Sede Amministrativa: Università degli Studi di Padova

Dipartimento di *Scienze del Farmaco*

SCUOLA DI DOTTORATO DI RICERCA IN : SCIENZE FARMACOLOGICHE

INDIRIZZO: Farmacologia, Tossicologia e Terapia
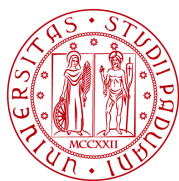
CICLO XXVI

GENDER DIFFERENCES IN THERAPIES AND OUTCOME IN CARDIOVASCULAR DISEASE

Direttore della Scuola : Ch.mo Prof. Pietro Giusti

Coordinatore d'indirizzo: Ch.mo Prof. Pietro Palatini

Supervisore : Ch.ma Prof.ssa Rosa Maria Gaion

Dottoranda : Julia Daragjati

University of Padua

DEPARTMENT OF PHARMACEUTICAL SCIENCES

SCHOOL OF PHARMACOLOGICAL SCIENCES

Pharmacology, Toxicology and Therapeutics

XXVI CYCLE

GENDER DIFFERENCES IN THERAPIES AND OUTCOME IN CARDIOVASCULAR DISEASE

School director: Professor Pietro Giusti

Coordinator: Professor Pietro Palatini

Supervisor: Professor Rosa Maria Gaion

PhD Candidate : Julia Daragjati

RIASSUNTO

La Medicina di Genere è una nuova dimensione della Medicina nata negli USA negli anni '90, quando l'OMS incluse un capitolo sull'Health Equity con il XXI Century Program.

Nasce come necessità di prevenzione e cura mirate per le malattie dell'uomo e della donna. Basti pensare agli studi clinici di tante malattie che colpiscono entrambi i sessi (es., le malattie cardiovascolari), ma che prevalentemente continuano ad arruolare gli uomini, o a patologie chiamate di genere femminile, come l'osteoporosi e il cancro alla mammella, che colpiscono anche la popolazione maschile.

Sulla base di tale premessa, l'obbiettivo iniziale della ricerca è stato quello di descrivere la storia prescrittiva di tutti i farmaci nell'anno 2010. Tramite l'analisi dei dati di prescrizione provenienti dall'Assistenza Farmaceutica Territoriale di Padova è stato possibile descrivere l'utilizzo di questi farmaci nella popolazione generale. Sono risultati maggiormente utilizzati: gli antibiotici (con 39% M vs 46 % F con almeno un antibiotico prescritto, $p<0,001$), gli antiulcera(13,20% M vs 16,68 % F, $p<0,001$), gli antireumatici (10,84% M vs 16,70 % F, $p<0,001$), gli antidepressivi (con 3,74% M vs 8,09 % F, $p<0,001$) etc., con una prevalenza di trattati del genere femminile. Una prevalenza di trattati del genere maschile è stata osservata invece per gli antitrombotici (con 12,11% M vs 11,33% F, $p<0,025$), gli antidiabetici di cui insulino-trattati 1,26% M vs 1,03 % F, $p<0,05$ ed i trattati con ipoglicemizzanti 3,73% M vs 2,83 % F, $p<0,05$) ed i dislipidemici (8,93%M vs 8,08%F, $p<0,025$) etc. Tutti questi dati riportati sono statisticamente significativi. Questa analisi indica anche che il genere femminile è in assoluto il maggior consumatore di farmaci antidolorifici, risultato che porta a dedurre che le donne soffrono maggiormente di dolore acuto e cronico, ma può essere anche un indicatore di una maggiore propensione della donna alla ricerca di una visita medica rispetto all'uomo, il quale forse preferisce rimedi autogestibili (OTC oppure a fumo e alcool). L'alto numero di donne fra i trattati con farmaci del sistema nervoso (antipsicotici, antidepressivi) fa pensare a questi "giorni moderni" in cui la donna è ancora vittima di violenza non solo fisica, ma anche psichica, e si trova spesso sottoposta a stress, come risultato dell'emancipazione. La moglie-madre-donna in carriera è esposta ad una vita frenetica e le tante responsabilità accumulate negli anni tendono a portarla alla parità col genere maschile.

Una analisi più approfondita è stata fatta nello specifico per i farmaci cardiovascolari. La maggior parte dei farmaci cardiovascolari è stato dispensato prevalentemente al genere maschile, ma bisogna sottolineare che le malattie cardiovascolari erano la causa principale di morte in entrambi i sessi. Non si è verificata alcuna differenza di genere nella prevalenza di trattati per i sottogruppi dei betabloccanti non associati, calcio antagonisti con effetto cardio-diretto e antagonisti dell'angiotensina II, mentre per gli antitrombotici, gli antiaritmici di classe sia I che III, gli ipocolesterolemizzanti e ipotrigliceridemizzanti si è osservato un utilizzo maggiore nel genere maschile.

Per quanto riguarda le malattie trombotiche, le femmine risultavano meno trattate dei maschi, in accordo con il fatto che il maschio adulto, a parità di età, è più propenso alla trombosi rispetto alla femmina adulta, perché con l'avanzare dell'età ha una maggiore aggregazione piastrinica rispetto alla femmina.

 Infine, l'attenzione è stata focalizzata sull'evento della sindrome coronarica acuta (SCA) per analizzare la presenza di eventuali differenze di genere in pazienti ospedalizzati per SCA in relazione ai seguenti indicatori: prevalenza di ricoveri per SCA, mortalità intra- ed extra-ospedaliera, tipologia di interventi di rivascolarizzazione, trattamento farmacologico alla dimissione, aderenza alla terapia e sopravvivenza.

Nel corso dell'anno 2008, sono stati ricoverati per SCA 1.204 pazienti (760 maschi e 444 femmine). La prevalenza dei ricoveri è stata significativamente superiore negli uomini (3,26‰) rispetto alle donne (0,92‰) con OR = 1,7 (IC 95% = 1,4-2,0). Dei 1.204 pazienti arruolati 142, ovvero 11,8%, sono andati incontro a decesso intraospedaliero. Sono state analizzate le recidive a breve e lungo termine. Le donne in entrambi i casi andavano in contro a recidive più frequentemente degli uomini (nel 2009 il 17,9% delle donne vs. 12,6% degli uomini e nel 2012 32% donne vs. 24% degli uomini, p<0,05). Una fotografia della terapia nei 12 mesi precedenti l'evento evidenziava un trattamento con antiipertensivi e antidepressivi maggiore nelle donne. Per quanto riguarda il trattamento del diabete e delle dislipidemie non si evidenzia nessuna differenza di genere nell'utilizzo dei farmaci riguardanti queste patologie. E' stata fatta una analisi degli interventi di rivascolarizzazione per rilevare eventuali differenze di genere e differenze di età. Il 40,12% della popolazione è andata incontro a rivascolarizzazione invece il 48,1% non è stata rivascolarizzata. Nella fascia di età 65-79 anni il 73,4% dei maschi ha subito un intervento di

rivascolarizzazione contro il 26,6% delle donne (OR=1,7 con IC 95% =1,2-2,5). Negli over 80, gli uomini sono sempre maggiormente rivascolarizzati (71,2%M vs 28,8F OR= 4,1 con IC 95% = 2,2-7,6). Questi dati hanno confermato che in generale gli uomini vengono sottoposti a questo tipo di interventi più delle donne. Per quanto riguarda l'aderenza alla terapia, i pazienti di sesso maschile sono stati più aderenti alla terapia limitatamente all'aspirina (92% M vs 82% F, OR = 2,4 IC 95% 1,2-4,6). L'analisi di sopravvivenza ha mostrato una prognosi migliore del genere maschile, con una mortalità più alta del genere femminile.

Merita porre l'accento sul fatto che in questi anni l'utilizzo di farmaci cardiovascolari da parte delle donne sta aumentando. La donna è sempre più esposta a rischi come fumo, alcool, condizioni di malessere che la portano alla ricerca di farmaci e a volte è esposta a politerapie poco controllate, che aumentano il rischio di reazioni avverse. Conseguenti costi inutili potrebbero essere evitati se ci fosse una terapia adeguata per genere ed età (soprattutto per gli anziani maggiormente soggetti a malattie croniche). Nasce così l'importanza di una cura appropriata della condizione di malessere o di malattia. La società di oggi si sta evolvendo verso abitudini sempre più consumiste, abusi di sostanze come fumo, alcol, droga da parte di entrambi i generi. Nasce così l'esigenza di agire in modo coerente in termini d'informazione del cittadino (assistibile/assistito) e di indurre una maggiore consapevolezza nel medico, che possa così mettere in atto una terapia adeguata, tenendo conto non solo delle funzioni biologiche e fisio-patologiche del paziente, ma anche dell'ambiente socio-culturale e delle differenze di genere!

Abstract

Introduction: It has been clearly evidenced that physiologic differences between men and women are numerous regarding every organ and apparatus as for nervous system, immune system and especially for cardio-vascular system. Epidemiology is of great help in analysing these differences by offering several measures to describe therapies outcome as predictors to health/disease patterns. Acute Coronary Syndrome (ACS) may occur in both men and women, but with different symptoms, risk factors or types at presentation. This leads to different clinical and pharmacological management and possibly in the health outcome.

Objective: The purpose of this analysis was to explore, by using an administrative database, gender and age differences in drug prescriptions of ordinarily residents, entitled to either free or subsidised approved prescribed drugs and medicines and and surgical interventions provided from the Local Health Service. Further analysis was performed in the cohort of patients that experienced an ACS during 2008.

Methods: All residents of the Local Health Service Area 16 of the Veneto Region (Italy) ages 15-44, 45-64, 65-79 and >=80 years in the period 1st of January until 31st of December 2010, were included in the study. The Local Health Service system, covering this area, keeps record of all drug prescriptions dispensed by public or private pharmacies. All medications dispensed during 2010 were considered and classified according to Anatomical Therapeutic Chemical (ATC) classification system. Results were reported as odds ratios (OR) of prescriptions dispensed to males and females with 95% confidence intervals (CI) to analyse the number of subjects that received at least one medication. A detailed analysis was conducted for Cardiovascular drugs (ATC: C) in the cohort of 1,204 ACS patients (760 men and 444 women) being admitted in Saint'Anthony Hospital. Data of therapies and interventions were collected from the hospital and local medical distribution database.

Results: Of the 491,261 included subjects, 255,026 were females and 236,235 males. Females were medicine dispensed in most of ATC subgroups as with antiulcer drugs (OR=0.80, 95% confidence interval [CI] 0.74-0.86), antibiotics(39% M vs. 46% F, p<0.001) as for tetracyclines (OR=0.91 95% CI 0.85-0.93), penicillins (OR=0.90 in the 95% CI 0.83-0.94), antimigraine preparations (OR 0.34 95% CI 0.0.31-0.36), antipsychotics (OR=0.86, 95% CI 0.81-0.90), antidepressants (3.74%M vs. 8.09% F, OR=0.44, 95% CI 0.40-0.52) diuretics (OR=0.72, 95% CI

0.66-0.80). On the other hand, males were dispensed more with antidiabetic drugs, insulin therapy (OR= 1.24 95% CI 1.21-1.30) and with oral hypoglycaemic (OR=1.37 95% CI 1.33-1.40), more exposed to treatment for cardiovascular disease with antithrombotic agents (12.11% M vs. 11.33%F, OR=1.16 95% CI 1.14-1.20), betablockers (OR=1.15 95% CI 1.10-1.20), ACE-inhibitors (OR=1.25 95% CI 1.20-1.30). Males were generally more prescribed with cardiovascular medications than their female counterparts. An obvious gender difference in drug utilisation was noticed during the 15-44 years of age, this difference decreased with aging, but still the medication use difference remained statistically significant.

The prevalence of ACS was 2.5 ‰ (3.26‰ in male patients and 0.92‰ in female patients, OR=1.7 95% CI 1.4-2.0). Of the ACS patients, 142 (11.8%) died in hospital without any gender and age difference. Thus, for further investigations a cohort of 1,062 ACS patients (688 male and 374 female patients) was considered. Of these patients 40.12% underwent a revascularization intervention and 48.1% were not revascularised. Male patients over 65 years of age (73.4%) were significantly more likely to have a revascularization than the female patients (26.6%) of the same age (age group: 65-79, OR=1.7 95%CI 1.2-2.5; age group >=80, OR=4.1 95%CI 2.2-7.6).

Six months after hospital discharge antiaggregation therapy was analysed. In the ACS population 82% received at least one antiaggregant. The remaining population 18% did not receive any antiaggregant at all, generally those were female patients (OR=2.8 95%CI 2.1-3.8).

Aspirin was used in 35% of the non- revascularized vs. 28 % of the revascularized patient especially in non-revascularized female patients; Thienopyridines were dispensed in 8% of the non-revascularized vs. 5% of the revascularized patients especially in revascularized female patients, dual antiplateletes therapy was more dispensed in revascularized patients (61% vs. 29%), especially in male non-revascularized patients. For the other non mentioned therapies male and female patients were treated equally.

Regarding to therapy adherence, male patients were in general more adherent to Aspirin (92%M vs. 82%F, OR=2.4 95%CI 1.2-4.6) on the other hand, to Thienopyridines (87%M vs. 84%F, OR=1.3 95%CI 0.3-5.0) and to Dual-antiplateletes therapy (76%M vs.74%F, OR=1.1 95%CI 0.7-1.8) both male and female patients were adherent without gender differences.

Conclusions: As women are more exposed to chronic and acute conditions, especially in the reproductive years 15 to 44 and in pre- and post-menopausal age, according to the literature, our results support the suggestion that females are dispensed more medicines than males in general. On the contrary, men were more exposed to cardiovascular drugs than women. ACS occured more frequently in men than in women. In general men were more revascularized than women.

On discharge, female patients were not usually treated with antiaggregant therapy, more often than their male counterparts. Revascularized patients compared to non-revascularized patients did not have any gender difference in terms of therapy, but an evaluation between non-revascularized patients indicated an inequity between male-female patients use of antiaggregants. On the whole, both female and male ACS patients were adherent to therapy. In general, men had a better survival than women.

