 1 % in men are associated with the so-called Takotsubo syndrome (see below).[82, 83]

Some important findings from highly qualified papers that were included in the literature search:

- Smaller intrinsic diameter coronary arteries in women, after correction for body size.
- Men have more atheroma burden, calcifications, functional abnormalities and focal obstructive disease than women.[42]
- Higher mortality in younger women (< 65 years) with acute coronary syndromes compared to men, despite having less obstructive disease. Coronary plaque ruptures are more associated with thrombus formation in women than in men.[84, 85]
- Takotsubo cardiomyopathy, coronary microvascular dysfunction, and spontaneous coronary artery dissection occur more often in women.[19]
- Different genetic variants involved in coronary microvascular dysfunction in women compared to men.[86]
- Evidence for gender-related differences between the regulation of vasomotor function of microvessels of female and males.[87]
- Spontaneous coronary artery dissection is an important cause of acute coronary syndrome and sudden death in young persons, particularly women. Associated conditions are fibromuscular dysplasia, peripartum status, and episodes of extreme emotion or exercise.[44, 88, 89]

- In the absence of obstructive coronary artery disease, microvascular coronary spasm is more often present and inducible in symptomatic women compared to men.[90]
- Gender differences in circulating cytokines and other markers of inflammation in-patient with macrovascular coronary artery disease.[91]
- Inflammation is also involved in coronary microvascular dysfunction. Increasing evidence for gender difference in relationship between cardiovascular burden and systemic autoimmune diseases that is mainly due to inflammation and autoimmunity.[37]

Gender differences in vascular stiffening with ageing, this is much more present in women.[92]

In summary, it has become literally visible that important sex and gender differences exist in the early onset and progression of atherosclerosis and myocardial ageing, for yet unknown reasons. At autopsy studies and coronary intervention studies it has clearly been demonstrated that men develop more and earlier coronary plaques than women during their life. Men present more frequently with more extensive coronary artery disease than women. The reasons for this are still unknown, it is speculated that inflammatory mechanisms play a greater role in men. This needs to have more consequences in clinical practice and is a plea for a more gender-sensitive approaches to our cardiac patients. Inflammation is importantly involved in the process of atherosclerosis, not only in the larger coronary arteries, but also in the coronary microvasculature.

d) Clinical symptoms and diagnosis

In acute coronary syndrome, patient-delay before seeking medical help is longer in women than in men.[24, 53] It has recently been postulated that a sex specific threshold for high- sensitive biomarker Troponin I (reflects myocardial damage) may improve the diagnostic accuracy of this most important laboratory test for diagnosis of acute coronary syndrome in women.[47] [93]

The interpretation of non-invasive diagnostic testing is less reliable in women compared with men, especially in the age group below 60 years when the prevalence of obstructive coronary artery disease is still relatively low.[94] Non-specific ECG changes at rest and a lower exercise capacity contribute to the lower sensitivity and specificity of non-invasive exercise testing in women. [28, 95] As most exercise testing scores have been developed from populations that were composed primarily of men, only few scores have been designed especially for women. [39, 96] The current ESC guidelines advise stress imaging techniques (e. g. SPECT, stress echocardiography) when available as first test of choice, with a preference for non-radiation diagnostics in younger women.[94, 97]

In the Swedish coronary angiography and angioplasty register, almost 80% of women with stable angina symptoms below age 60 had no visible coronary obstructions at angiography, compared to 40% of men. [50] Thus, primary diagnostic strategies in women searching for the classical 'male' pattern of obstructive coronary artery disease, may be suboptimal, increasing the risk for procedural complications and leave vascular dysfunction or coronary micro vessel disease in symptomatic women underdiagnosed.[33] In 2014 the American Heart Association (AHA) launched evidence-based gender-related guidelines for non-invasive testing promoting selective functional and anatomic testing with non-invasive imaging techniques in women at intermediate risk.[94] These are helpful to avoid the still too large number of unnecessary and inconclusive angiograms in this patient population. Women at low ischemic heart disease risk most often require no testing. Women at low-intermediate or intermediate ischemic heart disease risk who can exercise adequately should be referred to an ETT-first strategy. Coronary artery disease imaging is indicated for intermediate-risk or high ischemic heart disease risk women with functional disability or an abnormal rest ECG. Diagnostic modalities for assessment of coronary microvessel disease include measurement of coronary blood flow reserve by transthoracic echocardiography or PET-CT perfusion or calculation of microcirculatory

resistance indexes during coronary catheterisation (coronary flow reserve).[15, 98]

Women with recurrent chest pain syndromes and non-obstructive coronary artery disease need to be diagnosed and treated since they have a twofold increased risk to develop obstructive coronary artery disease events in the next 5-8 years and have a four times higher risk for re-hospitalisations and recurrent angiograms than women without these symptoms.[48, 99] Shaw et al. (2009) reported an expected consumption of nearly \$750,000 of cardiovascular health care resources related to the burden of ongoing symptoms and medications.

Additional summarised findings from highly rated papers over the past decades: In 20-30% of females with an acute myocardial infarction no angiographic obstructive coronary artery disease (MINOCAD) is seen, this is two times as often as in men.[36, 46]

- A gender difference in plaque morphology, female pattern coronary artery disease in acute coronary syndrome has been identified (PROSPECT).[100] More angina and periods of ischemia have been found in women than in men (Merlin-TIMI 26).[101]
- Women experience and describe angina symptoms differently than men, both in stable and unstable angina syndromes. Women have more angina during stress, men more during exercise. Women have more referred pain in the neck and shoulders.
- Results from the landmark Women's Ischemia Syndrome Evaluation study: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis, macrovascular, and microvascular coronary disease.[6]
- Syndrome X replaced by "coronary microvascular dysfunction" to better define and classify this type of ischemic heart disease.[6]
- In women with premature coronary artery disease, other risk factors beyond the traditional risk factors are important.[41]

- ST-T abnormalities on resting ECG are less often related to obstructive coronary artery disease in women compared to men.[29]
- There is evidence for more diffuse and peripheral coronary artery disease in type 1 female diabetics compared to males with DM1. [102]
- Non-invasive imaging with CT scans to determine coronary calcium score (CAC) age- and gender-related nomograms have been developed. High sensitivity and negative predictive value in both genders, important tool for evaluation of intermediate risk patients.[13]
- With CCTA, gender differences in plaque morphology, women more NOCAD, less calcification and mixed plaques are been found.[103]
- Different standards are needed among men and women for normal values brachial artery flow-mediated dilatation.[104]
- Diameter ascending aorta increases with age more in men than women, but gender-related and age –adjusted normal values is needed.[105]
- Cardio-geriatrics: In the very old men beget more coronary artery disease, whereas women more LVH with HFpEF and valvular calcification. Gender-sensitive cardiac approach needed in the elderly.[106]
- Extent of NOCAD with CCTA predicts mortality in women but not in men. [107] CCTA however has limited prognostic value in women < 60 years, but not in younger men.[108]
- Indication that there are important gender-differences in resting coronary flow (CFR measures).[109]

Female gender, especially after menopause, dominates the occurrence of Takotsubo cardiomyopathy.[110] Domestic violence may be an important trigger for this syndrome and this needs further investigation.[111]

e) Management

Treatment of stable coronary artery disease and acute coronary syndrome should be performed according to the current guidelines in both genders.[97] It is now well accepted that women derive the same benefits from percutaneous coronary intervention as men. Previously, worse prognosis was attributed to smaller luminal diameters of the coronary arteries, risk factor

profiles, more comorbidities and referral bias in women. The Belgian Working Group on Interventional Cardiology registry analysed a large cohort of 130,985 percutaneous coronary intervention procedures in Belgium, from January 2006 to February 2011. Female gender remained an independent predictor of mortality after multivariable adjustment.[112] In most studies with second-generation drug-eluting stents sex and gender differences in long-term outcome after percutaneous coronary intervention are not supported further. However, female gender remains an independent predictor for peri-procedural myocardial infarctions and major bleedings after percutaneous coronary intervention which are associated with increased short-term morbidity and mortality.[4, 113] Due to the relative higher contribution of functional coronary abnormalities and a more diffuse pattern of atherosclerosis in female patients with coronary artery disease, residual symptoms of angina are often present after acute coronary syndrome or coronary interventions.[101, 114]

Using the transradial access for coronary interventions reduces the incidence of peri-procedural bleeding complications and improves clinical outcome.[10] The use of fractional flow reserve (FFR)-guided percutaneous coronary intervention has improved outcomes in both men and women.[22] Fractional flow reserve values are found to be higher in women after correction for visually assessed coronary anatomic severity. It is currently discussed whether gender-related guidelines in interpreting fractional flow reserve measurements are warranted.[52, 115]

Women have a higher mortality after elective coronary artery bypass surgery.[116] Major risk factors for women's mortality were low physical function, respiratory dysfunction, renal failure and old age.[117] A recent study identified a significantly higher prevalence of diastolic dysfunction among females presenting for elective cardiac surgery and reported that women had a prolonged hospital stay.[32] Women have poorer health related quality of life than men after coronary surgery.[55] Depression is a significant predictor of worse outcomes in women and men.[56]

Therapeutic options for coronary microvascular dysfunction are less well investigated than those for epicardial coronary artery disease; the efficacy of anti-anginal medications for symptom reduction is relatively poor and optimal treatment options are lacking.[97, 118] The presence of detectable peripheral coronary flow abnormalities in patients with microvascular dysfunction is associated with impaired prognosis in both men and women.[119, 120] Therefore this syndrome urgently needs more research.

The following important conclusions concerning management can be drawn from the GenCAD search:

- Less aggressive management approach is needed in women compared to men with acute coronary syndrome.[27]
- Women have fewer coronary interventions than men, also after correction for severity of disease.[121]
- In NSTEMI an early invasive strategy improves outcomes in men, but this is less clear in women (FRISC II).[122]
- The majority of studies show no gender differences in percutaneous coronary intervention results, but some found better results in women with DES compared to men.[43, 123]
- Acute coronary syndrome patients with non-obstructive coronary artery disease are less well treated with standard medication than acute coronary syndrome patients with obstructive coronary artery disease. This occurs more frequently in women than in men.[124]
- Evidence is lacking for the optimal treatment options in coronary microvascular dysfunction. B blockers have beneficial effect.[23]
- FFR guided percutaneous coronary intervention criteria should be different between men and women.[115]
- Lifestyle interventions with stress-reducing programs more effective in female than male coronary artery disease patients.[16]

In 2014 a consensus statement by Academic Emergency Medicine has been made to define optimal gender-related needs in management in emergency cardiac care. [125] Important included themes were:

- 1) The full spectrum of sex-specific risk as well as presentation of cardiac ischemia may not be captured by our standard definition of coronary artery disease and needs to incorporate other forms of ischemic heart disease,
- 2) Diagnosis is further challenged by sex/gender differences in presentation and variable sensitivity of cardiac biomarkers, imaging, and risk scores;
- 3) Sex-specific pathophysiology of cardiac ischemia extends beyond conventional obstructive coronary artery disease to include other causes such as microvascular dysfunction, Takotsubo, and coronary artery dissection, better recognised as ischemic heart disease
- 4) Treatment and prognosis are influenced by sex-specific variations in biology, as well as patient-provider communication; and
- 5) The changing definitions of pathophysiology call for looking beyond conventionally defined cardiovascular outcomes to patient-centred outcomes.

f) Outcomes

There is an ongoing debate whether outcomes are identical in women and men. Less aggressive management of coronary artery disease in general leads to worse outcomes. Other factors, such as older age, more co-morbidity and differences in the pathophysiology of underlying coronary artery disease contribute to our current understanding of gender differences in outcomes of coronary artery disease patients.

Due to the increased awareness of the prevalence of cardiovascular disease in women and coronary artery disease in particular, hard outcomes (mortality, events) have improved in female patients over the past decades. However, there is still a higher mortality in younger female acute coronary syndrome patients (< 65 years) and an important gender-gap in outcomes between the Eastern and Western European countries. Higher in-hospital mortality in

women with acute coronary syndrome has been attributed to a longer patient delay before admission, older age, a higher clustering of cardiovascular risk factors, lower use of invasive and medical treatment, and more bleeding complications after interventions.[9] In younger women (< 60 years) with STEMI, adjusted in-hospital mortality rates are nearly twice as high as in similarly aged men.[85, 126] More data are needed on gender differences in residual symptoms and softer endpoints related to QOL. Evolving knowledge has led to the first initiatives to implement gender-related strategies into the guidelines, such as the NSTEMI guidelines. Further progression is hampered by insufficient knowledge among cardiac care professionals and the need for more research in the field of (microvascular) coronary vascular dysfunction and gender differences in myocardial ageing (HFpEF).

The GenCAD search revealed some additional findings from the literature:

- Stress-related factors and social support important determinants of outcomes and QOL in female patients.[11, 127, 128]
- Prognosis of NOCAD is worse in women than men, 3x higher event rate in women.[129]
- More residual angina after coronary interventions in diabetic women with coronary artery disease than male counterparts. [114]
- In patients with coronary artery disease and reduced LVEF (HFrEF), women have poorer outcomes than men.[130]
- Physical exercise and fitness seems to improve outcomes even more in women than in men. However, women participate less often in cardiac rehabilitation programs than men.[5]
- More women than men hospitalised for acute decompensated heart failure (ADHF) related to diastolic dysfunction (HFpEF). Recognition and treatment needs to improve.[35]
- Coronary microvascular dysfunction is highly prevalent among at-risk individuals without objective signs of ischemic heart disease and is associated with adverse outcomes regardless of sex.[120]

- Women are still under-represented in clinical trials. This has several reasons:
 - lower awareness of cardiovascular disease risk in women and their doctors
 - lower willingness to participate is also based on distrust to medical researchers [25]
- Female participation can be enlarged by facilitation inclusion of elderly women. A more gender-sensitive approach for the work-up of chest pain is needed.[131]

Overlooking all studies, it became evident that the number of women included is still low in comparison to men, that sex and gender related questions are often not analysed in a prospective manner and in a state of the art randomized, double blind design, and therefore the studies are not suited for inclusion into guidelines.

2.1.4 Conclusions

In conclusion, important sex and gender differences have been found in all areas of coronary artery disease, but the studies do not offer a strong basis for inclusion of sex and gender in guidelines.

It is well known that women and men differ in the early onset and progression of atherosclerosis and myocardial ageing[77] Men develop the classical type of focal, obstructive coronary artery disease earlier in life compared to women, while the latter have a more diffuse pattern of coronary artery disease with relatively more microvascular coronary disease, plaque erosion, and thrombus formation.[30, 132] Sex and gender differences exist also in established and in novel risk factors.[3-7, 9-11, 13, 15-25, 133, 134] and in pathophysiology.[26-35] Accordingly, prevention strategies have a different weight in women and men.[36-42] Gender differences also exist in clinical manifestation, diagnosis and symptoms, in the sensitivity of laboratory and stress tests, and results from coronary angiography.[33, 43-50] However, most medical and interventional strategies have been developed for the male patient as the gold standard, which is less well suited for women in many ways.[33, 43, 51-56] This concerns dosages of medications, side effects,

interactions with other medications, size of devices, but also bleeding risks during percutaneous coronary intervention and morbidity and mortality after coronary artery bypass surgery etc. Evidence for optimal treatment options in coronary microvascular dysfunction is still scarce and in an exploratory phase. In summary, coverage of women specific or men specific risk factors, disease manifestations treatments and outcomes in the published literature is still insufficient and the quality of the studies is often limited by small numbers, retrospective and non-randomized design. Better studies with state of the art design for both sexes are needed as a basis for medical guidelines.

2.2. Sociodemographic and medical database analysis

2.2.1 Objectives

The aims for this second task in the first work package were to test

- a) whether large public sociodemographic and medical databases in the EU are suited for the analysis of sex and gender in coronary artery disease prevalence, outcomes, medical and socioeconomic risk factors,
- b) whether research databases from large cohort studies are suited for sex and gender analysis, and
- c) how was the awareness of holders of research databases on sex and gender related questions.

2.2.2 Methods

The following steps were taken to ensure the database analysis of work package 1 was completed:

- a) Assess sex specific coronary artery disease prevalence, incidence, mortality in public sociodemographic databases in different EU Member States.
- b) Correlate coronary artery disease prevalence, incidence and mortality with socio-demographic data and risk factors in the different Member States.
- c) Assess expert opinion on inclusion of sex and gender related outcomes, biomedical and sociocultural risk factors.

d) Survey coronary artery disease research database holders on awareness and inclusion of sex and gender related data

Selection of databases

We selected a number of sociodemographic and medical databases to collect coronary artery disease prevalence, incidence mortality, as well as classical risk factors (i.e. smoking, hypertension, hyperlipidaemia, obesity, diabetes, and alcohol use) based on whether the databases offered sex disaggregated data for a number of Member States, and how recent their results were (< 5 years). Based on these criteria, we identified the following as most indicative databases for our study and included them in our analysis:

Table 1: Databases analysed for coronary artery disease related sociodemographic and medical data and sex and gender related variables

Database	Type of database	Source	Database holder
European Cardiovascular Disease Statistics (2012)	Public sociodemographic and medical database	https://www.escardio.org/static_file/Escardio/Press-media/press-releases/2013/EU-cardiovascular-disease-statistics-2012.pdf	Nichols et al. (European Heart Network)
WHO European Health for all Database	Public sociodemographic and medical database	http://data.euro.who.int/hfad/	World Health Organization
Eurostat	Public sociodemographic and medical database	http://ec.europa.eu/eurostat/data/database	Eurostat
Tobacco consumption and gender socioeconomic differences in south Europe (2009)	Public sociodemographic and medical database	http://spoudai.unipi.gr/index.php/spoudai/article/view/1348	Nikolaou, K.
Tromsø heart study	Coronary artery disease research database	http://journals.sagepub.com/doi/abs/10.1177/1741826711421081	Maja-Lisa Lochen
Gutenberg heart study	Coronary artery disease research database	http://www.gutenberg-gesundheitsstudie.de/ghs/willkommen.html	Renate Schnabel
Monica/KORA	Coronary artery	https://www.helmholtz-	Renate Schnabel

	disease research database	muenchen.de/herzschlag-info/	
FADOI ATA AF (Atrial fibrillation)	Coronary artery disease research database	www.italjmed.org/index.php/ijm/article/view/649	Cecilia Politi
FADOI CoNFINE (Type 2 diabetes)	Coronary artery disease research database	http://www.sciencedirect.com/science/article/pii/S0167527311001847#!	Cecilia Politi
FADOI DIAMOND (Heart failure)	Coronary artery disease research database	https://link.springer.com/article/10.1007/s00592-014-0585-z	Cecilia Politi
Euroaspire III	Coronary artery disease research database	http://journals.sagepub.com/doi/abs/10.1097/hjr.0b013e3283294b1d	Christof Prugger
MONICA	Coronary artery disease research database	https://www.ncbi.nlm.nih.gov/pubmed/20471016	Renata Cifkova

Selected databases by type, source, and database holder

Next, we selected variables as indicators for outcomes and risk factors, based on their availability in as many databases as possible (table 2). Table 2 indicates whether these data are disaggregated for sex and if the data were collected in all 28 EU Member States.

Table 2: List of database variables related to coronary artery disease

<u>Variables</u>	<u>Data presentation</u>	<u>Sex disaggregated data</u>	<u>Available in all MS</u>
Mortality rate	Coronary artery disease mortality rate per 100,000 in 2012 or closest year (age under 65)	yes	yes
Ischemic heart disease discharges	Hospital discharge rate due to ischemic heart disease	no	yes
Stroke discharges	Hospital discharge rate due to stroke	no	yes
Income gap	Gender pay gap in unadjusted form 2013 (in %)	yes	yes
Smoking	Smoking prevalence in 2009 or closest year (in %)	yes	yes
Hypertension	Prevalence of hypertension in 2008 (in %)	yes	yes
Hyperlipidaemia	Hyperlipidaemia prevalence in 2008 (in %)	yes	yes

Obesity	Prevalence of obesity in 2010 or closest year (in %)	yes	no
Alcohol	Prevalence of lifetime abstainers in 2009 (in %)	yes	no
Diabetes	Diabetes prevalence in 2009 (in %)	no	yes

Based on availability of outcomes, we selected mortality and hospital discharges from stroke and ischemic heart disease as variables to represent the existing status quo of coronary artery disease in women and men. These variables were most frequently available and were collected from the European Cardiovascular Disease Statistics 2012 and originated from the WHO mortality database.

Coronary artery disease mortality in the databases was presented as cases per 100.000. It only included adults aged 65 and younger, and therefore excludes persons from an older age. Given the delayed incidence in women compared to men, this data does not represent the numbers in the female population appropriately.[2]

A representative parameter of coronary artery disease incidence could not be directly identified in the databases and therefore, the ischemic heart disease discharges was used as the closest possible proxy parameter that adhered to the two main variables. Stroke is also part of the “cardiovascular diseases” entity and is linked to coronary artery disease. We therefore included also stroke hospital discharge as an indicator for coronary artery disease.

Coronary artery disease prevalence, however, could not be found in any databases searched and neither could a proxy parameter, which is why it was left out altogether from the final set of variables.

For socioeconomic parameters, income gaps between women and men was selected to give better understanding to the gender dynamic of work forces and financial resources available to Europeans.[135] A number of publications have linked coronary artery disease manifestations to socioeconomic status. In

general, women in the EU earn 17% less per hour than men.[136] Large income gaps between women and men mean that pensions are lower and poverty risks are greater for women. The income gap is defined by the unadjusted gender pay gap that indicates the “difference in gross hourly earnings between male and female employees, as a percentage of average gross hourly earnings of male employees” and is collected via the Structure of Earnings Survey (Reg.: 530/1999).[136] We tested whether a very high gender pay gap would be associated with poverty of women and increased coronary artery disease rate because of this.

Risk factors were added to not only indicate the potential for individuals to suffer from coronary artery disease, but also to understand their lifestyle choices for themselves and their families. Smoking, hypertension, hyperlipidaemia, obesity, alcohol, and diabetes were selected as variables . All of these except alcohol and smoking were collected from the European Cardiovascular Disease Statistics 2012. More reliable data was found for lifetime abstainers than alcohol consumption, as it contained country complete data for all 28 EU Member States. The data for smoking was taken from Nikolaou’s (2009) “Tobacco consumption and gender socioeconomic differences in south Europe: evidence from panel data”, where it is defined as the proportion of adult smokers in the EU.

For the other risk factors (hypertension, hyperlipidaemia, obesity, and diabetes), their inclusions were collected in the European Cardiovascular Disease Statistics 2012. Hypertension and high blood cholesterol’s (hyperlipidaemia) data can be traced to the WHO global health observatory database, obesity’s data was collected from the IOTF Global Prevalence of Adult Obesity. The data of diabetes was collected from the WHO Europe, Health for All Database. Hyperlipidaemia was defined as the age-standardised estimate of prevalence of raised blood cholesterol (≥ 6.2 mmol/L).[2]

2.2.3 Results

- a) Assessment of sex and gender differences in coronary artery disease indicators in sociodemographic databases

We first aimed at analysing sex differences in coronary artery disease mortality and potentially related socioeconomic and biological outcomes and risk factors, in order to find out, if overarching sex and gender analysis including different regions and databases would yield scientifically sound results. We first compared CAD related variables in publically available sociodemographic databases from different countries and checked whether sex disaggregated data over a full age range were available.

We found high country specific differences in outcome variables. Latvia had the highest coronary artery disease mortality rate for both men and women aged 65 and under, as well as the largest difference between the rates of mortality for women and men. France had the closest men to women mortality rate, but it also had the lowest total mortality rate of all 28 EU Member States. (European Cardiovascular Disease Statistics 2012; WHO European Health for all Database (<http://data.euro.who.int/hfad/>), Interim Report 2, Attachment 2).

The discharges rates for ischemic heart disease and stroke showed similar trends as for coronary artery disease. Lithuania and Bulgaria had the highest rate of ischemic heart disease discharges and Cyprus and Spain the least. Hungary and Lithuania had the highest rate of stroke discharges and Cyprus and Malta the least. Sex disaggregated data on these variables were not available, which may be problematic as there tends to be a higher incidence of stroke amongst older women, which is not reflected in these combined data.[58]

The gender pay gap was the highest in Estonia and the lowest in Slovenia. Other countries with high gender pay gaps included Austria, Czech Republic, and Germany. It did however not correlate with coronary artery disease prevalence or outcomes.

Large country differences and sometimes sex differences were also found in risk factors such as smoking, hypertension, hyperlipidemia, obesity and alcohol consumption.

The analysis shows a large inhomogeneity between European regions in coronary artery disease mortality prevalence and outcomes, and its socioeconomic and biological risk factors. Analysis from the public databases is on one hand hampered by the fact, that the age dependency of the different variables cannot be assessed and the complete age range is not comprehensively covered in the statistics. For example, coronary artery disease mortality had a cut-off point at age 65.[2] However, the historically determined cut-off point of 65 years of age does not appear sensible anymore, given higher average life expectancies in Europe around 75 years.[135] Most of the DALYs (Disability-Adjusted Life Years) apply to these last 10 years of life and this should be considered in the databases. Even worse, for some important variables, sex disaggregated data are not available.

In summary we had to conclude that most databases have a limited sensitivity for analysing sex and gender differences, because they have a rather low cut-off point for age at inclusion, and variables were not always broken down to sex.

b) Correlation of coronary artery disease data with socio-demographic and risk factors

Even though we realised the limited power of the sociodemographic EU public databases to run a sex or gender specific analysis, we tried to identify sex and gender specific association of risk factors with outcomes. A gender-related correlation of the results from assessment in the previous section was therefore attempted. The data was correlated, based on a comparison of the mortality rate per 100,000 data and the percentages or rates of the risk factors and socioeconomic factors.

The review of the results shows that only a limited number of factors exhibit a strong correlation with coronary artery disease mortality. The main factor to show a strong correlation with coronary artery disease mortality (at least 0.7) is hypertension, which showed a positive relationship with coronary artery disease mortality in men, as well as in women. However, other risk factors did not show the expected correlation with outcomes and the results observed in our analysis were partially different from the results from large cohort studies

in several European countries (SCORE). Reasons may be that age dependency of risk factors or gradual expression of variables cannot be assessed in the public databases. In particular, the early cut-off of 65 leads to a loss of power and the data sources may not be as reliable as these from cohort studies. Therefore, we referred to other sources for these results in the project.

Furthermore, important sex specific variables (number of children, miscarriages, hormone therapy, andro- or menopause, etc.) are incompletely covered. True measures for gender has not been found in any database (2016).

In conclusion the expected associations between major risk factors, sex and surrogate markers for the disease prevalence and outcomes were surprisingly weak in the public EU sociodemographic databases, probably due to the limitations of the databases discussed below.

c) Investigate expert opinion on inclusion of sex and gender in coronary artery disease studies

We developed a questionnaire to obtain expert opinion on the inclusion of sex and gender related variables. Experts were contacted from a list of 56 identified stakeholders in the project. The questionnaire was prepared to be filled out anonymously and contained 32 statements about gender and coronary disease, including coronary artery disease risk factors, statement about coronary artery disease-related heart diseases, treatment, diagnosis, and prognosis. The responders were asked to identify how relevant each item was to healthcare professionals and the general population, based on a 5-point Likert-scale, ranging from not relevant to very relevant (see Table 3).

