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ASPECTOS EPIDEMIOLOGICOS, CRONOBIOLOGICOS Y ORIENTADOS EN EL GENERO DE ENFERMEDADES MÉDICAS

EPIDEMIOLOGICAL, CHRONOBIOLOGICAL, AND GENDER-ORIENTED ASPECTS OF MEDICAL DISEASES

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TITULO: *Aspectos epidemiológicos, cronobiológicos y orientados en el género de enfermedades médicas*

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EPIDEMIOLOGICAL, CHRONOBIOLOGICAL, AND GENDER-ORIENTED ASPECTS OF MEDICAL DISEASES

Tesis Doctoral presentada en la Universidad de Córdoba

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TÍTULO DE LA TESIS: Aspectos Epidemiológicos, Cronobiológicos y Orientados en el Género de Enfermedades Médicas

DOCTORANDO/A: Roberto Manfredini

INFORME RAZONADO DEL/DE LOS DIRECTOR/ES DE LA TESIS

Los Directores de la tesis "*Aspectos Epidemiológicos, Cronobiológicos y Orientados en el Género de Enfermedades Médicas",* desarrollada por el Doctorando Roberto Manfredini, han acompañado el proceso de elaboración de la misma con dedicación como corresponde a su función académica, pero sobre todo con admiración y respeto dada la categoría humana y científica del doctorando.

La trayectoria investigadora del Profesor Manfredini se refleja, entre otros méritos, en **400** publicaciones, y en un índice de impacto >**2050 (Web of Science & Journal Citation Reports. 2017)**.

Asimismo, los directores quieren hacer hincapié en las líneas que en el trabajo de tesis se han abordado, Cronobiología y Género, por su relevancia científica, social y sin lugar a dudas en el ámbito de la salud de las personas.

Con relación a los temas referidos, se relaciona una selección de publicaciones y presentaciones a congresos que el doctorando ha llevado a cabo en el presente año 2018 (Appendix I: Tables 1 & 2).

Por todo lo expuesto, los directores de la tesis refrendan que la misma cumple los requisitos formales de calidad y originalidad, mantiene el rigor científico y académico exigible, y viene respaldada por comunicaciones científicas en congresos y publicaciones, por lo que se autoriza la presentación de la tesis doctoral.

En Córdoba a 3 de diciembre de 2018

Fdo.: Pablo Jesús López Soto

Fdo: Juan Manuel Carmona Torres

A Raffaella

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Carissimi amici, cosa volete che aggiunga? Mi casa es tu casa. Vi aspetto a Ferrara. Anzi, vi aspettiamo.

Un abbraccio, e grazie ancora di tutto. Vi voglio bene.

Roberto

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LIST OF ABBREVIATIONS

ACS=acute coronary syndrome

AF=atrial fibrillation

CA=catheter ablation

CAD=coronary artery disease

CABG=coronary artery bypass grafting

CSI=coronary stent implantation

DAPT= dual antiplatelet therapy

DES= drug eluting stents

DM=diabetes mellitus

DOAC=direct oral anticoagulants

DtB=door to balloon

GI=gastrointestinal bleeding

HL=hyperlipidemia

HT=hypertension

ICH=intracerebral hemorrhage

IHM=in-hospital mortality

LVEF=left ventricle ejection fraction

LOS=length of stay

M= men

MACCE= major adverse cardiac and cerebrovascular events

MB=major bleeding

MI=myocardial infarction

NAA= newer antiplatelet agents

NACE= net adverse cardiac and cerebrovascular events

OA=oral anticoagulants

PCI= Percutaneous coronary intervention

RA=repeat ablation

TAVR=transcatheter aortic valve replacement

TE=thromboembolic event

TFA=transfemoral access

TIS=total ischemic time

TRA=transradial access

TVD=tricuspid valve disease

W=women

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RESUMEN

INTRODUCCIÓN:

Las mujeres y los hombres son biológicamente diferentes a nivel de células, órganos y organismos, y, por lo tanto, en el sistema cardiovascular (CV); diferencias que pueden generar variaciones en la prevalencia, la presentación e incluso los resultados de las afecciones cardiovasculares. En la enfermedad arterial periférica (EAP), hay una amplia serie de diferencias sexuales, que incluyen la epidemiología y el perfil de riesgo, la presentación clínica y el manejo de la misma. A pesar de que la EAP es la tercera manifestación más común de la enfermedad cardiovascular, después de la enfermedad coronaria y el accidente cerebrovascular, sigue siendo poco diagnosticada y poco tratada en las mujeres. Esto también se debe a que las mujeres tienen tasas más altas de enfermedad asintomática / subclínica y la mayoría tiene síntomas atípicos. La claudicación intermitente restringe la actividad y la movilidad afectando considerablemente la calidad de vida relacionada con la salud, por lo tanto, el objetivo principal del tratamiento en estos pacientes es mejorar su función de deambulación y calidad de vida. Aunque la importancia de la rehabilitación cardiovascular está bien establecida, está infrautilizada en todo el mundo, especialmente entre las mujeres.

La tesis está compuesta por dos partes. Por un lado, en base a la experiencia científica específica de mi grupo de investigación, decidí revisar los aspectos epidemiológicos y cronobiológicos de las enfermedades médicas, en particular con referencia a las enfermedades cardiovasculares, bajo una perspectiva de género. Se inició una búsqueda general en la base de datos PubMed con los términos “Género” y “Cardiovascular” (búsqueda cerrada el 1 de agosto de 2018). Se abordaron nuevas adquisiciones y datos, incluso resumiendo en una serie de Tablas los resultados más recientes de estudios que tratan las diferencias de género en términos de terapia,

procedimientos de intervención y resultados clínicos. La segunda parte se centra en el tema seleccionado de EAP, una vez más con una perspectiva definida por género. En particular, se discute la relevancia e importancia de la rehabilitación vascular, y se diseñó un estudio ad hoc para evaluar las diferencias relacionadas con el género en un nuevo programa de rehabilitación realizado por nuestro grupo de investigación.

OBJETIVOS:

General: Describir los aspectos epidemiológicos, cronobiológicos y orientados por género de las enfermedades médicas.

Específicos: Determinar diferencias cronobiológicas y por género en las enfermedades cardiovasculares, considerando tratamiento, intervenciones y resultados clínicos. Evaluar diferencias por género en la apliación de un programa de rehabilitación en pacientes con EAP.

SUJETOS Y MÉTODOS:

Se estudiaron los pacientes con EAP y claudicación inscritos en un programa domiciliario estructurado de 2003 a 2016. El programa se prescribió en el hospital y se basó en dos sesiones diarias de caminata sin dolor de 10 minutos a una velocidad cada vez mayor. Las medidas de resultado, que se evaluaron al inicio y al momento del alta, fueron la velocidad al caminar cuando existen síntomas (PTS) y la máxima (Smax) durante una prueba de esfuerzo y la distancia a pie sin dolor (PFWD) y la distancia total caminada en seis minutos (6MWD). Se determinó el índice tobillo-brazo (IAB), la duración del programa y la adherencia del paciente.

RESULTADOS:

Se incluyeron 1007 pacientes (mujeres, N = 264; 26%). Al inicio del estudio, en comparación con los hombres, las mujeres mostraron valores IAB similares, pero valores más bajos de PTS y PFWD (p <0,001).

En el momento del alta, con una adherencia similar (puntuación de ¾ ± 1 cada uno) en ambos grupos, se observaron importantes mejoras para PTS (0,8 ± 0,8 kmh-1 cada uno), Smax (0,4 ± 0,5 kmh-1 cada uno), PFWD (mujeres: 95 ± 100; hombres 86 ± 104), 6MWD (mujeres: 32 ± 65; hombres: 35 ± 58) y ABI (mujeres: 0.07 ± 0.12; hombres: 0.06 ± 0.11) sin diferencias entre grupos (confirmado después del análisis de propensión).