TABLE OF CONTENTS

List of abbreviations

ACS	Acute Coronary Syndrome
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
DDD	Defined Daily Dose
F	Female (patients)
GDM	Gestational Diabetes Mellitus
GERD	Gastro-Esophageal Reflux Disease
IQR	Interquartile Range
M	Male (patients)
MI	Myocardial Infarction
NSTEMI	without ST-segment elevation MI
OR	Odds Ratio
OTC	Over the Counter
SD	Standard deviation
STEMI	ST-segment elevation MI
UA	Unstable Angina
ULSS	Unità Locale Socio Sanitaria
WHO	World Health Organization
WHOCC	WHO Collaborating Centre

1   Introduction

A new dimension of medicine was stressed in the 90's, when WHO included in the XXI century Program the Health Equity chapter. It was stressed that women die from the same disease as men (e.g. heart disease, cancer and stroke), but women were not being enrolled in clinical studies. In Europe women live on average 6 years longer than men showing a difference in life expectancy, but living longer doesn't mean living better and healthy. Gender differences were noticed in morbidity and mortality anyway females were disqualified routinely from all medical researches. It has been clearly evidenced that physiologic differences between men and women are numerous regarding every organ and apparatus as for cardio-vascular system, nervous system and immune system. These differences affect drug efficacy and safety including pharmacokinetic and pharmacodynamic aspects.

The purpose of the present analysis was to explore , possible gender differences in drug prescriptions, utilizing an administrative database. Different studies reported that women were prescribed more drugs for all conditions and disease, except for cardiovascular disease. In addition, women were less adherent to therapies. Cardiovascular disease is the primary cause of death worldwide. Women think that cancer is the most dangerous disease and take more prevention cares to it. Instead they should think also about cardiovascular disease and undergo periodic heart checkups especially during post-menopause. This underconsideration makes women less prone to seek cardiac prevention and care. Even physicians underdiagnose and undertreat female patients in their first heart-coronary problems. Usually, specific symptoms are not recognised thus treatment may be delayed.

 According to the present analysis further investigation was done in a cohort of patients that experienced acute coronary syndrome and results were compared to th region population (Osmed, 2012) as our ACS patients (Saint'Anthony hospital) are a sub-population of the ARNO report (Veneto Region).

2   Review of the literature

2.1   Concepts of sex and gender in healthcare

In the latest years, an important factor that influences individual health and healthcare other then sex and age was shown to be the gender difference.

This factor has been neglected when in a variety of preclinical and clinical studies the male animals and men were used. It has been, thus important to consider other variables that can influence extremely male and female in prevention, healing and care.

Sex differences are related to biology: genetics, anatomy and physiology. Gender refers to socio-cultural phenomena related to rules, traditions and social relationships in cultures shaping the feminine and masculine behaviour. It is a complexity of norms, relations and individual identity. Gender norms consider the appropriate behaviour of men and women, gender relations evaluate the actual roles of individuals (men and women) in any one society, and the identity is the way that individuals (men and women) introduce themselves and are perceived by others (Gendered Innovations, 2013).

Sex and gender are analytically distinct but not independent. They interrelate in important and multifaceted ways: "Not only can gender relations influence expression and interpretation of biological traits, but also sex-linked biological characteristics can, in some cases, contribute to or amplify gender differentials in health" (Krieger, 2003).

2.2   Gender differences in therapies

There are sex-gender differences with regard to the prevention, epidemiology, evolution prognosis, therapy and outcome of diseases. Medications are used to treat morbidity, especially in older ages, but also to prevent health-related disorders among healthy individuals (Nilsson, 2006).

Therapies are mostly developed in males. Protective pathways in females are not well analyzed. Some of the drugs effective in males are not meant to be effective in females, too (Regitz-Zagrosek, 2006). Thus, therapies for patients with the same pathology are not the same (in terms of doses, gender related pharmacokinetic,

pharmacodynamic and effectiveness or kind of medications). In pharmacokinetics of drug administration, metabolism, absorption, distribution and elimination gender differences were observed, especially in activity of drug metabolizing enzymes and, to a less extent, for absorption. For example, the metabolisation is a process occurred in many drugs by enzymes of the cytochrome p450 (CYP) system. Hormones, including estrogens and progestins are metabolized via these enzymes. Women seem to have a higher clearance of CYP3A4 substrates, although findings are not consistent. Menstrual cycle, pregnancy and menopause can be associated with changes in pharmacokinetics, because of sex steroid concentrations and alteration of body water. In pharmacodynamics an there is an important relation between receptors and sex hormones (estrogens) which can modulate the regulation of receptors in heart, vessels etc, (e.g beta-adrenergic receptors and cardiovascular medications: estrogen deficiency up-regulate beta1 receptors, showing a good activity of beta blockers in men) (Jochamann et al., 2005). Another example of hormone influence was observed for estrogens and androgens in the immune reactivity. Estrogens induce inflammation; on the other hand androgens show anti-inflammatory effect. Immune reactivity is significantly higher in women, thus they use more anti-inflammatory drugs, also they perceive more pain and require higher doses of opioid analgesics (morphine) (Cepeda et al., 2003). Another study reported the connection between migraines and estrogen levels in women (Cornforth et al., 2009).

Physical abuse or sexual abuse and psychic abuse appear to be related to pain and mood disorders in women. Differences in therapies are related to sex differences as chromosomes, genes and hormones but also there is another social and environment impact. Women have larger number of comorbid pain conditions as depression and anxiety related to effects of living arrangements, employment history, social support, marital status and family composition (Greenspan et al., 2007).

An important determinant for greater dispensing medications to one gender as compared to the other is the behaviour of health seeking. Women are more likely to visit a physician than men. They discuss easier any kind of disorder. They report a higher grade of abdominal pain (Labus et al., 2008), or heartburn (Oliveria et al., 1999) and a higher frequency of migraine (Lipton et al., 2005).

In drug-prescribing some gender-related differences among physicians were noticed. If the physician was a male, hypertensive female patients resulted to be undertreated (Journath et al., 2008).

Compliance and adherence to therapy are very important. Better adherence is associated with better prognosis, survival and lower risk of hospitalization, especially in chronic diseases (Wu et al., 2006). To understand the reason associated with adherence may provide opportunities for intervention. Different studies reported conflictual results as women are the less adherent, or no gender difference in adherence to therapies were observed.

Another study (Dunbar-Jacob, 2002) reported that women, especially those under 75, are less adherent than men, and they are more likely to over-report adherence. Factors that may contribute to poor medication adherence are depression, cognitive impairment, social support, severity of illness (Brossworth et al., 2008; Stilley et al., 2004) etc. Most of psycosocial factors are more attributed to women. Smoke and alcohol abuse are associated with a poor medical adherence (Evangelista et al., 2001).

2.3   Cardiovascular system and gender

Cardiovascular disease remains the primary cause of death worldwide but age of onset, severity and fatalities differ between women and men. The number of women participating in studies on cardiovascular disease has increased since mid-1980s. However, physiological and molecular bases of differences between women and men which contribute to development of cardiovascular disease and response to therapy remain underexplored. Women are still under represented in trials as for arterial hypertension and heart failure (Stramba-Badiale, 2010). Women frequently respond in a different way from men to many cardiovascular medications as a result of different physiology, pharmacokinetics and pharmacodynamics.

Physiologic differences include smaller heart, larger proportion of body fat, lower glomerular filtration rate etc., observed in women. The complement of sex chromosomes and the influence of hormones affect all components of the vascular wall, the heart and autonomic nervous system. Sex and hormones, for example the menstrual cycle, menopause and pregnancy, fluctuate during those cycles and this can influence plasma levels of cardiovascular drugs as well as vascular healing and

development of atheroma which involve activation (or suppression) of blood elements including those of the immune system (Miller, 2008). Inflammation is an important prognostic indicator in women. "Basic science studies of the cardiovascular system must identify experimental material including species/strain characteristics, sex and hormonal status including the presence of gonadal steroids at the time of testing, during development or number of pregnancies" (Miller, 2009). There are differences in prevalence, incidence and severity of diseases. Major gender differences have been observed in heart failure and its most frequent causes hypertension, myocardial infarction, coronary artery disease, cardiomyopathies and atrial fibrillation. Hypertension, diabetes and myocardial hypertrophy are major risk factors for heart failure in women. There is a heart failure difference between men and women, showing that women suffer of diastolic heart failure and men more from systolic heart failure. Myocardial infarction is more relevant in men. Other factors such as composition of diets, stress due to handling, social interactions and disruption of sleep/wake cycles have the potential to impact experimental outcomes. Obesity and insulin resistance inhibit myocardial substrate metabolism and efficiency in young women. Obesity, hypertension and dyslipidemia are interrelated risk factors. They are associated with inflammation in women. Diabetes is a stronger risk factor for heart failure in women than in men. Metabolic syndrome has gender specific traits (Regitz-Zagrosek, 2007).

Medication therapies depend on the physician. It was observed that male physicians usually undertreat hypertensive women (Journath, 2008). Hypertensive women are usually treated with diuretics, hypertensive males are more often treated with Beta-blockers, Calcium Antagonist channel blockers and ACE-inhibitors.

Adherence to therapy is another important factor considered. Contrary to popular belief fewer medication was associated with lower adherence with chronic cardiovascular regimens (Shalansky, 2002), and men were more adherent to medication recommendations than females especially for hypertension (Shiah-Liah, 2011).

2.4   Definition of Acute Coronary Syndrome

Acute Coronary Syndrome (ACS) is a group of clinical conditions occurring when an atherotic plaque ruptures leading to thrombus formation within a coronary artery, or coronary thrombosis. It is an unstable atherothrombotic coronary disease. First symptoms occurring are chest pain and diaphoresis.

It is important to diagnose the ACS event with measurement of cardiac markers as troponins, and ST segment-evaluation on ECG for a better emergency management. ACS patients may experience:

- ST-segment elevation Myocardial Infarction (STEMI), the most dangerous infarction that occludes completely and steadily. It is observed that the coronary cardiac markers become abnormal and there is an elevation of the ST segment in the ECG.

- without ST-segment elevation of Myocardial Infarction (NSTEMI), it is a less dangerous infarction caused by the incomplete and temporary occlusion of the coronary. Myocardial biomarkers are higher, but there is not an ST-segment elevation.

- Unstable Angina (UA), occurring often at rest. In this case all ACS biomarkers and ECG are normal. (Van de Werf, 2008; Bassand, 2007)

The stable angina is not a type of ACS, because it occurs after an emotion, hard activity and does not resolve at rest. (MerckMedicus, 2009)

ACS is gender and age specific in both symptoms and risk factors at presentation. Women tend to present later than men, and usually with atypical symptoms (Goldberg, 2000).

Primary prevention of this disease consists in controlling risk factors as: healthy eating, making exercise, treatment for hypertension or diabetes, controlling cholesterol levels, and avoiding smoking. As society is in a continuous evolution thus starting with primary prevention can make a gender/age difference in ACS occurrence. Based on international literature (Saubouret, 2010; Akhter, 2009, Hee Tae, 2011), women at presentation are older and have higher rates of comorbidities such as diabetes and hypertension. Secondary prevention consists in pharmacologic therapy, coronary interventions, and concomitant therapy (Coven, 2012). There is also evidence that women are less likely to be treated for ACS, and even at discharge are less likely to be given aspirin, thienopyridines, beta-blockers

and statins. Often are less compliant to therapies (Akhter, 2009). Moreover they tend to be less revascularized than men (Sabouret, 2010, Hee Tae, 2011) although having higher rates of in-hospital complications, and higher mortality rates among young ages (Claassen, 2012). It is obvious that there is a gender difference among ACS patients.

3   Objectives

The objective of this analysis was to explore, by using an administrative database, gender and age-related differences in drug prescriptions dispensed by regional pharmacies of the National Health Service, Unità Locale Socio Sanitaria, ULSS 16 of the Italian city, Padua.

A major importance has been given to medications of the cardiovascular system,

Further analyses were done in a cohort of patients hospitalized at Saint'Anthony hospital following an acute coronary syndrome event during 2008 to investigate potential gender/age-related differences in:

- population-based prevalence on admission

- in-hospital mortality

- anti-aggregation therapy and related adherence to it six months after discharge

- coronary interventions (management of revascularization or not)

- pharmacologic therapy in the 12 months before the ACS event: hypertension, diabetes, dyslipidemias and depression treatments were considered as possible risk factor predictors

- short term relapse (1 year after discarge), long term relapse (3 years after discharge) and cohort survival rate until 30th of June 2012.

4 Population and Methods

4.1 Study design

This is an observational and retrospective study. The Local Health Sevice (Unità Locale Socio Sanitaria ULSS16) is a regional agency that provides care service to residents of the Veneto Region in Italy. Data were extracted from ARNO database, where all the so called "red prescriptions" entitled to either free or subsidised from the National Health Service (NHS), are registered. The study includes the number of individuals (population of ULSS 16) and all medications dispensed over one year. Medications were classified by ATC for easier and manageable view of results. Further analyses were done for ATC= C, the Cardiovascular System drugs.

Moreover, as coronary heart disease is the leading cause of morbidity and mortality in men and in women, as well, a cohort of patients with ACS was analysed (see below the study design, Figure 1)

Figure 1 Study project
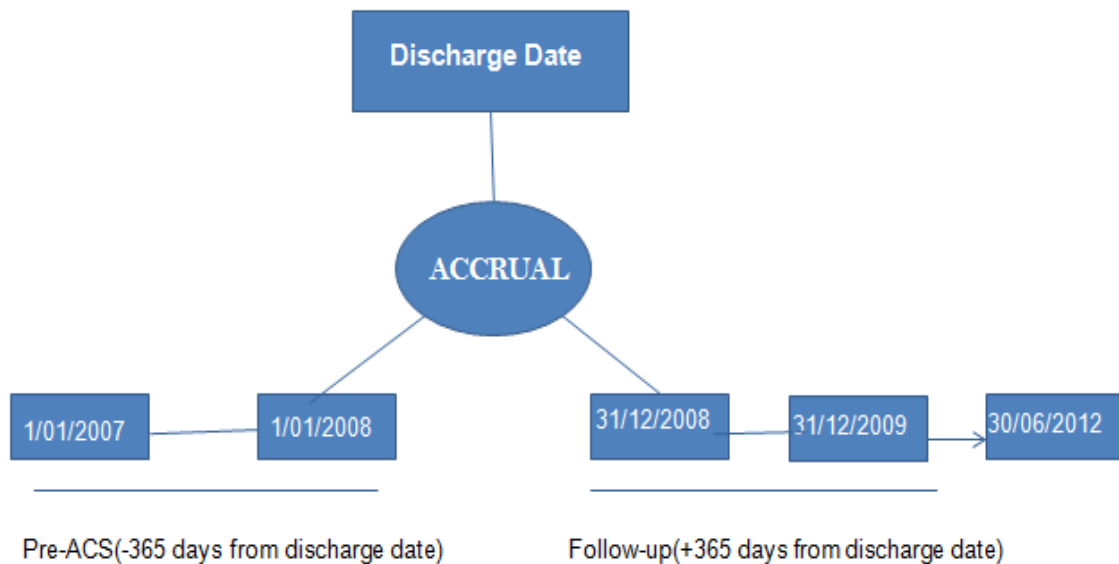
4.2 Population

4.2.1 Overall population

In 2010, the population of ULSS 16 was 491,261 residents (255,026 females and 236,235 males) and was evaluated anonymously based on demographic data, stratified by gender and five age groups (0-14, 15-44, 45-64, 65-79 and over 80).