Table 3: Percentage of expert responses based on the relevance of coronary artery disease and gender statements for healthcare professionals (HCP) /general public (lay)

	Type	Very irrelevant	Irrelevant	Undecided	Relevant	Very relevant

1. In the last 15 years smoking is increasing in younger women in many European member states compared to other population groups	HCP	0,0%	6,3%	6,3%	25,0%	62,5%
2. In the last 15 years smoking is increasing in younger women in many European member states compared to other population groups	Lay	0,0%	0,0%	6,3%	25,0%	68,8%
3. Systolic blood pressure rises more steeply in ageing (+60yrs) women compared with men of the same age.	HCP	0,0%	0,0%	5,9%	52,9%	41,2%
4. Systolic blood pressure rises more steeply in ageing (+60yrs) women compared with men of the same age.	Lay	0,0%	17,6%	17,6%	29,4%	35,3%
5. Hypertension results in a higher prevalence of strokes, left ventricular hypertrophy, and diastolic heart failure in women than in men.	HCP	0,0%	0,0%	5,9%	35,3%	58,8%
6. Hypertension results in a higher prevalence of strokes, left ventricular hypertrophy, and diastolic heart failure in women than in men.	Lay	0,0%	11,8%	5,9%	47,1%	35,3%
7. Diabetes worsens coronary artery disease outcome more in women than in men.	HCP	0,0%	0,0%	0,0%	47,1%	52,9%
8. Diabetes worsens coronary artery disease outcome more in women than in men.	Lay	0,0%	11,8%	11,8%	35,3%	41,2%
9. Depression and various forms of sustained mental stress are risk factors for coronary artery disease that occur more frequently in women	HCP	0,0%	11,8%	5,9%	47,1%	35,3%
10. Depression and various forms of sustained mental stress are risk factors for coronary artery disease that occur more frequently in women	Lay	0,0%	5,9%	47,1%	35,3%	11,8%
11. Symptoms of myocardial infarction (MI) and ischemic heart disease may differ in women and men.	HCP	0,0%	5,9%	0,0%	17,6%	76,5%
12. Symptoms of myocardial infarction (MI) and ischemic heart disease may differ in women and men.	Lay	0,0%	11,8%	0,0%	17,6%	70,6%
13. Ischemic heart disease develops on average 7-10 years later in women compared to men.	HCP	0,0%	0,0%	29,4%	35,3%	35,3%
14. Ischemic heart disease develops on average 7-10 years later in women compared to men.	Lay	0,0%	5,9%	29,4%	47,1%	17,6%
15. Tako-tsubo syndrome and acute coronary dissection are underestimated causes of acute coronary syndrome in women.	HCP	5,9%	5,9%	17,6%	35,3%	35,3%
16. Tako-tsubo syndrome and acute coronary dissection are underestimated causes of acute coronary syndrome in women.	Lay	17,6%	17,6%	35,3%	17,6%	11,8%
17. Sudden cardiac death occurs mainly in men.	HCP	0,0%	0,0%	11,8%	47,1%	41,2%
18. Sudden cardiac death occurs mainly in men.	Lay	11,8%	5,9%	11,8%	47,1%	23,5%
19. Erectile dysfunction can represent an early symptom of cardiovascular disease in men and should be investigated during history taking.	HCP	0,0%	0,0%	11,8%	35,3%	52,9%
20. Erectile dysfunction can represent an early symptom of cardiovascular disease in men and should be investigated during history taking.	Lay	0,0%	0,0%	23,5%	41,2%	35,3%
21. The current ESC guidelines advise stress-imaging techniques as first test of choice in intermediate or low risk women.	HCP	0,0%	6,3%	18,8%	43,8%	31,3%
22. The current ESC guidelines advise stress-imaging techniques as first test of choice in intermediate or low risk women.	Lay	25,0%	25,0%	12,5%	31,3%	6,3%
23. The number of acute coronary syndromes occurs 3-4 times more often in men than women in ages below 60.	HCP	0,0%	0,0%	23,5%	47,1%	29,4%
24. The number of acute coronary syndromes occurs 3-4 times more often in men than women in ages below 60.	Lay	0,0%	11,8%	29,4%	47,1%	11,8%
25. In many European countries, women with acute coronary syndromes have longer delays before hospital admission and treatment.	HCP	0,0%	5,9%	5,9%	23,5%	64,7%
26. In many European countries, women with acute coronary syndromes have longer delays before hospital admission and	Lay	0,0%	11,8%	23,5%	17,6%	47,1%

treatment.						
27. In many European countries, female patients with MI still have longer "door-to-needle" times than male patients when obtaining percutaneous coronary intervention.	HCP	0,0%	0,0%	17,6%	23,5%	58,8%
28. In many European countries, female patients with MI still have longer "door-to-needle" times than male patients when obtaining percutaneous coronary intervention.	Lay	5,9%	17,6%	23,5%	29,4%	23,5%
29. In some European countries, women at discharge after acute coronary syndrome receive less medical treatment, life style recommendations and secondary prevention measures according to European Society for Cardiology guidelines than men.	HCP	11,8%	5,9%	5,9%	11,8%	64,7%
30. In some European countries, women at discharge after acute coronary syndrome receive less medical treatment, life style recommendations and secondary prevention measures according to European Society for Cardiology guidelines than men.	Lay	5,9%	17,6%	23,5%	0,0%	52,9%
31. Coronary angiography is of limited value to establish ischemic heart disease in middle-aged women at intermediate/low risk.	HCP	5,9%	0,0%	29,4%	29,4%	35,3%
32. Coronary angiography is of limited value to establish ischemic heart disease in middle-aged women at intermediate/low risk.	Lay	23,5%	5,9%	29,4%	29,4%	11,8%

Rated from 1 to 10, where 1 is very irrelevant and 10 is very relevant

Experts attributed the greatest relevance to the increase in smoking in younger women, compared to other population groups. They further attributed great relevance to greater hypertension effects in women than in men and to the longer delay of treatment of acute coronary syndrome in European countries for women. In addition, the strongest relevance was the difference in symptoms of myocardial infarction and ischemic heart disease between men and women. However, the least relevant statement overall was the relevance of ESC guidelines on stress-imaging techniques.

These responses have since helped guide the factsheets of WP 3 and WP 1, Task 3 and the awareness questionnaires for WP 2 as to which facts could be influential in improving the understanding of gender in coronary artery disease across Europe.

- d) Analyse databases for sex and gender specific biological and sociocultural risk factors

The analysis began by contacting major coronary artery disease database holders in representative EU Member States, with the following studies submitting answered questionnaires: the Tromsø Heart Study, the Gutenberg

Health Study, the WHO Monica Project, the Euroaspire III Survey, the FADOI ATA AF, the FADOI Confine Study, and the FADOI Diamond Study. A questionnaire was sent to database holders in 2015 and 2016.

We first asked about inclusion of sex and gender related variables into their databases (Table 4). We used the literature search in from the bibliographic review to identify potentially sex specific risk factors and identified as such:

- Age of menarche
- Age of menopause
- Oral contraceptive use
- Other forms of hormone therapy including androgen use
- Data on childbirth and abortion
- Pregnancy history
- Pregnancy complications
- Indicators of polycystic ovary syndrome (pcos)
- Measurements of sexual hormone status
- Depression
- Specific forms of stress (job, private, etc.)
- Exercise
- Nutrition
- Exposure to environmental toxins
- Information on autoimmune diseases
- Inflammatory diseases

Table 4: Representation of sex and gender related variables in databases from European cohort studies.

	Gutenberg	Monica/ KORA	Tromso	FADOI – ATA AF	FADOI – DIAMOND	FADOI – CONFINE	Euroaspire III	MONICA
Anthropometric data (out of 3 in total)	3	3	3	2	2	2	3	3
Classical risk factors (out of 5 in total)	5	5	5	4	4	4	5	5
Socioeconomic factors (out of 3 in total)	3	3	2	0	0	0	2	2
Cardiovascular outcomes (out of 4 in total)	3	3	3	4	4	4	3	4
Sex and gender related variables (out of 6 in total)	2	2	4	2	2	2	N/A	N/A

Numbers indicate how many of the gender-sensitive variables in total were represented in each database

We next asked about the interest of database holders to study effects of sex and gender (Table 5).

Table 5: Relevance of sex and gender-related coronary artery disease statements and database holders' interest in such studies

	Gutenberg	Monica/ KORA	Tromso	FADOI – ATA AF	FADOI – DIAMOND	FADOI – CONFINE	Euroaspire III	MONICA
Interest in gender analysis?	X	X		X	X	X		X
Publication to target sex/gender issues?	X	X	X	X	X	X	X	X
Willingness to answer more questions?	X	X	X	X	X	X	X	X

X denotes a “yes” to the question, whereas blank answers are unanswered questions.

We found that a number of sex and gender specific indicators are included in major databases, but by far not enough to analyse the effect of sex and gender on CAD in a coherent manner.

2.2.4 Conclusions

A number of sex and gender specific variables are included in the public databases as well as in major coronary artery disease research databases , but by far not enough to analyse the effect of sex and gender on coronary artery disease in a coherent manner.

There is a need for more recent sex and gender disaggregated-data, for the inclusion of additional sex and gender related variables as well as increased age cut-offs to obtain a clearer picture of coronary artery disease in women and men across Europe.

Experts are only partially aware on the relevance of sex and gender and do not have the resources to include them in all studies. Therefore, awareness and funding for sex and gender inclusion into studies and databases must be improved.

2.3. EU Member State policy analysis

2.3.1 Objectives

The main aim of this WP was assessing member state policies in respect to sex and gender in health and more specifically in coronary artery disease prevention and management.

2.3.2 Methods

We planned to obtain an overview on European gender and health policies in the field of coronary artery disease prevention and management by contacting the governmental health care departments, national medical and public health societies, non-governmental organisations and societies in the field of gender medicine. The following activities were used:

- a) Identification of key informants
- b) Contacting key informants with details of the study and request for information
- c) To develop a database to collect retrieved documentation
- d) To develop and to pilot questionnaires to collect retrieved documentation
- e) Retrieval of cardiovascular policy
- f) Retrieval of national guidelines on cardiovascular prevention
- g) Retrieval of national guidelines on cardiovascular prognostic services
- h) Retrieval of national guidelines on cardiovascular treatment interventions
- i) Discussion of retrieved information at EUPHA symposium at Oct. 14th Milan
- j) Content analysis of retrieved documentation
- k) Qualitative analysis of retrieved documentation

- l) Policy environment analysis i.e. existing gender equality legislation / guidance
- m) Write up of findings
- n) Revision of documents

To determine the current policy climate for the recognition and the action on gender aspects in coronary heart disease, a gendered analysis of potential gender/coronary artery disease policies, guidelines and action plans from official entities within the 28 Member States was undertaken. This explored the policy process environment as well as policy content as we sought to determine the willingness of the EU Member States to embrace a more gender-equitable stance on cardiovascular risk and its management. Key contacts in all EU Member States were used to ensure we had a comprehensive view of the current cardiovascular treatment, prevention and rehabilitation environment.

The ongoing analysis of the data during the research period also included a round of 'data checking' by national experts on the data collected and an additional desk-based search of each Member State by the research team.

The raw data as provided by country experts and the desk searches were analysed using content analysis and an adapted Critical Frame Analysis approach.[137] The analysis explored the policy environment as well as the specific policies and guidelines that may influence gender and coronary artery disease within each Member State. The analysis comprises three levels:

- Meta frame – Equality / sex-discrimination policy.
- Issue frame – Sex and gender policy / guidelines focused on health (including coronary artery disease).
- Document frame – coronary artery disease policy / guidelines etc.

Detailed description of activities:

- a) Identification of key informants

Within EU Member States, policy documents needed were sourced from different layers of health care provision including:

- Ministries of Health
- General public health experts via EUPHA
- Specialists in Cardiovascular medicine via EACPR
- Specialists in Gender and Gender Medicine via personal contacts
- Other key organisations including:
 - National cardiology societies
 - National prevention societies
 - National public health societies
 - Active researchers
 - National doctors and nurses associations

Overall, **383 individuals/organisations** were initially identified and contacted.

b) Contacting key informants with details of the study and request for information

Letters were prepared for each different group of respondents. These were sent out from July 2015 onwards to our EACPR and EUPHA national contacts and to the contacts mentioned above to give general information on the project and invite them for participation. Incentives to participate were made – for those able to participate and provide substantial information an offer of support was made for conference fees and travel to either the main EUPHA conference in Milan or the EACPR conference in Istanbul. Following discussions with the EUPHA and EACPR representatives on the GenCAD collaboration a further letter was sent out in October from their main offices, signed by a leading figure within the two organisations. During November 2015, additional appeals for information were made to personal contacts within each country, drawing on existing gender networks.

c) To develop a database to collect retrieved documentation

The database was developed during earlier phases of the project. Detail of the process used to gather data from key informants was described in the second interim report:

- A two-stage survey was created to illicit information from organisations and individuals on general health policy and cardiovascular disease specific policy
- Knowledge of and expertise within specialist on-line survey software (SNAP Surveys) were developed which enabled the survey to be completed online. This allowed for an adaptable approach that could be utilised for other health conditions – this survey tool allows for monitoring of individual respondents to show where they are in the process of completion of the survey and sent reminders (one week and two weeks after the initial invitation) and a note of thanks on completion
- The survey software created an excel database of responses

To manage the letters and questionnaires being sent out to contacts and the return of completed questionnaires an excel database was established at Leeds Beckett University. This information was shared with project staff at the Charité Universitätsmedizin Berlin.

d) To develop and to pilot questionnaires to collect retrieved documentation

Two key questions needed to be addressed within the analysis:

- Is gender considered in the national policies concerning coronary heart disease and its prevention
- Is gender the starting point for policy development for coronary heart disease?

We structured the planned questionnaire in two levels. Level 1 included 4-5 questions about identifying national gender policies and national coronary artery disease policies and who to contact to help identify such policies. Level 2 was a more detailed questionnaire about specific aspects of the inclusion of sex and gender into these national policies. Both the level 1 and level 2

questionnaires were drafted and piloted, with the approval of DG Health and Food Safety.

Two versions of the level 1 and level 2 questionnaires were created; one for national organisations and coordinators for EACPR and EUPHA and other experts within each Member State and one for other relevant organisations that have a role in coronary artery disease. Online versions of these questionnaires were developed using Snap Survey software and hosted online using Leeds Beckett University’s Snap Survey webhost system (<https://surveys.leedsbeckett.ac.uk/snapwebhost/>).

Our research team undertook the analysis of responses in those countries where we had language competence. Students with foreign language skills were used to assist with the analysis of policy content where documents are not available in English or any language known to the GenCAD research team.

A breakdown of the contacts and responses is shown in tables 6 and 7 below.

Table 6: EU policy response by type of contact

Type of contact	Contacted	Engaged		
		Total Engaged	Completed level 1 only	Completed both
EACPR national coordinators	31	10	5	5
EUPHA national representatives	33	5	1	4
Active researchers/general experts/named in application	57	11	6	5

Cardiology including: cardiac institute/hospital; national medical cardiology societies; out of hospital cardiologist associations; paediatric cardiology society	41	1	1	0
Ministries: Ministries of health, governmental health care departments; Ministries of research, departments responsible for research on life sciences	79	6	4	2
Other: other health care professionals; national doctors associations; other health care professional organisations; family/community medicine society	80	1	1	0
National prevention societies	33	1	1	0
National public health societies	4	0	0	0
Gender network contacts	25	18	18	0
Total	383	53	37	16

Table 7: EU policy response by country

Country	Completed Level 1 only	Completed both surveys	Other
Austria	y		
Belgium			
Bulgaria	y		
Croatia		y	
Cyprus			Informed us they adopt the ESC guidelines
Czech Republic	y		
Denmark			
Estonia	y		

Finland			
France			
Germany		y	
Greece		y	
Hungary			
Ireland	y		
Italy		y	
Latvia		y	
Lithuania			
Luxembourg			
Malta			
Netherlands		y	
Poland		y	
Portugal			
Romania		y	
Slovakia			
Slovenia	y		
Spain		y	
Sweden	y		
United Kingdom			

e) Retrieval of cardiovascular policy

The process by which the country specific documents were obtained was outlined in the second interim report.

First strategy: survey

Altogether, completed surveys were obtained from 17 countries (Austria, Belgium, Bulgaria, Croatia, Czech Republic, Estonia, Germany, Greece, Ireland, Italy, Latvia, Netherlands, Poland, Portugal, Romania, Slovenia, Spain, Sweden). There was a significant lack of engagement from the Ministries of Health, where 79 individual requests were sent out, with only 6 (Austria, Estonia, Germany, Greece, Ireland, and Sweden) responding and just 2 (Germany, Sweden) completing the second level questionnaire. The contact to the Ministries involved an initial request to complete the survey sent out to the contact addresses provided at the homepages of the Ministries, with a follow-up email for those who did not respond and often an additional request.

Second search strategy: desk based search

In our second interim report, we also noted it was difficult to determine whether some nil responses from country representatives were a result of an absence of relevant policies or a lack of awareness in the respondent of existing policies.

This prompted the research team to move towards a detailed and extensive desk based search for policies within each EU Member States. For this process, online searches were conducted using the search words listed below (including their plural forms) translated into the national language using Google translate and/or supported by native speakers.

- Gender
- Sex
- Man/Woman
- Boy/Girl
- Male/Female
- Heart Disease
- Coronary
- Cardiovascular

Where search terms were located within foreign language documents, paragraphs of text were translated into English using Google translate. This phase of the search was found to be very fruitful, as it identified relevant material that had not previously been identified by the country experts.

An additional attempt to identify appropriate documents was through the contact with known gender specialists within each of the countries. This produced no new cardiovascular policies or guidelines, but did assist in the Issue frame analysis.

Data checking procedure

Finally, key informants and authors of the cardiovascular disease prevention reports published in the country of the month series of the European Heart

Journal were sent an overview of the gender and cardiovascular policies already located through previous data collection procedures.

This 'data checking' procedure was developed to verify completeness and accuracy of information used in the analysis. Following approval of our finds from those country representatives that responded additional searches continued, with more documents and policies being found and integrated into the analysis and country profiles.

Limitation

At the end of the process of data collection a large number of documents from all countries were obtained and searched. Nevertheless, it is recognised that this approach focuses on documents that are found online and it is not possible to be sure all policies and guidelines have been included in our study.

2.3.3 Results

Altogether, **273 policies and guidelines were identified across the 28 EU Member States** that made specific reference to sex and gender, either as part of their national gender equality legislation or in relation to cardiovascular disease (see Table 8). Overall, the analysis demonstrated a great variance in the importance sex/gender differences in policies and guidelines relating to coronary artery disease. In Appendix 3/ [Attachment 3/2016](#) there is an overview of the detailed findings for each country, broken down by the Meta frame, Issue frame and Document frame.

At the European level there are key organisations that have created cardiovascular guidelines that have been adopted by the majority of the EU Member States. The European Society of Cardiology (ESC) is preeminent in this role, and the majority of countries have endorsed those guidelines that most meet their needs (see Table 9). Other key sources of guidelines were the American Heart Association and the UK's National Institute for Health and Care Excellence guidelines. These sources recognise at least some sex and gender specific aspects in cardiovascular disease, most pronounced in the field of including sex specific risk calculators and prevention. However, altogether, sex

and gender differences in cardiovascular disease as they are described in recent publications [138] may be incompletely covered by these guidelines.

Table 8: Member State policies and guidelines

	Endorsed ESC guidelines per country	Meta frame: Gender legislation	Issue frame: Gender in health and coronary artery disease	Document frame: coronary artery disease policies/ guidelines that included reference to sex/gender
Austria	19	2	8	3
Belgium	24	7	0	3
Bulgaria	29	2	4	0
Croatia	27	4	1	3
Cyprus	1	2	0	0
Czech Republic	24	3	1	0
Denmark	18	3	4	8
Estonia	26	5	0	2
Finland	22	6	1	1
France	20	4	4	4
Germany	25	4	3	7
Greece	22	6	1	2
Hungary	24	2	3	1
Ireland	2	4	7	2
Italy	24	5	12	3
Latvia	26	7	1	4
Lithuania	28	3	0	3
Luxembourg	22	3	1	1
Malta	7	4	5	2
Netherlands	18	1	4	7
Poland	30	5	3	2
Portugal	30	5	2	2
Romania	22	2	1	1
Slovakia	28	6	0	0
Slovenia	8	6	0	1
Spain	32	4	4	3
Sweden	8	4	4	0
United Kingdom	14	9	4	12
		118	78	77

For the purpose of the analysis only country specific policies and guidelines were included as the focus of the study was on the EU Member States and not European wide legislation / guidelines. The website of the ESC (<http://www.escardio.org>) lists which of its guidelines have been adopted by each country and has been recorded in Table 9. – this detail is not available for the other internationally recognized guidelines.

f) Content analysis of retrieved documentation

Once the policy documents had been identified and classified each was the subject of a detailed content analysis. Fracturing of the policies into smaller segments enabled a deeper conceptual analysis on how sex/gender issues were integrated into cardiovascular disease policies within the following theoretical framework (see Table 9):

- Prevention of cardiovascular disease
- Acute care of cardiovascular events
- Disease management and health care
- Quality of life
- Evaluation of health programmes
- Implementation of health programmes
- Health policy actions

Table 9: Availability of health policy documents/guidelines with regard to gender/sex and cardiovascular disease according to country

	Prevention	Acute care	Disease management and health care	Quality of life	Evaluation of health programmes	Implementation of health programmes	Health policy actions
Austria	X, X, X, X	X, X	X, X	X, X, X			X, X, X
Belgium	X, X	X, X, X	X, X				X, X, X
Bulgaria	X, X, X						
Croatia	X, X	X, X, X					
Cyprus							

Czech Republic							
Denmark	X, X, X, X	X, X, X	X, X, X, X	X, X, X	X, X		
Estonia	X, X, X						X, X
Finland	X, X, X						
France	X, X, X, X	X, X, X, X	X			X, X	
Germany	X, X, X, X	X, X	X, X	X			
Greece	X, X, X	X					X, X
Hungary		X					
Ireland	X, X, X		X, X	X, X	X	X	
Italy	X, X, X	X	X		X, X		
Latvia	X, X	X, X, X	X	X			X, X
Lithuania	X, X, X	X, X					
Luxembourg	X, X, X						
Malta	X, X, X						
Netherlands	X, X, X, X	X, X		X, X			X, X, X, X
Poland	X		X, X				
Portugal	X, X, X			X			
Romania	X, X		X, X				
Slovakia							
Slovenia	X, X	X, X					
Spain	X, X, X, X	X, X				X, X	X, X, X
Sweden							X
United Kingdom	X, X, X, X	X, X			X, X, X	X, X	X, X

X – denotes inclusion within any policy document or guideline of a sex/gender component. Colour coding: Sex, gender, female / woman / women, male / man / men

g) Qualitative analysis of retrieved documentation

A critical frame analysis approach was utilised to further analyse the text identified through the content analysis. This approach is based around three main areas: the Meta frame, the Issue frame and the Document frame. The Meta frame relates to the policy environment within the country and allows for examination of how important gender, and gender equality, is within the Member State generally. The Issue frame relates to how well the 'issue' of sex/gender and gender equality with regard to cardiovascular disease is promoted within the country. The Document frame focuses directly on the policies that relate specifically to cardiovascular disease to identify the practical aspects of how sex and gender are recognised and acted upon. This has been utilised in other gender policy analyses, including the Quality in Gender+ Equality Policies' project. [137, 139] This approach allows a

gendered lens to be used to analyse not only the policy and national guideline content, but also the policy environment. By identifying a Member State's legal and constitutional perspective on sex discrimination and gender equality it allows a deeper insight into the possibility of a more gender sensitive cardiovascular disease prevention, diagnosis and management. Each countries profile can be found in Attachment 3/2016, with references to all the documents referred to in section h, below.

h) Policy environment analysis i.e. existing gender equality legislation / guidance

Meta frame

The policy environment analysis (the Meta frame) sought to determine the willingness of the EU Member States to embrace a more gender equitable stance on cardiovascular risk and its management through the broader analysis of the position of gender equality generally within their respective countries.

The analysis identified two key aspects of legislation: the EU Member States fundamental constitutional rights of the citizens with regard to gender equality; and any specific gender equality or anti-discrimination legislation. These were then analysed to explore if this covered health as well as issues such as reproductive rights, employment rights and other forms of potential discrimination.

Constitutional rights

The member states, apart from the UK, have formal constitutions where they lay out the fundamental rights and freedoms of the population. In the UK there is an 'unwritten constitution' which is formed through the legislature. Analysis of the constitutions demonstrated that they all state that everyone is equal before the law and no one shall be discriminated against on the basis of their sex. An example of this is "The Fundamental Law of Hungary", which states in Article XV that all are equal before the law, and guarantees the fundamental rights to everyone without discrimination, which includes sex.

Through the constitutions many countries have established ministerial / government bodies to support the equality agenda. Sweden has a Special Minister for Gender Equality, in Belgium "A Council of Equal Opportunities for Men and Women", In Slovenia their "Advocate of the Principle of Equality" leads the Office for Equal Opportunities and Estonia has a "Gender Equality and Equal Treatment Commissioner". In some countries, there is a specific focus on women and children, for instance Cyprus has established "The Ministerial National Machinery for Women's Rights (NMWR)" and France has "The Ministry for Families, Children and Women's Rights" and Spain has an "Observatory for Women and Health" within their Ministry of Health.

Equality and anti-discrimination legislation

As a pre-requisite for becoming a Member of the European Union all countries need to show they abide by the EU acquis [140]acquis is focused onto social policy and employment and includes minimum standards in the areas of labour law, equality, health and safety at work and anti-discrimination.

In some countries there is well developed equality legislation and anti-discrimination legislation. Some of the newer members of the European Union are still in the process of developing their equality legislation. Bulgaria has a National Strategy for Promotion of Gender Equality and a Protection against Discrimination Act, but it does not yet have specific gender equality legislation. Poland's Plenipotentiary for Equal Treatment is focused onto the employment rights for women and women's reproductive rights, but not to health. Other countries have recognised health within their general equality legislation, for instance Slovenia's "Law for Equality of Opportunity among Men and Women" prohibits any form of discrimination based on sex in terms of access for women and men at all levels of health care and illness prevention programmes and health promotion.

In addition to formal legislation, the countries of the EU have signed up to key international drivers for gender equality, including "The Convention on the

Elimination of All Forms of Discrimination Against Women”, the UN “Convention on civil and political rights”, and the “UN Convention on economic, social and cultural rights and the European Convention on Human Rights”.

Issue frame

For the Issue frame analysis the review was broadened to include any policy statements that related specifically to sex or gender in relation to health or cardiovascular disease. This included documents from key health charities or other health organisations that were specifically calling for sex or gender to be considered as a key factor in health decision making.

The Issue frame analysis demonstrated that there was a strong push within some of the Member States for the recognition of gender as an important factor in both health generally and cardiovascular disease specifically.

Some countries have extensive coverage of the risks women face with regard to their cardiovascular health, such as the ‘The Polish Women 50+ Report. Health and its threats’; Medical societies, such as the Italian Society for Cardiovascular Prevention which published a handbook on prevention of myocardial infarction in women; and key non-government organisations, such as the British Heart Foundation’s Women Room. There was less information relating to the needs of men and coronary artery disease, with the most notable exceptions being the Danish Men’s Health Report, the Irish Men’s Health Policy and the Men’s Health reports conducted by the Robert Koch Institute and the German Men’s Health Foundation.

There were 6 countries where there were no apparent policy statements relating to gender and health or coronary artery disease (Belgium, Croatia, Cyprus, Estonia, Lithuania and Slovenia). Some had policies relating to gender and health, but without reference specifically to coronary artery disease (Czech Republic, Portugal, Romania, Slovakia).

Document Frame

The policy guidelines and policies that help develop services directed specifically at sex and gender and cardiovascular disease are the focus of the Document frame analysis. Within each country report ([Attachment 3/2016](#)) we have stated 'none apparent' for each of the areas where no data could be found. For other countries, there was an extensive array of sex/gender policies and guidelines, with Denmark, Germany, the Netherlands and the UK standing out as having the most comprehensive coverage (see Table 9).

It is worth noting that in Sweden there was an absence of gender within their cardiovascular policies and guidelines, which for such a gender equal society seemed unusual – however the explanation from the country expert was that equality is so ingrained that it was not necessary to explicate it within each document. Whether this meant that the condition specific insight into the sex/gender differences that emanated from some countries guidelines was missed, is not possible to know.

The retrieved policies and guidelines were subjected to a content analysis to determine how sex and gender were reflected under the following headings (see Table 9):

- Prevention of coronary artery disease
- Acute care of cardiovascular events
- Disease management and health care
- Quality of life
- Evaluation of health programmes
- Implementation of health programmes
- Health policy actions

Prevention of cardiovascular disease

This category has been broken down into 6 themes: risk, biological risk factors, lifestyle risk factors, age, preventative medication and screening.

Risk

The majority of countries noted within their cardiovascular policy documents that the risk of cardiovascular disease differed by sex, however there were 6 countries that did not have any policy related statements that outlined the risk of cardiovascular disease by sex.

Italy noted the increased risk of sudden death in women and the need for gender sensitive family history taking. The National Strategy for the Prevention of Cardiovascular Disease in Estonia reported that in 2002 more women than men had a first occurrence of cardiovascular disease, which they attributed in part to the availability of diagnostic facilities. Cardiovascular disease was reported as being the leading cause of death for women in Croatia and Poland, with the UK reporting that women's death rates for cardiovascular disease were not falling as fast as they are for men.

Biological risk factors

The biological risk factors that contributed for the sex difference in cardiovascular disease were recognised in policy documents, with Austria, Belgium, Denmark, Malta, Spain, UK, identifying sex differences in diabetes. Hypertension was noted as a risk factor in Belgium, Bulgaria, Estonia, Luxembourg, Malta, Spain, and the UK. There were 7 (Belgium, Denmark, Hungary, Italy, Malta, Netherlands, UK) countries which report the sex differences with regard to cholesterol.

The impact of the menopause on women's increased risk of cardiovascular disease was noted by France, Germany, Latvia, Malta, Netherlands, Poland and the UK. The increased cardiovascular risk posed by pregnancy was reported by France, Italy, Netherlands, and the UK.

Lifestyle factors

The gendered nature of lifestyle on sex differences in cardiovascular disease were noted by many of the countries including: smoking (Denmark, Germany, Ireland, Italy, Latvia, Lithuania Luxembourg, Malta, Netherlands, Poland, Slovenia, Spain, UK), alcohol (Bulgaria, Denmark, Hungary, Ireland, Italy, Latvia, Malta, Netherlands, Poland, Slovenia, Spain, UK), overweight/obesity

(Ireland, Greece, Ireland, Hungary, Lithuania, Luxembourg, Malta, Slovenia, Spain, UK) and low physical activity (Denmark, Germany, Ireland, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, UK). Low physical activity was predominantly seen as an issue for women, but many countries also noted that men were also not reaching recommended levels. High alcohol was seen to be a particular risk for females in Spain, but generally it was seen as a male problem. Overweight and obesity were seen to be damaging to both males and females, but the differences in prevalence were noted to be higher in males.

Age

The higher incidence, prevalence and mortality of cardiovascular disease in younger men and older women was noted in 9 of the countries (Croatia, Estonia, Italy, Latvia, Lithuania, Malta, Netherlands, Slovenia, UK) in their policy documents.

Preventative medication

Aspirin as a preventative measure for men, but not for women was noted in Austria, Denmark, Germany and the United Kingdom.

Sex differences in the prescription of statins to lower lipid levels were reported by 5 (Denmark, Germany, Italy, Latvia, Netherlands) of the Member States, with Italy also noting that the differences in body composition between males and females affected the efficacy of lipid lowering drugs

Screening

The French Federation of Cardiology published an information booklet focused on women and heart disease, which called for improved screening and support in women, especially during pregnancy and following the menopause. Latvia calls for cardiovascular disease screening of high risk groups, which included younger men and older women.