CONCLUSIONES:

En comparación con los hombres, las mujeres con EAP y claudicación después de un programa personalizado estructurado de baja intensidad, realizado en el hogar durante unos minutos al día, obtuvieron el mismo beneficio en términos de reducción de la discapacidad para caminar y un grado de adherencia similar. Esta observación también se confirmó después del análisis de propensión, que equilibró a los dos grupos en las características iniciales y demostró que no existen diferencias en los resultados de rehabilitación entre los sexos. Según nuestro conocimiento, la literatura disponible sobre la respuesta de las mujeres a la rehabilitación en PAD es deficiente, y los resultados actuales representan un informe novedoso. Los programas que favorecen la adherencia y los resultados funcionales en mujeres deben probarse en estudios prospectivos.

ABSTRACT

INTRODUCTION:

Women and men are biologically different at the level of cells, organs and organism, and sex differences exist also in the cardiovascular (CV) system, so that they can result in variations in prevalence, presentation, and even outcomes of CV conditions. Also per peripheral arterial disease (PAD), there are a wide series of sex differences, including epidemiology and risk profile, clinical presentation, management. Despite PAD is the third most common manifestation of CV disease, following coronary artery disease and stroke, it remains underdiagnosed and under-treated in women. This also because women have higher rates of asymptomatic/subclinical disease and the majority have atypical symptoms. Intermittent claudication restricts activity and mobility considerably affecting the health-related quality of life, therefore the primary treatment goal in these patients is to improve their deambulatory function and quality of life. Although the importance of CV rehabilitation is well established, it is underutilized worldwide, especially among women.

This thesis is composed by two parts. On one hand, based on the specific scientific expertise of my group, I decided to review the epidemiological and chronobiological aspects of medical diseases, in particular with reference to CV diseases, under a gender-oriented perspective. A general search was launched on PubMed database with the terms ‘Gender’ and ‘Cardiovascular’ (search closed August 1, 2018). Novel acquisitions and data are recorded, even by gathering into a series of Tables the most recent results from studies dealing with sex-differences in terns of therapy, intervention procedures, and clinical outcomes. The second part is focused on the selected topic of PAD, once again with a defined perspective by gender. In particular, the relevance and importance of vascular rehabilitation is discussed, and a

ad-hoc study has been designed to evaluate the possible difference of sex-related differences in a novel rehabilitation program performed by our research group.

OBJECTIVES:

General: To describe epidemiological, chronobiological and gender-oriented aspect of medical disease

Specific: To determine chronobiological and gender differences in cardiovascular disease, considering therapy, intervention procedures and clinical outcomes. To evaluate gender-related differences in a novel rehabilitation program performed by peripheral arterial disease patients.

SUBJECTS AND METHODS:

Patients with PAD and claudication enrolled in a structured home-based program from 2003 to 2016 were studied. The program was prescribed at the hospital and based on two daily 10-minute pain-free walking sessions at progressively increasing speed. Outcome measures, which were assessed at baseline and discharge, were the walking speed at symptoms (PTS) and maximal (Smax) during a treadmill test and the pain-free walking distance (PFWD) and total distance walked in six minutes (6MWD). The ankle-brachial index (ABI), program duration and patient adherence were determined.

RESULTS:

A total of 1007 patients (women, n = 264; 26%) were enrolled. At baseline, compared to men, women exhibited similar ABI values but lower PTS and PFWD values ($p<0.001$).

At discharge, with similar adherence (score ¾±1 each) in both groups, superimposable improvements were observed for PTS (0.8±0.8 kmh^{-1} each), Smax (0.4±0.5 kmh^{-1} each), PFWD (women: 95±100; men 86±104), 6MWD (women: 32±65; men: 35±58), and ABI (women: 0.07±0.12; men: 0.06±0.11) without between-group differences (confirmed after propensity analysis).

CONCLUSIONS:

Compared to men, women with PAD and claudication following a structured low-intensity personalized program, performed inside the home for a few minutes a day, obtained the same benefit in terms of reduction of walking disability as well as a similar degree of adherence. This observation was also confirmed after propensity analysis, which balanced the two groups in baseline characteristics and proved that no differences in rehabilitation outcomes exist between sexes. To the best of our knowledge, the available literature on the response of women to rehabilitation in PAD is poor, and the present results represents a novel report. Programs favoring adherence and functional outcomes in women should be tested in prospective studies.