In 2008, the cohort of patients hospitalized after an ACS event was 1,204 out of 483,042 (250,143 females and 232,899 males).

4.2.2 ACS patients

Patients admitted in Hospital after an ACS-event during the time period 1/1/2008-31/12/2008 were analysed. ACS-events were classified by ICD IX-codes (International Statistical Classification of Diseases and related Health Problems). Data were collected from hospital database, hospital discharge forms, hospital pharmacies and local pharmacies evaluating: demographic data (age and gender), admission diagnosis (ACS), date of admission, discharge or transfer, previous 12 months therapy (drug prescriptions), 6 months follow-up (drug prescription records), possible coronary interventions (classified as revascularized and non-revascularized patients) [see Table1].

Table 1 Classification of Acute Coronary Syndrome

Type	ICD-IX Codes and description
ACS-Non revascularized patients	410 Acute Myocardial Infarction 411 Other acute and subacute forms of ischemic heart disease (only main diagnosis)
ACS-Revascularized patients	410 Acute Myocardial Infarction 411 Other acute and subacute forms of ischemic heart disease 36.01 Single vessel percutaneous transluminal coronary angioplasty without mention of thrombolytic agent 36.02 Single vessel percutaneous transluminal coronary angioplasty with mention of thrombolytic agent 36.05 Multiple vessel percutaneous transluminal coronary angioplasty [PTCA] performed during the same operation, with or without mention of thrombolytic agent 36.06 Insertion of non-drug-eluting coronary artery stent. (only main diagnosis)
Heart failure	428 Heart failure (only main diagnosis)

4.3   Medication

Drugs that were considered in the present study were: Antiinfectives (ATC J) for systemic use Tetracyclines (J01A), Penicillins (J01C), Beta lactam antibiotics (J01D), Macrolides and Lincosamides (J01F), Quinolone antibacterials (J01M), Antimycotics for systemic use and Antiparasitic products (J02A); Gastro-intestinal drugs (ATC A, Anti-acids A02A, Anti-ulcer drugs A02B, drugs of Biliar Therapy A05A, Intestinal Antibiotics A07A); Calcium & drugs affecting bone structure and mineralization (A12A); Potassium (A12B); Iron preparations (B03); Vitamin B12 and Folic acid (B03B); Anti-inflammatory and Anti-rheumatic products Non steroids (M01A); other Analgesics and Anti-pyretics (N02B); Opioids (N02A); Anti-migraine drugs (N02C); Antiepileptic drugs (N03A); Anti-parkinson drugs (N04A); Antipsychotic drugs (N05A); Antidepressant drugs (N06A); Corticosteroids (D07A); Thyroid and Anti thyroid drugs (H03); Anti-glaucoma preparations and Miotics (S01E); Antidiabetics (A10, Insulin therapy and Oral hypoglicemics); Anti-acne & Psoriasis drugs (D10B); Antigout preparations (M04A); Adrenergics, Inhalants; other Systemic drugs for Obstructive airway disease (R03), Dopaminergic Agents; other drugs for Obstructive Airway Diseases, Inhalants (N04); Antihistamines for systemic use, Antiadrenergic agents, centrally acting drugs (R06).

These are all cardiovascular medications with ATC C & A: Glycosides (C01A); Antiarithmics I and III class (C01B); Vasodilators used in cardiac diseases (C01D); Diuretics (low ceiling diuretics, Thiazides and low ceiling diuretics excluding Thiazides, high ceiling, Potassium-sparing agents, C03); Beta blockers (C07); Selective Calcium Channel Blockers With Mainly Vascular Effects and with direct cardiac effect (C08); Ace Inhibitors, Plain and ACE inhibitors, combinations; Angiotensin II Antagonists, Plain and Combinations (C09); Anti-thrombotic agents (B01A, B01B); HMG-CoA Reductase inhibitors Simvastatin and Ezetemibe, Fibrates (C10A).

4.3 Calculation of therapy adherence

The population on average gets a certain treatment daily.

The numbers of DDDs per inhabitant per year, gives an estimate of the number of days for which each inhabitant is on average treated annually.

The WHO's definition is: "The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults."

*Drug usage (DDDs)= Items issued **x** Amount of drug per item/DDD*

Adherence to antiaggregation therapy (over six months) was analysed using Defined Daily Doses DDDs. Patients were treated with one antiaggregant with a dosage of 150mg/day (Aspirin/ Thienopyridine). Some were treated with a dual-antiaggregation with a dosage of 300mg/day. Male and female patients were classified in 4 age groups for a better study comparison in: 15-44, 45-64, 65-79 and ≥ 80 years old. Patients transferred from a hospital to the other were excluded.

4.4   Statistical analysis

Data stratification was processed using Microsoft Access and the calculation of sum, mean, standard deviation, ratios using Microsoft Excel 2003. Results were reported as odds ratios of prescriptions dispensed to males and females with 95% confidence intervals (OR is a measure of association between an exposure and an outcome most commonly used in case-control studies) to report the number of individuals that were prescribed at least one medication. A ratio of 1 indicates there was equal prescription of drug to males and females. A ratio >1, more medications were prescribed to males, and a ratio <1indicates prescribed medications in favour for women. DDDs (Defined Daily Dose) were analysed to screen gender difference in adherence to therapies. Forest plots were used to illustrate gender/age differences in adherence and intervention analysis. Wilcoxon test was used to verify the significance of the intervention analysis. Statistical analysis was performed using R-project software version 2.15.1 for Windows (GNU project). Descriptive statistic included mean and standard deviation for normally distributed variables and median and interquartile range (IQR) for nonparametric variables. Study groups were compared using χ^2 or Fisher's exact test for categorical variables, the Student's *t*-test for normally distributed continuous variables and the Wilcoxon rank-sum test for nonparametric variables. The Kaplan Meier survival curves were performed using R-project a statistical computing and graphics program, significance was verified using the Shapiro test.

5   Results and Discussion

5.1   Dispensed medications to males and females stratified by ATC

Of the 491,261 included subjects, 255,026 were females and 236,235 males. Females were more likely to receive prescriptions of most of Chemical therapeutic subgroups, e.g. antiulcer drugs (OR=0.80, 95% confidence interval [CI] 0.74-0.86), antibiotics as for tetracyclines (OR=0.91 95% CI 0.85-0.93) and penicillins (OR=0.90 in the 95% CI 0.83-0.94), anti migraine products (OR 0.34 95% CI 0.0.31-0.36), antipsychotics (OR=0.86, 95% CI 0.81-0.90), antidepressants (OR=0.44, 95% CI 0.40-0.52) diuretics (OR=0.72, 95% CI 0.66-0.80). On the other hand, males were more likely to be treated with antidiabetic drugs, including insulin (OR= 1.24 95% CI 1.21-1.30) and oral hypoglycemics (OR=1.37 95% CI 1.33-1.40), with antithrombotic agents (OR=1.16 95% CI 1.14-1.20), betablockers (OR=1.15 95% CI 1.10-1.20), ACE-inhibitors (OR=1.25 95% CI 1.20-1.30). Moreover, for ACE-inhibitors a larger difference between males and females was noticed in the 15-44 years old group, decreasing with aging.

On the whole, males were more likely to receive cardiovascular medications. Females were medication dispensed in most of ATC subgroups than males. Results were given as odds ratio (OR) to compare the two population groups, males and females. An OR<1, is indicative for a higher proportion of treated females, a ratio >1 is indicative of higher dispensing to males. Medications with a prevalent use in females were: Anti-acids; Anti-ulcer drugs; drugs of Biliar Therapy; Intestinal Antibiotics; Calcium & drugs affecting bone structure and mineralization; Potassium; Iron preparations; Vitamin B12 and Folic acid; Antiadrenergic agents, centrally acting drugs; Diuretics; Potassium-sparing agents; Beta blockers and other Diuretics; Angiotensin II Antagonists, Combinations; Corticosteroids; Thyroid and Anti thyroid drugs, Antiinfectives for systemic use as Tetracyclines, Penicillins, Beta lactam antibiotics, Macrolides and Lincosamides, Quinolone antibacterials, Antimycotics for systemic use, Anti-inflammatory and Anti-rheumatic products, Non steroids; other Analgesics and Anti-pyretics; Opioids; Anti-migraine drugs; Antiepileptic drugs; Anti-parkinson drugs; Antipsychotic drugs; Antidepressant drugs; Anti-dementia drugs; agents against Amoebiasis and other Protozoal diseases; Anti-malarial drugs; agents against Leishmaniasis and Trypanosomiasis; Anti-glaucoma preparations and Miotics. Males were dispensed mostly with: Insulin

therapy and Oral hypoglicemics; Anti-thrombotic agents; Glycosides; Vasodilators used in cardiac diseases; Antiadrenergic Agents, Peripherally Acting drugs; Selective Calcium Channel Blockers With Mainly Vascular Effects; Ace Inhibitors, Plain; Lipid Modifying Agents, Plain; Anti-acne & Psoriasis drugs, Antigout preparations; Adrenergics, Inhalants; other Systemic drugs for Obstructive airway disease. There was no difference in the number of treated males and females for those therapeutic subgroups: Antiarithmics I and III class; ACE inhibitors, combinations; Dopaminergic Agents; other drugs for Obstructive Airway Diseases, Inhalants; Antihistamines for systemic use.

From 58 ATC subgroups, of our interest, 13 were dispensed mostly in males, 5 had no gender difference in dispensing and all the other were dispensed mostly in females. This first overview showed that females were more treated than males.

Anti-infectives are the most dispensed drugs, especially to women of all age groups, excluding 0-9 years (Macy, 2009). From our ATC groups, Penicillines were the most dispensed antibiotics, followed by Macrolides, Lincosamides, Quinolones, Betalactams and last Tetracyclines. During 2010, approximately 46% of women and about 39% of men were prescribed at least one antibiotic prescription. Frequently, antibiotics cause adverse reactions, e.g. Penicillines give side effects as hyper sensibility, especially in females over 80, or allergies most frequently in males under 9 years old; Tetracyclines can induce the immunologic reaction Lupus Eritematosus in females (Minocicline); Meflochine, an antimalarial agent gives Central Nervous System side effects as sleep disorders, depression, epileptic crisis much more in females than males due to a different drug distribution, because it is known that females have a higher emetic cerebral flux.

After Anti-bacterials, the *Analgesics and Anti-inflammatory* agents were the most dispensed drugs, especially in females. This could be an explanation of more Adverse Drug Reactions in females as compared to males (Zopf, 2009).

A large number of prescriptions for non steroidal inflammatory drugs, NSAIDs (M01), muscle relaxants (M03B), opioids (N02A), other analgesics (N02B) and anti migraine products (N02C) were prescribed in favour of women.

Over the Counter (OTC) pain relieving drugs and medications dispensed without a prescription were not included in this survey as they are not subsidized from the SSN (National Health Care).

Females have more chronic pain conditions. Most common diagnosed pain symptoms in females are chronic musculoskeletal pain, followed by arthritis/osteoarthritis, back pain, headache, migraine, unspecified pain, malignancies. The prescribing rates increased with patients' age, especially over 70 years old patients. There is a high proportion of elderly women taking these drugs due to the increased prevalence of arthritis/osteoarthritis. Females experience a lower pain tolerance and higher subjective pain ratings than males another reason of a more frequent administration of these drugs by females (Weisenfeld-Hallin Z, 2005).

Antidepressanst, Antidementia Agents, Antipsychotics and *Anticonvulsants* were all medicines with odds ratio<1, indicating a higher proportion of treated females than males. There was no difference in treated patients with the *Dopaminergic agents. Antidepressants* were the most used medicines in patients with mental health problems. 3.74% of the studied male population was treated at least once with antidepressants vs 8.09% of female patients suggesting that depression occurs in females more commonly than in males (2:1). This suggests that women are more prone to depression, they also report greater fear and are more likely to develop anxiety disorders than men (McLean, 2009).

Epidemiological studies of different nations suggested that females are more likely to be treated with antidepressants, antipsychotics, antidementia agents, but no significant sex-related difference of therapy was stressed for Dopaminergic and Cholinergic agents (Statistics: Norway 2008, Wettermark, 2007 Sweden, US).

Gastrointestinal drugs: Antiacids and Antiulcer drugs: these drugs were prescribed more to females than to males. Antiacids are used in case of indigestion, heartburn, gastritis, and gastroesophageal reflux disease (GERD). Females display less physiologic episodes of gastroesophageal reflux than males, but symptoms are tolerated better by males. Quality of life is significantly worse for women with GERD (Lippmann, 2009). Females report more intense abdominal pain when exposed to the same stimulus as males (Labus, 2008). This could be an explanation why they seek care to physicians for heartburn more than men.

Another difference in visiting a physician has been reported with proton pump inhibitors for individuals with GERD conditions. Antiulcer drugs are prescribed for gastric or duodenal ulcer, gastro-esophageal reflux, and co-prescribed with NSAIDs. Comparing treatment of patients with NSAIDs and treatment with COX-2 inhibitors

would suggest that the second group of treated patients use less antiulcer drugs than the first group, but when adjusted for age, gender and number of prescriptions, patients in the COX-2 inhibitor group were still co-prescribed anti-peptic ulcer drugs more frequently than patients prescribed nonselective NSAIDs). These drugs were one of the most dispensed (13.18% M vs. 16.78%F). In UK it is reported that antiulcer drugs made up 6.1% of all prescriptions dispensed and are the second most expensive group of drugs to the government (Teeling, 2004).

Antiasthma drugs: It was noticed a gender difference in Antiasthma drugs utilisation for the Adrenergic Inhalants and other antiasthmatic for systemic use. Antiasthma drugs were dispensed to both male and female patients but with a higher dispensing to male patients. There was no significant gender-related difference in prescribed antihystamines for systemic use and other drugs for obstructive airway disease, inhalants.