The UK has a national screening programme for cardiovascular disease, which differentiates the risk by sex. Many other countries have adopted the ESC risk

assessment tool or have made adaptations for their own country, such as the Finnish FINRISK calculator or the Greek Heart Score Greece, which recognise sex differences in risk.

Belgium's 'Early detection of cardiovascular risk factors and diabetes' report recognises that women were more likely to have their blood pressure, cholesterol and blood sugar measured as compared to men. This was also noted in Luxembourg's 'Observatoire de la santé de la province de Luxembourg'.

The UK and Spain were amongst 10 countries that highlighted that there may be an awareness issue for women and that greater effort should be made to educate the general public about the warning signs of coronary artery disease. The need for men to also be informed more clearly about their cardio-vascular risks was made in the Irish Men's Health Policy.

Acute care of cardiovascular events

There were 15 EU Member States that had developed their own statements on the implication of sex on the acute care of cardiovascular events (see Table 9). These were mostly focused onto the recognition that female signs and symptoms of coronary artery disease and infarction differed from those seen in males and the need for improved diagnosis and treatment for females.

The sex differences in presentation of acute coronary events were highlighted in policy documents in Austria, Denmark, France, Germany, Hungary, Spain and the UK. Females were more likely to present with non-classical signs and symptoms that were often mistaken for other conditions. Specific signs and symptoms reported were women being at greater risk of a clinically silent infarction (Austria), and presenting with nausea and vomiting (Germany, Spain), shortness of breath (Netherlands, Spain) and fatigue (Netherlands). That the ECG and stress tests may be less sensitive and underestimate risk in females were seen as an issue within the Italian guidelines.

Greece noted that women were more likely to be admitted with a second heart attack, with the first one having been missed. Latvia proposed that the identification of angina should take the sex of the patient into account.

Disease management and health care

Of the 28 Member States, 10 made some comment on the sex/gender differences in disease management and health care (see Table 6). There were three main subthemes in this category: Drug treatment and reperfusion, psychological support, and lifestyle interventions.

Drug treatment and reperfusion

The Austrian Ministry of Health guidelines on cardiovascular health state that there may be sex differences in the efficacy of drug treatments and side effects due to physical and physiological reasons. There were conflicting messages about medicine usage, with Belgium reporting greater prescription rates for males, and Denmark that more were used by females. The German Society for Prevention and Rehabilitation reported that females have higher plasma levels of beta-blocker Metoprolol under treatment, and suffered twice as often from the principle side effect of ACE-inhibitors.

Women's poorer adherence to treatment regimens were noted in Austria, Germany and Portugal.

The avoidance of hormone replacement therapy for the purpose of cardio-protection in females was specifically mentioned in the German and Dutch guidelines.

Psychological support

Three of the countries (Austria, Germany and Portugal) had made note of the gender differences in psychological support following coronary artery disease. The Austrian Medical Association report that women were more likely to be

prescribed sedatives and anxiolytics following their cardiac event. In Germany it was proposed that women do better if offered psychotherapy, but that psychoeducational interventions are mainly offered to men. Portugal considered the increased susceptibility of women to psychiatric problems as a reason for their poor compliance to treatment.

Lifestyle interventions

The German Society for Prevention and Rehabilitation commented that increasing women's levels of physical activity for secondary prevention was important, with Romania stipulating that controlling alcohol intake was necessary for both men and women.

Quality of life

There were 7 countries (Austria, Denmark, Germany, Ireland, Latvia, the Netherlands and Portugal) where there could be found specific reference to gender and quality of life with regard to coronary artery disease (see Table 9).

For disability free years of life, both Ireland and the Netherlands noted women fared worse than men following coronary artery disease, but this may be due to women tending to be older, with more pre-existing comorbidities than men.

The negative consequences of anxiety and depression on quality of life were made in the Danish National clinical guideline for cardiac rehabilitation and by the German Society of Cardiology, with women being found to have more negative consequences. Men were found to have better outcomes if offered psychological support. The German Society for Prevention and Rehabilitation also noted that women had poorer quality of life if they were physically inactive as a result of their coronary artery disease.

Evaluation of health programmes

There were 6 countries (Denmark, France, Germany, Ireland, Italy and the UK) that made reference to issues of gender within their evaluations of health programmes relating to coronary artery disease, (see Table 9) with the

majority focused onto the gender split in the uptake of cardiac rehabilitation programmes or the effectiveness of programmes aiming to reduce risk factors.

Accessing cardiac rehabilitation

The 'Reabilitação Cardíaca: Realidade Nacional e Recomendações Clínicas' in Portugal warned that women were twice as likely as men to abandon their cardiac rehabilitation programmes. The Danish national clinical guidelines commented that women were less likely to be offered cardiac rehabilitation, as did an analysis of an Irish rehabilitation programme. The French Société Française de Cardiologie also noted a lower medical prescription for women accessing rehabilitation, but in addition suggested poor compliance related to lacking familial support or help in organization of household, fear of non-adapted training particularly in older adults, and comorbidity. Lower socio-economic level was also associated with less women attending.

The Belgian health care knowledge centre added a male perspective as to why cardiac rehabilitation may not be suitable: citing that men found the cardiac centre being too far from residence; believing they can handle their own problems; no time to go to the centre; and no transportation to go to the centre.

Reducing risk factors

The Latvian National cardiovascular guidelines reported an improvement in women's smoking cessation outcomes following an exercise intervention post infarction. The UK's National Institute for Health and Care Excellence evaluation of intervention programmes for risk factor reduction reported that women were more likely to have negative attitudes towards positive health choices.

Implementation of health programmes

Only 4 countries (Germany, Ireland, Spain and the UK) offered gendered suggestions for the implementation of health programmes with regard to coronary artery disease (see Table 9).

The German 'Physical activity guideline for secondary prevention and treatment of cardiovascular diseases' recommended the development of programmes that reach out to women to help them engage in exercise based cardiac rehabilitation. The Irish College of General Practitioners similarly suggested that rehabilitation should be tailored to enable more women to attend. In the UK family doctors were supported to invite women in for cardiovascular assessment and the UK has also invested in interventions aimed at improving nutrition in pregnant women and young children as a means of reducing cardiovascular risk. In Spain, their Quality Plans aims to help set up services that are more gender sensitive.

Health policy actions

There were 10 countries that had made some kind of policy action recommendations to tackle gender issues with regard to coronary artery disease (see Table 9).

Improved monitoring of registers and improved data collection to explore sex differences in coronary artery disease were called for by Austrian Ministry of Health, and in the Swedish National Guidelines for cardiovascular disease. There was also support for gender sensitive interventions, with, for example, the development of health programmes for boys and girls in Spain and more focused cardiac rehabilitation (UK). There was also a call, from Spain, for more sex specific clinical guidelines. Both Estonia, in their National Strategy, and Spain's Ministry of Health, Social Policy and Equality, called for gendered campaigns to tackle smoking.

In Germany there was a call for more prospective cohort studies to explore the gendered nature of coronary artery disease. The Greek National Plan for Cardiovascular Disease, and the Spanish Ministry of Health, Social Policy and Equality also recommended more research into sex differences, with the

Netherlands seeking a broad programme of research to help eliminate all sex and gender knowledge gaps by 2040.

Discussion

The purpose of the analysis was to explore how explicitly sex and gender had been recognised as an important factor in cardiovascular disease, within the 28 EU Member States. From the analysis it can be seen that there was a very good level of awareness shown in some countries to the differing risks and needs of men and women. This was reflected in high level policy documents and guidelines that offered concrete guidance on how services should be adapted to meet the different risks and needs of men and women. However, in other countries a significant lack of documents is recognized. Furthermore, existing policies may cover incompletely the sex and gender differences in cardiovascular disease that are well recognised by experts, and have been published and retrieved in our bibliographic study.

What the Meta frame analysis revealed is that all the countries state a fundamental requirement that all people have equal rights and freedoms, whether this be through a formal Constitution or through legislation (as with the Equality Act in the UK). All the EU Member States have, in addition, further legislation that supports gender equality, but the focus of this legislation do differ from country to country, with some just focused onto anti-discrimination in the workplace, or in strengthening women's rights with regard to their family role, [pregnant workers and parental leave] (for instance Poland). At the other end of the spectrum there are countries with broad ranging legal requirements that protect both men and women within all aspects of life (for instance the Nordic countries have a very deep rooted gender equal environment). For some of the more recent Members of the EU there has been rapid change in their gender equality legislation and this has not yet had time to fully embed within the whole of society.

The Issue frame analysis demonstrated that there was a strong push within some of the Member states for the recognition of gender as an important

factor in both health generally and cardiovascular disease specifically. This included Ministry of Health level support and leading health organisations within the countries. In some countries, such as Ireland and Italy, this was extensive and offered a clear model for other countries to follow.

This recognition is building on a worldwide increase in awareness of the role of gender in health, from the most fundamental science of sex difference, as with GenderBasic (<http://www.genderbasic.nl/>), through to a wide range of resources available to those wishing to develop research, practice and policy, through European initiatives such as Gendernet (<http://www.gender-net.eu/>), Portia (<http://www.portiaweb.org.uk/>), EUGenMed (<http://www.eugenmed.eu/>), genSET (<http://www.genderinscience.org/>) and international resources, such as Gender Innovations (<https://genderinnovations.stanford.edu/>). In addition, there are non-government organisations that are advocating on behalf of both women and men in health, including the European Institute of Women's Health (<http://eurohealth.ie/>) and the European Men's Health Forum (<http://emhf.org/>).

The European State of Men's Health Report (EC 2011b; EC 2011a), reported that there were 160,000 male deaths and 60,000 female deaths before the age of 65 across the EU in 2008, with substantially greater numbers of male deaths in the Eastern European countries. It is noticeable that there are only three countries that have statements about the need to focus on men's health – Denmark, Germany and Ireland, with only Ireland being the only Member State to have a men's health policy.

The risks women face with regard to cardiovascular disease have similarly been well reported in the academic literature, with a greater number of women dying than men across the lifespan, with different signs and symptoms, different management needs from diagnosis through to rehabilitation. [8, 141-144] These have been recognised by some Member States and there are very good models that could be adopted across the EU, for instance, Slovenia's national prevention programme having different ages for targeting men and women.

The document frame analysis demonstrated that there was a growing level of awareness of the implications of sex and gender on coronary artery disease within some countries, with good coverage within policy documents and guidelines (the most notable examples are: Austria, Denmark, France, Germany, Ireland, Italy, The Netherlands, Spain and the UK).

There are countries, such as the Czech Republic, where there is a reliance on the use of ESC guidelines, with no specific health policies with regard to cardiovascular disease. With there being no over-arching country policy, the health system is reliant on the interpretation of each individual guideline, with no centralised push for sex and gender to act as an important element in strategy development or the allocation of resources. Even in EU Member States that were evidently strong on gender equality, there were some that had not seen this translated into specific policies or guidelines to help guide service change with regard to cardiovascular disease (for example Sweden).

It is important to recognise, as noted elsewhere [145], that although there may be health policy or guidelines it is not possible to know whether these are being enacted by practitioners. This analysis therefore has been an attempt to demonstrate the state of policy and guideline development that could influence how practice develops within each member state, rather than what is currently happening 'on the ground'.

2.3.4 Conclusions

The overall conclusions from this analysis is that for all EU Member States there is a policy environment that should ensure gender equality and an absence of sex discrimination. There is also a growing body of recommendations from leading health organisations supporting more gender sensitive and gender aware health care. At the level of detailed policy and guidelines guiding practice for coronary artery disease however, it is necessary to recognise simultaneously high reliance on the ESC guidelines in many countries and incomplete endorsement of these guidelines in some (Table 8). Thus, their role in ensuring gender sensitive care is very important and

coverage of gender aspects in these guidelines seems mandatory for successful implementation of gender sensitive treatment and prevention strategies.

2.4. Deliverables and performance indicators

WP 1				
	Deliverable	Start (month)	End (month)	Responsible
1.	Comprehensive report on gender differences in coronary artery disease in Member States from bibliographic studies	1	18	CH; RUMC
2.	Database investigation on gender-related risk factors, manifestations and treatments of coronary artery disease	1	18	CH
3.	Review of member state policies prevention and treatment guidelines	1	18	BSPH, CMH

All deliverables in this WP were reached in time.

The key performance indicators (KPIs) for this chapter are:

- Number and quality of publications retrieved
- Number of databases contacted
- Cooperation of database holders
- Number of EU Member States reached for policy analysis
- Content analysis for policies performed

Number and quality of publications retrieved.

We were satisfied with both, however there is no true external standard. Best comparators could be expert opinions, like the category C in guidelines. In guidelines, statements that are not based on clinical studies, but only on expert opinions are usually included and considered as category C. We compared our results to the discussions at international congresses and discussed them with international experts. A few more publications and ideas could be added by these means. Altogether, the list of publications and retrieved facts was well in agreement with the state of the art presented at

international congresses and by recognized experts. Qualitative external standardization was obtained by our network of experts in several rounds of reviews and confirmed the high quality of the analysis.

The number of databases contacted

We able to reach the European databases contacted, as intended in the project. The database analysis resulted in full cooperation of the contacted database holders.

Number of EU Member States reached

We obtained coverage across all EU states for the policy analysis, through a combination of key informants, official ministry's and organisation's website searches, endorsed ESC policy guidelines, and desk research, and thereby reached our goal.

Content analysis for policies performed

We performed policy analyses in all Member States and thereby reached our goal.

3. Needs assessment

A needs assessment was undertaken to assess how best to raise awareness about coronary artery disease in all Member States of the European Union. The objectives in work package 2 were organized into three tasks, the first of which is a survey for health professionals; the second is a survey of the general population in several European Member States, and the last part is an assessment of ongoing EU research activities in the area:

- a) Study of Awareness among Healthcare Professionals
- b) Study of Awareness among the General Population
- c) Overview EU research activities

3.1. Study of Awareness among Healthcare Professionals

3.1.1. Aims

The aim of the survey was to assess the degree of awareness of sex and gender differences in coronary artery disease, among professionals of different health specialties, work settings and European Member States.

3.1.2. Methods

Survey questionnaire

We did an extensive review of the scientific literature on awareness studies among health professionals of any discipline or specialty, and on any aspect related to health. Also, we used the conceptual framework of "awareness" developed along this project.

The questionnaire includes questions related to risk factors, symptoms, diagnosis, treatments, prevention, community programs, and the degree of information on these differences. In addition, some questions on key sociodemographic aspects of the participant were included.

A first draft of the questionnaire was prepared. In addition, a guide was also developed to help evaluate the questionnaire. This first draft and the guide were sent to the partners for comments and suggestions. Based on that, we developed a second draft of the questionnaire. The second draft was validated

by different experts. After several revisions, the final questionnaire was translated into the 6 languages of the countries chosen for the general population survey: Germany, Sweden, Czech Republic, Croatia, Bulgaria, and Spain. These countries were selected according to previously defined criteria. They should be representative of the European Member States mix, according to some key factors or indicators relevant for coronary artery disease. The criteria and indicators used were: epidemiology of coronary artery disease in Europe (mortality rates from coronary artery disease), economic performance (GDP -gross domestic product), population size, and East/West divide. According to partners' suggestions, some questions were modified and the most recent version is attached (see Attachment 4/2016).

Selection of medical and nursing specialties

We identified the medical and nursing specialties, health care institutions (hospitals, health centers, universities, etc.) and health care levels (primary care, specialty care, emergency services), to be included into the survey. These specialties are nursing and medical professionals in the primary health care level, and the following medical/nursing specialties: gynecologists, cardiologists, intensive care unit specialists, and medical rehabilitation specialists.

To reach these specialties, we considered the different medical/organizational approaches to health care for coronary artery disease provided in the different EU Member States, exemplified by the differences among GenCAD partners. We were aware that some of these specialties might not be present as such in the different Member States. We were also aware that, potentially, we could find some other medical or nursing areas that might have some relevant role for coronary artery disease in some Member States.

For these reasons, we kept open the listing of medical/nursing specialties, until the closing of the survey, to maximize the opportunity of identifying new medical/nursing specialties, given the limitations signaled above.

3.1.3. Results of healthcare professionals awareness study

Socio-demographics

Health professionals from 11 European countries completed the survey. Three countries, Italy, Germany, and Spain provided almost two thirds of the respondents. The mean age of respondents was 46 years of age, more often females, and with an average number of 22 years in professional practice.

A large majority of respondents works in a hospital setting, and more than 90% report working in a public setting. Half of respondents are physicians in primary care or hospital settings and only 6% are nurses. Almost one third are cardiologists and another third medical internists. Some 15% are primary care physicians. Finally, 20% hold some kind of clinical authority (Chief of Staff, Clinic Director, Head of Department, etc.).

Causes of death and symptoms

Professionals selected the three major causes of death from a listing of twelve. For females and males the three causes selected more often correspond with the three leading causes of death in Europe. However, the order of causes is not fully correct. Respondents identified ischemic heart disease as the leading cause of death for both sexes. But breast cancer and lung cancer were identified as the second cause of death, for women and men respectively. Nevertheless, the second cause of death for both sexes in Europe are cerebrovascular diseases. Regarding the symptoms of myocardial infarction, the participants mostly agree that women complain less frequently than men do of chest pain. Also, they mostly agree that in women, myocardial infarction may manifest with dyspnea and fatigue only, more often than in men. Both results agree with the evidence available in the scientific literature: myocardial infarction in women can present clinically with an intensity of pain and with symptoms different from the typical male pattern.

Family and primary care physicians are specialty that in a smaller proportion identify ischemic disease as the leading cause of death among women (68%), compared with cardiologists and internists (93%), and with the rest of specialties (82%). However, these differences do not occur for men.

Risk factors and clinical manifestations

Respondents were presented with a series of statements regarding differences in risk factors for coronary artery disease between men and women, and to indicate how much they agree or disagree with each one of them. Most respondents correctly agree that dyslipidemia is an equally large risk factor for women and men, that diabetes is a stronger risk factor for women, and that early menopause is a risk factor of coronary artery disease in women.

A majority of professionals agree that high blood pressure at a young age is more common in men than in women. Additionally, more than 90% agree that depression is an underestimated risk factor in men and women, and some 65% agree that emotional stress is a more frequent trigger for myocardial infarction in women than in men. Regarding the clinical manifestations of coronary artery disease, there is a clear agreement among respondents that men develop arteriosclerosis more easily than women, that women have coronary spasms more frequently than men do, and that men die more frequently from sudden coronary death than women. But there is no agreement for other clinical manifestations.

In general, there is high agreement among respondents from the different specialties on major risk factors and main clinical manifestations of coronary artery disease. For instance, there are no differences between the different specialties in that chest pain is the leading symptom of myocardial infarction in both men and women, nor in that women report chest pain as a dominant symptom less frequently than men do.

Diagnosis, treatments, and prevention

Regarding the sensitivity of some diagnostic procedures for men and women, some 68% agree that exercise testing is the first choice for diagnosing coronary artery disease in all women and men that can exercise, and some 64% agree that biomarkers may have sex specific threshold values. Respondents were asked about differences in some aspects of therapeutic drugs used to treat coronary artery disease between men and women. Some 64% do not agree that women and men respond in the same manner, with the same adverse event rate, to cardiovascular drugs such digitalis, ACEI, b-

blockers, etc. In addition, some 52% do not agree that adverse events in elderly women are not more frequent than in men. However, there is not a clear agreement on some side effects of antiarrhythmic drugs.

There is a clear agreement among respondents that women are less aware that coronary artery disease is a personal risk factor for them. But other than that, there is not a clear agreement on that campaigns on primary prevention address women and men equally, or that more women than men participate or have participated in coronary artery disease prevention programs.

Another significant difference is that cardiologists and internists indicate less frequently that exercise testing is the first choice for diagnosing coronary artery disease in all women and men that can exercise. Also, almost a quarter of family doctors and primary care physicians, as well as all other specialists, are unaware that imaging procedures are more necessary to diagnose women, compared to cardiologists and internal medicine specialists.

Awareness in coronary artery disease and preventive activities

Respondents were asked about the awareness of sex and gender differences in coronary artery disease in their country. More than 80% of respondents agreed that patients are not well informed about gender and sex differences in coronary artery disease, and that women with acute myocardial infarction are more likely than men to suffer delays between onset of symptoms and the arrival at the hospital.

A majority of respondents agreed that the sex of the health professional influences the care provided to men and women with coronary artery disease, that women with cardiovascular disease are less diagnosed than men, that women with cardiovascular disease have a worse general prognosis, and that women are not well represented in cardiovascular research. In addition, most did not agree that men have more knowledge about coronary artery disease than women.

The different specialties had significant differences in some questions. Among the respondents, there was no agreement that men and women are equally

well informed about the risk factors for coronary artery disease. The different specialties had significant differences in some questions. There was not an agreement that men and women are equally well informed about risk factors for coronary artery disease. Another important difference was that 70% of family and primary care physicians do not believe that the sex of the healthcare professional has an influence on the approach of coronary artery disease in men and women. This percentage was much lower in the other groups. Also, there were no differences in that women are worse diagnosed than men, nor were there differences in the fact that women with acute myocardial infarction will encounter more delays than men, between the onset of symptoms and the arrival at the hospital.

A majority of the respondents stated that they knew of activities developed in the consultation and plans and programs to promote cardiovascular health in their geographical area. However, only a minority knew if collective actions are being developed in health centers, in the community, or through media campaigns.

Less than 50% of the respondents reported that gender and sex differences are taken into account in the medical consultation. Also, only a minority reported that these differences are reflected in group actions in the context of health centers, in the actions developed in the community, in health promotion plans and programs, or in the media campaigns.

3.1.4. Conclusions

The results of the survey show that there is a high degree of consensus among professionals in some important aspects of sex and differences in coronary artery disease. However, in many of the issues there are between 20% and 25% of respondents who either disagree with one of the many aspects included in the survey, or do not know how to answer the question. In addition, for some clinical and preventive aspects the consensus among professionals is not large. To this, it must be added that in some aspects the different specialties have different opinions or practices. Due to the low number of respondents, it was not possible to explore the differences between countries. But all in all, the results are not satisfactory. Results indicate an insufficient degree of awareness among professionals in relation to the

differences and similarities between men and women on coronary artery disease. These lack of agreement could be reflected in the professional practice and in clinical and preventive activities, giving rise to gender inequalities in the approach to coronary artery disease, among the different specialties, or settings (hospital, primary care, emergencies, public health), or countries. All of this demands for the establishment of a European strategy to promote broad and clear professional consensus on sex and gender differences in the prevention and treatment of coronary artery disease in the Member States.

3.2. Study of Awareness among the General Population

3.2.1. Aims

The second aim of the needs assessment WP was to assess current levels of awareness on coronary artery disease among the general population of European countries.

3.2.2. Methods - Awareness study general public

We did an extensive review of the scientific literature, searching for studies on awareness, and overall, on awareness on cardiovascular diseases among the general population. We obtained and revised the questionnaires used in these studies. Additionally, we used questionnaires on different aspects of heart disease developed in other projects by partner organizations, like the Institute of Gender Medicine (GIM) and the Andalusian School of Public Health (EASP).

The questionnaire included questions relative to coronary artery disease, the perception of its relevance for health, the identification of risk factors and lifestyles, preventive measures, information needs, and the family and personal conditions. Additionally, questions were included to examine factors associated to knowledge and ability to search for emergency medical care in case of a coronary artery disease emergency. Finally, questions on basic demographic and socioeconomic data were also included.

The result of this work was the elaboration of a first draft of the questionnaire. Additionally, we developed a guide to help to evaluate the questionnaire. This first draft and the guide were sent to partners for comments and suggestions.

A content validation of this first "pilot" questionnaire was done through a focus group. For this, participants applied a series of criteria to evaluate appropriateness and quality of the questionnaire. Thereafter, we developed a second draft of the questionnaire. This second draft was used for validation with the participation of different experts. After several revisions, the final version of the questionnaire was translated to the 6 corresponding languages of the participant countries.

Finally, to organize and execute the survey, a global market research company, TNS Investigación de Mercados y Opinión S.L (TNS), was subcontracted. TNS adapted the questionnaire for a telephone survey. We have attached the questionnaire in English version, as well as the evaluation guide (see Attachment 4/2016).

To comply with the objective, within the project resources, it was decided to do the survey in a selected number of Member States, with a total sample size of 2,600 participants. In order to select the countries to be included in the survey, they should be representative of the European Member States mix, according to some key factors or indicators relevant for coronary artery disease. We selected the following criteria and indicators: epidemiology of coronary artery disease in Europe (mortality rates from coronary artery disease), economic performance (GDP -gross domestic product), population size, and East/West divide.

According to these criteria, selected countries were Bulgaria, Croatia, Czech Republic, Germany, Spain and Sweden. The 2,600 surveys were distributed from 300 to 500 for each country according to their population size: large countries like Germany and Spain, 500 subjects; medium countries, like Sweden and Czech Republic, 450 subjects; smaller countries like Bulgaria 400 subjects; and the smallest, Croatia, 300 subjects. Within each country, the sample distribution was representative by region and size of habitat. We used the Nomenclature of Territorial Units for Statistics (NUTS 1), to define regions for each country. Finally, the selection of the final individual was done through

sex and age quotas. The sample within each country consisted of adults older than 25 years of age.

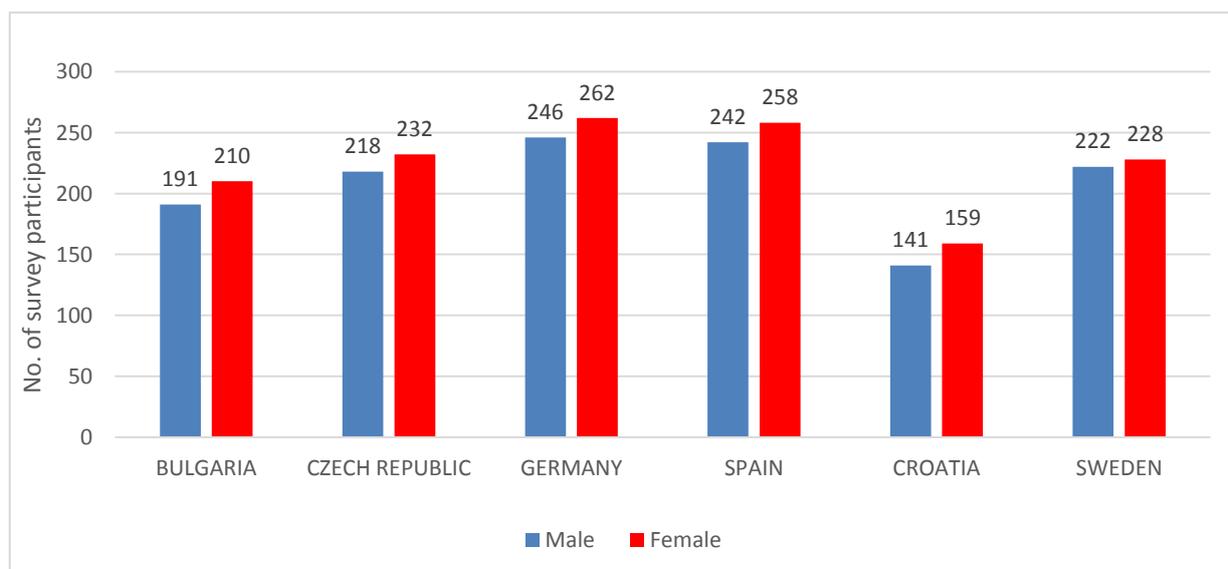
Computer Assisted Telephone Interviewing (CATI) system was used, included landline and mobile phone calls in order to ensure maximum representativeness.

3.2.3. Results

Socio-demographics

A total of 1260 men and 1349 women completed the survey, distributed among the six participating countries according to population size.

Figure 6: Number of participants in the survey by sex and selected country.



In the sample, half of the population has secondary education and 37.8% of men and 35.8% of women have a university degree. A 60% of men and 48.6% of women are workers, 5.5% and 6.1% are unemployed, 29.8% and 34.5% are retired, and 1.6% and 0.7% are studying, respectively. In addition, 7.3% of women are dedicated to care within the home while the percentage of men, 0.2%, is imperceptible.

Concerning household income, 21.1% of women lived in a household with less than 500€ per month, the lowest level, compared to 14.3% of men. And

13.1% of men and 9.8% of women live in households with incomes above € 5000, the highest level of income. These differences are strongly influenced by the country of residence. A 70.2% of women and 66.1% of men have public health insurance, less than 6% have only private health insurance, and 23.8% of men and 22.3% of women have both types of health insurance. In addition, 1.7% of men and 0.7% of women do not have health coverage. Regarding habitat size, 25.5% of the sample resides in urban cities of more than 100000 inhabitants, 19% in cities between 10000 and 100000 inhabitants, and 24.5% in cities under 10,000 inhabitants.

General and cardiovascular health

For 22.3% of women and 24.6% of men, the main health problem that affects women is breast cancer. Another 17.1% of women and 17.4% of men contemplate cancer in general. Only 5% of women and 16.4% of men consider cardiovascular disease or heart attack as the greatest health problem for women.

With regard to the greatest health problem for men, both men and women, 34.9% and 32.6% respectively, consider a variety of causes. A smaller percentage, a 19.6% of men and 18.6% of women, consider that cancer in general is the greatest health problem. Only 16.4% of men and 17.4% of women perceive cardiovascular disease or heart attack as the main health risk for men. These data reflect that awareness on cardiovascular disease is very limited among the sampled population. And that this limitation is more intense in relation to women.