STATE OF ART

GENDER-ORIENTED MEDICINE

Women and men are biologically different at the level of cells, organs and organism. Sex and gender are not interchangeable terms. Sex refers to biological differences between males and females, in terms of genetics, epigenetics and endocrinology, gender refers to sociocultural status, and sex differences can be studied in animal models and also in isolated cells. Sex differences exist also in the cardiovascular (CV) system, due to differences in gene expression from the sex chromosomes, further modified by sex differences in hormones resulting sex-unique gene expression and function. These differences result in variations in prevalence and presentation of CV conditions, including autonomic regulation, hypertension, diabetes, vascular and cardiac remodeling. In contrast, gender differences are unique to the human, and arise from sociocultural practices (behaviors, environment, lifestyle, nutrition) (Garcia et al, 2016; Ventura-Clapier et al, 2017).

The inclusion of gender in clinical data analysis could represent an important opportunity to discover differences in the relationship between exposure and outcomes for men and women, and arrange strategies for intervention. Currently, international funding agencies have established policies focused on the integration of sex and gender in grant application to strengthen science and guarantee quality and generalisability of biomedical research. Thus, it will be mandatory to study the interaction of sex with age in women and men, and a higher proportion of women must be enrolled to draw final conclusions through a well-powered sex stratify analysis (Ventura-Clapier et al, 2017; Raparelli et al, 2018). It is known that women are under-represented in research on CV disease. A study aimed to investigate, through an on-line survey, the willingness to participate (WTP) and other attitudes towards aspects of clinical research studies in a cohort of men and women, did not show differences in WTP in patients with CV

disease compared to patients with other chronic diseases, and no differences by sex. Thus, the lower levels of participation by women are due to factors other than a lower WTP (Gruca et al, 2018). On the other hand, the role of gender has been largely neglected despite being a critical determinant of CV health. The American Heart Association's Social Determinants of Risk and Outcomes of Cardiovascular Disease Scientific Statement strongly suggested to look beyond breakthroughs in biological science toward a social determinants approach that focuses on socioeconomic position, race and ethnicity, social support, culture and access to medical care, and residential environments to curb the burden of CVD going forward. In fact, there is a need for CV treatment and awareness campaigns and gender equality strategies, in the view of reducing the burden of CV disease for men and women at the population level (O'Neil et al, 2018).

Based on the specific scientific expertise of my group, I decided to review the epidemiological and chronobiological aspects of medical diseases, in particular with reference to cardiovascular (CV) diseases, under a gender-oriented perspective. This work was done either on the more than 30-year of personal studies and on the recent data from the medical Literature. A general search was launched on PubMed database with the terms 'Gender' and 'Cardiovascular', and I retrieved 2514 items (search closed August 1, 2018) (*Appendix II*).

ATHEROTHROMBOSIS AND GENDER

Sex-specific differences exist in the presentation, pathophysiological mechanisms, and outcomes in patients with acute myocardial infarction (AMI). Recently, a scientific statement has been released by the American Heart Association dealing with AMI in women (Mehta et al, 2016), providing a comprehensive review of the current evidence of the clinical presentation, pathophysiology, treatment, and outcomes of women with AMI. Again, in the same year the American Heart Association released also a more general scientific statement on ischemic heart disease in women (McSweeney et al, 2016). Increased recognition of the prevalence of traditional CV risk factors, and their differential impact in women, as well as emerging, nontraditional risk factors unique to, or more common in women, contribute to new understanding of mechanisms leading to these worsening outcomes for women (Garcia et al, 2016). Here some recent findings on risk factors.