According to literature in childhood males are more prone to get asthma or asthmatic symptoms, but there is a switch in adulthood with a major occurrence of asthma among women. This suggested a role for estrogen and progesterone in asthma incidence. Female sex is an important risk factor. Male sex was associated with a significantly increased risk of death and with a significantly increased risk of re-hospitalisation for obstructive airways disease. Mean survival and time to rehospitalisation for obstructive airways disease are significantly better for female patients (Gonzalez, 2010).

Females visit the emergency department for asthma more frequently than males do (Watson, 2003) and are more likely to report asthma attacks. Environmental exposures such as pollution, passive smoking are risk factors. Indoors activity as cooking with gas has been shown to be associated with respiratory symptoms and a small lung reduction another risk factor especially for women. It is well known that smoke causes problems to the respiratory tract (without mentioning all the other harmful risks). Smokers are undertreated with inhalants (Gonzalez, 2010). In our case adrenergic inhalants were more dispensed to males and for the other inhalants there was no difference in dispensing. Could this be due to the increased number of young female smokers? Another hypothesis could be that physicians prescribe to females more glucocorticoids than other antiasthma drugs especially for chronic asthma. Interaction between gender and asthma should be more studied and further examined. Generally, different international studies report unequal treatment between men and women (Anthony, 2008 & Loikas, 2013)

ATC	Description ATC	OR (IC-95%)
A02A	ANTIACIDS	0,6 (0,6-0,7)
A02B	ANTIULCER DRUGS	0,8 (0,7-0,8)
A05A	BILIAR THERAPY	0,8 (0,7-0,9)
A07A	INTESTINAL ANTIBIOTICS	0,7 (0,6-0,7)
A10A	INSULIN THERAPY	1,2 (1,2-1,3)
A10B	ORAL HYPOGLICEMICS	1,3 (1,3-1,4)
B01A	ANTITHROMBOTIC AGENTS	1,1 (1,1-1,1)
C01A	GLYCOSIDES	0,7 (0,6-0,7)
C01B	ANTIARITHMICS I & III CLASS	1,1 (1,0-1,2)
C01D	VASODILATORS used in CD	1,2 (1,1-1,2)
C03A	Low-Ceiling DIURETICS, Thiazides	0,8 (0,7-0,9)
C03B	Low-Ceiling DIURETICS, excl. Thiazides	0,6 (0,5-0,6)
C03C	High-Ceiling DIURETICS	0,8 (0,8-0,9)
C03D	POTASSIUM-SPARING agents	0,9 (0,8-0,9)
C03E	POTASSIUM-SPARING agents, Comb.	0,5 (0,4-0,5)
C07C	BETA BLOCKERS and other DIURETICS	0,6 (0,6-0,7)
C08C	Ca CHANNEL BLOCKERS with Vascular Effects	1,1 (1,1-1,1)
C09A	ACE INHIBITORS, Plain	1,2 (1,2-1,3)
C09B	ACE INHIBITORS, Combinations	0,9 (0,9-1,0)
C09D	ANGIOTENSIN II ANTAGONISTS, Comb.	0,9 (0,9-0,9)
C10A	LIPID MODIFYING agents, Plain	1,1 (1,1-1,1)
H03A	THYROID drugs	0,2 (0,2-0,2)
H03B	ANTITHYROID drugs	0,4 (0,3-0,4)
J01A	TETRACYCLINES	0,9 (0,8-0,9)
J01C	PENICILLINS	0,9 (0,9-0,9)
J01D	BETALACTAM antibiotics	0,9 (0,8-0,9)
J01F	MACROLIDES and LINCOSAMIDES	0,8 (0,8-0,8)
J01M	QUINOLONE antibacterials	0,8 (0,8-0,8)
J02A	ANTIMYCOTICS for systemic use	0,6 (0,5-0,6)
M01A	NSAIDs	0,6 (0,6-0,6)
M04A	ANTIGOUT PREPARATIONS	1,9 (1,8-2,1)
M05B	DRUGS affecting MINERALIZATION	0,1 (0,1-0,1)
N02A	OPPIOIDS	0,5 (0,5-0,6)
N02C	ANTI MIGRAINE products	0,3 (0,3-0,3)
N03A	ANTICONVULSANTS	0,8 (0,8-0,8)
N04A	ANTICOLINERGIC agents	0,7 (0,6-0,9)
N04B	DOPAMINERGIC agents	0,9 (0,8-1,0)
N05A	ANTIPSYCHOTICS	0,8 (0,8-0,9)
N06A	ANTIDEPRESSANTS	0,4 (0,4-0,5)
N05B	ANTIDEMENTIA agents	0,5 (0,4-0,6)
R03A	ADRENERGIC Inhalants	1,1 (1,1-1,1)
R03B	Other drugs for ASTHMA/BPCO	0,9 (0,9-1,0)
R03D	Other ANTIASTHMATIC for systemic use	1,1 (1,1-1,2)
R06A	ANTHYSTAMINES for systemic use	0,9 (0,9-1,0)
S01E	ANTI-GLAUCOMA preparations	0,8 (0,7-0,8)

Table 2. **Odds Ratios for medications classified by ATC.**

Red reported medications are indicative of a larger number of treated females OR<1. Blue reported medications are indicative of a larger number of treated males, OR>1 and grey reported medicationsn show equal in drug dispensation to males and females. Analysis has been done in patients who received at least one prescription of the reported drugs.

5.2 Gender differences in cardiovascular therapies

5.2.1 General overview

A major difference in prescribing was observed with cardiovascular medications. Although Cardio vascular Disease (CVD) is the number one cause of morbidity and mortality in both genders, males received this type of prescription adolescence more than females. For the age group 45-64 at least one Cardiovascular drug was dispensed to 32.2% of male patients and 26.5% to their female counterpart, increasing as patients get older (Figure 2).

Males were more likely to receive prescriptions for cardiovascular medications, such as beta-blockers, ACE-inhibitors, antithrombotic agents (OR 1.16 95% CI 1.14-1.20), and also more treated with antidiabetic drugs: insulin therapy (OR=1.24 95% CI 1.21-1.30) and with oral hypoglycaemics (OR=1.37 95% CI 1.33-1.40). Females were more exposed to diuretics (OR=0.72, 95% CI 0.66-0.80). A larger gender difference was noticed between 15-44 years old males and females and this difference decreased with aging, still remaining statistically significant. Results show that in general men were more likely to be adherent to therapy as compared to women. Differences in adherence were more pronounced among patients under 80 years of age. Young women were less adherent than the older ones.
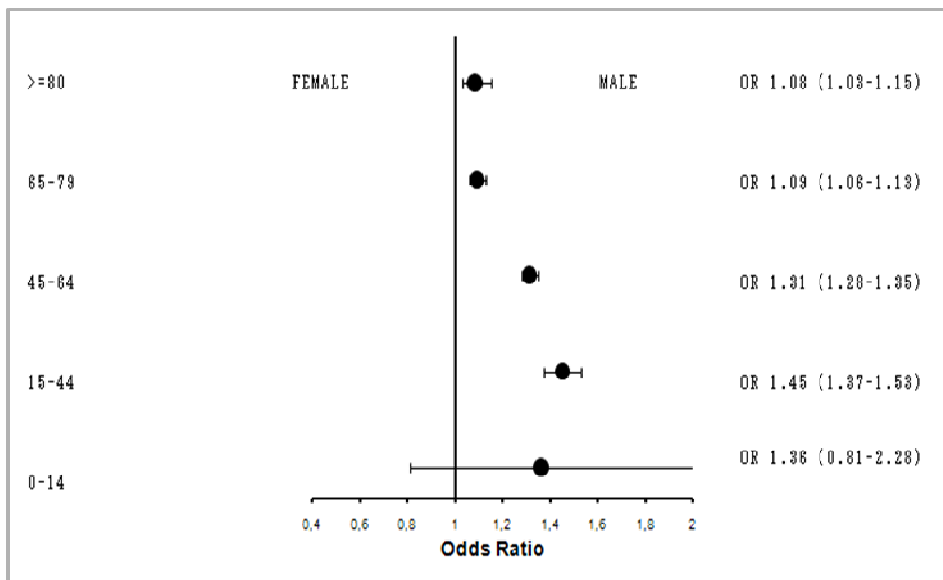

Figure 2 Odd Ratios Gender/Age difference in Cardiovascular treatment.

It can be clearly seen that males of age 45-64, 65-79 (68.6% males vs. 66.6% females) and over 80 (75.1% males vs. 73.5% females) used cardiovascular drugs more than females. It is known that CVD affects men earlier in life and the incidence of heart disease increases in women with age (Melloni, 2010).

Figure 3 shows that in general men of all age groups were more adherent to therapies than women. All the differences were statistically significant. Male patients were more adherent to ATC-C medicines than female patients with statistically significant outcome for the age groups of 15-44, 45-64, 65-79 and over 80. An increased adherence for both men and women was noticed for the age group 65-79 and over 80. Differences in adherence between women and men were more pronounced among patients under their 80s. Some factors that affect patient's adherence to medication are age, personal control such as living alone (Saito, 2005), identity, emotional representations (Shiah-Lian, 2011), severity of illness, number of concomitant diseases, complexity of medication regimen (Granger, 2008), depression (Bosworth, 2008), cognitive disorders (Stilley, 2004), health literacy and addictive behavior such as smoking or alcohol abuse (Evangelista, 2009). Understanding all these factors that interfere with patient's adherence could provide a better intervention. Women are less adherent comparing to their men peers to Cardiovascular medicines, thus gender is another major factor to be be considered and further studied.
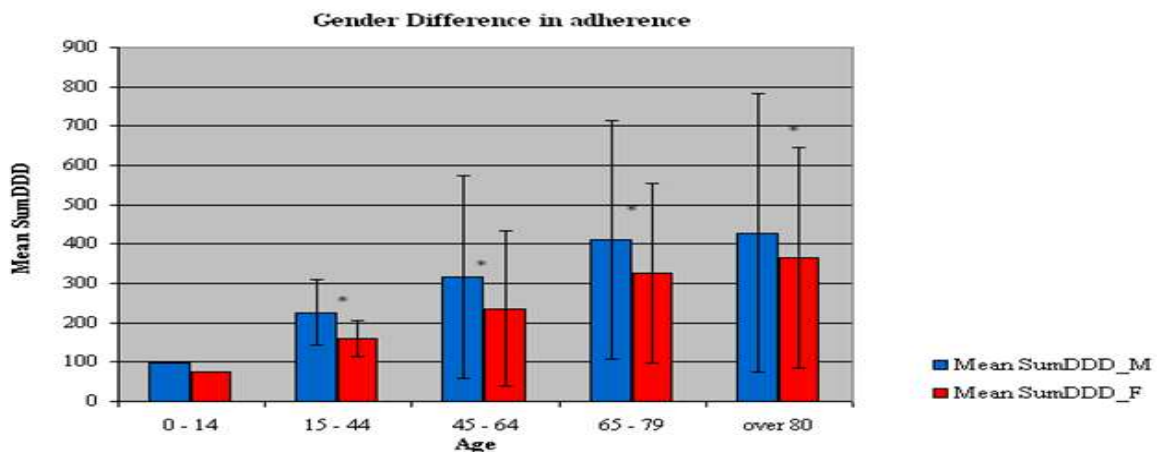

Figure 3 Gender/ Age difference in adherence to Cardovascular Disease

5.2.2 Insulin therapy and Oral Hypoglycaemics

Diabetes and gender: For the insulin therapy and oral hypoglycaemics it was observed that females were less treated than males. The number of male patients that received at least one oral hypoglycaemic was 8,810 (3.73% of all the male treated population) vs. 7,224 of females (2.83% of all female treated population) with an odds ratio of 1.3 and confidence interval 95% CI=1.3-1.4. On the other hand there were 2,981 (1.26%) males vs. 2,630 (1.03%) females receiving at least one medicine of the insulin therapy and an odds ratio of 1.2, 95%CI= 1.2-1.3.

It is known that women with diabetes and hyperlipidemia receive a less aggressive therapy especially in the young age (Vilamananda, 2011). 5% of all diabetes are Type 1 Diabetes (T1DM). In some studies it was noticed a different incidence on diabetes related to age and gender. Under 15 years of age, men have a higher incidence rate: 23/100,000 male vs. 4.5/100,000 women and for the age group 15-40 years: still 3:2 male excess was noticed (Gale, 2001) wondering if T1DM is genetic, sex, gender or age dependent. Women and men show slightly different incidence rates of diabetes mellitus, T2DM. Prevalence increases dramatically all over the world and is accompanied by a parallel rise of obesity. Diabetic men and women differ in the prevalence of pre-diabetes, diabetic complications, adherence to recommendations regarding lifestyle and drug therapy (Carstensen, 2008) .

In some studies of drug administration usually men were prescribed Metformin and Glitazone at a younger age, women instead were prescribed Acarbose over 55 years because Rosiglitazone was found to increase the risk for bone fracture (Kautzky-Willer, 2009). There are some risk factors influencing the incidence of T2DM as ethnicity, family history (GDM=gestational diabetes mellitus), obesity (visceral). In Africa, Japan and other less or more developed countries the incidence of Diabetes is lower.

The increase in incidence of diabetes in developing countries follows the trend of urbanization and lifestyle changes, perhaps most importantly a "Western-style" diet. The World Health Organization (WHO) suggested that obesity accounts for 80% of diabetes. Abdominal obesity increases mortality (+33%M, 28% F).