There are statistically significant differences between countries. Heart diseases are considered as the most important health problem for women in a range of 1.8% to 9.5% between countries. For men, this range goes from 9.3% to 25.9%. These differences also exist between age groups. The percentage of women who point to heart disease as their main health problem is greater the greater the age. Among men, this difference is not so clear.

In relation to the main cause of death, 30.8% of men and 40.3% of women report that cancer is the main cause of death for women. However, heart problems are the leading cause of death for women, only for 14.3% of men and 14% of women. When asked about the leading cause of death for men, 41.6% of men and 43.2% of women point to heart problems, followed by 22.4% of men and 2.8% of women who identify cancer. Both men and women consider that cardiovascular diseases are not a major cause of death for women, in contrast to men. Also, differences between countries are large. For example, the percentage of people who identify heart disease as the main cause of death for women varies between countries from 7% to 29%.

A 6.8% of men and 4.2% of women in this population have suffered a heart attack (myocardial infarction or angina). Additionally, 12.5% of men and 11.5% of women have had a diagnosis of another cardiovascular problem. Also 60% of men and 62.5% of women know a relative or a friend who has suffered a heart attack, and 40.2% of men and 43.5% of women to a family member or a friend with some other cardiovascular disease. That is to say, the cardiac disease is present among the European population. These figures vary by age. For instance, only 1,2% of those younger than 44 have had a heart attack, compared to a 12,2% of those older than 65. Similarly, the percentage reporting a heart attack in the past is higher among the lower income group.

A 45.3% of men confirm having undergone some type of screening for cardiovascular disease, compared to only 32.2% of women, a difference of 13.1 percentage points. This difference is a little higher in older age groups. Among countries, the differences vary between 11.7% and 52.5%.

The few studies on awareness in coronary artery disease show very similar results. An unsatisfactory level of awareness, especially among women. This is due to several reasons. The absence of informative, comprehensive and effective campaigns on the relevance of coronary artery disease for population health. In addition, the differences between men and women are also due to differences in the information and approach that men and women with

cardiovascular disease receive from their doctor or healthcare provider. On the other hand, in European countries there are frequent campaigns in the media about cancer in general, and very common about breast cancer. Hence, women consider it their biggest health problem. Finally, there is an old general belief that cardiovascular disease belongs to men. It seems that this belief remains.

Knowledge and perceptions about cardiovascular disease, symptoms and risk factors

Both men and women identify the three most important signs associated with a heart attack: chest discomfort, pain radiation, and pain in the chest. But there are important differences between countries. For instance, radiation of pain is considered a warning sign of heart attack for women, in a range from 9% to 49%, depending in the country.

For a majority of the people interviewed, 77.1% of men and 65.5% of women, "men have more heart disease than women". Likewise, for 82.5% of men and 82.3% of women agree that "men who work as highly stressed professional executives are more likely to have heart attacks". Only a minority of the sample, 33.1% of men and 27.5% of women believe that "young women, below 50, do not have heart attacks". Also, 23.4% of men and 24.2% of women agree that "in women, the likelihood of a heart attack increases after menopause". A majority of the population interviewed, 69.62%, disagrees with that "only women who adopt behaviors and lifestyles of men will have heart disease". In addition, 89.96% disagree with the statement that "only women who have raised their children will have heart disease".

Stress, smoking, unhealthy diet, a sedentary lifestyle, alcohol consumption, obesity and high blood pressure are considered risk factors for men and women. Stress is considered the greatest risk factor for suffering heart disease by 67.4% of women and 64.7% of men. A 57.7% of men and 49.9% of women consider smoking as the second risk factor. Drinking alcohol is the third risk factor, according to 43.9% of men, and eating habits are the third

risk factor, according to 39.2% of women, for their own health. And 40.4% of men and 37.1% of women consider a sedentary lifestyle as the fourth risk factor for their health. For instance, the differences in stress vary between 56.4% and 73.8%. For smoking, the differences vary between 36.0% and 66.4%.

There is a large difference between the percentage of men and women informed by their doctor on cardiovascular disease. A 45.95% of men and a 31.08% of women report to have been informed by their doctors about risk factors for heart disease. Also, 44.9% of women and 42.47% of men would like to have more information on heart disease. Among countries, the differences in the sources of information on CVD are relatively large. Those informed by your doctor vary between 31.4% and 58.9%. The media and internet are the first source of information in all countries.

Awareness about prevention strategies and what to do in case of experiencing a heart attack

Men and women agree in identifying the three factors that best may prevent heart disease: first, physical activity (67.7% of men and 63.3% of women), secondly not smoking (47% of men and 44% of women) and thirdly, increasing the intake of fruits and vegetables (42.1% of men and 44.1% of women).

Given the signs of a heart attack, 55.4% of men and 56% of women, would call health emergency services as their first reaction. A 13.5% of men and 15.9% of women would choose to call a doctor, a 8.9% of men and 8.5% would go to a hospital, and 7.4% of men and 7.1% of women would call a family member. To call emergency services varies between countries from 46% to 62%.

Additionally 74.4% of men and 77.24% of women would call health emergencies as the first reaction if in the presence of another person with

signs of suffering a heart attack. Also a large majority, 94.7% of men and 94.8% of women, report to have access to a telephone emergency service in their area of residence.

While men and women correctly point to adequate preventive strategies, almost half of the population would choose a different way of acting than calling to emergency medical services, in case of a heart attack. Moreover, this happens in a context of practically universal access to such services.

Information and communication strategy about heart diseases

Relative to sources of information on cardiovascular diseases and their prevention, 61.4% of men and 61.1% of women state that their main source of information is the media (TV / Radio / newspapers / other). A 49.6% of men and 48.3% of women have internet as the main source of information. The doctor is the informative reference for 48.7% of men and 39.6% of women, and their family and friends for 34.2% of men and 35.5% of women. Individuals obtain information on cardiovascular disease from a large variety of sources. It is important to use adequately all these sources to improve the amount and quality of the circulating information on heart disease.

Participants were asked about how well informed they are on the risks associated with heart attacks and other heart diseases. On a scale from 1 to 5, in which 1 indicates "not having information" and 5 "being very well informed", the majority of the population, 38.3% men and 38.9% women, place themselves on the 3 of that scale. Moreover, when asked about their information on what to do and how to act to prevent a heart attack, on a scale where 1 indicates "Nothing" and 5 "Completely", the majority place themselves in position 3, a 35.8% of the men and a 36.6% of women. Between countries, differences are relatively small.

The majority of participants would like to have more information about: the management of the onset of symptoms (52.8% of men and 54.3% of women); to detect symptoms (45.2% of men and 47.8% of women); to

prevent the risks that affect them personally (43.8% of men and 44.5% of women); and how to detect the symptoms in other people (42.8% of men and 43.2% of women). Only 14.4% and 12.8% of men and women respectively prefer not to receive any information.

Clearly, general population demands more information on specific aspects of cardiovascular disease.

3.2.4. Conclusions

Some results of this study have also been found in other studies. The main one is that the general population does not have an adequate level of awareness about coronary artery disease. The most important study on this, conducted in the United States, found, for example, that 56% of women identified heart disease as the leading cause of death among women, compared to 14% in our study. That percentage in the US increased very significantly with respect to previous years, after intense campaigns in the media and other strategies to increase awareness.

Also, this study shows that some erroneous beliefs regarding cardiovascular disease remain. And, healthcare professionals do not seem to inform adequately or sufficiently their patients about coronary artery disease. A majority of respondents claims more information about various aspects of coronary artery disease, ranging from identifying symptoms of heart attack to prevention strategies. Most people surveyed know what to do in case of having a heart attack. But there is still a significant percentage that would adopt erroneous behaviors in that situation, that will delay their arrival to proper hospital care.

Finally, the results show important differences between countries. The survey was not designed to examine differences among participating countries. Therefore, these differences may be due to a combination of elements. First, they are due to random variation. The design of the survey guarantees a relatively small error for the global estimates. But the error is larger for any country specific estimation. Also, selected countries are different in many

social, economic or environmental factors. More relevant for our results, are the differences that these countries may have in the organization of health services, the variability in professionals practice, the information strategies of health authorities and institutions, the quality of media information about CAD, etc. And finally, the epidemiology of CAD is different among these countries. All of these are reasons behind differences in the results among the selected countries.

In any case, and as the Americans have shown, improving coronary artery disease awareness is a matter of putting in place the right strategies. This should be a key element of health policies in Europe, given the great importance that cardiovascular disease has on the continent, the large epidemiological inequalities among Member States, and the enormous costs involved.

3.3. Overview EU Research Activities

At the inception meeting it was discussed that prevention and care are the priorities in this project, and to a lesser extent the research activities. Furthermore, research activities are the main topic in other calls. Therefore, this part of the project was considered not to be of particular interest to DG Health and Food Safety and can refer to the results of the other projects in its report. Indeed, two recent EU projects, EUGENMED and GenderNet aimed at answering these questions in a systematic manner have been finished.

EUGENMED was coordinated by Charite and the team of the present application. The EUGenMed project was started in 2013 in order to introduce sex and gender aspects into medicine as an innovative way to improve biomedical and health research and thereby the health of European citizens. A first step was the assembly of sex and gender stakeholders in biomedical European research and identification of all ongoing research activities. Cardiovascular disease was chosen as an exemplary field. EUGenMed identified stakeholders by systematic literature searches (all published research results)

and invited them to a) a kick-off conference; b) 4 workshops in clinical research and pharmacology, prevention and public health, basic research and medicines regulation and medical education, and to a c) an International Gender conference in Berlin September 2015, and d) an EUGENMED final conference in June 2016. EUGenMed tried to enlarge the network as much as possible and to be inclusive for all ongoing EU research activities in gender medicine. This project has published three major papers, that summarize the ongoing research activities in prevention and public health, in clinical medicine and basic research:

- Oertelt-Prigione S, Dalibert L, Verdonk P, Stutz EZ, Klinge I. Implementation Strategies for Gender-Sensitive Public Health Practice: A European Workshop. *J Womens Health (Larchmt)*. 2017 Nov;26(11):1255-1261.
- Ventura-Clapier R, Dworatzek E, Seeland U, Kararigas G, Arnal JF, Brunelleschi S, Carpenter TC, Erdmann J, Franconi F, Giannetta E, Glezerman M, Hofmann SM, Junien C, Katai M, Kublickiene K, König IR, Majdic G, Malorni W, Mieth C, Miller VM, Reynolds RM, Shimokawa H, Tannenbaum C, D'Ursi AM, Regitz-Zagrosek V. Sex in basic research: concepts in the cardiovascular field. *Cardiovasc Res*. 2017 Jun 1;113(7):711-724.
- EUGenMed Cardiovascular Clinical Study Group, Regitz-Zagrosek V, Oertelt-Prigione S, Prescott E, Franconi F, Gerds E, Foryst-Ludwig A, Maas AH, Kautzky-Willer A, Knappe-Wegner D, Kintscher U, Ladwig KH, Schenck-Gustafsson K, Stangl V. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. *Eur Heart J*. 2016 Jan 1;37(1):24-34.

Furthermore, Gendernet, coordinated by France, focused on the integration of gender dimension in European research contents and programmes and therefore aimed to identify European gender research activities in all fields, including medicine. The project was completed in 2016 and its coordinators reported on its results at the GenCAD first Brussels conference. Reports and materials of this project may be found at: <http://www.gendernet.eu/spip.php?article55&lang=en>

Gender equality is a key priority of the European Research Area. A number of projects focusing at developing Gender equality strategies have already been funded by Horizon 2020 and a number of projects have also been run in FP 7 (Libra, Integer, Trigger, GenderTime, Egera, Genera, http://ec.europa.eu/justice/gender-equality/eu_funded_projects/ index_en.

htm). Most of these projects looked however at gender equality only and not at the gender dimension in research, with the exception of Trigger (<http://triggerproject.eu/>), coordinated in Italy.

Furthermore, at European level, H2020 is asking since 2014 for the integration of the gender dimension into biomedical research, in particular in the area of Societal Challenge 1 Health, Demographic Change and Well-being. First results were presented at the first GenCAD Brussels conference by Vivianne Willis-Mazzichi.

An ERA NET on gender research has just been founded in 2016 by those countries who are interested – France, Spain, Norway, UK, Ireland, Belgium, Slovenia, Cyprus, Germany as an observer. However, as of the date of this report, results are not yet available.

A number of countries have established their own calls on gender research in the biomedical field: The Netherlands with the “Queens of heart programme”, Germany with “Gender in prevention”, Italy with “Progetto Strategico Salute Donna”. An overview on research policies at different funding bodies from in- and outside Europe is found at the gendered innovations in science website (<https://genderedinnovations.stanford.edu/>).

3.4. Deliverables and performance indicators

WP 2				
	Deliverable	Start (month)	End (month)	Responsible
1.	Survey on awareness in health care professionals	1	32	EASP
2.	Survey on awareness among the general population	1	24	EASP (+subcontract)
3.	Report on EU research activities	12	24	EASP

We completed deliverables numbers 2 and 3 at the scheduled time, in the first 24 months of the project. Product number 1 was completed in month 32. The delay was due to the fact that the EASP decided to conduct the general population survey first (Deliverable nº 2). The reason for this change was that this deliverable needed of a subcontracting process. And this process involved some administrative procedures of uncertain duration. And indeed, the administrative procedure for the subcontracting was very long, which delayed the subcontracting, and the implementation of the field work of this survey of the general population. With the resources assigned to the project, it was impossible for the EASP team to manage and execute two surveys at a European level simultaneously. Therefore, the operational work for the survey of health professionals (Deliverable nº 1) began once the subcontracting process was resolved. This caused a delay of some months in the development of the survey.

The results indicators for this for this section are:

1. Elaboration and quality of the questionnaires
2. Number of people participating in both surveys
3. Number and representativeness of Member States participating in the surveys

Preparation and quality of the questionnaires used.

The questionnaires used in both surveys were elaborated using questionnaires of studies published in the scientific literature and questionnaires developed in other studies by some of the partner institutions. Subsequently, the questionnaires were submitted to an organized process of discussion and validation among the partners and among experts in gender medicine, public health, psychology, and survey design. For this process, we used well-known formal participation methodologies.

Respondents completed the questionnaires with no major problems identified in any particular question. In both surveys, questions related to sociodemographic factors were introduced. In the general population survey,

age, social class, and country,, in addition to sex, are the most useful variables to describe the variability of the European population. In the survey of health professionals, specialty and work environment assumed that role. The small number of respondents in this survey prevents a reliable analysis of these factors.

Number of people participating in both surveys

The target number of individuals (2,600) for the general population survey was reached in less than one month in the six countries. The survey had a response rate (number of questionnaires completed /number of targeted persons contacted by phone) of 16%, higher than usual in telephone surveys. In addition, there was a small number of refusals to complete the survey, less than 6% on average, due among other factors, to the short time needed to complete the questionnaire.

The survey of professionals did not have a defined universe, because it was unknown. The number of respondents obtained is lower than expected, mainly due to the short period of time that the survey was open to answer on the internet, of only 5 weeks. For this reason, the distribution of the sample among Member States reflects also the special effort made by some partners. In addition, the low participation of nurses seems to indicate that the survey did not adequately capture the interest of this professional group to identify sex and gender differences from their professional perspective and their participation in the coronary artery disease process. On the other hand, the distribution of participants among medical specialties, mainly cardiology, internal medicine and family medicine, reflects well the specialties that participate more directly in coronary artery disease in Europe.

Number and representativeness of the Member States participating in the surveys

The methodology for selecting the six participating countries guarantees the representation of the great variability of the Member States, in terms of the epidemiology of coronary artery disease, economic development, geography,

and political and historical tradition. Given the limited resources of the work package and the large differences in population size among the selected countries, it was not possible to select a sample size proportional to the population size of the countries. The chosen design maintains a balance between the size of the population of the countries, and the size of the sample. The survey of the general population was designed with a margin of error of +/- 1.96% and a confidence interval of 95.5%, which offers a relatively high precision for European-level results. In addition, we used calls to fixed and mobile phones, to ensure maximum representation. Finally, the distribution of the sample at the national level was representative by regions (NUTS 1) and habitat size.

4. Factsheets

4.1. Objectives

The third work package aimed at developing factsheets on gender aspects in coronary artery disease in all EU languages. They should communicate the results of the bibliographic study and should include also insights gained from need assessment by the expert interviews and the awareness study. These factsheets should on one hand reach health care professionals and on the other hand be also developed in a second version in an easy and understandable laymen-style for general population.

4.2. Methods:

a) Medical content factsheets

Based on the literature search in task 1 of work package 1, the expert opinions and results from the awareness study, we developed the key messages and information for the factsheets. These factsheets reflect the results of the state of the art reports, however, because of the large amount of materials that were available we had to make a selection of contents. We tested the validity of our selection, and the adequacy and meaningfulness of

the medical content of factsheets by making use of the expertise and experience of the consortium partners and their networks.

Thus, the key messages were circulated and discussed in our groups of experts for scientific validity. A number of comments were integrated and general agreement was reached for all statements before final inclusion into the factsheets.

b) Draft factsheets for healthcare professionals and general public

In a next step, the factsheets were drafted with the help of a professional health journalist under the supervision of EUPHA. However, data were reorganized to be more presented convincingly and in a more didactic manner. The initial drafts of the factsheets for healthcare professionals and general public were created by the Charité team and built on the medical content derived from the first and second work packages. Drafts were again circulated to all partners and our group of experts and were tested among health professionals from different EU Member States and focus groups of general public and policy makers.

c) Finalised (content) factsheets, English and linguistic adaptation

Thereafter, the content of both factsheets was discussed with DG Health and Food Safety and finalized according to their suggestions.

e) Factsheets translation in 24 official EU languages

Once the factsheets were finalised in English they were translated into all 24 official EU languages by a subcontractor. Thereafter, quality-control was achieved by contacting medical experts from all 24 official languages and following their advice to improve the translations in a gender sensitive medical language of the different countries.

4.3. Results - final versions of the factsheets

The final versions of the factsheets for both healthcare professionals and the general public are depicted below. The translated copies of both factsheets can also be found on the homepage of DG Health and Food Safety

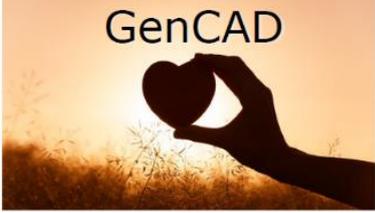
(https://ec.europa.eu/health/social_determinants/projects/ep_funded_projects_en#fragment3).

4.4. General public factsheet

Figure 7: General public factsheet



How to protect your heart - are women and men different?



Being a woman or a man and having a heart disease

Does it make a difference if you are a woman or a man when it comes to coronary artery disease and heart attack? Doctors say it does, and it's important to understand how it appears in women and men so you know what to look out for and how best to deal with it if you have it.

Are women and men different?
Women and men get different forms of heart disease at different ages, with different symptoms and may need different types of prevention and therapy.

Some risk factors for heart disease differ in women and men

Age: Men develop coronary heart disease early, mainly in their sixties, and women in their seventies, but throughout their lives, both have the same risk for getting it.

High blood pressure is most common in young men and old women. High blood pressure causes more strokes and heart failure in women than in men.

Diabetes increases the risk of coronary heart disease more in women than in men. This makes women with diabetes high-risk patients who need intense treatment.

High cholesterol levels are equally dangerous and must be treated in both women and men.

Young women who smoke increase their risk for heart disease more than men. Smoking, being overweight and taking hormone therapy is a very dangerous combination.

Depression and stress are risk factors for women. They are often overlooked in men. Both must be treated by doctors.

Rheumatic diseases, like arthritis, and other **diseases of the immune system** cause heart disease more often in women than in men.

Pregnancy: Women who have high blood pressure during pregnancy – or pre-eclampsia – are more likely to develop heart disease and hypertension later in life and should have their blood pressure monitored after pregnancy.

Erectile dysfunction may be an early sign of coronary heart disease in men.

Differences in risk factors between women and men:

- Age
- High Blood pressure
- Diabetes
- Smoking
- Depression and stress
- Rheumatic diseases
- Pregnancy complications
- Sexual hormones



Heart disease may differ in women and men

Large and small coronary arteries: Men and older women usually have atherosclerosis (lipid deposits) in their large coronary arteries. Women before age 65 have more frequently spasms (cramps) of their coronary arteries or disease of the small vessels. This may lead to different symptoms.

Stress induced heart disease: Women after menopause may develop acute stress induced heart disease – severe chest pain that can mimic myocardial infarction. This condition is called broken heart syndrome and is rare in men. It is usually cured by medical treatment.

During and shortly after pregnancy very special acute forms of heart disease with severe chest pain may arise that require immediate medical attention.

Women and men can have different types of heart disease

- Stress induced heart disease is more com- mon in women.
- Pregnancy can lead to special forms of heart disease.



Prevention in women and men

What can women and men do to reduce their risk of coronary heart disease?
Be aware - Don't underestimate your risk. Women often do.

Know your normal values and take action if your values are higher:
Blood pressure: optimal <120/80 mmHg, pharmacotherapy is indicated when ≥140/90 mmHg
Blood glucose level: <100 mg/dl (5.6 mmol/l)
Blood lipid levels: LDL-Cholesterol ≤115 mg/dl
Waist circumference: women ≤80 cm, men ≤94 cm

- **Stay healthy** - Adopt a healthy lifestyle to reduce your risk of coronary heart disease.
- **Quit or don't start smoking:** It is more difficult for women to stop smoking. Try to stop and get help if needed.
- **Exercise regularly:** Women and men can make big improvements to their heart health by exercising regularly. Take time (e.g. 30 minutes per day/ 5 days a week) for walking.
- **Eat a healthy diet:** Eat plenty of whole grains, a wide variety of fresh fruits and vegetables, low-fat or fat-free dairy products, and lean meats. Avoid saturated or trans-fat, added sugars, and especially salt. Maintain a normal weight for optimal health and longevity.
- **Alcohol:** limit your alcohol consumption.

Women and men should be aware of their risk of coronary heart disease.

- Women and men can prevent coronary heart disease by adopting a healthy lifestyle.
- In some cases, drugs are needed.



Managing heart disease may differ in women and men

Drug therapy:
High blood pressure and high blood lipids should be treated in both women and men.
Aspirin does not prevent coronary heart disease in healthy women below 65 years.
Hormone therapy after menopause does not prevent heart disease.
Drugs may act differently in women and men and they may have different adverse effects. Adverse effects are more frequent in women and should be reported to the doctor.

What else can be done? — Interventions:
Both women and men can benefit greatly from invasive therapy, e.g. catheters, balloon dilatations, cardiac surgery and advanced pacemakers. However, women are treated less frequently. Talk to your doctor.

Recovery and rehabilitation:
Women take longer to recover than men after a heart attack or surgery. This may be due to the early resumption of household activities, family care, and missing out on cardiac rehabilitation. It's important that both men and women go to cardiac rehabilitation.

Optimal doses and adverse effects of drugs may differ in women and men.

- Women and men benefit from surgery and modern interventions.
- Both men and women need rehabilitation after myocardial infarction or surgery.



Heart attack symptoms and help seeking in women and men

Symptoms:
The most common heart attack symptom in women and men is pain, pressure or discomfort in the chest. It is not always the most prominent symptom.

Women with heart attacks frequently experience other symptoms, in addition to or without chest pain, such as:

- Neck, jaw, shoulder, upper back or abdominal discomfort
- Shortness of breath
- Pain in one or both arms
- Nausea or vomiting
- Sweating
- Lightheadedness or dizziness
- Unusual fatigue

Help seeking: Because women often do not recognise they are having a heart attack, they tend to arrive later at hospitals than men.

Symptoms of a heart attack can differ in women and men.

- Women more often have a heart attack without chest pain.



Diagnosis of coronary heart disease

The tests doctors choose to diagnose chronic coronary artery disease can differ in women and men.

Exercise testing and coronary angiography is usually used in men and can be used in women if they have a number of risk factors and they can exercise sufficiently.

If women are younger, cannot exercise and have no other risk factors, alternative diagnostics may be preferred.

There are different ways to diagnose coronary heart disease, and your doctor can choose the most effective method.

In a nutshell!

- Heart disease can manifest differently in women and men, in risks, symptoms, causes and diagnosis. Be aware - know your risk factors.
- Exercise regularly, eat a healthy diet, maintain a healthy weight, and quit or don't start smoking. Be active.
- There are various ways to diagnose heart problems. Listen to options - protect yourself from delayed diagnosis.
- Best medications and doses may differ in women and men. Talk to your doctor.
- Both women and men benefit from cardiac interventions, surgery, pacemakers and cardiac rehabilitation.

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GenCAD project: Institute of Gender in Medicine, North School of Public Health, Institute School of Public Health, European Public Health Association, Institute of Health and Wellbeing, National University Health Centre, European Association for Cardiovascular Prevention & Rehabilitation.

GenCAD is an initiative of an experimental nature designed to test the feasibility of an action and to co-ordinate and provide appropriate care to be entered in the EU budget for more than ten consecutive financial years.

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4.5. Healthcare professionals factsheet

Figure 8: Healthcare professionals factsheet



FACTSHEET for healthcare professionals

GENCAD

Gender differences in coronary artery disease in Europe



Gender differences in classical risk factors

- Coronary heart disease develops 7-10 years later in women compared to men. Overall, more women are affected, since they live longer and the disease develops in old age.¹
- Hypertension occurs more frequently in men before the age of 50, and in women after the age of 50. Hypertension leads to more strokes and heart failure in women than in men.^{2,3}
- Diabetes increases the risk of cardiovascular disease more in women than in men.⁴ Women with diabetes and associated risk factors are high risk patients, and need intense management and treatment.⁴
- Dyslipidemia is an equally strong risk factor in women and in men. Lipid lowering therapy should therefore be used in both.¹
- Smoking is a relatively greater risk factor in younger women than in men and smoking rate in women has been reduced less than in men.⁵

Gender differences in non-classical risk factors

- Poor socioeconomic status contributes to gender disparities in cardiovascular health.^{6,7}
- Depression and sustained mental stress occur more often in women than in men and are more important risk factors in women.^{10,11}
- Autoimmune and rheumatic diseases occur more often in women and are frequently associated with cardiovascular disease.¹²
- Preeclampsia is an increasingly recognized risk factor in women.¹³ Women who develop preeclampsia have a twofold elevated risk of developing cardiovascular disease later in life.^{14,15}
- Genetic factors are important in premature heart disease in women and in men.¹⁶
- Estelle Dysfunction is associated with general metabolic and cardiovascular health risks in men.¹⁷
- Menopause, polycystic ovary syndrome, andropause and hypogonadism are associated with increased cardiovascular risk in women and men.^{18,19,20,21}

Gender-specific mechanisms of disease

- In men, arteriosclerosis of large coronary arteries is the dominant mechanism leading to myocardial ischemia and infarction.²²
- Middle-aged women frequently have angina pectoris and myocardial ischemia in the presence of normal coronary arteries. The term ischemic heart disease is suitable for this form of disease.^{23,24}
- Functional disorders and spasms of large arteries and the smaller vessels (the microcirculation) of the heart or an increased demand of the myocardial tissue may cause ischemic heart disease, which occurs preferentially in women.^{23,25}

- Age
- Hypertension
- Diabetes
- Smoking



- Socioeconomic status
- Mental stress
- Autoimmune & rheumatic diseases
- Preeclampsia
- Sex hormones



- Large coronary artery arteriosclerosis
- Ischemic heart disease
- Non-obstructive functional coronary artery disease
- Stress-induced heart disease, spasms and dissections
- Heart disease in pregnancy and peripartum period

Gender in prevention

- Stress induced heart disease, coronary artery spasms and spontaneous coronary artery dissections (longitudinal ruptures in the wall) cause relatively more acute coronary syndromes in women than men.^{26,28}
- In pregnancy and the peripartum period, preeclampsia, peripartum cardiomyopathy and coronary artery dissection should be suspected in symptomatic women.^{29,31}

Gender in clinical manifestation and diagnosis

- Women with myocardial ischemia and infarction may have a greater variety of symptoms than men.²⁹
- The ECG normally is an indicator of myocardial ischemia. However, women exhibit changes in ECG more often than men, caused by factors other than myocardial ischemia.^{38,40}
- Women have relatively lower exercise tolerance than men and the exercise-ECG is less sensitive for CAD.^{38,40}
- The use of high-sensitive Troponins and sex-specific thresholds improve the diagnosis of myocardial infarction in women.^{41,43}
- Coronary angiography should not be used as a first test to diagnose myocardial ischemia in young or middle-aged women that have few other risk factors for CAD.⁴⁴ Newer imaging techniques are recommended by the ESC Guidelines in these patients.^{38,40}
- Non-radiation imaging techniques should be preferred in younger women with suspected myocardial ischemia.^{38,40,45,48}

Gender, management & outcomes

- Women and, in particular, elderly women with suspected myocardial infarction arrive later at hospital emergency units than men.²⁹
- Cardiovascular rehabilitation after myocardial infarction is not equally available for women and men.⁴⁷
- Treatment of CAD should be performed according to the current guidelines for women and men. Women derive the same benefits from bypass surgery and percutaneous coronary intervention as men.²⁹
- Women have more complications and more residual chest pain after coronary interventions for myocardial ischemia.^{48,49}
- Women have higher mortality and poorer health related quality of life after elective coronary artery bypass surgery.^{12,50,52}

Conclusion

- Coronary artery disease differs significantly in European women and men, in age distribution, prevention, clinical manifestation, in response to therapies and outcomes.
- Whenever managing women and men with risk factors or coronary artery disease, think about the differences in prevention, diagnosis, and therapy.
- Take conventional risk factors seriously in women and men. Hormonal dysfunction and poor lifestyle increase the risk in both.
- Choose proper and risk-adapted non-invasive and invasive tests for diagnosis of coronary artery disease in women and men.
- Choose proper and risk-adapted pharmaceutical and invasive management for therapy of coronary artery disease in women and men.