HYPERTENSION

Men and women differ in prevalence, awareness, and control rate of hypertension in an age-dependent manner. Sex hormones changes play a pivotal role in the pathophysiology of hypertension in postmenopausal women, and estrogens influence the vascular system inducing vasodilatation, inhibiting vascular remodeling processes, and modulating the renin-angiotensin aldosterone system and the sympathetic system. The final result is a protective effect on arterial stiffness during reproductive age, that is dramatically reversed after menopause (Di Giosia et al, 2018). Level of intensity of blood pressure (BP) programs is matter of debate, particularly in women. Recent data seem to indicate that women do not benefit from intensive compared to standard BP control. Data from the Systolic Blood Pressure Intervention Trial (SPRINT), matching patients with standard therapy (systolic BP <140 mm Hg) to

those with intensive therapy (systolic BP <120 mm Hg; n = 9,106), found that men on intensive therapy had a lower risk of the composite outcome compared to those on standard therapy (HR 0.70, p = 0.001), but women did not. In fact, in women there were no differences between therapy groups (HR 0.82, p = NS) (Ochoa-Jimenez et al, 2018). Hypertension in pregnancy deserves a consideration apart. In accordance to current guidelines, the diagnostic approach does not differ between men and women, although the cardiac response to pressure overload may suggest greater sensitivity in women, and may vary according to age, ethnic background and obesity. It seems that peculiar abnormalities by gender in left ventricle (LV) systolic and diastolic function exist. The increase in LV mass in response to chronic pressure overload is associated with higher LV ejection fraction in women than in men and LV torsion is maintained with aging in women but not in men. Interstitial fibrosis may reduce circumferential shortening and early diastolic strain rate, in the presence of a preserved ejection fraction in women, favoring the development of heart failure with preserved ejection fraction. Changes in aortic stiffness with aging may influence cardiac structural and functional changes, and isolated systolic hypertension is frequent in women and may be associated to a greater development of concentric LV hypertrophy. Moreover, the regression of hypertensive LVH is more difficult in women, and residual hypertrophy is more common in women than in men despite effective antihypertensive treatment (Muiesan et al, 2018).

LIPIDS & DIABETES

A Spanish study on more than 1000 subjects, investigated possible sex differences with regard to lowering lipid levels, and found that, compared with men, women were less likely to be treated with more potent statins (9.2% vs. 14.4%, p=0.009), and received lower doses (45±59 mg/day vs. 56±71 mg/day, p=0.004).

Moreover, total cholesterol and LDL-C levels were significantly higher in women than in men (5.7±1.3 mmol/l vs. 5.2±1.2 mmol/l, and 3.5±1.2 mmol/l vs. 3.1±1.0 mmol/l, respectively) (Moreno-Arellano et al, 2018). As for diabetes mellitus (DM), there is strong evidence to suggest that it is a stronger risk factor for vascular disease in women than men. (Peters et al, 2018). Type 1 DM affects adipose and skeletal muscle insulin sensitivity to a greater extent in women than in men, perhaps contributing to the greater relative increase in CV risk in women with type 1 DM (Millstein et al, 2018). In fact, young adults with type 1 DM present gender differences with regard to glycemic control, prevalence of some cardiovascular risk factors, sexual dysfunctions and circulating levels of endothelial progenitor cells (EPCs), most often to the detriment of women. In fact, as compared to men, women with type 1 DM had significantly higher HbA1c levels, BMI, HDL-cholesterol, and also a lower count of EPCs (Maiorino et al, 2018).

SEX HORMONES & INFLAMMATION MARKERS

Higher androgen and lower estrogen levels are associated with CV disease risk factors in women. In a study on near 3000 post-menopausal women participating in the MESA (Multi-Ethnic Study of Atherosclerosis), Zhao et al. found that a higher testosterone/estradiol ratio was associated with an elevated risk for incident CV disease, coronary heart disease (CHD), and heart failure (HF) events, higher levels of testosterone associated with increased CV disease and CHD, whereas higher estradiol levels were associated with a lower CHD risk. Thus, sex hormone levels after menopause are associated with women's increased CVD risk later in life (Zhao et al, 2018). On the other hand, soluble receptors for tumor necrosis factor α (sTNFR1 and sTNFR2) have been associated with CV diseases, and there is evidence of a difference

in associated risk between men and women. Data from a Swedish study found an association between circulating sTNFR1 and sTNFR2 and an increased risk for AMI. Women with a combination of elevated CRP and values in the upper quartile of TNFR1 or TNFR2 had a 5-fold higher risk of AMI versus those with normal CRP and values in the lower three quartiles of TNFR1 or TNFR2 (Carlsson et al, 2018).