Visceral adiposity, fasting glucose concentration of >110mg/dl and impaired glucose tolerance(>risk in women), blood pressure of >130/85 mmHg and atherogenic lipid profile are all risk factors that impair myocardial metabolism more severely in women than in men (Regitz-Zagrosek, 2007). Men and women with similar amounts

of liver fat do not exhibit sex-differences in insulin resistance. (Westerbacke, 2004). Liver fat strongly increases when glycaemia and glucose tolerance deteriorate and this depends on age but not on sex (Kantartzis, 2010). Pre-diabetic and diabetic women are at much higher risk for vascular disease than diabetic men. In the fertile age between 20 and 35 years of age, the incidence rate for women is twice larger than the one for men of the same age (Carstensen, 2008). Over 45 years, men have in general a higher risk of developing T2DM at younger age (Rathmann, 2009). Women show glucose intolerance more often at all ages and have a slightly higher prevalence of T2DM possibly caused by a prolonged gut glucose time (Anderwald, 2011) and a lower height, less physical activity, socioeconomic status, hormones fluctuation (female: high testosterone; low plasma SHBG more prone to diabetes; male: low testosterone, erectile dysfunction and diabetes). Endogenous hormones may influence insulin sensitivity via their effects on adiposity. Testosterone is inversely associated with adiposity in men, but positively associated with adiposity in women. Clinical trials show that androgen deprivation increases adiposity and insulin resistance in men, while testosterone therapy decreases adiposity and improves insulin sensitivity. In women androgen therapy increases adiposity and antiandrogen therapy decreases adiposity (Ding, 2006). Although men have higher risk factors, progression rate is similar to women. Diabetes is a risk factor by itself leading to greater increase of cardiovascular disorders. Women with diabetes compared with those without are suffering from cardiovascular disease twice as common, they are four times as likely to be hospitalized, but less likely to be treated than men (Regitz-Zagrosek, 2007).
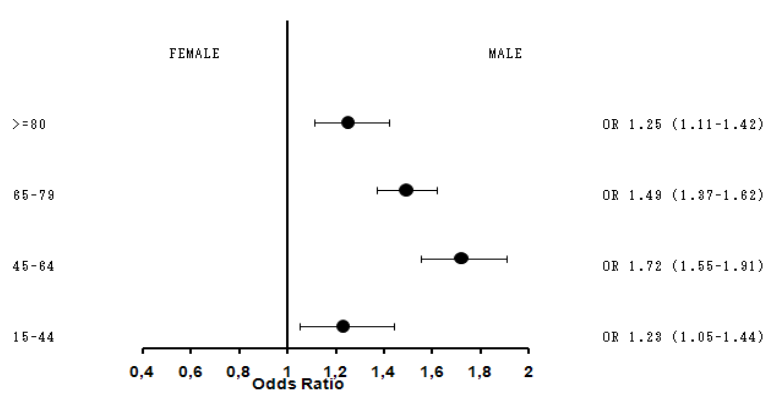

Figure 4 Gender/Age difference in patients treated with insulin therapy
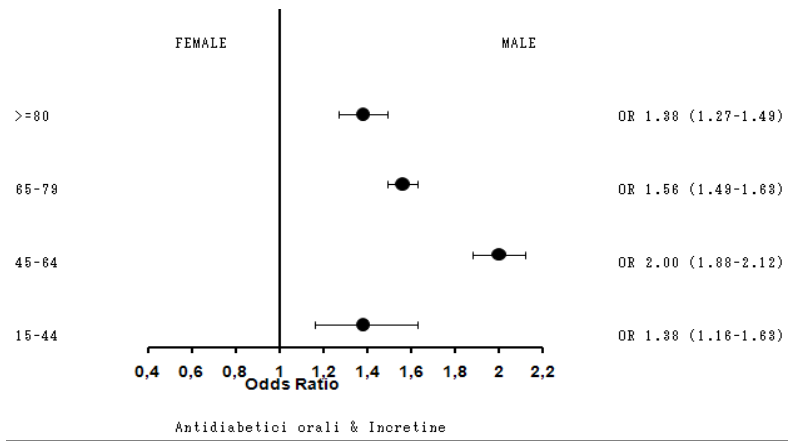
Figure 5 Gender/Age difference in patients treated with oral-hypoglycaemics.

Men were more likely to be treated with antidiabetic drugs, including insulin (OR= 1.24 95% CI 1.21-1.30) and oral hypoglycaemics (OR=1.37 95% CI 1.33-1.40).

5.2.3 Beta-blockers, Diuretics, ACE-inhibitors, Lypid Modifying Agents

*Beta-blockers***:** For all age groups, beta-blockers were more prescribed among males than females with significant OR-result. Men were more treated with betablockers (OR=1.15 95% CI 1.10-1.20) than women.
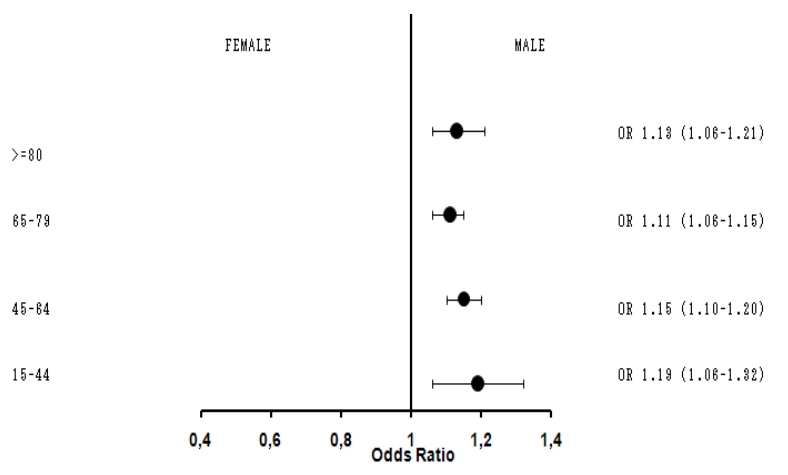

Figure 6 Gender/Age difference in patients treated with Betablockers

Diuretics: Women administered more diuretics (OR=0.72, 95% CI 0.66-0.80). Diuretics are used especially on monotherapy for hypertension in women and in the elderly, usually causing adverse drug reaction as vertigo and osteoporosis for both genders (Lim, 2009).

The use of thiazides is associated in some patients with erectile dysfunction, even when the dose is kept as low as possible, thus males should be less exposed to those medicines, but no gender difference in prescription was noticed. Furosemide, a high ceiling diuretic is associated with a major mortality in women as compared to men with heart failure (Cohen, 2004). Hypopotassemia caused by diuretics is more frequent in females. This would be the reason of a higher dispensation of Potassium sparing diuretics to women. Some gender differences in adherence were observed for the high ceiling diuretics and potassium sparing diuretics.
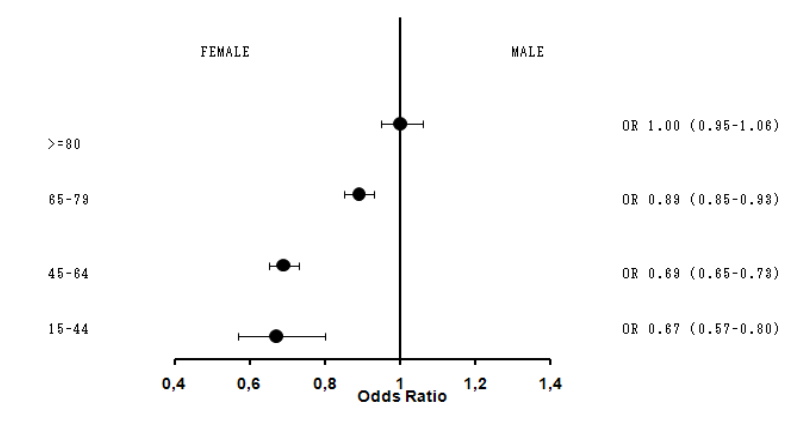

Figure 7 Gender/Age difference in patients treated with diuretics.

ACE-inhibitors (OR=1.25 95% CI 1.20-1.30): In the studied population on monotherapy with ACE-inhibitors, women were less likely than men to be prescribed an angiotensin converting enzyme for all groups of age. Although older women were prescribed more ACE-inhibitors, than the young one, men were still more prescribed with ACE-inhibitors (Figure 8). The question of whether ACE-inhibitors have a more favorable impact for men than for women cannot be a valid explanation on the basis of the small proportion of women included in ACE-inhibitors studies (Jochmann, 2005). A larger difference in ACE-inhibitors use between males and females in the 15-44 years group was noticed, decreasing with aging, but still the difference remained statistically significant.
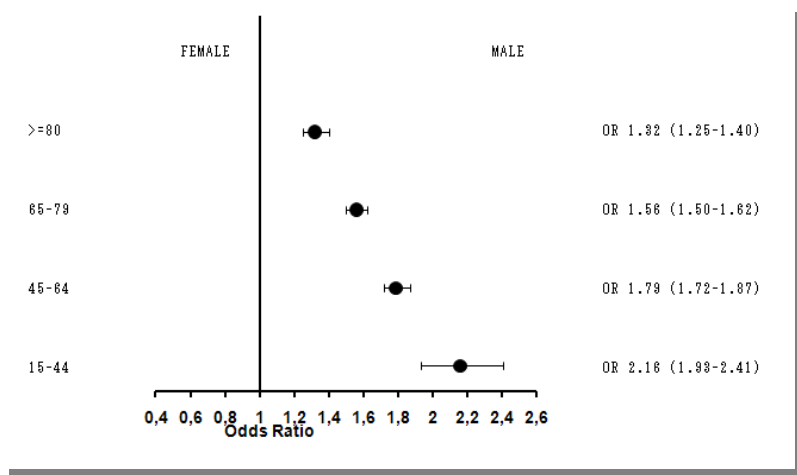
Figure 8 Gender/Age difference in patients treated with ACE-inhibitors.

Lypid Modifying Agents (OR= 1.53 95% CI 1.48-1.59)*:* Pharmacokinetic gender-specific differences with respect to statins are slight. Primary and secondary prevention of cardiovascular disease studies have revealed beneficial effects for both genders, but with a minor use in women than in men (Jochmann, 2006). Anti hyperlipidemics were prescribed less frequently in the age groups 45-64. In the age groups 65-79 there was a higher dispensing. In literature the lipid lowering therapy is associated with better outcomes for postmenopausal women. Substantially women have been undertreated for hyperlipidemia (Figure 9).
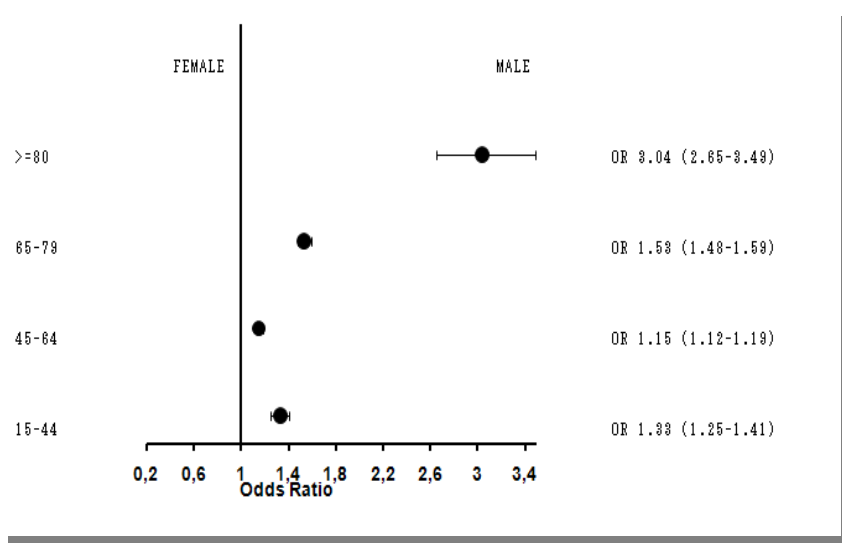

Figure 9 Gender/Age difference in patients treated with lipid modifying agents.

5.3 Interventions in Acute Coronary Syndrome

A total of 1204 (2.5‰) patients, 760 (3.26‰) males and 444 (0.92‰) females patients, with an ACS-event during 2008 admitted in Saint Anthony hospital were recruited in this study.

Table 3 Demographic characteristics of enrolled patients

			OR MvsF	95%IC
Sex	_N_	_‰_		
Male	760	3.26		
Female	444	0.92	1.7 (1.4-2)	M
Total	1204	2.5		
Age in years (n)	_Male(n,‰)_	_Female (n,‰)_		
15-44 (18)	15 (1.57)	3 (0.03)	4.9 (1.6-15)	M
45-64 (264)	220 (3.43)	44 (0.65)	5.3 (4.0-7.0)	M
65-79 (506)	343 (10.81)	163 (4.11)	2.6 (2.2-3.2)	M
≥80 (416)	182 (21.25)	234 (12.79)	0.8 (0.7-1.0)	NS
Inhospital-mortality (Total 142=11.8%)	72	70	1.0 (0.6-1.7)	NS
Previous Hospitalization (2007) (Total 1204)	66(5.48%)	26(2.16%)	1.5 (1.0-2.4)	NS
Re-hospitalization until 31/12/2009	87(12.6%)	67(17.9%)	0.7 (0.5-0.9)	F
Re-hospitalization until 30/06/2012 (Total 1062)	165(24%)	120(32%)	0.7 (0.5-0.9)	F

Revascularized vs. Non Revascularized

Tot	M	F	M	F	OR	
1062	375	108	313	266	1.2 (1.0-1.6)	NS

The population was subdivided in four age classes. For each class a gender difference consideration was made. Overall men had higher prevalence to develop ACS. Considering age groups men up to79 years had a higher prevalence in developing ACS, while the over 80 population did not show any gender difference. Elderly women were larger in number, but comparing to the whole population, there was no significant difference between genders in ACS prevalence of this age group. Of the 1204 enrolled patients, 142 (11.8%) died in hospital before the follow-up without any gender difference in mortality rate, in accordance with other national and international studies (Osservatorio ARNO Cardiovascolare, 2012 & Akhter, 2009). Short term and long term re-hospitalization was analysed showing that women had higher relapse rates than men in both cases: in 2009, 17.9% women vs.12.6% men and on 30th June 2012 32% women vs. 24% men (Table 2).

A previous 12 month analysis of those patients was done to verify hospitalization and pharmacological history to understand if patients received other therapies related to hypertension, diabetes, dislypidemia and depression that are all ACS risk factors. This analysis showed that no gender difference was noticed in hospitalization. A drug prescription analysis showed: 77% of women and 69% of men (OR=0.7 95%CI 0.5-0.9) had an antihypertensive medication and 17% of women and 8% of men (OR=0.4 95%CI 0.3-0.6) were treated at least once with an antidepressant. This may be potentially indicative of higher rates of hypertension and depression among ACS women. There was no difference in drug utilization for diabetes (21%M and F), nor for dyslipidemia treatment [37% M vs. 32% F, OR=1.3 95%CI 1.0-1.6, NS-(not significant)]. Age group subdivision did not show significant difference in utilizations of these drugs between genders with the exception of a major antidepressant use among women of 65-79 years old (Table 4). Other studies confirm that women with ACS tend to have more cardiovascular risk factors such as diabetes, hypertension andì hypercholesterolemia and the possible explanation was that women in pre-menopause are protected from estrogens, but in post-menopause they start to loose hormone protection thus they present with ACS 10 years later than men and at this time they have a higher cardiovascular risk factor (Claassen, 2012). First co-morbidity of ACS patients, seems to be depression especially in the female population and diabetes is present in their medical history in one fourth of the subject (Osservatorio ARNO Cardiovascolare, 2012).