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GENCAD project partners: Institute of Gender in Medicine, Berlin School of Public Health, Andalusian School of Public Health, European Public Health Association, Institute of Health and Wellbeing, Aristotle University Medical Centre, European Association for Cardiovascular Prevention & Rehabilitation.

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This document has been revised in accordance with recommendations from DG Health and Food Safety.

4.6. Deliverables and performance indicators

WP 3				
	Deliverable	Start (month)	End (month)	Responsible
4.	Medical content factsheets	6	18	CH
5.	First draft factsheets for healthcare professionals and general public	8	14	EUPHA
6.	Finalised (content) factsheets, English and Linguistic adaptation	15	26	EUPHA
7.	Factsheets translation 24 official EU languages	26	32	EUPHA, (+subcontract)

The key performance indicator identified for this work package was the development and translation of the two types of factsheets. Through the feedback from all our workshops and conferences, coupled with the suggestions from external experts, we were able to thoroughly plan and deliver the factsheets in all official EU languages on time.

Thus, all deliverables and key performance indicators were reached on time.

5. Conferences

5.1. Objectives

The main goals of WP 4 was to communicate and disseminate the findings of the state-of-the-art study, the needs assessment, and the factsheets to specific target audiences, to improve the knowledge and awareness in the EU for gender aspects in coronary artery disease. For this purpose, one preparatory workshop and two conferences were organized.

5.2. Workshop Luxembourg

Aims: The first workshop was planned to outline the project design and the detailed work plan, including the next two conferences. The partners also planned to set out the framework for the finalisation of the project.

Participants: The workshop included about 20 external participants, project partners, and Commission staff from DG Health and Food Safety, DG RTD (Directorate General for Research and Innovation), DG JUST (Directorate General for Justice and Consumers), and the European Institute for Gender Equality (DG JUST's Gender Equality unit). Because of its limited size and preparatory character, complete coverage of all EU Member States was not intended.

Participant information is included in the participant list ([Attachment 5](#))

Role of participants:

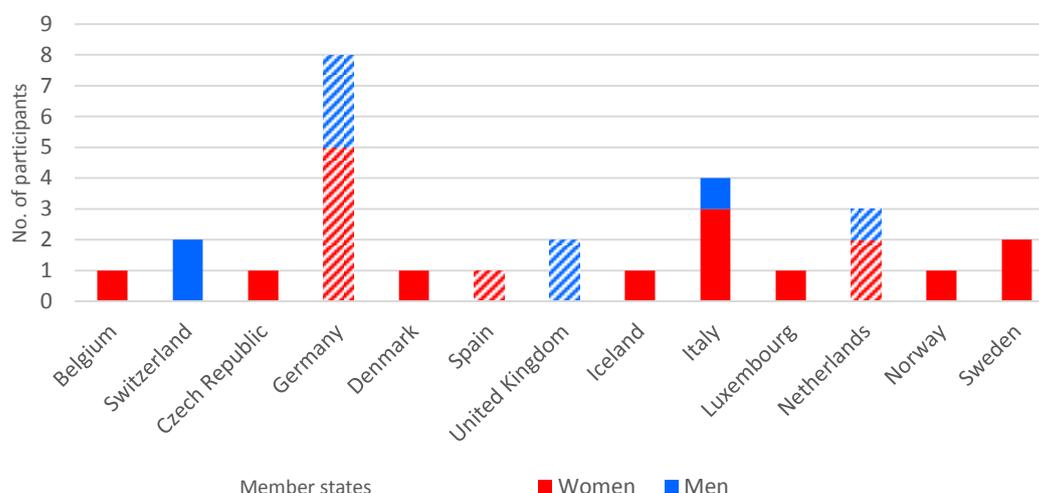
Partners: present work accomplished so far.

Advisory board members: expected to read report and to comment on the whole project during or after workshop. They received an information letter and whole 2nd interim report and information letter on the 18th Jan.

External experts: invited to read WP reports and to discuss specific issues based on their expertise. They received an information letter and reports on the WP or tasks to which they are assigned at the 18th Jan.

Commission staff: comment on the work

Figure 9: Participation of Member States in the preparatory Workshop, February 2016 (Luxembourg)



No of contributors per member states. Partner Member States are indicated as diagonal stripes. Women and men are shown in blue and red.

Workshop Content

In the welcome by Isabel de la Mata of DG Health and Food Safety, she outlined the necessity to recognize sex and gender differences in health.

The GenCAD overview by Vera Regitz-Zagrosek, GenCAD coordinator, Charite Universitaetsmedizin Berlin emphasised the discussion and feedback from participants on the project.

Bibliography review

Sabine Oertelt-Prigione and Vera Regitz-Zagrosek presented the most recent results of the literature search, as well as the importance of which items should be included in the factsheets and which of those were still missing:

- Renate Schnabel mentioned new studies on acute coronary syndrome patients: time-to-treatment very similar in women and men in Germany. Referral to this study will be important.
- Ulrich Keil asked for inclusion of notion that cardiovascular disease prevention is a success story in medicine, by increasing life expectancy and suggested use of Science 2012 paper, as well as SCORE project for references. It was also noted that the ESC guidelines only contain a small

focus on gender and asked for more weight to be given to sex and gender. Formal contact of our project with ESC offices may be helpful.

- Renata Cifkova asked for more focus on menopause and premature menopause for women
- Peter Ong made a suggestion to include of management of patients with chest pain and normal coronary arteries after angiography
- Marco Stramba Badiale mentioned paper on "Red Alert for Women" for reference in factsheets as well as the need to question why younger women have worse coronary artery disease diagnoses than young men
- Eva Swahn also mentioned the aspect of cardiovascular disease being a success story (i.e. reduction in morbidity and mortality). She also made note of the myth around women having atypical symptoms in coronary artery disease, which is not true and this needs to be addressed. Further discussion can be made of what physicians define as "typical" symptoms. More publications from the Sweetheart project should be included in references – they outline the reason for delays to treatment in women in Sweden.
- Colette Andree stated that lifestyle changes in women and men ought to be included

Database analysis

Nicholas Alexander GenCAD project manager, *Charite Universitaetsmedizin Berlin* and researcher discussed the database analysis of work package 1 and the inclusion of indicators relating to sex and gender variables in coronary artery disease. Comments from the discussants included:

- Katrin Fjeldstedt asked for data to be included from Iceland and asked for a more differentiated categorization of indicators like smoking. Comment U Keil: This may however be less important in cardiology than in oncology.
- Elisabeth Zemp Stutz emphasized the need to have more data for age groups of 65 years and above

- Isabel de la Mata emphasized the focus on this task should be on the impact of sex and gender in disease prevention (i.e. coronary artery disease)

EU Member State policy analysis

Alan White, *Center for men's health, Leeds Beckett University*, presented the overall concept of inclusion of gender into policies at different levels (meta frame, issue frame, document frame) and how to access additional experts who have access to policies. Further comments on the presentation were:

- Ineke Klinge suggested that all EU member states ought to adopt existing guidelines that cover sex and gender issues in coronary artery disease. However this is problematic, as the ESC Strategy for 2010/15 only has a small reference to this.
- Ulrich Keil confirmed these comments, stating that the ESC could give more focus on gender, but there is a lack of instruction.

Needs assessment

Mariola Bernal (replacement for Antonio Daponte) presented the methods and plan for the questionnaires of needs assessment in work package 2. Comments from the discussion after the presentation:

- Karolina Kublickiene suggested to include the European Institute for Gender Equality and the Standing Committee of European Doctors as reference contacts in reviewing questionnaires. Also mentioned that questionnaires for Sweden can be made in English and require no translation.
- Marco Stramba Badiale suggested the ESC website as a starting point for contacts of national websites on the subject matter
- Ulrich Keil confirmed this point, stating that each country of the month publication by the ESC has contact information which could be helpful. There are now 26 countries on the ESC homepage. Also of interest for the EU policy analysis of work package 1.

Factsheets

Presentation by Vera Regitz-Zagrosek and Floris Barnhoorn on content and design of factsheets. Comments:

- Use of social media was suggested by a number of participants, however Isabel de la Mata mentioned that one must consider the expenses and target audience
- Vera Regitz-Zagrosek stated that there would be two versions of the factsheets – one for lay people and one for healthcare professionals

Discussion of conference organization

Presentation by Vera Regitz-Zagrosek, who clarified differences between two conferences – 1st to focus on medical content, 2nd to focus on public health, prevention, and population measures

- Location and date of Bratislava for 1st conference to be changed. Replacement suggestion is Brussels in February 2017.
- Participants at 1st conference will be 2 per state (1 from public health policy and 1 from medicine with background in cardiovascular disease prevention) with this list being confirmed by February 2016
- Members of parliament were also to be invited
- Katrin Fjeldsted and Jannis Papazoglou asked for greater representation of students at these conferences
- Thereafter it was confirmed that there will be no entrance fee to the conference, however audience will be limited.

The Luxembourg workshop was characterized by constructive, open and successful discussions. After a presentation of each work package, the main outcomes were a review of facts collected in Task 1 of WP 1, comments on the proposed surveys in WP 2, as well as a clarification on the upcoming conference locations and targets.

5.3. Conference 1 - Brussels

The 1st GenCAD Conference was held in Brussels on 1st March 2017.

Goals, topics and agenda: The main focus of the 1st conference was on gender-related disease manifestations, treatments and outcomes, as these are a core elements to raise awareness in the general population and in

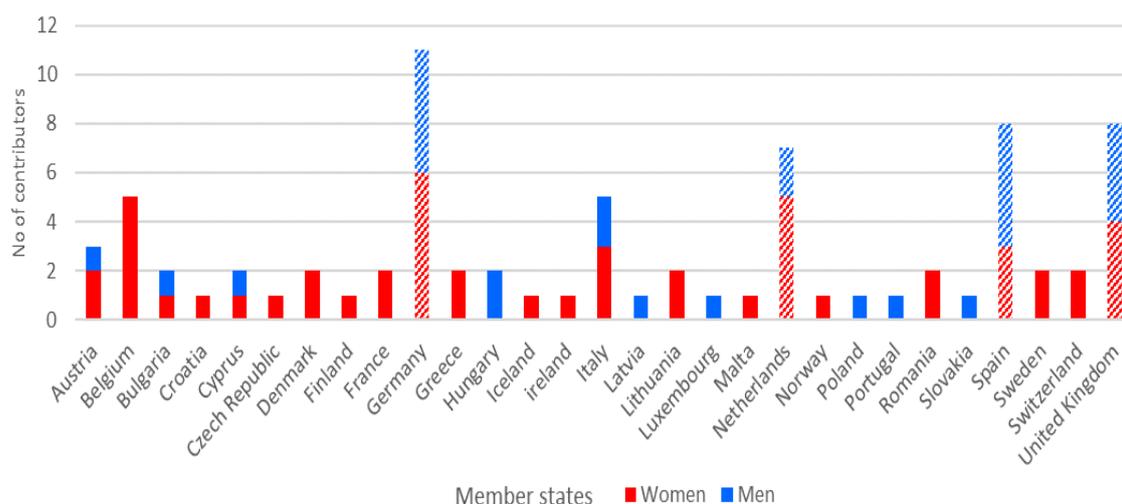
physicians. The initial results of the project including the needs assessment and factsheets were presented.

Invited persons: The targeted representation of all 28 EU Member States was one national representative (in accordance to the GenCAD contract) and one national expert (proposed by the national representatives involved in the project). Invitation lists were agreed upon with DG Health and Food Safety and invitations were successfully sent out.

Among those we invited were experts in gender and cardiovascular disease (group 1), persons with interests in policymaking and gender (group 2) and experts in gender/representatives of European organisations (group 3) (Figure 10). Furthermore, all ministries of health in all 28 EU Member States were contacted, some by several persons, and also by phone. Overall, we had representation from all EU Member States.

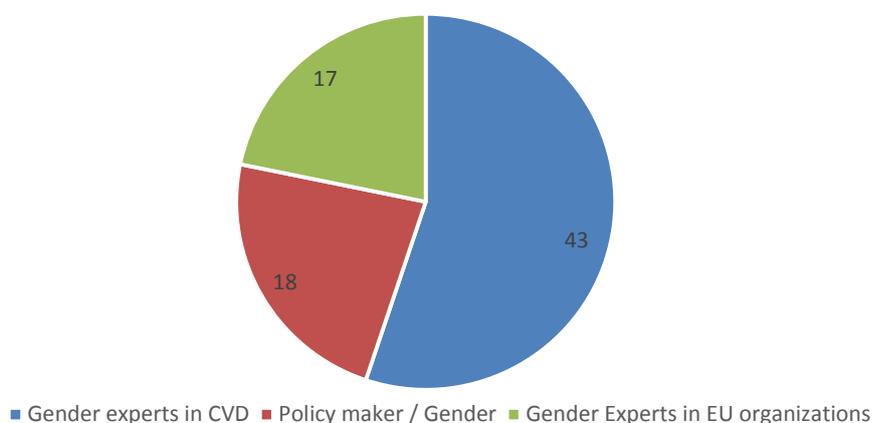
Invitations lists were sent to DG Health and Food Safety in June and were finalized in October. Thereafter, invitations and registration form were sent. The conference announcement was placed at DG Health and Food Safety homepage in November 2016.

Figure 10: Participants from Member States at 1st GenCAD conference, March 2017 (Brussels)



No. of participants per Member State. Partner Member States are indicated in diagonal stripes. Women and men are shown in blue and red, respectively.

Figure 11: Participant distribution in 1st GenCAD conference, March 2017 (Brussels)



Conference participants joined with diverse backgrounds, as gender experts in cardiovascular disease, policy makers with an interest in gender and gender experts in European organizations.

Conference Content

In her welcome address, Isabel de la Mata, DG Health and Food Safety, Luxembourg emphasized the importance of sharing information on gender-sensitive facts related to coronary artery disease, as an example for frequent diseases, and to discuss the implications on health in Europe as well as regional differences in gender specific disease manifestations, treatments and outcomes.

The conference was structured into four major areas, discussed in 4 blocks:

1. Gender and health - the challenge for the 21st-century

In the first block, new knowledge was discussed - most impressive results from the GenCAD literature search on sex and gender differences in coronary artery disease and in pharmacology, as well as gender specific risk factors and manifestations in European databases were presented. This included an overview on worldwide trends on an increase in non-communicable diseases and the importance of gender specific risk factors and comorbidities. In recent European surveys, women now have more classical cardiovascular risk factors than men.

Gender differences in coronary artery disease prevention, diagnosis, treatment and outcomes, based on more than 1000 references, were presented that were the basis of GenCAD factsheets. Coronary artery disease is increasing in younger women, probably due to life style changes. New gender sensitive risk factors, such as depression, stress, sexual dysfunction, sex hormone disturbances and unfavourable socioeconomic conditions have to be considered as well as pregnancy complications. The pathophysiological spectrum of coronary artery disease manifestations differs in women and men: some yet under-researched syndromes are more frequent in women, including microvascular disease, coronary spasms, and coronary dissections, the latter frequently seen in pregnant women. Sudden cardiac death in contrast is more frequent in men.

Applicability of drug therapy to women and men is not equal; in the cardiovascular field more data are available for men. The therapeutic response is a complex effect that depends among others, on hormonal status and lifestyles, comorbidities, genetic factors, foods and environmental contaminants, co-treatments, racial and ethnic differences, access to healthcare systems, adherence and psychosocial factors. The Swedish Sex, Gender and Medical Drugs database offers information on gender specific effects for some important drugs.

Focussing on prevention, we also discussed strength and weaknesses of the presentation of Gender specific risk factors and manifestations in European databases. Inclusion of the elderly, socioeconomic background, reproductive history, number of pregnancies, sexual function/ dysfunction, sex hormone status, mental health indicators and environmental toxin exposure, variables that vary significantly with gender, are often missing. However, database holders were mostly open to study gender aspects in coronary artery disease.

2. Member State policies in gender and health, focus on coronary artery disease

GenCAD looked at Member State policies in gender and health in a complex framework. At the meta frame, in all EU Member States, there is a policy

environment that should ensure gender equality and an absence of sex discrimination. There is a positive trend, where leading health organisations are supporting more gender-sensitive and gender-aware health care - the issue frame. Although some member states do not have any policies regarding sex and gender, others do. For example, Member States, such as Denmark, Germany, the Netherlands and the UK, have well-established policies. The inclusion of sex and gender in actual coronary artery disease guidelines and policies occurs at the document frame. Some countries tend to rely mainly on the ESC guidelines, thus their role in ensuring gender sensitive care is very important in the implementation of gender sensitive treatment and prevention strategies.

Gender-NET (EU-FP7 project) has carried out a mapping and analysis of existing national strategies and programmes promoting the integration of sex and Gender Analysis into research contents (IGAR), for funding agencies, peer-reviewers and grant applications. 13 national ministries, funding agencies, national research organisations from 12 countries across Europe joined forces to promote gender equality in research, and in particular to advance the (IGAR). It was discussed that the upcoming gender-NET PLUS project, an ERA-NET Cofund scheme funded through Horizon 2020 will follow up on gender-NET in summer-fall 2017.

The Brussels EU perspectives and gender aspects in Horizon 2020 aimed at implementing gender aspects in European research at multiple levels. Horizon 2020 received more than 270.000 proposals for evaluation in the first 2 years. Evaluation of all proposals has to be done by gender experts. Therefore, they implemented a database, which now comprises 6.000 experts, women and men. In 2017 there was be a call for "Gender Equality Plans" and in 2018 will be reported about the "National Action Plans".

The gender summits are reporting on gender-related aspects in European policies, focus on health, at the gender summit. They are organized in different regions in the world to bring the facts showing impact of sex/gender differences on research outcomes together. The growing trend to use

Information and communications technology in health is a new area of concern. Data mining used to examine large databases in order to generate new information and may be helpful but the analytic engine must recognize potential shortcoming in the data used, in particular, the missing sex/gender aspects.

3. Session Gender awareness and factsheets

The GenCAD survey on the awareness of gender differences in coronary artery disease along with the initial results in general population were presented. This first survey in 6 countries showed that almost 50% of the participants would not call emergency services in case of heart attack, as a first reaction and more than 50% of men and women want to have more information on prevention and management of cardiovascular disease.

Surveys in the HC professionals are under way.

The factsheets on gender aspects in coronary artery disease were presented. The main goal of the projects is to disseminate a summary of the gender differences in coronary artery disease, emerging from our bibliographic study presented in block 1 - to health professionals and EU citizens in all Member States in the 24 official EU languages.

The standing committee of European doctors is interested in gender issues. A representative of the Standing Committee of European Doctors presented their activities: they recently adopted a Standing Committee of European Doctors policy sex and gender in medicine in April 2016 (<http://www.cpme.eu/cpme-policy-on-sex-and-gender-in-medicine/>) which will be synergistic with our project.

4. Gender in chronic diseases and impact on policies

In this block, we offered best practice examples from different states and diseases. A representative from the Gender Medicine Unit at the Medical University of Vienna discussed sex and gender differences in Diabetes mellitus. Sex and gender are important variables for diabetes management, which are

currently not included, and thus they need to be considered in modern personalized medicine. The German Federal Ministry of Education and Research reported on a case study from Germany titled the "Health Across the Life Span". The aim is to develop novel and effective concepts for health promotion, prevention and care which take into account the specific characteristics and developments in children and adolescents, the elderly, working people, women and men. A representative of the Women's Health Centre at the Innsbruck University Hospital presented a case study how they implemented Gender Medicine into the work of all health care professionals, starting with lecture series, elective and finally mandatory courses. The director of Biocenter Finland reported on policies to tackle gender inequalities in research and health in the Nordic countries. Sweden, Finland and Denmark were on the top ranking of surveys asking for gender equal rights but it was pointed out that lack of women in academic positions is a problem.

5. Comments from the advisory board and conclusions

The advisory board pointed out that a large number of facts on sex and gender differences in cardiovascular disease have been identified in the first part of the GenCAD project. These are all agreed among experts but did not make the way to policies so far. Representatives of the advisory board underscored that factsheets for health care professionals and citizens are important to raise awareness. However, it needs about 10 years to change a simple thing as it is discussed in the ACC/AHA clinical practice guidelines implementation strategies. Messages must be clear and simple and adapted to the listener. Identifying the target audiences for sex and gender facts and communicating clear and convincing messages will be the challenge for the next year.

Evaluation

We asked for feedback from all participants after the conference by email. The feedback we received was overwhelmingly positive. Out of the participants that responded, the vast majority agreed that the conference was a major

success. In particular, a number of them were grateful for the broad participant range and the new information presented.

5.4. Conference 2 - Brussels

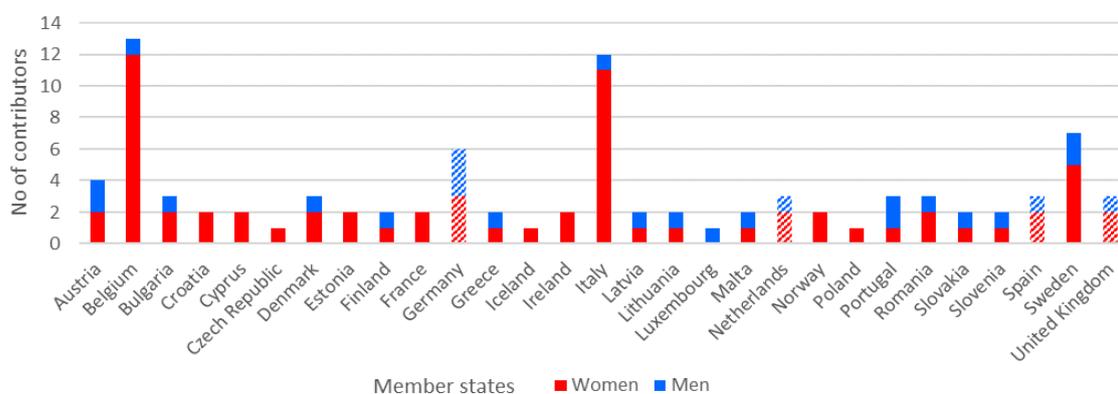
The 2nd GenCAD Conference was held in Brussels on 11th October 2017.

Goals, topics and agenda: The main focus of the second GenCAD conference was on gender specific disease prevention. In particular, greater details was given population measures, experiences within the single Member States and regional differences. The conference contained two moderated round table discussions that allowed for in-depth discussion about the report and future policy needs.

Invited persons: As in the first conference, the targeted representation of all 28 EU Member States (one national representative and one national expert) was achieved. In comparison with the first conference, a wider participation of policymakers was invited. Special focus was given to representatives of health ministries and politicians within health- and gender-related fields.

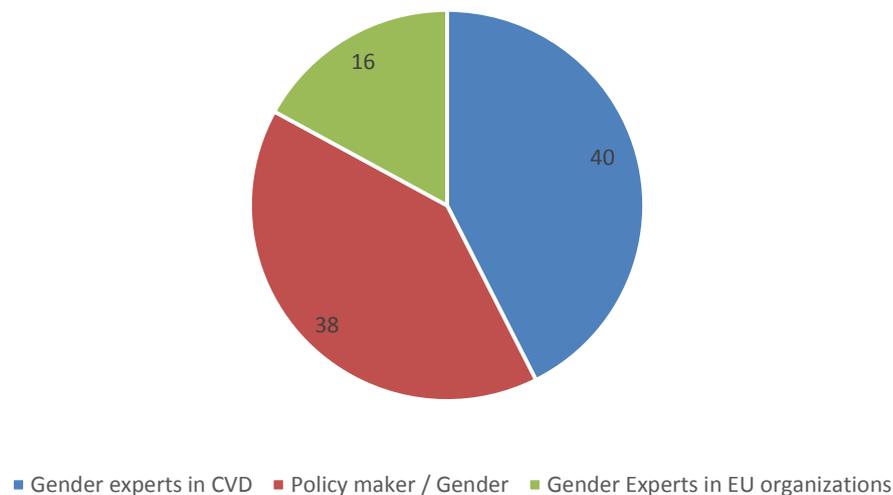
Once the invitation lists were agreed upon and invitations were successfully sent out.

Figure 12: Participant distribution in 2nd GenCAD conference, October 2017 (Brussels)



Number of participants per Member State. Partner Member States are indicated as diagonal stripes. Women and men are shown in red and blue.

Figure 13: Participants distribution – 2nd GenCAD conference, October 2017 (Brussels)



Participants distribution of 2nd GenCAD conference. In comparison with first conference, a greater percentage of policy makers contributed.

Conference Content

Welcome by the chair Vera Regitz-Zagrosek, GenCAD coordinator, Institute of Gender Medicine, Charité-Universitaetsmedizin Berlin

Introduction and welcome of Isabel Pena Rey Lorenzo, policy officer in *DG Health and Food Safety* (DG Health and Food Safety) *representing the European Commission*.

Gender mainstreaming is a long-established EU principle to be taken into account in all policy areas and the Commission have a solid determination to act and to implement this commitment. EU health policy takes the gender dimension in health into account in its activities, in the broader context of its work to support Member States in reducing health inequalities between and within them. Many chronic diseases differ significantly in women and men in risk factors, prevention, clinical manifestation, response to therapies and outcomes. There is a need to improve the understanding of sex and gender differences in regarding treatment and prevention activities in European countries. EU financed the GenCAD project with the aim to focus on awareness

and knowledge about gender-related prevention of cardiovascular diseases as an example to other chronic diseases.

EU and WHO actions on gender and health

- Greet Vermeylen, *DG Justice - European Commission EU*, talked about actions to promote gender equality in health and mentioned the “entry points”: The European Pillar of Social Rights, the Strategic Engagement for Gender Equality and the UN sustainable development goal on gender equality. She underlined two elements with potential associations with health issues: violence against women on the one hand and quality of work, including work-life balance on the other hand. Next to the important Istanbul Convention, the Commission has set up a number of actions to combat violence against women. She next referred to the issue of gender segregation in the labour market with associations with health, the fact that men and women do different jobs, in different sectors, the 'double burden' and engagement of men and women in so-called 'unpaid work' (care and domestic work in the private sphere). She linked it with gender pay gap and the gender pension's gap. It is important to consider these issues with a view to make work sustainable over the life course. Both healthy work environments as well as reconciliation between work and private life, with a more equal sharing of work done in the private sphere, can contribute to the health of women and men throughout one's life.
- Teresa Moitinho de Almeida, *DG Employment, Social Affairs and Inclusion - European Commission*, focused her talk on the occupational perspective, in particular the promotion of a gender-sensitivity approach through EU Occupational Safety and Health actions. Goodhealth and safety conditions for women and men at work are beneficial for the workers and employers as well as for society as investment on prevention of health and safety at work risks pays off. “Gender sensitivity approach” in Occupational Safety and Health is an ongoing exercise, not an one-off activity. Therefore, sharing and exchange of experiences, practices and tools need to continue and be promoted. The Commission and the European Agency on Safety

and Health at Work carry out many actions to support employers to properly deal with these themes.

- Isabel Yordi Aguirre, *WHO*, talked about WHO actions in Europe on Gender and health within the WHO Regional policy framework Health 2020 and the 2030 Agenda for sustainable development. Two main WHO initiatives are the report and the Women's health strategy (2016), the report, and the Men's Health strategy, which are currently under development. The WHO Strategy for women's health and well-being aims at: - strengthening governance for women's health and well-being; - eliminating discriminatory values, norms and practices; tackling the impact of gender and other social economic, cultural and environmental determinants; and improving health systems responses to women's health and wellbeing. The men's health strategy addresses the impact of masculinities and socioeconomic determinants of the exposure to risk factors and on the responses from the health systems. It also focuses on strengthening men's engagement in gender equality in health. The main objectives are: reducing premature mortality of men and improve their health and wellbeing across the life course; reducing inequalities between men of all ages across the region and within countries; improving gender equality by engaging men in fatherhood, unpaid care, preventing violence and in sexual and reproductive health.

Implementing a gender dimension in health research

- Gesa Hansen, *DG Research and Innovation, European Commission* pointed out that achieving gender equality is not only a matter of social justice but also of enlarging the pool of talents and the innovation potential. Including sex and gender analysis in research enhances the quality and the societal relevance of the produced knowledge, technologies and innovations. The European Commission has defined a strategic engagement for gender equality¹ in EU policies. Its third objective, the integration of the gender dimension in Research and Innovation content aims to ensure that the biological characteristics and the social/cultural features of both women and men are taken into account as relevant. Currently 70 % of the funded

health research projects under Horizon 2020 have integrated an explicit gender dimension into their research approach, including several sex specific projects mainly dealing with female diseases. There are various good examples of funded projects in pre-clinical and clinical research integrating both sexes/genders into their approach to produce sex/gender disaggregated data in areas such as cardiovascular disease, mental health, cancer etc. By referring to sex-and/or gender analyses in the proposal templates and in many health-related call topics the European Commission has brought these issues a major step forward and will continue to do so in the future.

Gender inequalities in health

Round table discussion, moderated by Jürgen Scheftlein, DG Health and Food Safety – European Commission Participants: Alan White, Center for men's health, Leeds Beckett University Alessandra Caré, Centre for gender-related Medicine in Italy, Ineke Klinge, Chair of H2020 Advisory Group for Gender, Jürgen Harreiter, Center for Gender Medicine, University of Vienna

- Alan White, *Center for men's health, Leeds Beckett University* started with a statement about *Understanding of the gender concept from the men's perspective*. He pointed out that the men's health perspective is often focused onto the high rates of premature death. However, the health and wellbeing of men covers many more issues, including their use of preventative health services, their mental health, their lack of access to weight loss services, and recognition of the impact of the wider social determinants of health. Studies that have looked into health policies locally, nationally and internationally have found that men are mostly invisible, with little recognition of the specific health needs they may have or how they may be addressed. In Leeds, following on from the State of Men's Health in Leeds report there is now a much more concerted effort to reach out and target men more effectively. This work is now being followed up with a State of Women's Health in Leeds report, with the intention of making Public Health in Leeds fully gender aware. Thus, the

WHO (Europe) men's health report and strategy, which is in the process of being developed, is an important development.