ISCHEMIC HEART DISEASE & ACUTE MYOCARDIAL INFARCTION

Atypical presentation

CV disease remains the leading cause of morbidity and mortality for both women and men. Emerging evidence supports that ischemic heart disease may manifest differently in women and men, in ways ranging from the clinical presentation, diagnosis, and management of disease to the basic biology and biomechanics of cardiomyocyte function and the coronary circulation. Women consistently present with a higher burden of symptoms and comorbidities as compared with men and experience worse outcomes. The atypical presentation of women with acute coronary syndrome (ACS) has been related to delayed diagnosis and treatment, which may explain worse outcome compared with men. A study was conducted on 2009 women and 976 men (aged 18 to 55 years) hospitalized for AMI at US hospitals participating in the VIRGO study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients). The majority of women (87.0%) and men (89.5%) presented with chest pain (defined as pain, pressure, tightness, or discomfort). Women were more likely to present with ≥3 associated symptoms than men (eg, epigastric symptoms, palpitations, and pain or discomfort in the jaw, neck, arms, or between the shoulder blades; 61.9% for women versus 54.8% for men, $p<0.001$). In adjusted analyses, women with an ST-segment-

elevation AMI were more likely than men to present without chest pain (OR 1.51). In comparison with men, women were more likely to perceive symptoms as stress/anxiety (20.9% vs 11.8%) but less likely to attribute symptoms to muscle pain (15.4% vs 21.2%,). Approximately 29.5% of women and 22.1% of men sought medical care for similar symptoms before their hospitalization but, interestingly, 53% of women reported that their provider did not think these symptoms were heart-related in comparison with 37% of men (Lichtman et al, 2018). Analysis of pooled data of more than 2500 patients of two prospective cohorts in terms of differences in presentation and management of women and men suggestive of ACS, women were older than men, had more often dyspnea, nausea or vomiting and radiating chest pain, and women less frequently had classical risk factors (smoking, diabetes mellitus, dyslipidemia or known CAD). There were no significant sex-related differences in diagnostic performance, but women underwent coronary angiography and revascularization less frequently (73.8% vs 84.3%, and 53.8% vs 70.1%, respectively). However, two-year incidence of MI and death was similar in both sexes. (Sorensen et al, 2018). Reported sex differences have long been influenced by the practice of defining heart disease primarily as obstructive CAD, but obstructive plaque is now recognized as neither necessary nor sufficient to explain symptoms of ischemic heart disease, and it is no longer adequate to tailor diagnostic and treatment strategies only to this subset of patients. Smaller epicardial coronary arteries in women as compared to men, coupled with differences in shear stress and inflammatory mediators over the life span, may modify the development of CAD in susceptible patients into a diffuse pattern with more contribution from coronary vasomotor dysfunction than focal obstruction. Symptomatic women are more likely than men to present with nonobstructive CAD and coronary microvascular dysfunction.

When present, these processes increase CV risk in both women and men but may constitute an especially malignant phenotype in a subset of severely affected women, with implications for the management (Taqueti, 2018).

Diagnosis

Elevated cardiac troponin, with signs/symptoms of ischemia, represents crucial point in a diagnosis of myocardial infarction (MI). A study on more than 27,000 patients with ischemic chest pain presenting to a series of Canadian hospitals showed that cardiac troponin testing was quite similar in women and men, except among young women aged <50 years, where it was markedly lower (OR 0.78). In any case, the odds of cardiac catheterization within 90 days of ED presentation were lower in women (OR 0.52) and, even in the presence of chest pain, only 17.7% of women vs 32.7% of men had cardiac catheterization (Humphries et al, 2018). A study conducted over a 5-year period on more than 7200 patients presenting to the ED (41% females) showed that, among patients with chest pain with cardiac features/history and cTn > 99th percentile, females were less likely to be diagnosed with MI (46.4% vs 57.5%). Females in the cTnI > 99th percentile group had the worst outcomes with a 1-year MACE rate of 22.7% vs 18.8%. Overall, females underwent fewer diagnostic catheterizations than males within 7 days of admission to the ED. Even when cTn was above the 99th percentile and the chest pain was cardiac in nature, 48% of females underwent a diagnostic catheterization compared to 64% of males. Moreover, within 90 days of discharge, females were less likely to use the evidence-based cardiac medications. The most striking sex differences were noted when cTnI levels were > 99th percentile and when the chest pain was cardiac in nature; males filled 25% more prescriptions for statins than their female counterparts (Humphries et al, 2018).