Table 4 Previous 12 months pharmacological treatment as an ACS-risk factor predictor: gender/age based evaluation.

	M (n)	(%)	F(n)	(%)	TOT		OR (95%CI)	M vs. F
Hypertension therapy					M	F		
15-44	5	33%	2	67%	15	3	0,3(0-0,3)	**F**
45-64	111	50%	26	59%	220	44	0,7(0,4-1,4)	NS
65-79	271	79%	121	74%	343	163	1,3 (0,8-2)	NS
≥80	135	74%	193	82%	182	234	0,6 (0,4-1)	NS
TOT	522	69%	342	77%	760	444	0,7 (0,5-0,9)	**F**
Diabetes								
15-44	2	13%	0	0%	15	3	0	NS
45-64	30	14%	4	9%	220	44	1,6 (0,5-4,7)	NS
65-79	93	27%	35	21%	343	163	1,4 (0,9-2,1)	NS
≥80	31	17%	54	23%	182	234	0,7 (0,4-1,1)	NS
TOT	156	21%	93	21%	760	444	1 (0,7-1,3)	**NS**
Dyslipidemia treatment (C10A)								
15-44	4	27%	1	33%	15	3	0	
45-64	72	33%	12	27%	220	44	1,3 (0,6-2,7)	NS
65-79	144	42%	68	42%	343	163	1 (0,7-1,5)	NS
≥80	63	35%	61	26%	182	234	1,5 (1-2,3)	NS
TOT	283	37%	142	32%	760	444	1,3 (1-1,6)	**NS**
Depression (N06A)								
15-44	0	0%	0	0%	15	3	0	
45-64	16	7%	6	14%	220	44	0,5 (0,2-1,3)	NS
65-79	21	6%	29	18%	343	163	0,3 (0,2-0,5)	**F**
≥80	23	13%	40	17%	182	234	0,7 (0,4-1,2)	NS
TOT	60	8%	75	17%	760	444	0,4 (0,3-0,6)	**F**

After excluding patients that died in-hospital, further analysis was performed in 1,062 ACS patients: 483 (40.1%) underwent revascularization and 579 (48.1%) were not revascularized. A general gender anlysis did not show any differences in interventions, but a further evaluation by age revealed major revascularization in the 65-79 and ≥80 year old male populations (Figure 11). Median age of revascularized men was 67 years (interquartile range [IQR] 58-74 years old) and age of women was 72 (IQR 66-78 years old). Median age for the non-revascularized population was men 75 years (IQR 64-81), women 82 years with IQR 75-88.

Female patients are generally older and with more comorbities when diagnosed with an ACS and anatomically have smaller vessels, thus are less likely than male patients to undergo invasive evaluation and surgery intervention. Women have higher rates of bleeding complications, consistently seen in trials (Redberg, 2006).
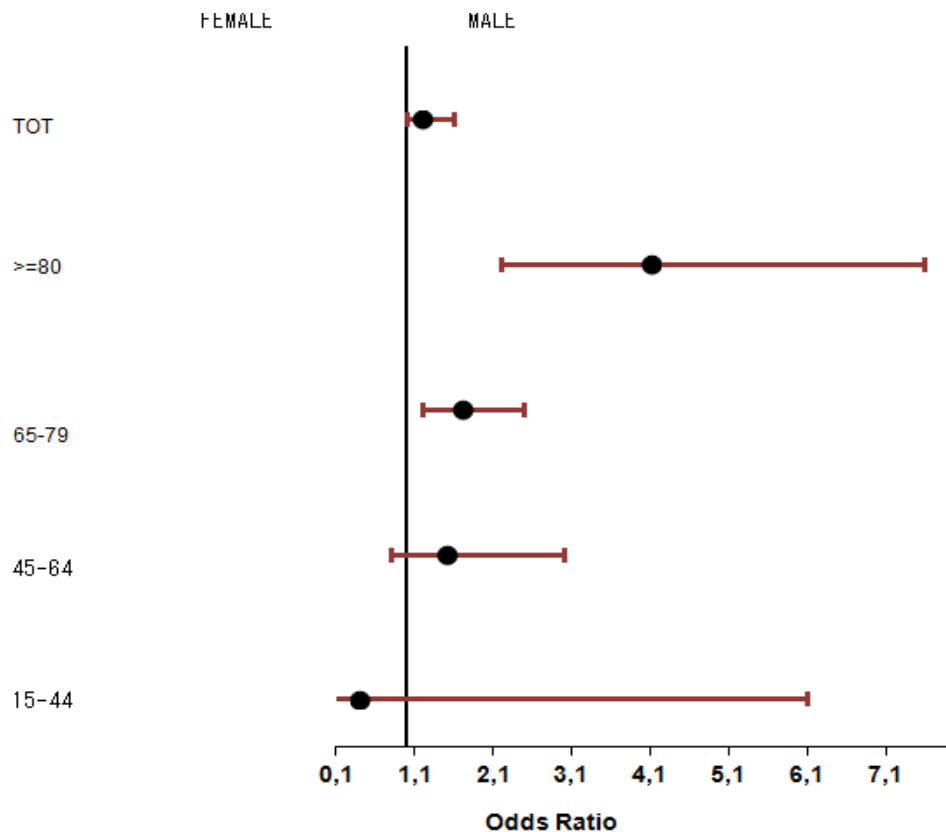

Figure 10 Gender/age difference in revascularized vs. non revascularized ACS patients

An analysis of pharmacological therapy showed a total lack of anti-aggregants use in 191 (18%) patients during the first semester of follow up after the ACS event. Gender classification showed a larger number of untreated women 12.4%M vs. 28% F, OR=2.8 95%CI 2.1-3.8 p<0.01.

The evaluation of antiaggregant use was done for revascularized and non-revascularized patients. Female non-revascularized patients were larger in number than their male counterparts not receiving any antiaggregant 36%F vs. 20%M, OR=2.2 95%CI 1.5-3.2. Non-revascularized women were treated mostly with aspirin 36%F vs. 35%M, OR=0.6 95%CI 0.4-0.9. On the other hand men were treated mostly with dual antiplatelet therapy (36%M vs. 20%F OR=1.8 95%CI 1.2-2.7). Most patients underwent revascularization. A gender difference was noticed in thienopyridines use between revascularized patients. Women were prescribed more thienopyridines than (men 9%F vs. 3%M, OR=0.3 95%CI 0.1-0.8) (Table 5).

Table 5 Anti-aggregation therapy six months after ACS-event: gender based evaluation.

	M	%	F	%	TOT	%	OR (95%CI)	p-value	MvsF
No therapy	85	12.4%	106	28%	191	18%	2.8 (2.1-3.8)	<0.01	F
Aspirin	217	31.5%	124	33%	341	32%	0.7 (0.5-0.9)	<0.05	F
Thienopyridines	39	5.7%	31	8%	70	7%	0.5(0.3-0.9)	<0.025	F
Dual antiplatelets	347	50.4%	113	30%	460	43%	1.9(1.4-2.5)	<0.005	M
Total therapy	603	87.60%	268	71.7%	871	82,02	2.8 (2.1-3.8)		M

Revascularized patients were younger than the non revascularized ones for both genders. The median age of revascularized men is lower than that of women. This shows that physicians postpone females'revascularization and older non revascularized patients were still female patients. This confirms that women are less likely to be revascularized than men (Figure 12). The problem is that non revascularized patients were prescribed guideline-recomendation therapies less frequently than revascularized patient. Thus, female patients seem to be the population under greater risk (Sabouret, 2010)
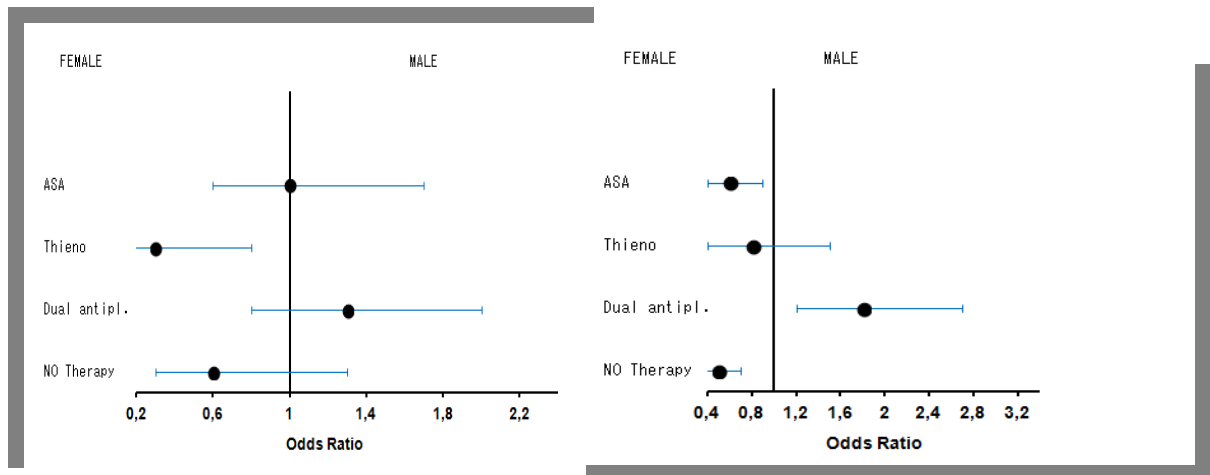
Figure 11 Antiaggregant therapy of revascularized vs. non revascularized

The Fisher's exact test for count data confirmed that both for men and for women adherence to conservative therapy and invasive interventions reduces mortality (Table 6)

Table 6 Mortality vs Adherence and vs Intervention: a gender difference analysis

Mortality	TOTAL	M	F
Adherence	OR 0.16	OR 0.23	OR 0.11
	95%CI 0.12-0.25	95%CI 0.15-0.34	95%CI 0.07-0.18
Intervention	OR 0.13	OR 0.18	OR 0.16
	95%CI 0.09-0.18	95%CI 0.11-0.28	95%CI 0.04-0.18

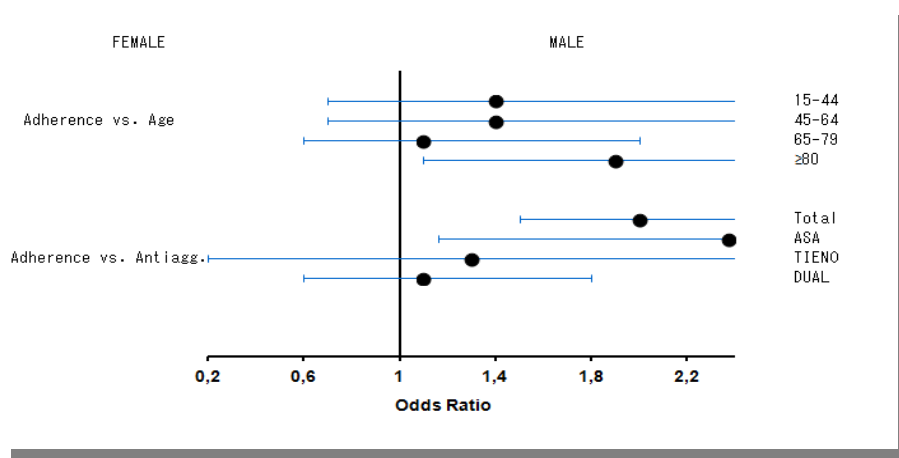**Figure 12 Adherence analysis**

Figure 12 and Table 7 reports a good adherence >=74% to antiplatelet therapies for both genders. A significant gender difference was detected in general for all antiplatelets use and especially in the aspirin use. An age related adherence difference was noticed in the very old population. Male patients over 80 years old were significantly more adherent than their female counterparts of 90%, OR=1.9 95%CI 1.1-3.4. After antiplatelet subdivision in aspirin, thienopyridines and double antiagregation therapy, women were less adherent than men and especially less adherent than young men (total patients adherent to aspirin 92%M vs. 82% F, OR=2.4 95%CI 1.2-4.6, and age 45-64 year old patient adherent to aspirin 95%M vs. 79% F, OR=5.0 95%CI 1.1-22.5).

Table 7 Gender/Age difference between adherent to Antiaggregants and not adherent patients to Antiaggregants.