- Alessandra Caré, *Centre for gender-related Medicine in Italy*. Participating on behalf of the Center for Gender Medicine recently established at the Istituto Superiore di Sanità (Rome Italy) she illustrated the Italian scenario on gender-related medicine. She underscored that, thanks to the interest of Health Minister Beatrice Lorenzin and to Laura Boldrini member of the Parliament, a law article sustaining the inclusion of sex and gender in the National Health System has recently been submitted to the Italian Parliament. She highlighted the absolute requirement for recommending the inclusion of both genders not only in clinical trials, but also in preclinical studies, and the opportunity of sustaining those projects correctly balancing male and female samples as these studies require doubled amounts of subjects and, in turn, budgets. The conclusion was that the new vision of Gender Medicine requires additional investment in research, reform of medical teaching and, primarily, the political willingness to change the health approaches.
- Ineke Klinge, *Chair of H2020 Advisory Group for Gender*, described the Dutch initiative: In 2013, the bottom-up multi stakeholder Alliance for Gender and Health, brought together policy makers, scientists, medical professionals, gender experts, and knowledge institutes around the theme gender and health, coordinated by Women Inc. This Alliance successfully implemented the Gender and Health research program at the Dutch Organisation for Health Research and Development at (ZonMw), financed by the Ministry of Health (12 million euro – 4 years). This programme is explicitly aimed at reducing health inequalities by stimulating sex and gender analysis in research in order to address the gaps in knowledge. This grant programme profits from the Gendered Innovations methods and case studies, as well as from materials and online trainings developed by the Canadian Institute for Gender and Health GH at developing instructions for applicants and evaluators. At the national congress Gender and Health of October 5 2017 The Dutch Society for Gender and Health was launched: <http://genderengezondheid.nl>

- Jürgen Harreiter, *Center for Gender Medicine, University of Vienna* pointed out that sex and gender differences can be found in nearly all fields of clinical medicine, which is being reported in a growing body of evidence. However, there is still a lack of awareness and an insensitivity about these issues and how to apply them in daily routine. Many guidelines and recommendations for health professionals do not include sex and gender differences and thus the transmission from research to clinics is limited and hampered. Sex and gender are important variables for clinical care of patients in all fields of medicine, which are currently often neglected or even ignored. They need to be considered in modern personalized medicine to further improve and individualize clinical care for women and men.

Awareness on gender inequalities in cardiovascular disease in Europa and factsheets

- Vera Regitz-Zagrosek, *Charite Universitaetsmedizin Berlin*, presented the results of the 2 surveys conducted by GenCAD Partner EASP on knowledge and awareness of gender specific aspects in coronary artery disease. The first was conducted with the general public in 6 selected EU-representative countries and their 6 languages. Laywomen were less likely to recognize heart disease as relevant to them, and do not identify heart disease as a leading cause of female death. They cited stress is the most important risk factor, with the risk of smoking, exercise, and diabetes underestimated. Almost 50% of women reported that they would not call emergency services in case of heart attack, as a first reaction. Less than half of participants are well informed on cardiovascular disease. Mass media and internet are the main sources of information on cardiovascular disease. A second survey was conducted with health care professionals across Europe, in 7 languages. They recognized coronary artery disease as the most frequent cause of death in women and men. However, knowledge on lack of exercise, diabetes as risk factors, and on optimal diagnosis of coronary artery disease and therapy in women and men needs improvement. Patient information campaigns must be improved.

- Based on the identified knowledge gaps, the GenCAD factsheets, which have been produced in 24 languages, are very important. They describe gender differences in both the well-known and the newly recognized risk factors, e.g. socioeconomic status, depression, inflammatory and rheumatic diseases, preeclampsia, genetic factors, menopause and andropause and erectile dysfunction. They also include important information on the gender aspects in prevention, clinical manifestation, diagnosis, management and outcomes of coronary artery disease. All the data used for the factsheets are based on a structured literature search of over 1000 references
- Finally, she discussed the potential impact of GenCAD, on the behaviour of the patients and the medical community, which in the long run is only affected by guidelines. She reported a major step forward in that the, guidelines of the ESC from August 2018, will include a requirement that sex and gender-related facts should be considered.

Implementation of gender specific prevention

- Michel Wensing, *University of Heidelberg Dept. of General Practice and Health Services Research and Nimwegen*, discussed Implementation of gender specific prevention. The publication of valid scientific studies, practice guidelines and information syntheses is a crucial for the uptake of new insights into healthcare practice. However, additional strategies are often needed to achieve rapid and comprehensive change. Such strategies include: continuing professional education, computerized decision support, performance feedback, patient involvement, organisational change, financial incentives and regulations. None of these strategies are universally effective, because local conditions determine which strategies are needed to overcome barriers of implementation. Implementation science offers a set of concepts and methods to develop and evaluate implementation programs, which help to escape from narrow-minded quickly chosen approaches, which often not evaluated. Implementation science recommends taking a stepwise approach: determine goals for implementation, scan the local context, analyze the implementation

challenge in-depth, tailor strategies to the most relevant barriers, apply and evaluate the strategies. It is also important to realize that major change may take time.

Sustainability, future research and implementation in all member states

Round table discussion moderated by Ellen Kuhlmann, *Senior Researcher at Public Health School in Hannover*.

Participants: Alexandra Kautzky-Willer (President, International Society for Gender Medicine, Dept Gender Medicine, University of Vienna), Isabel Saiz (Head of unit on international topics, incl Gender, Spanish Ministry of Health), Alessandr  Car  (Center of Gender Medicine, Rome), Renata Cifkova (Thomayer Teaching Hospital, Prague), and Christopher Mayer (AIT Austrian Institute of Technology, Vienna).

The discussion brought together a broad range of expertise and diverse perspectives, which helped to better connect researchers, policymakers and practitioner. They offered rich insights into the implementation of gender specific approaches across various European countries and illustrated the future needs of the field. The keynote statements of the five participants in the Round Table highlighted an urgent need for action in many different areas as well as on macro- and micro-levels of healthcare. The following priority areas have been identified:

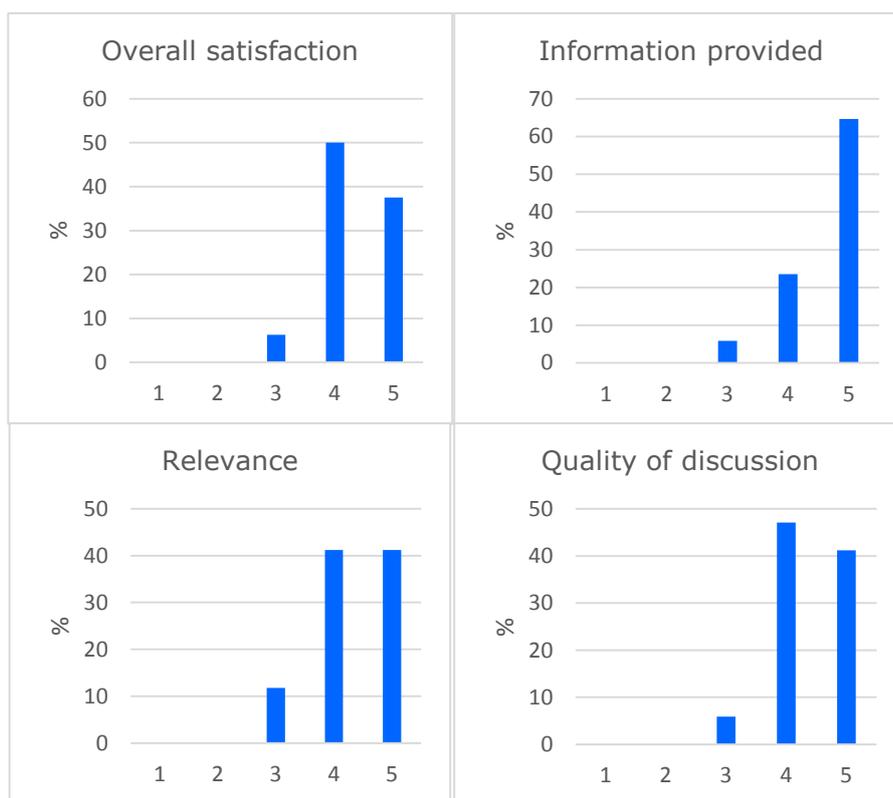
- Strengthen gender approaches in medical curricula and in guidelines
- Bringing gender into a national health policy strategy and connecting gender to quality indicators
- Improving information and knowledge transfer and involving medical leaders to strengthen gender approaches
- Improving funding for gender research and integrating gender in guidelines and funding decisions
- Addressing specific needs of women and developing guidelines for hypertension and pregnancy

- Bringing gender into EU research. The EU has recently stated that bringing gender into a network is not enough, and more has to be done on implementation.

In conclusion, this European GenCAD conference illustrated the benefits of EU coordinated networking and explored the future direction of travel of EU policy to strengthen gender-sensitive medicine.

A formalized short evaluation questionnaire was distributed to the participant which included 4 basic questions on the satisfaction level using scale value (5=Excellent to 1=Dissatisfied). Overall, the agreement with the conference was very good to excellent and this reflected the vivid discussions.

Figure 14: Evaluation by participants of 2nd GenCAD conference, October 2017 (Brussels)



Evaluation of the conference by the participants

Responses: 5 = Excellent 4 = Very satisfied 3 = Satisfied 2 = Less than satisfied 1 = Dissatisfied

5.5. Conclusions

The conferences showed in an impressive manner how big the benefit from interdisciplinary and trans-sectoral collaboration really was. We had vivid discussions and the interaction between clinicians, public health researchers, policymakers from all Member States was outstanding. All groups claimed to have learned from each other and new ideas were developed.

5.6. Deliverables and performance indicators

WP 4				
	Deliverable	Start (month)	End (month)	Responsible
5	Workshop	8	14	CH
6	Workshop report	14	15	CH
7	Conference 1 (Brussels) and minutes	14	27	CH
8	Conference minutes	28	29	CH
9	Conference 2 (Brussels)	29	34	CH
10	Conference minutes	35	36	CH

As mentioned in the Overview section, the dates and locations of the deliverables for the Conferences work package were changed after discussions with DG Health and Food Safety to reach more EU parliamentary experts and advisors. The workshop and both conferences were held within the agreed timeframes and the minutes of all meetings were consolidated and presented to DG Health and Food Safety, as well as all participants, as planned.

The performance indicator in this work package was the participation of all Member States representatives in all conferences. We were able to have at least one representative from every Member State, in the very most number

of cases two, for each of the conferences. Additionally, the evaluation of both organised conferences was very good to excellent and pointed to well organised events that contained novel information that were attractive to broader audiences.

6. Dissemination

6.1. Objectives

Communication and dissemination strategies were developed to go beyond our conferences and to reach greater target audiences to work towards growing and building of the understanding of sex and gender effects in coronary artery disease.

6.2. Methods

In the initial phase of the project, a communication and dissemination plan was created to support internal and external communication, dissemination across the twenty-eight Member States, to assure that the different activities, factsheets, conferences, internet activities and conventional media activities are well interrelated.

To do so, the following activities were undertaken:

- Development of overall communication strategy and corporate identity
- Development of dissemination plan: target audiences, messages and distribution actions and channels, Sustainability plan
- Dissemination activities, including social media platforms, website and conferences presentations
- Linguistic adaptations of all materials

6.3. Results

6.3.1. Communication strategy

A communication strategy was developed and adapted in the first project months, with the final plan discussed at the Luxembourg workshop.

Communication and dissemination for the project had two primary focal points: development of an effective project communication programme that

clarifies key messaging and communicates achievements, calls to action and progress of the project to health and non-health stakeholders; and the development of easy to use (and understand) messages, communication framework, information and online resources for use across Europe. The key messages for project communication were agreed upon by the partners at the onset to focus project activities.

The communication and dissemination strategy targeted health professionals and general practitioners; EU citizens and interest groups; and patients. The project worked towards growing and building on gender and coronary artery disease understanding, gender impact on health, actions health professionals can take to deliver effective advice, treatment and information to citizens and actions citizens can take to maintain coronary artery disease health.

As a part of the overall communication strategy, we developed a coherent program for communication in the scientific area and in the general public. It assured that the different activities, factsheets, brochures, newsletters, conferences, internet activities and conventional media activities were well interrelated and promoted the same mission and messages to their specific relevant target audiences.

The communication strategy also considered potential communication barriers and obstacles. Potential barriers identified included, but are not limited to resources, reputation, and openness/willingness to change issues.

As such, we began by generating a corporate identity and then contacted our stakeholders in regular intervals. We developed together with DG Health and Food Safety a project website, and contacted our potential stakeholders with project brochures and newsletters, conferences, internet activities and conventional media activities

6.3.2. Website

To communicate the project and its results in a sustainable manner, we developed a homepage hosted by DG Health and Food Safety. The main site is

in English with additional materials like factsheets, and executive project summary, made available in all EU official languages. Event links to both Brussels conferences were also hosted on this website.

6.3.3. Newsletters, flyers

We developed regular project newsletters in basic English. Each contained information about the project—its design, objectives, research themes, findings, interventions and assessment procedures, dissemination activities and initiatives. The newsletters have been published electronically. They were distributed by the network partners in the different Member States in English and in translated versions. The newsletter was disseminated through various listings of people and groups interested in the project subject and its work.

6.3.4. Stakeholders

We identified the following audiences of various target groups: policymakers and stakeholders within public health, healthcare, gender sectors, business, media, and the general public. For a broader audience, networks of consortium and cooperation partners were used. In particular, these networks helped to reach our aims of the involvement of all Member States as well as going beyond typical healthcare and public health networks to reach citizens through channels, based in their local community.

Involvement of target groups and stakeholder groups

Stakeholder lists were generated for distribution of specific project news, materials and events, based on strategies from previous projects, like EUGenMed, from participants of the conferences of the International Society of Gender medicine (Berlin 2015) and from members of national societies of gender medicine. We started with the members of our EUGenNet network, a group of ca 80 scientists that was generated by the Institute of Gender in Medicine Berlin, based on the EUGenMed project and included former consortium partners, active researchers in gender medicine, active stakeholders and policy makers. This was the starting point for international communication activities.

A larger stakeholder list was generated with the help of this EUGenNet network partners that all have their own networks and therefore served as multipliers. Furthermore, systematic searches in the internet were done to identify groups and persons interested in gender and health. In this second stakeholder list, we assembled more than 550 contacts, building a comprehensive pan-European list of stakeholders. This list became the basis for conference announcements, invitations, networking, newsletter distribution.

We also built a gender expert multi-sectoral advisory group with 30 opinion leaders from healthcare, public health, gender studies, business, European citizens, media/public relations, journalism and others deemed as relevant to consult with throughout the project, particularly regarding sustainability and dissemination. The comments of these experts were particularly valuable for discussing quality of bibliographic analysis, database analysis and assembly of factsheets.

6.3.5. Presentation of GenCAD at Conferences

GenCAD Conferences:

Presentation of the project at the two GenCAD Conferences described above was part of the dissemination plan. The main focus of the 1st conference was on gender-related disease manifestations, treatments and outcomes, as these are a core element to raise awareness in the general population and in physicians.

The main focus of the second GenCAD conference was on gender specific disease prevention. In particular, greater details were given on population measures, experiences within the single Member States and regional differences. The conference contained two moderated round table discussions that allowed for in-depth discussion about the report and future policy needs. Factsheets were also part of the dissemination activity at this conference.

We made sure that the key messages presented at these conferences were well in agreement with our communication and dissemination plan and the messages distributed at the conferences listed below.

External conferences:

Project results and factsheets were announced and communicated at different congresses, including the various ones listed below:

- 16.10.2015 8th European Public Health (EPH) Conference in Milan, presented by Vera Regitz-Zagrosek and Floris Barnhoorn. The first results of the project were shared with about 20 conference delegates in a meeting of the EUPHA Section on Chronic diseases.
- 20-23.09.2015 International Society for Gender Medicine conference 2015 in Berlin, presented by Nicholas Alexander in the form of a project poster. Flyers were distributed throughout the conference, which hosted delegates from all over the world. A GenCAD meeting and an open GenCAD session were organized.
- 15-18.05.2017 Organization for the Study of Sex Differences conference 2017 in Montreal. Results from GenCAD project was presented and discussed with delegates from more 20 countries by Vera Regitz-Zagrosek.
- 28.8-1.9.2017 European Society of Cardiology Conference in Barcelona. Factsheets and overall strategy of GenCAD were presented by Vera Regitz-Zagrosek to a large audience of the "Women in Cardiology" group at ESC, from all ESC member countries (more than 47).
- 31.08-02.09.2017 European Congress for Internal Medicine 2017 in Milan. Drafts of the factsheets and overall strategy of GenCAD were presented by Vera Regitz-Zagrosek to a large audience of European doctors, mainly specialists in Internal medicine.
- 14.09.2017 10th Annual Meeting of the Japanese Association of Gender medicine. Drafts of the factsheets, GenCAD results were presented by Vera Regitz-Zagrosek in a keynote lecture mainly to physicians and researchers interested in Gender Medicine in Japan.
- 14-16.09.2017 International Society for Gender Medicine 2017, Sendai, Japan. Drafts of the factsheets and overall strategy of GenCAD were

presented by Vera Regitz-Zagrosek to a large audience of doctors and students, Japanese and international researchers.

- Press conference of the 10th EPH Conference: In addition, both Vera Regitz-Zagrosek and Karin Schenck-Gustafsson participated in the press conference of the 10th EPH Conference. Karin Schenck-Gustafsson was interviewed for the 6 o'clock news by the main Swedish TV channel, SVT, and spoke about gender differences in cardiovascular therapy. The interview can be seen here: <https://www.svtplay.se/video/15723856/rapport/rapport-2-nov-18-00-1?cmpid=del:an:11-02-2017:rapport:pla:lp-app>
- 16.10.2017 World Health Summit in Berlin from 15-17 October 2017, The World Health Summit brings together about 2,000 decision-makers and representatives from the entire spectrum of health-related fields and industries. Factsheets were handed over to the delegates at the lunch breaks.
- 06.11.2017 Gender Summit 2017 in Montreal, presented by Vera Regitz-Zagrosek. Among others, the printed factsheets were disseminated here.
- 02.11.2017 10th EPH Conference in Stockholm, presented by Vera Regitz-Zagrosek at a lunch symposium. Presentations were made by Vera Regitz-Zagrosek, Alan White and Karin Schenck-Gustafsson to an audience of 30 persons. The session was chaired by Floris Barnhoorn. Topics included: GenCAD project introduction and overview, Cardiovascular therapy – are women and men different?, Gender policy analysis in the EU and Presentation of GenCAD factsheets.
- 23.11.2017 INSERM study day on Sex and Gender in Paris. Factsheets and key messages of GenCAD were presented by Vera Regitz-Zagrosek to a distinguished audience of approx. 150 researchers from all over the world and from France.
- 25.11.2017 Hausärztetag Saarbrücken. Factsheets and key messages of GenCAD were presented by Vera Regitz-Zagrosek to approx. 150 primary care physicians.

- 14.12.2017 Lisbon conference on gender. Factsheets and key messages of GenCAD were presented by Vera Regitz-Zagrosek to an international audience.

6.3.6. Dissemination via conventional and electronic media

The factsheets were sent to a number of medical societies, communicated via the homepages of all partners and a number of others. Table 10 below lists the medical societies/organizations who agreed to the electronic dissemination of the factsheets as of December 1st or are discussing it.

Furthermore, a large number of articles for TV and radio broadcasts appeared in the lay press in the countries of the partners.

Table 10: List of medical societies/organizations

Website	Organization	Status
http://gender-tagung.dgesgm.de	Working group „Kompetenzen in der Gendermedizinischen Lehre“	Completed
http://dgesgm.de	German Society for Gender-related Medicine	Completed
https://www.cpme.eu/?s=GenCAD&cat=0	The Standing Committee of European Doctors	Completed
http://www.ehnheart.org	The European Heart Network	Completed
https://www.ccr.charite.de/	Center for Cardiovascular Research (CCR)	Completed
https://eupha.org/GenCAD	The European Public Health Association	Completed
http://www.pgeu.eu/en/	The Pharmaceutical Group of the European Union (PGEU)	Completed
http://www.isogem.com/	International Society for Gender Medicine (IGM)	Completed
http://www.cihr-irsc.gc.ca/e/32019.html	Canadian Institutes of Health Research	Completed
	Italian society of gender medicine	agreed
http://www.eu-patient.eu/	The European Patients' Forum (EPF)	Pending
http://www.age-platform.eu/	AGE Platform Europe	Pending
https://www.idf.org/	The International Diabetes Federation (IDF)	Pending
http://www.mhe-sme.org/	The Mental Health Europe	Pending
http://eige.europa.eu/	The European Institute for Gender Equality (EIGE)	Pending

http://www.uemo.eu/	European Union of General Practitioners	Pending
http://www.eahp.eu/	The European Association of Hospital Pharmacists	Pending
http://www.combarriers.com/	Communication Across Barriers (CAB)	Pending

List of the medical societies and organizations who were approached to electronically list general public and healthcare professional factsheets on their websites.

Completed: Dissemination activity was completed or the factsheets were uploaded to the respective website.

As for the GenCAD partners, both factsheets for health professionals and for the general public (available in all Member States languages), have been uploaded to the EUPHA webpage https://eupha.org/general_page.php?p=155. Furthermore, the factsheets were distributed to all national public health associations in the European Union that are associated with EUPHA by a monthly newsletter and made available for distribution through the channels of the national associations in those EU countries where EUPHA member associations are present.

Radboud dissemination activities included the translation of the factsheets into the Dutch language and distribution of these nationally to several organizations/authorities and expert groups on sex and gender in healthcare:

- Dutch alliance Gender and Health, which is an important advisory organ to the ministry of Health
- Working Group Gender, Dutch Society of Cardiology
- Attached to course material for Cardiology training general practitioners and young cardiologists
- Delivered as hand-outs on lectures for the public
- Present as promotion material on Cardiology outpatient clinics
- Provided as promotion material for the Dutch Heart Foundation
- Provided as promotion material for patient organizations ("hartenvaatgroep')

The BSPH team collaborated with Association of Schools of Public Health in the European Region in promoting and disseminating the project results via its website, among its social media networks, and its newsletter.

6.3.7. Social media

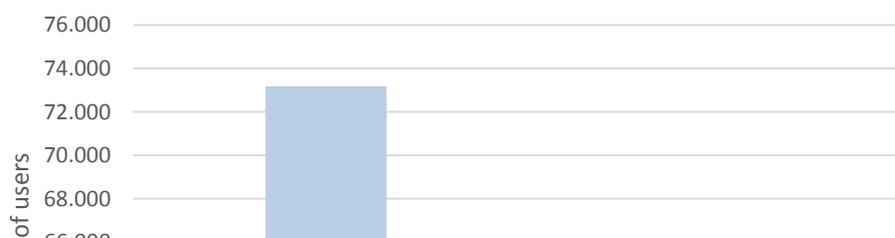
Social media has a huge potential to reach out to the general public and also to healthcare and medical organizations along with their followers. Therefore, we also communicated the project in the social media like Twitter and Facebook to reach our target audiences. Our target audiences included healthcare, health and wellness personnel, health organizations, non-governmental organisations in a population that was above 21 years old, an arbitrary age limit proposed by the facebook system, to target an adult audience. Tweets of the factsheet statements and a Facebook fan page is a regular activity until end of 2018. Furthermore, we were also using Facebook and Twitter to address the local target audiences in the desired age groups in all Member States. YouTube is additionally used to reach the further audience using video content.

GenCAD partners used the 2nd GenCAD conference as a means to communicate the project results and factsheets via social media, including but not limited to webpages, Facebook, Twitter, cited on radio, newspapers, etc.

Facebook activities

For each Member State a separate activity with the native language was launched for the user age above 21 and with interests in health and wellness, patient safety and preventive healthcare. The activities were run by the members of GIM. Total of 73,177 targeted Facebook audience was reached for General Public factsheets together with 61,979 for Healthcare Professional factsheet in English language (Figure 15). 2,381 times General Public factsheet link was opened while 1,704 times Healthcare Professional factsheet link was clicked.

Figure 15: General Public and Healthcare Professional Factsheet Facebook activity across European Member States in English language.

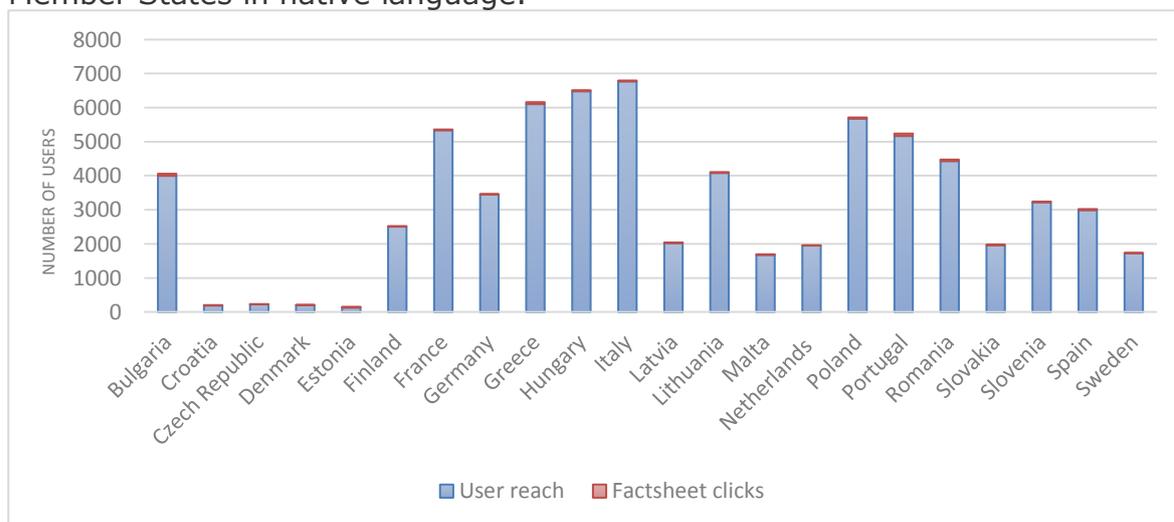


More Facebook target audience saw the general public factsheets compared to healthcare Professional factsheets.

Among those who received our messages, different numbers of people opened the factsheets in the different Member States.

The General Public factsheet was opened by, for example, 6778 persons on Facebook from Italy in their native language whereas only approx. 133 persons from Estonia clicked on the factsheet in their native language (Figure 16). These differences in numbers could be due to the fact that there are more active Facebook users in Italy compared to other Member States in this respective target audience.

Figure 16: General Public Factsheet Facebook activity across European Member States in native language.

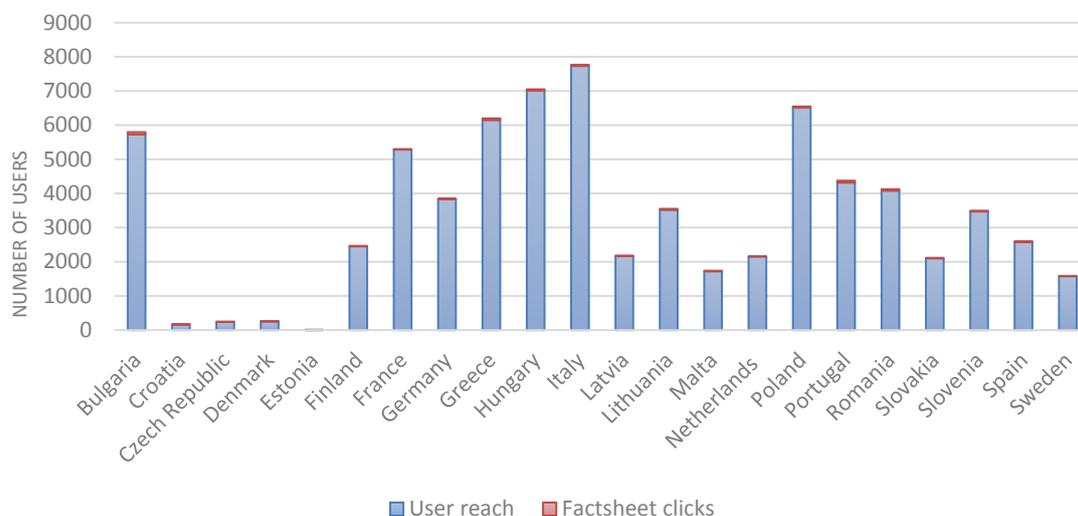


Number of users in each Member State who viewed the General Public Factsheet in their native language (blue) and number of users who clicked on the factsheet (red).

User Reach: is the number of unique people who looked at the content.

The Healthcare Professional factsheet in the native language was opened and seen by the almost 8000 users in Italy, whereas the lowest number of readers was found again in Croatia and Estonia with user reach as 165 and 129 respectively.

Figure 17: Healthcare Professional Factsheet Facebook activity across European Member States in native language.



Number of users in each Member State who read the Healthcare Professional Factsheet in their native language (blue) and those who clicked on the factsheet (red).