Outcomes

Acute myocardial infarction. It is known that women generally have worse mortality outcomes than men with regards to ST-elevation myocardial infarction (STEMI). A study on 16861 patients who presented directly to the ED with NSTEMI (38.6% women) showed that, at baseline, women were older and presented with history of prior CV disease more often than men. Women had higher unadjusted in-hospital mortality rates than men (4.8% vs. 3.9%, $p < 0.001$). Women also had 23 min longer ED lengths of stay ($p < 0.001$) and were much less likely to receive diagnostic coronary angiography within 24 h of arrival than men (47.0% vs 54.4%, $p < 0.001$). (Langabeer et al, 2018).

Out-of-hospital cardiac arrest (OHCA). Female sex was independently associated with worse neurologic recovery (OR 0.94), lower rates of treatment at a 24/7 PCI center (OR 0.89), lower rates of cardiac catheterization (OR 0.61), and with do-not-resuscitate (DNR) orders within 24 h of admission (OR 1.16) (Casey et al, 2018).

Cardiac resynchronization therapy defibrillator (CRT-D) implantation. A study based on the US Nationwide Inpatient Sample on 378,248 CRT-D cardiac resynchronizations found that female gender and age (≥ 65 years) (OR 1.08, $p<0.001$), and Charlson comorbidity score ≥3 (OR 1.52, <0.001) were significantly associated with increased mortality/complications (Patel et al, 2018).

Coronary artery bypass grafting (CABG). A study based on US Medicare-based data on 1863719 patients (33.6% women), evaluated for differences by sex for CABG utilization and post-CABG outcomes (in-hospital, 30-day, and 1-year mortality and 30-

day readmission), reported that women had persistently higher CABG mortality than men (Angraal et al, 2018).

Major surgery. A study assessed the effect of gender on 30-day morbidity and mortality after major surgery in 1409131 patients (57.2% women) found that overall morbidities were lower in women versus men (with the exception of after cardiac surgeries and vascular surgeries where overall morbidities were higher) (Al-Taki et al, 2018).

SUDDEN CARDIAC DEATH (SCD)

Data from the WISE (Women's Ischemia Syndrome Evaluation) study found that SCD contributes substantially to mortality in women with and without obstructive CAD. In addition to traditional risk factors (age, diabetes mellitus, smoking), a history of depression and longer corrected QT interval were independent SCD predictors in the entire cohort, but only corrected QT interval was an independent predictor of SCD in women without obstructive CAD (Mehta et al, 2017).

HEART FAILURE (HF)

Cardiovascular diseases increase with age in both men and women, and it is likely that age itself is a major independent risk factor for cardiovascular disease. It seems that the heart and blood vessels accumulate cellular and subcellular deficits with age, capable to increase susceptibility to disease in older individuals, and age-dependent remodeling of the heart and blood vessels also shows differences by sex (Kane et al, 2018). HF affects more than 25 million adults worldwide. Roughly, 50% of HF patients exhibit a reduced ejection fraction (HfpEF), and 50% have preserved (HfpEF) or mid-range ejection fraction (HfmrEF). Men more frequently show an ischemic etiology and

are characterized by HfrEF or HfmrEF, whereas women more frequently show hypertension, diastolic dysfunction, valvular diseases, and are characterized by HfpEF (Savarese & D'Amario, 2018; Beale et al, 2018). Females are older, have a higher EF, higher frequency of HF-related symptoms, lower NYHA functional status, and more comorbidities such as atrial fibrillation, diabetes, hypertension, anemia, renal disease, arthritis, frailty, depression, and thyroid abnormalities. However, overall, females have better prognosis in terms of mortality and hospitalization risk compared with men, regardless of EF (Savarese & D'Amario, 2018). As for dilated cardiomyopathy (DCM), although women were more likely to present with HF and had more severe symptoms compared to men, they have better survival (Halliday et al, 2018).