ASA

	ADHERENT				NON ADHERENT				TOT		OR (95%IC)	M vs F
	M	%	F	%	M	%	F	%	M	F		
15-44	2	100%	1	100%	0	0%	0	0%	2	1	Ns	Ns
45-64	73	95%	11	79%	4	5%	3	21%	77	14	5 (1,1-22,5)	M
65-79	87	92%	50	98%	8	8%	1	2%	95	51	0,2 (0,0-1,5)	Ns
>=80	37	86%	40	69%	6	14%	18	31%	43	58	2,8 (1,0-7,6)	Ns
TOT	**199**	**92%**	**102**	**82%**	**18**	**8%**	**22**	**18%**	**217**	**124**	**2,4 (1,2-4,6)**	**M**

THIENOPYRIDINES

	ADHERENT				NON ADHERENT				TOT		OR (95%IC)	M vs F
15-44	0	0%	0	0%	0	0%	0	0%	0	0	_	_
45-64	6	100%	3	75%	0	0%	1	25%	6	4	_	_
65-79	21	84%	10	91%	4	16%	1	9%	25	11	0,5 (0,1-5,3)	Ns
>=80	7	88%	13	81%	1	13%	3	19%	8	16	1,6 (0,1-19,3)	Ns
TOT	**34**	**87%**	**26**	**84%**	**5**	**13%**	**5**	**16%**	**39**	**31**	**1,3 (0,3-5,0)**	**Ns**

DUAL ANTIPLATELETES

	ADHERENT				NON ADHERENT				TOT		OR (95%IC)	M vs F
15-44	9	82%	1	100%	2	18%	0	0%	11	1	_	_
45-64	95	79%	17	85%	25	21%	3	15%	120	20	0,7 (0,2-2,5)	Ns
65-79	131	76%	51	77%	41	24%	15	23%	172	66	0,9 (0,5-1,8)	Ns
>=80	30	68%	15	58%	14	32%	11	42%	44	26	1,6 (0,6-4,3)	Ns
TOT	**265**	**76%**	**84**	**74%**	**82**	**24%**	**29**	**26%**	**347**	**113**	**1,1 (0,7-1,8)**	**Ns**

5.3.1 Survival of the general and ACS population

Information to draw the survival curve was collected on 413,148 residents (198,704M and 214,444F). There was no gender difference in the survival in 55 months of followup of the general population (Figure 13).
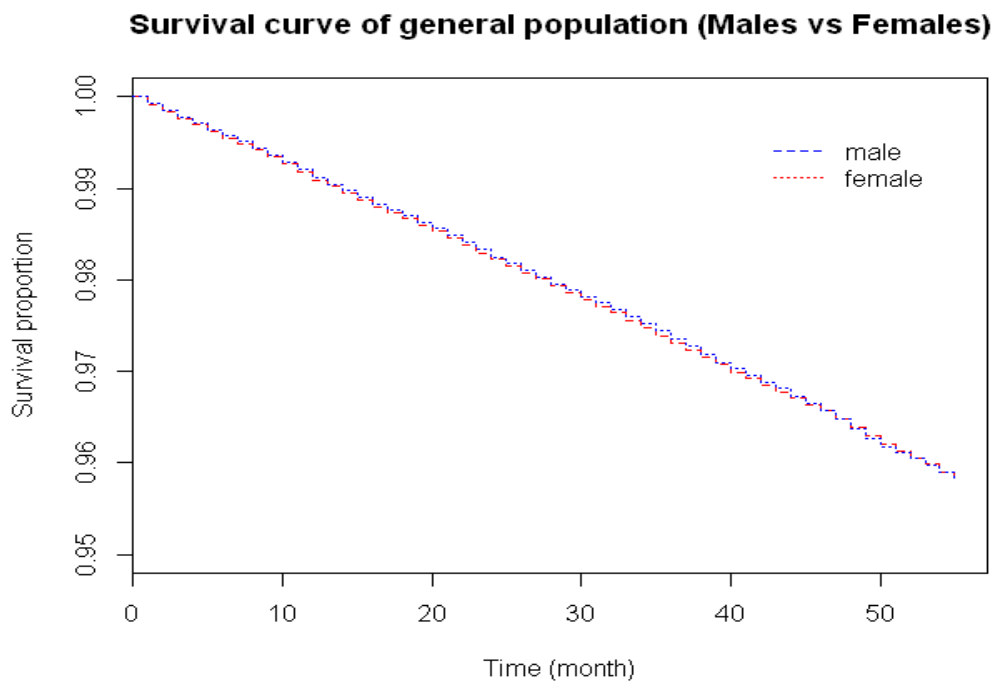

Figure 13 Survival curve of general population since 1/01/2008 until 30/06/2012 (55 months of FU).

A difference in survival was noticed when the overall population was subdivided in <80 years old and ≥80 (see Figure 14). In general women live longer and have a better survival than men.
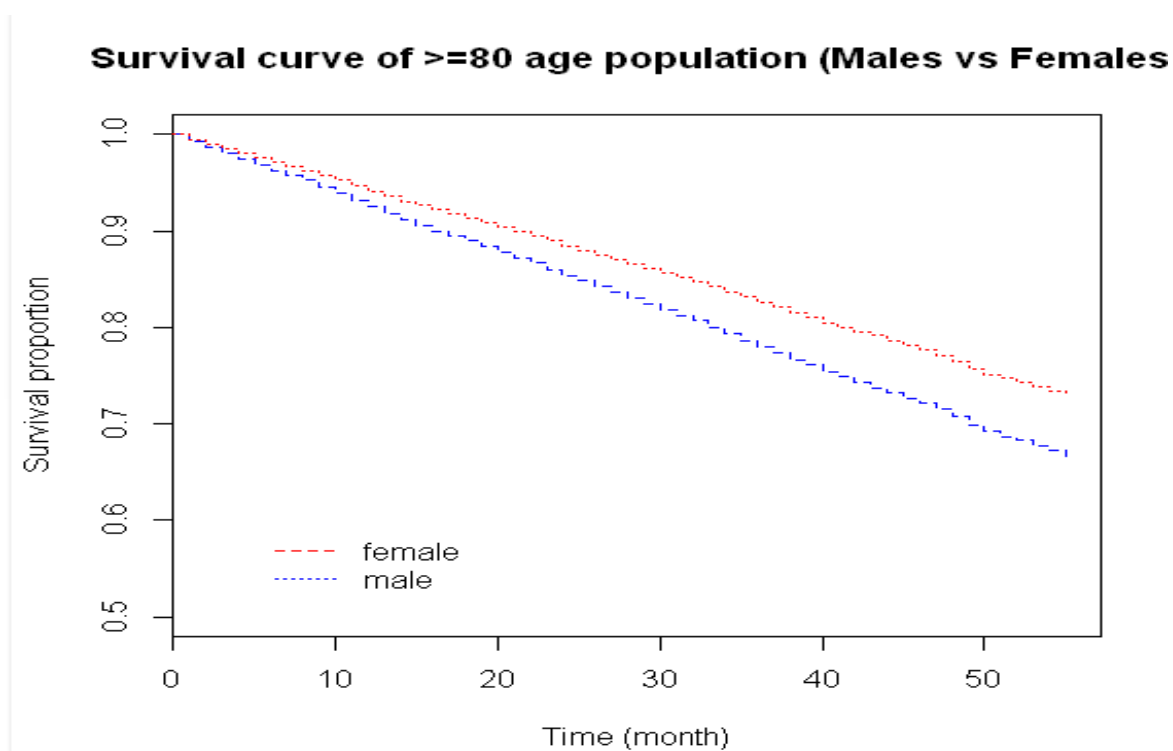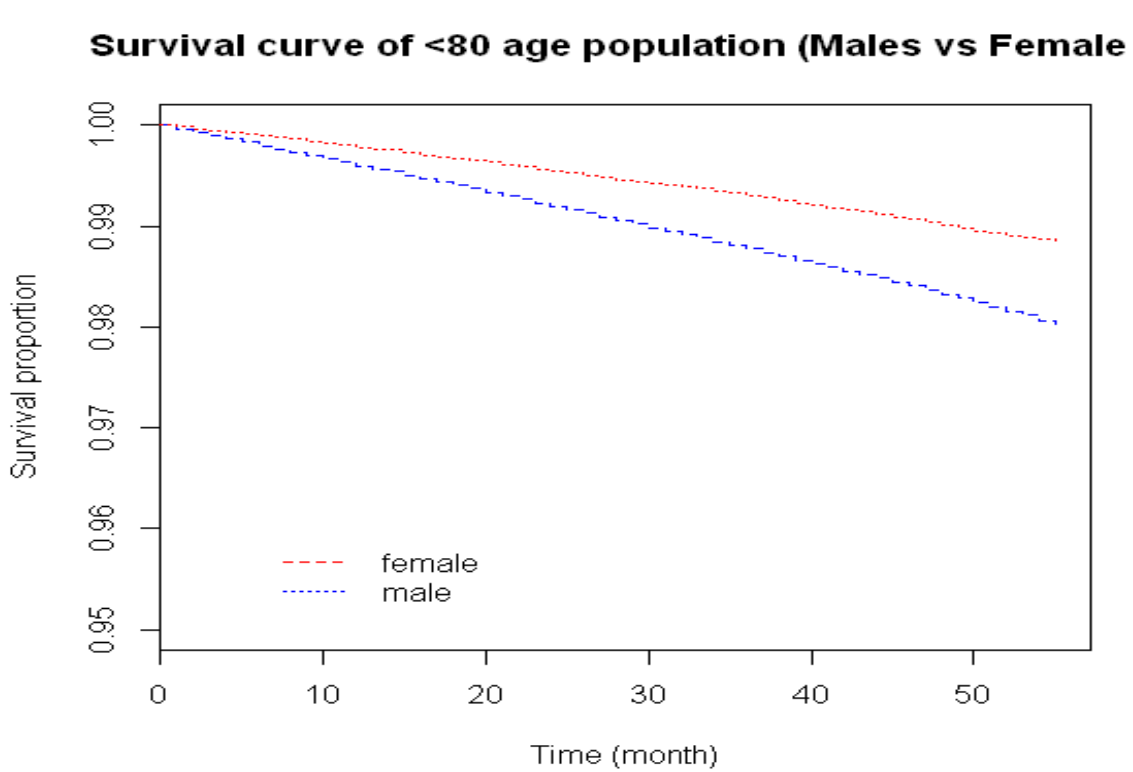
Figure 14 Survival curves of the overall population (younger than 80 years old and the very old population, the over ≥80)

The Kaplan-Meier survival curve was performed to understand the survival to 55 months post ACS event on 1,204 patients. A significant difference between genders of ACS patients was detected. Men survive longer than women. Accross two age groups: under and over 80 years old, this tendency of a higher survival between men is maintained. Of the under 80 years old group no difference beteween genders was detected (OR=1.3 95%CI 0.9-2.0). This disparity between men and women increased and became significant in the very old population (OR=1.7 95%CI 1.1-2.5). Throughout the first year of follow-up no difference in mortality rate was reported. Very old women presented 70% higher risk mortality rate than men after 4 years of follow-up.
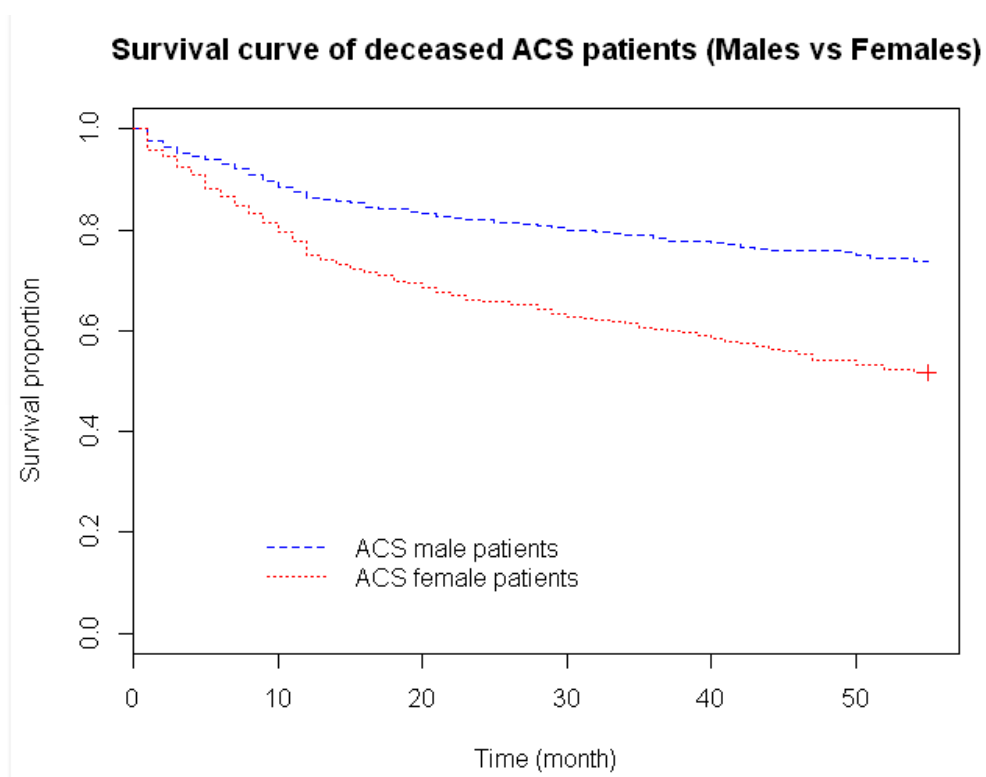