Twitter activities

Twitter target audience was set using following parameters:

1. Users with similar interests to the followers of following Twitter user accounts:

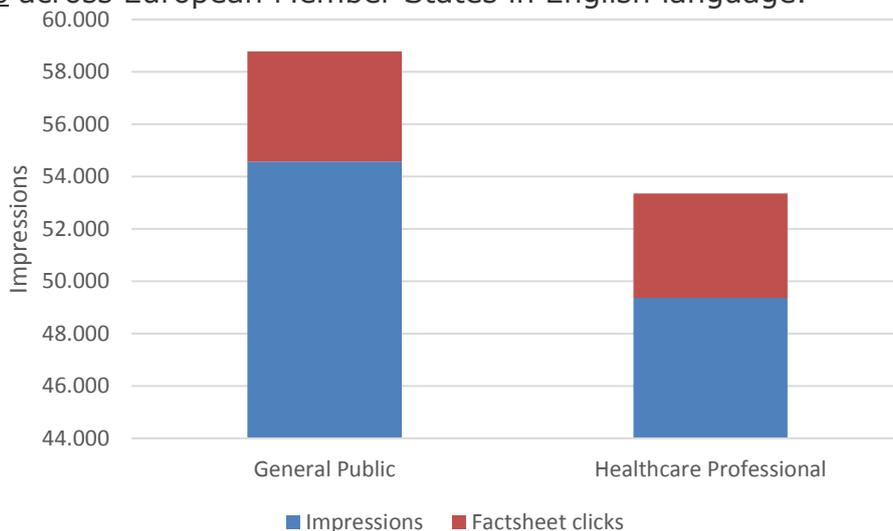
PublicHealthEngland @PHE_uk
 Public Health PHAC @PHAC_GC
 Women's Health @WomensHealthMag
 Ottawa Public Health @ottawahealth
 DZHK Germany @dzhk_germany
 Public Health @EPCPublicHealth
 Harvard Health @HarvardHealth
 BBC Health News @bbchealth
 HEALTH @_HEALTH_
 HarvardPublicHealth @HarvardChanSPH
 JHU Public Health @JohnsHopkinsSPH
 NBC News Health @NBCNewsHealth

CNN Health @cnnhealth
 Health @goodhealth
 APHA @PublicHealth
 Men's Health Mag @MensHealthMag
 European Commission @EU_Commission
 ColumbiaPublicHealth @ColumbiaMSPH

2. Age above 21 years old
3. Women and Men
4. Factsheet link in English or in the respective language of the Member State.

A total of 54,577 times the English version General Public factsheet was shown to targeted Twitter audience, and a total of 49,363 times Healthcare Professional factsheet was seen (Figure 18). 4,201 times General Public factsheet link was opened while 3,987 times Healthcare Professional factsheet link was opened.

Figure 18: General Public and Healthcare Professional Factsheet Twitter activities across European Member States in English language.



The general public factsheet was seen and opened more often by the Twitter targeted audience, compared to the healthcare professional factsheets. Impressions: no. of times the ad was shown to the Twitter targeted audience users.

6.3.8. Further dissemination activities

The GenCAD project used additional opportunities to inform the scientific community about its ongoing activities.

A project brochure was finalised and has been translated and made available in all EU official languages for the DG Health and Food Safety homepage.

In addition, the project poster was developed and can also be found on the DGS

homepage: https://ec.europa.eu/health/social_determinants/projects/ep_funded_projects_en#fragment3.

Both can be downloaded from the website and will be distributed to medical societies and interested parties, i.e. regional policy makers.

6.4. Sustainability

In order to ensure that knowledge and materials generated by the project continued to be circulated to healthcare professionals, patients and EU citizens after the project's end, we developed a sustainability plan.

Sustainability will be ensured by dissemination of the factsheets through the websites of medical societies like international or national societies of gender medicine, schools of public health, like EUPHA and others, and medical organizations (see table 10) that will keep it for years on their websites. Also all the materials on the DG Health and Food Safety stay available for download after the end of project lifetime.

Furthermore, the contribution of schools of public health through the involvement of EUPHA, the contribution of medical doctors' organizations (Standing Committee of European Doctors) and the contribution of the International Federation of medical students will ensure that gender related aspects of coronary artery disease are integrated into the curricula of Europe's future health professionals. As a best practice example, Charité is active in integrating gender in medical curricula for years and will integrate facts and factsheets into its curricula.

In particular, the website containing all project information and all factsheets will be maintained by DG Health and Food Safety.

6.5. Conclusions

In summary, the dissemination part of this project worked towards broadening the networks and including as wide a variety of stakeholders through conventional, as well as through novel media. The GenCAD partners developed targeted communication plans and key messages for their target audiences and distributed them in an efficient way. These aspects are pivotal to ensure that the sustainability plan comes to fruition.

6.6. Deliverables and performance indicators

WP 5				
	Deliverable	Start (month)	End (month)	Responsible
17.	Overall communication strategy and corporate identity	1	3	CH
18.	Dissemination plan: target audiences, messages and distribution actions and channels, Sustainability plan	1	12	CH
19.	Dissemination activities, including novel media	13	36	EUPHA
20.	Linguistic adaptations of all materials	1	36	EUPHA

The deliverables for the work package on dissemination included the communication strategy, dissemination plan, dissemination activities, and the linguistic adaption of all materials. The first two deliverables were achieved within the target timeframe of the first year. The dissemination began in the third year of the project and, with the sustainability plan in mind, has made material available for the foreseeable future, thereby reaching all deliverables in time.

In accordance with our key performance indicators, we reached a large number of societies, groups, non-governmental organisations, individual

persons with our factsheets. A significant number of them contributed to the presentation of GenCAD key strategies, key messages and factsheets via their homepages, at conferences and in press releases. This was also extended to include the groups of health/medical societies, non-governmental organisations, and individuals with interests in gender and health via the newsletters, project links on associated websites and conferences.

7. Management

7.1. Objectives

The management of the GenCAD project aimed to fulfil the needs of DG Health and Food Safety in a timely and high-quality manner with the support of meetings and reports to deliver work of the highest quality. In particular, the management of internal communication, development of a homepage, the installation of a steering board, advisory board, and multi-sectoral expert team, as well as the development of a risk and contingency plan were aimed to be completed over the course of the project.

7.2. Project meetings

Interim meetings were held as teleconferences with partners, as well as DG Health and Food Safety representatives. Other internal meetings were organised via teleconferences and are listed below:

Jan 28th: Teleconference GenCAD consortium

Feb 2nd: Meeting Luxembourg – DG Health and Food Safety, GenCAD consortium and advisory board

April 28th: Teleconference GenCAD consortium

Jul 28th: Teleconference GenCAD consortium

Sep 7th: Teleconference GenCAD consortium

Oct 27th: Teleconference GenCAD consortium

7.3. Installation of boards

The members of the advisory board were selected in an open and transparent vote following suggestions from all partners. Their relevant backgrounds are as follows:

Table 11: Advisory board members

Name	Country	Background
Prof. Ineke Klinge	The Netherlands	Associate Professor of Gender Medicine, Maastricht University
Dr. med. Fernando Rosell-Ortiz	Spain	Coordinator of cardiological processes emergencies EPES
Juan Carlos Kaski	United Kingdom	Professor of Cardiovascular Sciences and Head of the Cardiovascular Sciences Research Centre at St George's, University of London

The steering board has been constituted by one nominee from each partner and administration officer Carola Schubert. Nominated board members are Vera Regitz-Zagrosek (Charité), Antonio Daponte (Andalusian School of Public Health), Alan White (Centre for Men's Health), Floris Barnhoorn (EUPHA), and Angela Maas (Radboud University Medical Center).

The multi-sectoral expert team as proposed in the application was confirmed and is listed below:

Table 12: Multi-sectoral expert team

Name of Expert	Position/ Organisation	Country
Margarethe Hochleitner	Director / Innsbruck University Hospital, Women's Health Centre	AT
Alexandra Kautzky-Willer	Head of the Diabetes, Lipid and Obesity Outpatient Clinics at Department of Medicine III / Medical University of Vienna, Vienna	AT
Burkert Pieske	Head of Department of Cardiology and Head, University Heart Center Medical University Graz	AT
Klara Dokova	Department of Social Medicine and Health Care Organization, Faculty of Public Health, Medical University, Varna, Bulgaria	BG
Christiana Kouta	Department of Nursing , School of Health Sciences, School of Health Sciences, Cyprus University of Technology	CY
Ekaterina Lambrinou	Cyprus University of Technology/ Nursing Department	CY
Renata Cifkova	Department of Preventive Cardiology, Institute for Clinical and Experimental Medicine, Prague	CZ

Stefan Blankenberg	Director / Universitäres Herzzentrum Hamburg, Clinic for General and Interventional Cardiology	DE
Ulrich Kintscher	Head of Institute for Pharmacology / Charité Universitätsmedizin Berlin, Berlin	DE
Eva Prescott	Head of EACPR section on prevention, epidemiology; Dept of Cardiology Bispebjerg University Hospital Copenhagen, Denmark	DK
Jaan Eha	Head of Clinic / Tartu University Hospital, Clinic of Cardiology	EE
Miguel Angel Royo Bordonada	Instituto de Salud Carlos III, National School of Public Health, Madrid, Spain	ES
Nuria Romo, PhD.	Director of the Research Institute for the Study of Women and Gender at the University of Granada, and Professor in the Department of Social Anthropology at the same university, Granada, Spain	ES
M ^a Teresa Ruiz Cantero, PhD	Grupo de Investigación de Salud Pública, Universidad de Alicante, Alicante, España	ES
Carmen Saurina, PhD	Grup de Recerca en Estadística, Econometria i Salut, (GRECS) Departament d'Economia. Universitat de Girona	ES
Jean-Francois Arnal	CHU et Université de Toulouse UPS- Faculté Médecine, INSERM	FR
Claudine Junien	PU-PH Génétique Médicale, UVSQ Professor of Medical Genetics, Professor of Medical Genetics, SF-DOHaD, Présidente, President,	FR
Jadranka Božikov	Chair/Department of Medical Statistics, Epidemiology and Medical Informatics, Andrija Štampar School of Public Health, Medical School, University of Zagreb, Croatia	HR
Flavia Franconi	Center for Biotechnology Development and Biodiversity Research, University of Sassari, Osilo-Sassari	IT
Giovanni de Simone	Dprt of Translational Medical Sciences, Federico II University Hospital, Napoli	IT
Elisa Manacorda	CEO, Galileo Servizi Editoriali, Rome, Italy	IT
Ramune Kalediene	Dean, Lithuanian University of Health Sciences, Kaunas, Lithuania	LT
Daniel Wagner	Head, Dept of Cardiology / Centre Hospitalier de Luxembourg, Clinique d'Eich, Service de Cardiologie and Soins Intensifs Coronariens	LU
Maja-Lisa Lochen	Dept. of community medicine, Faculty Health Sciences, The Arctic University of Norway, Tromsø, UiT,	NO
Eva Gerdts	University of Bergen / Department of clinical science	NO
Marta Pereira	Department of Clinical Epidemiology, Predictive Medicine and Public Health, University of Porto Medical School	PT
Karin Schenck-Gustafsson	Chair and Founder, Centre for Gender Medicine / Karolinska University Hospital, Karolinska Institute	SE
Magdalena Piscova	Deputy Director, Institute for Sociology, Slovak Academy of Sciences, Bratislava	SK
Andrzej Pajak/Roman Topór-Madry	Institute of Public Health, Jagiellonian University Medical College, Krakow, Poland	PL

7.4. Quality control, risk and contingency plan

Plans to adapt the project to some potential difficulties are laid out below and were updated over the course of the project:

Table 13: Contingency plan

	Potential Hazard or risk	The immediate impact may be that:	Mitigating measures available include:	Likelihood	Impact
WP1	Database format inhomogeneous, difficult to analyse	Time schedule shifts, need for additional negotiations	<ul style="list-style-type: none"> - Involve local experts - Request further information from database holders - Offer incentives such as inclusion in publications 	Medium	Medium
WP1	Some studies are too weak or numbers are too small to empower the intended statistical analysis.	Insufficient statistical power for first round of analysis, time schedule shift	<ul style="list-style-type: none"> - Include a larger set of databases as primary source - Combine studies, use meta-analysis, and /or focus on the single aspects that can be analysed 	Medium	Low
WP2	Insufficient response rate from HCPs	Longer recruiting times, need for further active action	<ul style="list-style-type: none"> - Increase active search for participants - Include further professional bodies - Intensify liaison efforts with professional bodies 	Medium	Low
WP2	Insufficient willingness to participate by the general public	Lack of adequate information to make inferences on awareness	- Recruitment needs will be specified at the beginning of the telephone study and the performing institute will be allocated more time to obtain the needed number of participants	Low	Medium
WP4	Unforeseen cancellation by delegates	Loss of credibility of the consortium, Damage of image of DG Health and Food Safety	<ul style="list-style-type: none"> - A risk management strategy will be developed and included as part of the conferences and Workshop planning. - Delegations are constituted by at least two representatives per country to guarantee presence of all involved - Participants will be invited to identify potential substitutes in case of unforeseen events 	Low	Medium
WP4	Unavailability of suitable venue	Loss of credibility of the consortium, Damage of image of DG Health and Food Safety	Every effort will be made from the start of the project to find an adequate venue and make reservations on time to guarantee the success of the workshop and conferences	Low	High
WP4	Difficulty to recruit	Lack of professional	- A risk management strategy will be	Low	Medium

	Potential Hazard or risk	The immediate impact may be that:	Mitigating measures available include:	Likelihood	Impact
	sufficient numbers of expert reviewers from the different sectors.	feedback	developed as part of the factsheet development - Pools of suitable experts have already been identified - Well established consortium in the field with good connections and ability to identify alternatives		
WP5	Unexpected technical and IT difficulties	Inability to perform the communication tasks	- Backup server for services available - Intensive internal and external IT support will allow for rapid development of an alternative route of communication and identify fee-based providers to allow for uninterrupted services during the Institutes difficulties	Low	High
WP6	Unforeseen loss of services of a member of the team, for example through long term illness, or leaves.	The work does not run to agreed schedule. Loss of expertise informing the project.	- Ability to share out the remaining tasks which can be undertaken by existing project team members. - Recruit in other staff from European partners - Contracting more days from the external consultants who form part of the team - Loss of expertise not a particular concern due to the strength in depth of the international network.	Low	Medium
G	'Peak' in GIM workload if a number of concurrent bids are successful leading to overload of staff resources.	Staff unable to commit capacity to various contracts, lack or prioritisation, delay in schedule and loss of quality.	- Head of Institute for Gender in Medicine Cardiovascular Research Centre has overall view of workload and contracts on a weekly basis and can prioritise in the team accordingly. - Large and diverse project team includes access to additional staff and also freelance associates, the use of which provides additional 'overflow' capacity should it be needed. - Regular project progress reports/discussions initiated amongst the team and also with the client by project lead will ensure any concerns on quality or slippage are picked up early and addressed	Low	Medium

	Potential Hazard or risk	The immediate impact may be that:	Mitigating measures available include:	Likelihood	Impact
G	Work across the project team is unconnected and progressed in isolation from that of others	Disjointed approach to the project lacking coherency and ultimately lacking in rationale.	<ul style="list-style-type: none"> - Project lead to convene regular internal team communications between all involved. - Clear leadership in the large team with one individual having overall responsibility for each phase of the work. - Project team members allocated tasks in each phase to build familiarity and cohesiveness across the work streams 	Medium	Medium
G	Work undertaken by the project team does not meet client expectations	Client unhappy, poor working relations, loss of reputation for all consortium Participants.	<ul style="list-style-type: none"> - Regular communications between client and project team should identify concerns as soon as they occur. - Head of Institute for Gender in Medicine, Cardiovascular Research Centre providing strategic supervision and able to use experience to advise staff team and client on any potential unforeseen circumstances. - Presence of a project collaborative culture that sees staff take personal responsibility for the nature of their work and outputs to meet and exceed partner's needs. - Flexible approach of project leadership to readjust approach in line with client needs as project progresses if necessary. - Client able to invoke quality assurance procedure in place as outlined in the bid involving senior Faculty management at Charité - Universitätsmedizin Berlin. 	Low	High
G	Major incident at Charité closes premises or leads to loss of work space and semi-permanent evacuation of staff	Research work interrupted, delay in delivering work, loss of data.	<ul style="list-style-type: none"> - Faculty recovery plan activated including provision of temporary premises elsewhere in university and data recovery 	Low	High

7.5. Interim reports and final report to DG Health and Food Safety, as well as interim meetings in Luxembourg

The inception meeting took place in February 2015. A second meeting with DG Health and Food Safety took place at the Luxembourg workshop in February

2016 and the comments of DG Health and Food Safety are included in the minutes of this workshop. A second meeting took place on the 7th February 2017 in Luxembourg at the DG Health and Food Safety offices. The final report was submitted to DG Health and Food Safety in December 2017.

7.6. Deliverables and performance indicators

WP 6				
	Deliverable	Start (month)	End (month)	Responsible
21.	Project Office and electronic tools, management, internal communication	1	36	CH
22.	Establishment of Steering Board, Advisory Board, Multi-sectoral expert team	1	3	CH
23.	Risk and contingency plan	1	6	CH
24.	Inception meeting	1	1	CH
25.	Inception report	2	2	CH
26.	First Interim report to DG Health and Food Safety	5	6	CH
27.	Second draft Interim Report	10	12	CH
28.	Second meeting DG Health and Food Safety	12	12	CH
29.	Third draft Interim Report to DG Health and Food Safety	22	24	CH
30.	Third meeting DG Health and Food Safety	24	24	CH
31.	Final Report to DG Health and Food Safety	35	36	CH

All deliverables were targeted and reached within the allocated timeframe. Performance indicators were also reached. All reports were submitted in time and accepted by DG Health and Food Safety.

Highly qualified scientists accepted to work in the advisory board and highly qualified experts agreed to serve in our steering board and multi-sectoral expert group.

8. General conclusions and recommendations

8.1. General conclusions

Sex and gender related knowledge in coronary artery disease

Our bibliographic study revealed important sex and gender differences in the early onset and progression of coronary artery disease, of atherosclerosis and myocardial ischemia. We conclude that sex and gender related approaches are needed for women and men to identify their risk factors for coronary artery disease. In women, pregnancy related issues need more attention, as well as rheumatic and autoimmune diseases. In men, hormone related and behavior related conditions also need more attention. Socioeconomic conditions play an underestimated role in both sexes. Considering the pathophysiological basis for coronary artery disease, it is getting clear that most research focused on the male condition of atherosclerosis of large coronary arteries so far. In contrast, women characteristic conditions, e.g. dissections, spasms or microvascular disease received less research attention. A different pattern of coronary artery disease translates into different symptoms of ischemic heart disease. Unfortunately, age and gender related diagnostic algorithms have not yet been sufficiently well developed. Under-treatment of female cardiac patients is still actual and may contribute to the low quality of life and health problems of women at old age. This concerns medications, adverse effects, drug interactions but also bleeding risks during percutaneous coronary intervention and morbidity and mortality after coronary artery bypass surgery etc.

Limited studies quality

Even though a large number of publications is available, altogether, the quality of the gender related analysis is often limited by retrospective, non-randomized, non-blinded study design with low numbers. Studies often include women in insufficient numbers to draw conclusions on them, sex and gender

related research questions are not included into the protocols in a prospective manner, and sex and gender related confounders are not considered. Better studies must be planned and this needs training of the research community since they were not trained at the universities in sex and gender related research. They must be trained in identifying the right topics as well as methods.

Gaps in knowledge

A lot of knowledge exists, but is dispersed, largely unknown and frequently not at the level to be included in guidelines. Furthermore, some areas can be identified where studies are lacking in one sex.

Gaps in knowledge still exist in risk factors and disease mechanisms that mainly affect women – mechanisms of greater coronary artery disease risk in diabetic women, cardiovascular risk associated with pregnancy related complications, stress-induced cardiomyopathy, microvascular and functional coronary disease. Furthermore, lacking are large state-of-the-art prospective studies on optimal diagnostic or therapeutic strategies separately or in parallel in women and men, powered to reach valid diagnostic conclusions for both sexes, based on their specific pathophysiology, as well as studies on women specific approaches.

Some men specific areas are also understudied: depression in men, role of sexual dysfunction as a risk factor for coronary artery disease, mechanisms of sudden death in sports, role of men in caring.

Furthermore, there is a lack of research on the relevance of the sociocultural dimension gender on cardiovascular outcomes.

This leads to a lack of women and men specific diagnostic and therapeutic recommendations which causes poor quality and high costs of the system.

Sociodemographic and medical databases

From our analysis, we concluded that a number of sex and gender related indicators are included in public sociodemographic databases as well as in major research databases, but by far not enough to analyse the effect of sex and gender related factors and covariates on coronary artery disease and its

prevention in a coherent manner. Sex and gender related covariates such as number of children, miscarriages, hormone therapy, andro- or menopause, or true gender variables are incompletely covered in the public as well as in the research databases and therefore, sex or gender-related analyses often fail.

There is a need for more sex or gender disaggregated-data, more comprehensive inclusion of sex and gender related variables as well as increased age cut-offs to obtain a clearer picture of coronary artery disease and its risk factors, prevention and outcomes in women and men across Europe.

Researchers are only partially aware on the relevance of sex and gender and do not have the resources to include it in all studies. Therefore, awareness and funding for sex and gender inclusion into studies and databases must be improved.

In summary, we do ask now for inclusion of sex and gender related factors in the design of research, but the situation in the databases still predominantly reflects the sex and gender blind past.

Policies

The overall conclusions from the GenCAD analysis is that for all EU Member States there is a policy environment that ensure gender equality and prohibits gender based discrimination in most MS. There is also a growing body of recommendations from leading health organisations supporting more gender sensitive and gender aware health care. However translation of these recommendations into policies is still lacking and should be achieved in a next step.

Awareness studies

Results of the survey among health care professionals indicate an insufficient degree of knowledge and awareness among professionals in relation to the differences and similarities between men and women on coronary artery disease. This lack of knowledge and awareness will be reflected in the professional practice and in clinical and preventive activities, giving rise to gender inequalities in the approach to coronary artery disease, its prevention, diagnosis and treatment. This is true among the different specialties, or

settings (hospital, primary care, emergencies, public health), or countries. All of this demands an establishment of a European strategy going beyond ESC guidelines to promote broad and clear professional consensus on sex and gender related aspects in the prevention and treatment of coronary artery disease in the Member States. This strategy should include also research and training activities, as well as a clear definition of health professional competences in gender and CVD.

The main results in the general population survey show that there is no adequate level of awareness about coronary artery disease and this is more pronounced in women than in men. Women still heavily underestimate their risk from coronary artery disease. Intervention studies in the US showed that these numbers can be changed and knowledge and awareness in the US have improved. Their most important and recent study on this found that 56% of women identified heart disease as the leading cause of death among women, compared to 30% some years earlier. Also, our survey shows that healthcare professionals do not seem to adequately or sufficiently inform their patients about coronary artery disease. A majority of respondents claims more information about various aspects of coronary artery disease, ranging from identifying symptoms of heart attack to prevention strategies. Less than 2/3 of people surveyed know what to do in case of having a heart attack and the reactions towards women and men with suggestive symptoms still seem to differ. Finally, there are important differences among the countries in several of the items explored in the survey. For example, the percentage of people who identify heart disease as the leading cause of death for women varies between 7% and 29%. A four-fold difference between the country with the highest percentage and the country with the lowest percentage. These large differences indicate that there are countries that through formal or informal strategies get their population, especially women, better informed. Exploring the determinants of these differences could be very useful for the development of an effective strategy in Europe.

In summary, our awareness studies yielded the following major conclusions:

From healthcare professionals survey:

- ❑ Doctors are not well informed on women-specific diagnosis and therapies
- ❑ Doctors are aware that information campaigns do not reach women and men equally.
- ❑ Doctors are aware that, in general, men and women with coronary artery disease are not treated equally throughout the health process, from prevention to treatment of the disease.

From general public survey:

- ❑ Large differences between countries exist in all indicators
- ❑ Significant inequalities exist according to educational level
- ❑ Women attribute less relevance to heart disease and do not identify heart disease as their leading cause of death
- ❑ Stress is the most cited risk factor. Knowledge and awareness on smoking, lack of exercise and diabetes needs improvement
- ❑ Almost 50% will not call emergency services in case of heart attack, as a first reaction
- ❑ Less than half of participants are well informed on cardiovascular disease
- ❑ Mass media and internet are two important sources of information on cardiovascular disease

Improving coronary artery disease awareness and sex and gender awareness in coronary artery disease should be a key element of health policies in Europe, given the great importance that cardiovascular disease has on the continent, the large epidemiological inequalities among Member States, and the enormous costs involved.

Conferences and dissemination

Organizing conferences is always a great challenge and sometimes appears to be anachronistic considering all the possibilities for electronic communication. However, our conferences showed in an impressive manner how big the

benefit from personal interdisciplinary and trans-sectoral collaboration really was. We had vivid discussions and the interaction between clinicians, public health researchers, policy makers was outstanding. All groups claimed to have learned from each other and new ideas were developed and novel plans for actions were identified. Exchange with members of national parliaments helped to understand specific situations in different countries and gave best practice examples of how much can be achieved by well designed campaigns, as done in Italy, for example.

To disseminate the knowledge beyond the conferences, we worked on a large number of societies, groups, non-governmental organisations, individual persons with our factsheets. A significant number of them contributed to the presentation of GenCAD key strategies, key messages and factsheets via their homepages, at conferences and in press releases. It will be important to maintain their interest in the future.

The power of social media to reach different population groups is great. We also reached a large number of individual persons using approaches in the social media strategies in Facebook and Twitter. This was also extended to include the groups of health/medical societies, non-governmental organisations, and individuals with interests in gender and health via the newsletters, project links on associated websites, and conferences.

Applicability to other chronic diseases

Overall, the structure of the project is well suited to transfer to other chronic diseases. The strategy of the bibliographic study, as described in section 2.1.2 and in Fig 3, the database analysis, the policy analysis and the needs assessment can be immediately transferred to other studies.

8.2. Recommendations

- EU: The Commission Services should aim at reinforcing the gender dimension in the Horizon 2020 and FP 9 calls and make more tailored suggestions for topics in cooperation with the Advisory Group for

Gender of H2020. For example, calls for additional studies on sex and gender in coronary artery disease designed in a way to become suitable for guideline development are needed. Studies should include sufficient numbers of women and men to draw conclusions for both sexes, they should have a state of the art design and should be focused on gender analysis in a prospective manner. This will lead to closing gaps in knowledge regarding sex and gender related factors in cardiovascular diseases.

- Member State Level

- National health and research administrations or planning bureaus should be stimulated to include sex and gender related variables in databases.
- National research councils should support training of the biomedical research community in sex and gender related research since the present generation was not trained in these topics at universities. Researchers must be trained in identifying the right topics – this requires sex and gender knowledge - as well as choosing appropriate methods.
- Doctors professional organisations should train doctors systematically (post academic courses) and activities of CPME (Standing committee of European doctors) should be supported. Doctors in different disciplines should document a basic training and knowledge in sex and gender aspects in their respective discipline to obtain and to maintain their license, see example of Innsbruck Medical school. Furthermore, there should be a (voluntary) certificate on gender medicine in all countries.
- Universities should assure that sex and gender related issues become enclosed in medical curricula at universities, at medical and biomedical faculties. A European curriculum on gender medicine should be developed. There is already a draft curriculum and a broad knowledge basis available (among others from our

EUGIM project in FP 6) and the greatest deficits are in the regulatory aspects and the motivation of the universities.

- Medical and Public Health societies:
 - ESC should support and set incentives for developing sex and gender related knowledge, founding working groups on sex and gender in cardiovascular diseases, supporting gender training for cardiologists and inclusion of sex and gender into guidelines. Improving the inclusion of sex and gender into ESC research and training programmes and finally in guidelines may be a major step forward to implement sex and gender aspects in Member States health care programmes in the cardiovascular field.
 - Societies of Public Health, internal medicine and national societies of cardiology should keep distributing factsheets systematically, to doctors, to patients, to the general public.

- National health services:
 - Should improve the awareness of the relevance of sex and gender factors in coronary artery disease/other chronic diseases that should be a key element of health policies in Europe, given the great importance that cardiovascular disease has on the continent, the large epidemiological inequalities among Member States, and the enormous costs involved.
 - Should develop more campaigns to inform citizens on the relevance of coronary artery disease for their quality of life, not only on mortality that target women and men specifically and use electronic media (and/or TV spots) for reach-out to patients and general public.

- DG Health and Food safety:
 - Apply the structure of the work to other chronic diseases. Most studies can be easily adapted to other diseases.

9. List of submitted deliverables

WP 1				
Del. N°	Deliverable	Start (month)	End (month)	Responsible
1.	Comprehensive report on gender differences in coronary artery disease in Member States from bibliographic studies	1	18	CH; RUMC
2.	Database investigation on gender-related risk factors, manifestations and treatments of coronary artery disease	1	18	CH
3.	Review of member state policies prevention and treatment guidelines	1	18	BSPH, CMH
WP 2				
4.	Survey on awareness in health care professionals	1	24	EASP
5.	Survey on awareness among the general population	1	24	EASP (+subcontract)
6.	Report on EU research activities	12	24	EASP
WP 3				
7.	Medical content factsheets	6	18	CH
8.	First draft factsheets for healthcare professionals and general public	8	14	EUPHA
9.	Finalised (content) factsheets, English and Linguistic adaptation,	15	26	EUPHA
10.	Factsheets translation 24 official EU languages	26	32	EUPHA, (+subcontract)
WP 4				
11.	Workshop	8	14	CH
12.	Workshop report	14	15	CH
13.	Conference 1 (Berlin)	14	22	CH
14.	Conference minutes	23	24	CH
15.	Conference 2 (Brussels)	26	34	CH

16	Conference minutes	35	36	CH
WP 5				
17	Overall communication strategy and corporate identity	1	3	CH
18	Dissemination plan: target audiences, messages and distribution actions and channels, Sustainability plan	1	12	CH
19	Dissemination activities, including novel media	13	32	EUPHA
20	Linguistic adaptations of all materials	1	36	EUPHA
WP 6				
21	Project Office and electronic tools, management, internal communication	1	36	CH
22	Establishment of Steering Board, Advisory Board, multisectoral expert team	1	3	CH
23	Risk and contingency plan	1	6	CH
24	Inception meeting	1	1	CH
25	Inception report	2	2	CH
26	First Interim report to DG Health and Food Safety	5	6	CH
27	Second draft Interim Report	10	12	CH
28	Second meeting in DG Health and Food Safety	12	12	CH
29	Third draft Interim Report to DG Health and Food Safety	22	24	CH
30	Third meeting DG Health and Food Safety	24	24	CH
31	Final Report to DG Health and Food Safety	35	36	CH

All deliverables were reached in time, as outlined in the respective sections of the chapters.