Figure 15 Survival curve of ACS population since 1/01/2008 until 30/06/2012 (55 months of FU).
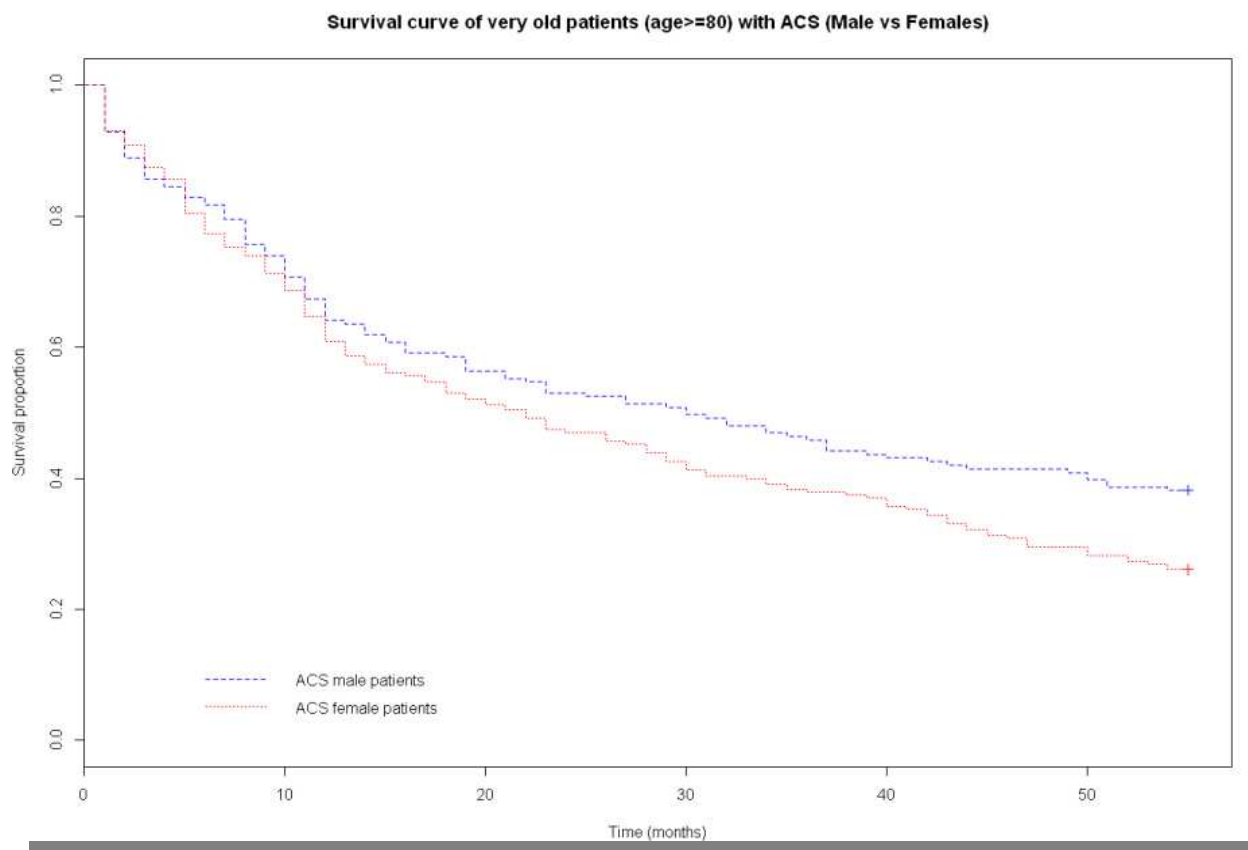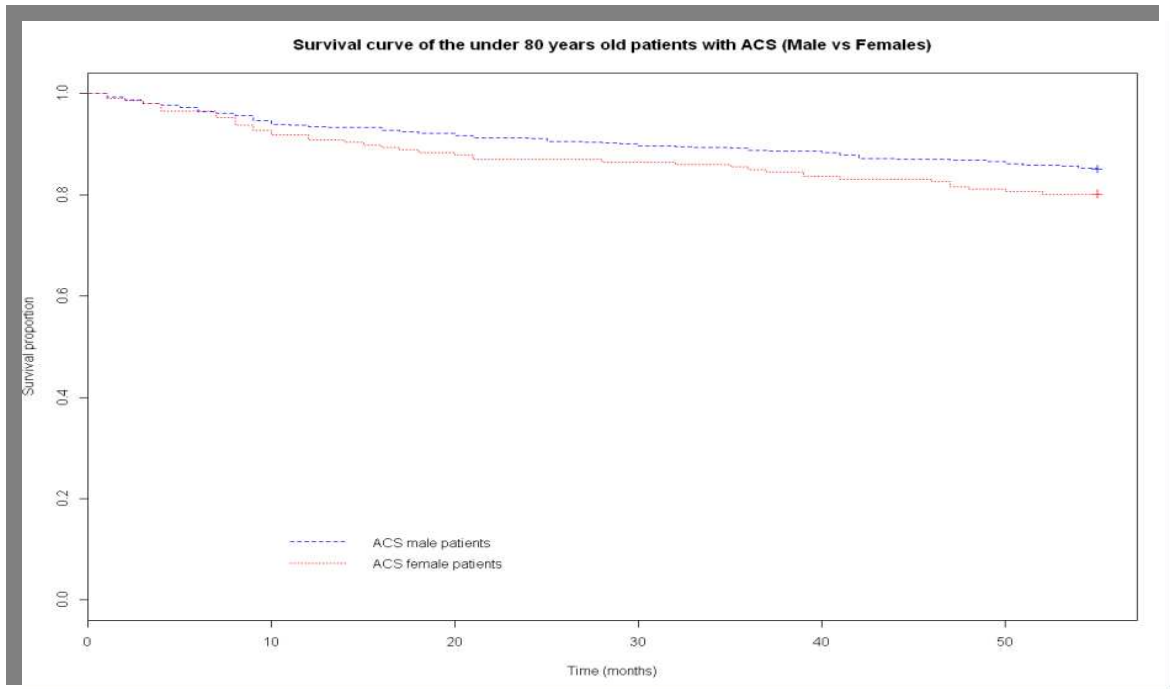
Figure 16 Survival curves of the ACS population (younger than 80 years old and the very old population, the over ≥80)

This study enrolled a high proportion of patients with acute coronary syndromes and these results can be compared with other international ones. Women with ACS have an increased mortality risk (Figure 15). In a review this higher mortality is reported among young women and it disappears with age (Claassen, 2012), but in our case even old women have higher mortality risk than their men counterparts (Figure 16). In order to better confirm a worse outcome in women different studies report later arrival at the hospital, longer hospital stays (Hee Tae, 2011) higher rates of in-hospital complications (Akheter, 2009), inadequacy of therapeutic management of especially non-revascularized patients (the female patient in our case).

Standard treatment guidelines and educational interventions are important strategies to improve the quality of health care

6   Conclusions

A limited number of studies have examined sex and age differences in overall therapies for the global population. Results of this study confirm that women especially over their 50s are the larger number of customer comparing to men.

These data collected and statistically performed are a valuable source of information on the characteristics, treatment of the italian population for physicians and all people working in the Sanitary and should serve for continuing improvements in patients' quality of care and prevention.

An importance has been given to cardiovascular therapies and especially to the acute coronary syndrome therapy management. Gender/age bias were noticed.

Despite our study and the international literature reporting bias in gender ACS management in favour of men, there are other studies that do not report such differences. However, standard treatment guidelines and educational interventions are required for an effective cardiac treatment modalities.

A review of drug prescriptions and ACS management is warranted in Italy to ensure that female and male patients are receiving the adequate treatments to reduce mortality, morbidity thus providing a better health outcome.

Cited References

- Akhter et al., (2009) Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). Am Heart J;157: 141-148.

- Anthony et al., (2008) Gender and age differences in medications dispensed from a national chain drugstore. J of women's health; 17: 735-743.

- Anderwald CH et al., (2011) Mechanism and effects of glucose absorption during an oral glucose tolerance test among females and males. JCEM; 96 (2): 515-524

- Bassand et al., (2007) Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. The task force for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes of the European Society of Cardiology. Eur Heart J; 28:1598-1660.

- Brosworth et al., (2008) The effects of the antidepressant medication adherence as well as psychosocial and clinical factors on depression outcome among older adults. Int J Geriatr Psychiatry; 23: 129-134.

- Carstensen et al., (2008) The Danish National Diabetes Register: trends in incidence, prevalence and mortality. Diabetologia; 51 (12): 2187-2196.

- Cepeda et al., (2003) Women experience more pain and require more morphine than men to achive a similar degree of analgesia. Anestesia and Analgesia 97, 5: 1464-1468.

- Cohen et al., (2004) Sex-related bedside clinical variables associated with survival of older in patients with heart failure. The European J of Heart Failure; 6: 781 – 786

- Cornforth et al., (2009) Why women have more migraines: The role of hormones. Migraine information. NINDS. http://www.ninds.nih.gov/disorders/migraine.htm Accessed 8/24/2013.

- Claassen et al., (2012) Gender gap in acute coronary heart disease: Myth or reality? World J Cardiol; 4 (2): 36-47.

- Osservatorio ARNO Cardiovascolare (2012) La prevenzione secondaria dopo un evento di Sindrome Coronarica Acuta. CINECA; Vol XVIII: 45-59.

- Coven et al., (2012) Acute Coronary Syndrome treatment and management. Medscape Reference: Drug and diseases and procedures.

- Ding et al., (2006) Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systemic review and meta-analysis. JAMA; 15,295 (11): 1288-1299.

- Dunbar-Jacob et al., (2003) Medication adherence in persons with cardiovascular disease. J Cardiovasc Nurs; 18: 209-218.

- Evangelista et al., (2001) Relationship between psychosocial variables and compliance in patients with heart failure. Heart Lung 30: 294-301.

- Franconi et al., (2011) Farmacologia di genere. Torino: SEED.

- Gale et al., (2001) Diabetes and gender Review. Diabetologia; 44: 3-15.

- Gendered Innovations. How gender analysis contributes to research (2013)

- Goldberg et al., (2004) Six month outcomes in a multinational registry of patients hospitalized with an acute coronary syndrome (the Global registry of patients of Acute Coronary Events GRACE. Am J Cardiol; 93: 288-293.

- Gonzales et al., (2010) Gender differences in survival following hospitalisation for COPD. Thorax; 66:38-42.

- Granger et al., (2009) Adherence to medication according to sex and age in the CHARM programme. Eur J of Hear Failure; 11: 1092-1098.

- Hake et al., (2008) KNOX lost the OX: the Arabidopsis KNATM gene defines a novel class of KNOX transcriptional regulators missing the home o domain. Plant Cell; 20(4): 875-887.

- Hee Tae et al., (2011) Gender-based differences in the management and prognosis of Acute Coronary Syndrome in Korea. Yonsei Med J; 52 (4): 562-568.

- Jochmann et al., (2005) Female specific aspects in the pharmacotherapy of chronic cardiovascular disease. Eur Heart J; 26: 1585-1595.

- Journath G et al., (2008) Sex Differences in risk factors control of treated hypertensives: a national primary healthcare-based study in Sweden. Eur J Cardiovasc Prev Rehabil; 15 (3): 258-262.

- Kantartzis et al., (2010) Diabetologia webpage. Accessed on 24/11/2013.

- Kautzky-Willer et al., (2009) Metabolic diseases and associated complications: Sex and gender matter! Eur J Clin Invest; 39(8): 631-648.

- Krieger (2003) Gender, sexes and health: What are the connections and why does it matter. International J of Epidemiology; 32(4): 652-657.

- Labus JS et al., (2008) Sex differences in brain activity during aversive visceral stimulation and its expectation in patients with chronic abdominal pain: a network analysis. Neuroimage. 41 (3): 1032-1043.

- Lim et al., (2009) Loop diuretic use and rates of hip bone loss and risk of falls and fractures in older women. J Am Geriatr Soc; 57: 855-862.

- Lippman et al., (2009) Quality of life in GERD and Barret esophagus is related to gender and manifestation of disease. Am J Gastroenterol; 104(11): 2695–2703.

- Lipton R, Bigal M (2005) Migraine: Epidemiology, impact and risk factors for progression. Headache 45 (Supl 1): S1

- Loikas et al., (2013) Differences in drug utilisation between men and women: a cross-sectional analysis of all dispensed drugs in Sweden, BMJ Open http://bmjopen.bmj.com/content/3/5/e002378.full Accessed on December 2013

- Macy et al., (2009) Self-reported antibiotic allergy incidence and prevalence: age and sex effect. Am J Med; 122: 778-788.

- McLean & Andreson (2009) Gender differences in fear.

- Melloni et al., (2010) Representation of women in randomized clinical trials of cardiovascular disease prevention. Duke Clin Research Inst Circ Cardiovasc Qual Outcomes; 3: 118-119.

- Merck Medicus (2009)

- Miller et al., (2008) Vascular actions of estrogens: Functional implications. Pharmacol Rev; 60 (2): 228-239.

- Miller et al., (2009) Usimg basic science to design a clinical trial : baseline characteristics of women enrolled in the Kronos Early Estrogen Prevention Study (KEEPS). J Cardiovasc Transl Res; 2 (3): 228-239.

- Nilsson et al., (2006) Increased introduction, advertising and sales of preventive drugs during 1986-2002 in Sweden. Ambul Care Manage; 29 (3): 238-249.

- Norway site: www.Norgeshelsa.no, (2004) Statistical Norwegian studu Accessed on 23/11/2013.

- Rathman et al., (2009) Incidence of type 2 diabetes in the elderly German population and the effect of clinical and lifestyle risk factors. Kora S4/F4 cohort study. Diabetic Medicine; 26(12): 1212-1219.

- Redberg RF (2006) Gender differences in acute coronary syndrome: invasive versus conservative approach. Cardiol Rev; 14 (6): 299-302.

- Regitz_Zagrosek V et al., (2006) Role of gender in heart failure with normal left ventricular ejection fraction. Prog Cardiovasc Dis; 49: 241-251.

- Regitz_Zagrosek V et al., (2007) Gender aspects of the role of the metabolic syndrome as a risk factor for cardiovascular disease. Gend Med; 4 Supl B: 162-177

- Saito et al., (2005) Social support as a predictor of health status among older adults living alone in Japan. Nurs Health Scie; 7: 29-36.

- Saubouret et al., (2010) Observational study of adherence to European clinical practice guidelines for the management of acute coronary syndrome in revascularized versus non revascularized patients- the CONNECT Study. Archives of Cardiovasc Disease; 103: 437-446.

- Shalansky et al., (2002) Effect of number of medications on cardiovascular therapy. Ann J Pharmacother; 36 (10): 1532-1539.

- Shiah Lian (2011) Gender differences in medication adherence among patients with hypertension (Abstract of 22nd International Nursing Research Congress)

- Stilley et al., (2004) Psycological and cognitive function: predictors of adherence with cholesterol lowering treatment. Ann Behav med; 27: 117-124.

- Stramba-Badiale M (2010) Women and research on cardiovascular diseases in Europe: a report from the European heart Health Strategy (Euro Heart) project. Eur Heart J 31: 1677-1681.

- Teeling et al., (2004) Have COX-2 inhibitors influenced the co-prescription of anti-ucer drugs with NSAIDs? Br J Clin Pharmacol; 57(3): 337-343.

- Van de Werf et al., (2008) Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. Eur Heart J; 29: 2909-2945.

- Vilamananda et al., (2011) Gender disparities in lipid lowering therapy among veterans with diabetes. Womens Health Issues; 21 (4): 1762-181

- Watson et al., (2003) Differences between males and females in the natural history of asthma and COPD. European Respiratory Monograph; 25: 50–73.

- Weisenfeld-Hallin (2005) Sex differences in pain perception. Gend Med 2:137.

- Westerbacke et al., (2004) (2010) Diabetologia webpage: Accessed on 23/11/2013

- Wettermark B et al., (2007) The new swedish prescribed Drug Register opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf; 16(7): 726-735.

- WHO Collaborating Centre for Drug Statistics Methodology (WHOCC): DDD Definition and general considerations

- Zopf et al., (2009) Gender-based differences in drug prescription: Relation to adverse drug reactions. Pharmacology; 84: 333–339.

Acknowledgments

There are many people I wish to gratefully acknowledge for these years of my PhD.

First I would like to express my gratitude to my supervisor Professor Rosa Maria Gaion. Without her help it would have not been possible the accomplishment of thesis. She has provided assistance in numerous ways with her kind and respectful manners.

I would like to extend special acknowledge to Dr Anna Maria Grion, who gave me the opportunity to carry out my PhD in their study staff of the Local Health Service. She gave me encouragement to go forward in my research studies.

A special thank to Dr Umberto Gallo. Thanks for your continuous help, guidance and support. You gave me extraordinary experience throughout the work.

Sincere acknowledgement go also to the school of Pharmacology mentioning Prof. Giusti, Daniela and Fabio who where always there to support any request and suggestion.

Special people that made easier this goal achievement need to be mention: Geti, Matilda, Don Giovanni, Marcella, Marsela e Maria.

Finally, my gratefulness goes to my family for their inseparable support and prayers. What I have accomplished is all because of your immense love and trust in me.