10. References list

1. Perk, J., et al., *European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts)*. *Atherosclerosis*, 2012. **223**(1): p. 1-68.
2. Nichols, M., et al., *European cardiovascular disease statistics*. 2012: European Heart Network.
3. Abdelaal, E., et al., *Risk score, causes, and clinical impact of failure of transradial approach for percutaneous coronary interventions*. *JACC Cardiovasc Interv*, 2013. **6**(11): p. 1129-37.
4. Ahmed, B. and H.L. Dauerman, *Women, bleeding, and coronary intervention*. *Circulation*, 2013. **127**(5): p. 641-9.
5. Aragam, K.G., et al., *Trends and disparities in referral to cardiac rehabilitation after percutaneous coronary intervention*. *Am Heart J*, 2011. **161**(3): p. 544-551.e2.
6. Bairey Merz, C.N., et al., *Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease*. *J Am Coll Cardiol*, 2006. **47**(3 Suppl): p. S21-9.
7. Barrett-Connor, E.L., et al., *Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study*. *JAMA*, 1991. **265**(5): p. 627-31.
8. Baviera, M., et al., *Sex differences in cardiovascular outcomes, pharmacological treatments and indicators of care in patients with newly diagnosed diabetes: Analyses on administrative database*. *European journal of internal medicine*, 2014. **25**(3): p. 270-275.
9. Berger, J.S., et al., *Sex differences in mortality following acute coronary syndromes*. *JAMA*, 2009. **302**(8): p. 874-82.
10. Bertrand, O.F., et al., *Comparison of transradial and femoral approaches for percutaneous coronary interventions: a systematic review and hierarchical Bayesian meta-analysis*. *Am Heart J*, 2012. **163**(4): p. 632-48.
11. Boutin-Foster, C. and M.E. Charlson, *Do recent life events and social support explain gender differences in depressive symptoms in patients who had percutaneous transluminal coronary angioplasty?* *J Womens Health (Larchmt)*, 2007. **16**(1): p. 114-23.
12. Brevetti, G., et al., *Women and peripheral arterial disease: same disease, different issues*. *J Cardiovasc Med (Hagerstown)*, 2008. **9**(4): p. 382-8.
13. Budoff, M.J., et al., *Electron beam tomography and angiography: sex differences*. *Am Heart J*, 2002. **143**(5): p. 877-82.
14. Bushnell, C., et al., *Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart*

- Association/American Stroke Association. *Stroke*, 2014. **45**(5): p. 1545-88.
15. Camici, P.G., G. d'Amati, and O. Rimoldi, *Coronary microvascular dysfunction: mechanisms and functional assessment*. *Nat Rev Cardiol*, 2015. **12**(1): p. 48-62.
 16. Casey, A., et al., *A model for integrating a mind/body approach to cardiac rehabilitation: outcomes and correlators*. *J Cardiopulm Rehabil Prev*, 2009. **29**(4): p. 230-8; quiz 239-40.
 17. Champney, K.P., et al., *The joint contribution of sex, age and type of myocardial infarction on hospital mortality following acute myocardial infarction*. *Heart*, 2009. **95**(11): p. 895-9.
 18. Charchar, F.J., et al., *Inheritance of coronary artery disease in men: an analysis of the role of the Y chromosome*. *Lancet*, 2012. **379**(9819): p. 915-22.
 19. Chou, A.Y. and J. Saw, *Basis for sex-specific expression of Takotsubo cardiomyopathy, cardiac syndrome X, and spontaneous coronary artery dissection*. *Can J Cardiol*, 2014. **30**(7): p. 738-46.
 20. Daugherty, S.L., et al., *Patterns of use and comparative effectiveness of bleeding avoidance strategies in men and women following percutaneous coronary interventions: an observational study from the National Cardiovascular Data Registry*. *J Am Coll Cardiol*, 2013. **61**(20): p. 2070-8.
 21. De Backer, G., et al., *European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice*. *Eur Heart J*, 2003. **24**(17): p. 1601-10.
 22. De Bruyne, B., et al., *Fractional flow reserve-guided PCI for stable coronary artery disease*. *N Engl J Med*, 2014. **371**(13): p. 1208-17.
 23. Di Franco, A., et al., *Correlation between coronary microvascular function and angina status in patients with stable microvascular angina*. *Eur Rev Med Pharmacol Sci*, 2014. **18**(3): p. 374-9.
 24. Diercks, D.B., et al., *Gender differences in time to presentation for myocardial infarction before and after a national women's cardiovascular awareness campaign: a temporal analysis from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation (CRUSADE) and the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network-Get with the Guidelines (NCDR ACTION Registry-GWTG)*. *Am Heart J*, 2010. **160**(1): p. 80-87 e3.
 25. Ding, E.L., et al., *Sex differences in perceived risks, distrust, and willingness to participate in clinical trials: a randomized study of cardiovascular prevention trials*. *Arch Intern Med*, 2007. **167**(9): p. 905-12.
 26. Donahue, R.P., et al., *Sex differences in endothelial function markers before conversion to pre-diabetes: does the clock start ticking earlier among women? The Western New York Study*. *Diabetes Care*, 2007. **30**(2): p. 354-9.
 27. Donataccio, M.P., et al., *In-hospital outcomes and long-term mortality according to sex and management strategy in acute myocardial infarction. Insights from the French ST-elevation and non-ST-elevation*

- Myocardial Infarction (FAST-MI) 2005 Registry*. *Int J Cardiol*, 2015. **201**: p. 265-70.
28. Douglas, P.S. and G.S. Ginsburg, *The evaluation of chest pain in women*. *N Engl J Med*, 1996. **334**(20): p. 1311-5.
 29. Elhendy, A., et al., *Gender differences in the relation between ST-T-wave abnormalities at baseline electrocardiogram and stress myocardial perfusion abnormalities in patients with suspected coronary artery disease*. *Am J Cardiol*, 1999. **84**(8): p. 865-9.
 30. Elias-Smale, S.E., A. Gunal, and A.H. Maas, *Gynecardiology: Distinct patterns of ischemic heart disease in middle-aged women*. *Maturitas*, 2015. **81**(3): p. 348-52.
 31. Eskerud, I., et al., *Global Coronary Artery Plaque Area is Associated with Myocardial Hypoperfusion in Women with Non-ST Elevation Myocardial Infarction*. *J Womens Health (Larchmt)*, 2015. **24**(5): p. 367-73.
 32. Ferreira, R.G., et al., *Sex differences in the prevalence of diastolic dysfunction in cardiac surgical patients*. *J Card Surg*, 2015. **30**(3): p. 238-45.
 33. Flammer, A.J., et al., *The assessment of endothelial function: from research into clinical practice*. *Circulation*, 2012. **126**(6): p. 753-67.
 34. Ford, E.S. and S. Capewell, *Coronary heart disease mortality among young adults in the U.S. from 1980 through 2002: concealed leveling of mortality rates*. *J Am Coll Cardiol*, 2007. **50**(22): p. 2128-32.
 35. Galvao, M., et al., *Gender differences in in-hospital management and outcomes in patients with decompensated heart failure: analysis from the Acute Decompensated Heart Failure National Registry (ADHERE)*. *J Card Fail*, 2006. **12**(2): p. 100-7.
 36. Gehrie, E.R., et al., *Characterization and outcomes of women and men with non-ST-segment elevation myocardial infarction and nonobstructive coronary artery disease: results from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) quality improvement initiative*. *Am Heart J*, 2009. **158**(4): p. 688-94.
 37. Gianturco, L., et al., *Cardiovascular and autoimmune diseases in females: The role of microvasculature and dysfunctional endothelium*. *Atherosclerosis*, 2015. **241**(1): p. 259-63.
 38. Gloria-Bottini, F., et al., *Coronary artery disease: a study on the joint role of birth weight, adenosine deaminase, and gender*. *Cardiol Res Pract*, 2009. **2009**: p. 860328.
 39. Gulati, M., et al., *The prognostic value of a nomogram for exercise capacity in women*. *N Engl J Med*, 2005. **353**(5): p. 468-75.
 40. Gulati, M. and C.N. Merz, *New cholesterol guidelines and primary prevention in women*. *Trends Cardiovasc Med*, 2015. **25**(2): p. 84-94.
 41. Hahmann, H.W., et al., *The significance of high levels of lipoprotein (a) compared with established risk factors in premature coronary artery disease: differences between men and women*. *Atherosclerosis*, 1999. **144**(1): p. 221-8.
 42. Han, S.H., et al., *Sex differences in atheroma burden and endothelial function in patients with early coronary atherosclerosis*. *Eur Heart J*, 2008. **29**(11): p. 1359-69.

43. Hansen, K.W., et al., *Improved two-year outcomes after drug-eluting versus bare-metal stent implantation in women and men with large coronary arteries: importance of vessel size*. *Int J Cardiol*, 2013. **169**(1): p. 29-34.
44. Hayes, S.N., *Spontaneous coronary artery dissection (SCAD): new insights into this not-so-rare condition*. *Tex Heart Inst J*, 2014. **41**(3): p. 295-8.
45. Herrmann, J., J.C. Kaski, and A. Lerman, *Coronary microvascular dysfunction in the clinical setting: from mystery to reality*. *Eur Heart J*, 2012. **33**(22): p. 2771-2782b.
46. Hochman, J.S., et al., *Outcome and profile of women and men presenting with acute coronary syndromes: a report from TIMI IIIB. TIMI Investigators. Thrombolysis in Myocardial Infarction*. *J Am Coll Cardiol*, 1997. **30**(1): p. 141-8.
47. Huynh, K., *Biomarkers: High-sensitivity troponin assays for the diagnosis of AMI-sex-specific differences?* *Nat Rev Cardiol*, 2015. **12**(3): p. 129.
48. Jespersen, L., et al., *Burden of hospital admission and repeat angiography in angina pectoris patients with and without coronary artery disease: a registry-based cohort study*. *PLoS One*, 2014. **9**(4): p. e93170.
49. Johnston, N., et al., *Effect of Gender on Patients With ST-Elevation and Non-ST-Elevation Myocardial Infarction Without Obstructive Coronary Artery Disease*. *Am J Cardiol*, 2015. **115**(12): p. 1661-6.
50. Johnston, N., K. Schenck-Gustafsson, and B. Lagerqvist, *Are we using cardiovascular medications and coronary angiography appropriately in men and women with chest pain?* *Eur Heart J*, 2011. **32**(11): p. 1331-6.
51. Kalyani, R.R., et al., *Sex differences in diabetes and risk of incident coronary artery disease in healthy young and middle-aged adults*. *Diabetes Care*, 2014. **37**(3): p. 830-8.
52. Kang, S.J., et al., *Sex differences in the visual-functional mismatch between coronary angiography or intravascular ultrasound versus fractional flow reserve*. *JACC Cardiovasc Interv*, 2013. **6**(6): p. 562-8.
53. Kaul, P., et al., *Temporal trends in patient and treatment delay among men and women presenting with ST-elevation myocardial infarction*. *Am Heart J*, 2011. **161**(1): p. 91-7.
54. Kaushik, M., S.P. Sontineni, and C. Hunter, *Cardiovascular disease and androgens: a review*. *Int J Cardiol*, 2010. **142**(1): p. 8-14.
55. Kendel, F., et al., *Gender differences in health-related quality of life after coronary bypass surgery: results from a 1-year follow-up in propensity-matched men and women*. *Psychosom Med*, 2011. **73**(3): p. 280-5.
56. Kendel, F., et al., *Predictive relationship between depression and physical functioning after coronary surgery*. *Arch Intern Med*, 2010. **170**(19): p. 1717-21.
57. Pelletier, R., B. Ditto, and L. Pilote, *A composite measure of gender and its association with risk factors in patients with premature acute coronary syndrome*. *Psychosomatic medicine*, 2015. **77**(5): p. 517-526.

58. Lisabeth, L. and C. Bushnell, *Stroke risk in women: the role of menopause and hormone therapy*. *The Lancet Neurology*, 2012. **11**(1): p. 82-91.
59. Oertelt-Prigione, S., et al., *GenderMedDB: an interactive database of sex and gender-specific medical literature*. *Biology of sex differences*, 2014. **5**(1): p. 7.
60. Puymirat, E., et al., *Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction*. *JAMA*, 2012. **308**(10): p. 998-1006.
61. Tunstall-Pedoe, H., et al., *Comparison of the prediction by 27 different factors of coronary heart disease and death in men and women of the Scottish Heart Health Study: cohort study*. *BMJ*, 1997. **315**(7110): p. 722-9.
62. Kotseva, K., et al., *EUROASPIRE III: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries*. *European Journal of Cardiovascular Prevention & Rehabilitation*, 2009. **16**(2): p. 121-137.
63. Prescott, E., et al., *Smoking and risk of myocardial infarction in women and men: longitudinal population study*. *Bmj*, 1998. **316**(7137): p. 1043.
64. Vaccarino, V., et al., *Ischaemic heart disease in women: are there sex differences in pathophysiology and risk factors? Position paper from the working group on coronary pathophysiology and microcirculation of the European Society of Cardiology*. *Cardiovasc Res*, 2011. **90**(1): p. 9-17.
65. Staessen, J.A., J.-G. Wang, and L. Thijs, *Cardiovascular protection and blood pressure reduction: a meta-analysis*. *The Lancet*, 2001. **358**(9290): p. 1305-1315.
66. Coylewright, M., J.F. Reckelhoff, and P. Ouyang, *Menopause and hypertension*. *Hypertension*, 2008. **51**(4): p. 952-959.
67. Vasan, R.S., et al., *Impact of high-normal blood pressure on the risk of cardiovascular disease*. *New England journal of medicine*, 2001. **345**(18): p. 1291-1297.
68. Silber, T.C., et al., *Cardiac rehabilitation after spontaneous coronary artery dissection*. *J Cardiopulm Rehabil Prev*, 2015. **35**(5): p. 328-33.
69. Yusuf, S., et al., *Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study*. *Lancet*, 2004. **364**(9438): p. 937-52.
70. Parashar, S., et al., *Impact of depression on sex differences in outcome after myocardial infarction*. *Circ Cardiovasc Qual Outcomes*, 2009. **2**(1): p. 33-40.
71. Xu, X., et al., *Sex differences in perceived stress and early recovery in young and middle-aged patients with acute myocardial infarction*. *Circulation*, 2015. **131**(7): p. 614-23.
72. Miner, M.M. and A.D. Seftel, *Erectile dysfunction and testosterone screening with prostate specific antigen screening at age 40: are these three gender specific determinants additive for overall men's health and do they improve traditional non-gender specific determinants to lessen cardiovascular risk and all-cause mortality?* *Int J Clin Pract*, 2010. **64**(13): p. 1754-62.

73. Hoffmann, B., et al., *Residential exposure to traffic is associated with coronary atherosclerosis*. *Circulation*, 2007. **116**(5): p. 489-96.
74. Vaidya, D., et al., *Incidence of coronary artery disease in siblings of patients with premature coronary artery disease: 10 years of follow-up*. *Am J Cardiol*, 2007. **100**(9): p. 1410-5.
75. Ranthe, M.F., et al., *Family history of premature death and risk of early onset cardiovascular disease*. *J Am Coll Cardiol*, 2012. **60**(9): p. 814-21.
76. Towfighi, A., et al., *A midlife stroke surge among women in the United States*. *Neurology*, 2007. **69**(20): p. 1898-904.
77. Shaw, L.J., R. Bugiardini, and C.N. Merz, *Women and ischemic heart disease: evolving knowledge*. *J Am Coll Cardiol*, 2009. **54**(17): p. 1561-75.
78. Yahagi, K., et al., *Sex differences in coronary artery disease: Pathological observations*. *Atherosclerosis*, 2015. **239**(1): p. 260-267.
79. Reynolds, H.R., et al., *Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease*. *Circulation*, 2011. **124**(13): p. 1414-25.
80. Thygesen, K., et al., *Third universal definition of myocardial infarction*. *Circulation*, 2012. **126**(16): p. 2020-35.
81. Regitz-Zagrosek, V., et al., *ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC)*. *Eur Heart J*, 2011. **32**(24): p. 3147-97.
82. Komamura, K., et al., *Takotsubo cardiomyopathy: Pathophysiology, diagnosis and treatment*. *World J Cardiol*, 2014. **6**(7): p. 602-9.
83. Sharkey, S.W. and B.J. Maron, *Epidemiology and clinical profile of Takotsubo cardiomyopathy*. *Circ J*, 2014. **78**(9): p. 2119-28.
84. Ruiz-Garcia, J., et al., *Age- and gender-related changes in plaque composition in patients with acute coronary syndrome: the PROSPECT study*. *EuroIntervention*, 2012. **8**(8): p. 929-38.
85. Otten, A.M., et al., *Is the difference in outcome between men and women treated by primary percutaneous coronary intervention age dependent? Gender difference in STEMI stratified on age*. *Eur Heart J Acute Cardiovasc Care*, 2013. **2**(4): p. 334-41.
86. Yoshino, S., et al., *Single nucleotide polymorphisms associated with abnormal coronary microvascular function*. *Coron Artery Dis*, 2014. **25**(4): p. 281-9.
87. Koller, A., *Perspectives: Microvascular endothelial dysfunction and gender*. *Eur Heart J Suppl*, 2014. **16**(Suppl A): p. A16-A19.
88. Tweet, M.S., et al., *Spontaneous coronary artery dissection: revascularization versus conservative therapy*. *Circ Cardiovasc Interv*, 2014. **7**(6): p. 777-86.
89. Tokura, M., et al., *Clinical features of spontaneous coronary artery dissection*. *J Cardiol*, 2014. **63**(2): p. 119-22.
90. Ohba, K., et al., *Microvascular coronary artery spasm presents distinctive clinical features with endothelial dysfunction as nonobstructive coronary artery disease*. *J Am Heart Assoc*, 2012. **1**(5): p. e002485.

91. Tayebjee, M.H., et al., *Plasma matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-2, and CD40 ligand levels in patients with stable coronary artery disease*. *Am J Cardiol*, 2005. **96**(3): p. 339-45.
92. Kingwell, B.A., et al., *Large artery stiffness: structural and genetic aspects*. *Clin Exp Pharmacol Physiol*, 2001. **28**(12): p. 1040-3.
93. Shah, A.S., et al., *High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study*. *BMJ*, 2015. **350**: p. g7873.
94. Mieres, J.H., et al., *Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: a consensus statement from the American Heart Association*. *Circulation*, 2014. **130**(4): p. 350-79.
95. Mieres, J.H., et al., *Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: Consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association*. *Circulation*, 2005. **111**(5): p. 682-96.
96. Morise, A.P., M.S. Lauer, and V.F. Froelicher, *Development and validation of a simple exercise test score for use in women with symptoms of suspected coronary artery disease*. *Am Heart J*, 2002. **144**(5): p. 818-25.
97. Montalescot, G., et al., *2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology*. *Eur Heart J*, 2013. **34**(38): p. 2949-3003.
98. Knaapen, P., et al., *Coronary microvascular resistance: methods for its quantification in humans*. *Basic Res Cardiol*, 2009. **104**(5): p. 485-98.
99. Robinson, J.G., et al., *Cardiovascular risk in women with non-specific chest pain (from the Women's Health Initiative Hormone Trials)*. *Am J Cardiol*, 2008. **102**(6): p. 693-9.
100. Lansky, A.J., et al., *Gender and the extent of coronary atherosclerosis, plaque composition, and clinical outcomes in acute coronary syndromes*. *JACC Cardiovasc Imaging*, 2012. **5**(3 Suppl): p. S62-72.
101. Mega, J.L., et al., *Clinical features and outcomes of women with unstable ischemic heart disease: observations from metabolic efficiency with ranolazine for less ischemia in non-ST-elevation acute coronary syndromes-thrombolysis in myocardial infarction 36 (MERLIN-TIMI 36)*. *Circulation*, 2010. **121**(16): p. 1809-17.
102. Pajunen, P., et al., *Angiographic severity and extent of coronary artery disease in patients with type 1 diabetes mellitus*. *Am J Cardiol*, 2000. **86**(10): p. 1080-5.
103. Qureshi, W., et al., *Gender differences in coronary plaque composition and burden detected in symptomatic patients referred for coronary computed tomographic angiography*. *Int J Cardiovasc Imaging*, 2013. **29**(2): p. 463-9.
104. Patel, A.R., et al., *Gender-based differences in brachial artery flow-mediated vasodilation as an indicator of significant coronary artery disease*. *Am J Cardiol*, 2005. **96**(9): p. 1223-6.

105. Mao, S.S., et al., *Normal thoracic aorta diameter on cardiac computed tomography in healthy asymptomatic adults: impact of age and gender.* Acad Radiol, 2008. **15**(7): p. 827-34.
106. Koster, N.K., et al., *Gender-specific echocardiographic findings in nonagenarians with cardiovascular disease.* Am J Cardiol, 2010. **105**(2): p. 273-6.
107. Shaw, L.J., et al., *Sex differences in mortality associated with computed tomographic angiographic measurements of obstructive and nonobstructive coronary artery disease: an exploratory analysis.* Circ Cardiovasc Imaging, 2010. **3**(4): p. 473-81.
108. Yiu, K.H., et al., *Age- and gender-specific differences in the prognostic value of CT coronary angiography.* Heart, 2012. **98**(3): p. 232-7.
109. Kobayashi, Y., et al., *Effect of Sex Differences on Invasive Measures of Coronary Microvascular Dysfunction in Patients With Angina in the Absence of Obstructive Coronary Artery Disease.* JACC Cardiovasc Interv, 2015. **8**(11): p. 1433-41.
110. Templin, C., et al., *Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy.* N Engl J Med, 2015. **373**(10): p. 929-38.
111. Rich-Edwards, J.W., B.R. McCaw, and A. Lewis-O'Connor, *Domestic violence may trigger Takotsubo.* Am J Med, 2015. **128**(4): p. e9.
112. Lempereur, M., et al., *Impact of gender difference in hospital outcomes following percutaneous coronary intervention. Results of the Belgian Working Group on Interventional Cardiology (BWGIC) registry.* EuroIntervention, 2014.
113. Park, D.W., et al., *Frequency, causes, predictors, and clinical significance of peri-procedural myocardial infarction following percutaneous coronary intervention.* Eur Heart J, 2013. **34**(22): p. 1662-9.
114. Tamis-Holland, J.E., et al., *Sex differences in presentation and outcome among patients with type 2 diabetes and coronary artery disease treated with contemporary medical therapy with or without prompt revascularization: a report from the BARI 2D Trial (Bypass Angioplasty Revascularization Investigation 2 Diabetes).* J Am Coll Cardiol, 2013. **61**(17): p. 1767-76.
115. Li, J., et al., *Sex-related differences in fractional flow reserve-guided treatment.* Circ Cardiovasc Interv, 2013. **6**(6): p. 662-70.
116. Regitz-Zagrosek, V., et al., *Gender as a risk factor in young, not in old, women undergoing coronary artery bypass grafting.* J Am Coll Cardiol, 2004. **44**(12): p. 2413-4.
117. Lehmkuhl, E., et al., *Gender-specific predictors of early mortality after coronary artery bypass graft surgery.* Clin Res Cardiol, 2012. **101**(9): p. 745-51.
118. Kothawade, K. and C.N. Bairey Merz, *Microvascular coronary dysfunction in women: pathophysiology, diagnosis, and management.* Curr Probl Cardiol, 2011. **36**(8): p. 291-318.
119. Pepine, C.J., et al., *Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study.* J Am Coll Cardiol, 2010. **55**(25): p. 2825-32.

120. Murthy, V.L., et al., *Effects of sex on coronary microvascular dysfunction and cardiac outcomes*. *Circulation*, 2014. **129**(24): p. 2518-27.
121. Nante, N., et al., *Sex differences in use of interventional cardiology persist after risk adjustment*. *J Epidemiol Community Health*, 2009. **63**(3): p. 203-8.
122. Lagerqvist, B., et al., *Is early invasive treatment of unstable coronary artery disease equally effective for both women and men? FRISC II Study Group Investigators*. *J Am Coll Cardiol*, 2001. **38**(1): p. 41-8.
123. Kornowski, R., et al., *A comparative analysis of major clinical outcomes with drug-eluting stents versus bare metal stents in male versus female patients*. *EuroIntervention*, 2012. **7**(9): p. 1051-9.
124. Ramanath, V.S., et al., *Receipt of cardiac medications upon discharge among men and women with acute coronary syndrome and nonobstructive coronary artery disease*. *Clin Cardiol*, 2010. **33**(1): p. 36-41.
125. Safdar, B., et al., *Gender-specific research for emergency diagnosis and management of ischemic heart disease: proceedings from the 2014 Academic Emergency Medicine Consensus Conference Cardiovascular Research Workgroup*. *Acad Emerg Med*, 2014. **21**(12): p. 1350-60.
126. Champney, K.P., et al., *The joint contribution of sex, age and type of myocardial infarction on hospital mortality following acute myocardial infarction*. *Heart*, 2009. **95**(11): p. 895-9.
127. Norris, C.M., et al., *Women with coronary artery disease report worse health-related quality of life outcomes compared to men*. *Health Qual Life Outcomes*, 2004. **2**: p. 21.
128. Norris, C.M., et al., *Sex and gender discrepancies in health-related quality of life outcomes among patients with established coronary artery disease*. *Circ Cardiovasc Qual Outcomes*, 2008. **1**(2): p. 123-30.
129. Sedlak, T.L., et al., *Sex differences in clinical outcomes in patients with stable angina and no obstructive coronary artery disease*. *Am Heart J*, 2013. **166**(1): p. 38-44.
130. Kwon, D.H., et al., *Gender differences in survival in patients with severe left ventricular dysfunction despite similar extent of myocardial scar measured on cardiac magnetic resonance*. *Eur J Heart Fail*, 2009. **11**(10): p. 937-44.
131. Nugent, L., P.K. Mehta, and C.N. Bairey Merz, *Gender and microvascular angina*. *J Thromb Thrombolysis*, 2011. **31**(1): p. 37-46.
132. Pepine, C.J., et al., *Emergence of Nonobstructive Coronary Artery Disease: A Woman's Problem and Need for Change in Definition on Angiography*. *J Am Coll Cardiol*, 2015. **66**(17): p. 1918-33.
133. !!! INVALID CITATION !!! [36, 57, 64, 84, 95, 98, 99, 111, 113, 115, 120, 124-128].
134. Bushnell, C., et al., *Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association*. *Stroke*, 2014. **45**(5): p. 1545-88.
135. Organization, W.H., *Global Health Observatory Data Repository, Mortality and global health estimates: Life expectancy*. 2013.

136. Justice, E.C.D.-G.f., *Tackling the gender pay gap in the European Union*. 2013: Publications Office of the European Union.
137. Dombos, T., et al., *Critical Frame Analysis: A Comparative Methodology for the 'Quality in Gender+ Equality Policies'(QUING) Project*. 2012, CPS working paper available at <https://cps.ceu.edu/publications/workingpapers/critical-frame-analysis-quiring>.
138. EugenMed, et al., *Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes*. Eur Heart J, 2015.
139. Verloo, M. and E. Lombardo, *Contested gender equality and policy variety in Europe: Introducing a critical frame analysis approach*. 2007.
140. Commission, E. *Aquis*. 2016; Available from: https://ec.europa.eu/neighbourhood-enlargement/policy/glossary/terms/acquis_en.
141. Kautzky-Willer, A., et al., *Sex-specific differences in metabolic control, cardiovascular risk, and interventions in patients with type 2 diabetes mellitus*. Gender medicine, 2010. **7**(6): p. 571-583.
142. West, R.R., D.A. Jones, and A.H. Henderson, *Rehabilitation after myocardial infarction trial (RAMIT): multi-centre randomised controlled trial of comprehensive cardiac rehabilitation in patients following acute myocardial infarction*. Heart, 2012. **98**(8): p. 637-644.
143. Ren, J. and R.O. Kelley, *Cardiac health in women with metabolic syndrome: clinical aspects and pathophysiology*. Obesity, 2009. **17**(6): p. 1114-1123.
144. Regitz-Zagrosek, V., et al., *Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes*. European heart journal, 2016. **37**(1): p. 24-34.
145. Prior, L., et al., *Translating policy into practice: a case study in the secondary prevention of coronary heart disease*. Health Expectations, 2014. **17**(2): p. 291-301.
146. EUGenMed Cardiovascular Clinical Study Group, et al., *Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes*. Eur Heart J, 2016. **37**(1): p. 24-34.
147. Ventura-Clapier, R., et al., *Sex in basic research: concepts in the cardiovascular field*. Cardiovascular Research, 2017. **113**(7): p. 711-724.