PULMONARY EMBOLISM (PE)

Data from a Japanese registry database (n=1428, 55.7% women) showed that women exhibit more severe cases and have a poor prognosis. Compared with men, women had more complaints of dyspnea and disturbed consciousness, lesser complaints of leg symptoms, and chest pain. Women also had higher pulmonary arterial systolic pressure and serum B-type natriuretic peptide level on admission. Also, cases with massive embolism were more frequent in women compared with men (14.6% vs. 9.2%). Due to these reasons, 30-day PE-related mortality was significantly higher in women than in men (5.0% vs. 2.8%) (Tanabe et al, 2018).

STROKE

Recent data seem to show that the risk of stroke is lower in women than in men under the age of 75 but is similar when comparing women and men after that age. Nevertheless, a higher absolute number of strokes in women than in men is the result of

the longer survival of women compared with men (Meirhaeghe et al, 2018). As for functional outcome, data from stroke incidence studies at 1 year (10 studies, n = 4852) and 5 years (7 studies, n = 2226) showed that women experienced worse results after stroke than men: unadjusted RR 1.32 at 1 year, and 1.31 at 5 years, and adjusted (age, prestroke dependency, stroke severity) RR 1.08 at 1 year, 1.05 at 5 years. This can be explained mostly by age, stroke severity, and prestroke dependency (Phan et al, 2018).

Stroke risk in atrial fibrillation is assessed by using the CHA_2DS_2-VASc score, where sex category (Sc, ie, female sex) confers 1 point. Nielsen et al (2018) performed a study on 239671 patients with AF (48.7% women), and concluded that female is a stroke risk modifier, rather than an overall risk factor, when added to a CHA_2DS_2-VA (sex-independent thromboembolism risk) score scale. Mean CHA_2DS_2-VA scores were 2.7 for women and 2.3 for men. The overall 1-year thromboembolic rate per 100 person-years for women was 7.3 and 5.7 for men. The 1-year absolute risk of thromboembolism was 0.5% among men and women with a CHA_2DS_2-VA score of 0 and increased up to >7% among very comorbid patients (score >5). The risk ratio (male as reference) across points >1 indicated that women exhibit a higher stroke risk. (Nielsen et al, 2018).

COMORBIDITIES

Women live longer and outnumber men, but older women develop more chronic diseases and conditions such as arthritis, osteoporosis and depression, leading to a greater number of years of living with disabilities (Corrao et al, 2014).

DRUGS & TREATMENT

Statins

Sex and gender disparities play a role in determining the efficacy and safety of the most commonly used medications suggesting the need for a sex-tailored approach in prescription. Statins are a cost-effective strategy for CV disease prevention. On one hand, statins are similarly effective in secondary CV disease prevention. However, conflicting data have been reported in primary prevention clinical trials, may be secondary to the small representation of women in clinical trials and the fewer rates of events due to the lower female baseline CV disease risk. In particular, benefits outweigh disadvantages of statin therapy in women with a high CV disease risk, while some doubts exist for the primary prevention of women at low-intermediate risk. Furthermore, disparities between women and men in medication adherence may influence statin efficacy in CV disease prevention. The sex-dependent impact of adverse side effects is one of the reasons advocated for explaining the gender gap, but it is not evidence-proved (Raparelli et al, 2017). Analysis of data from 32258 patients (VOYAGER study) showed that, even if all statins and doses gave significant dose-dependent reductions in LDL-C and non-HDL-C, and increases in HDL-C, a 2.1% greater reduction in LDL-C was observed in women, compared with men ($p < 0.0001$). Men experienced a significantly greater increase in HDL-C than women. While statins improve the lipid profile in all gender groups, the improvements are greater in women than in men (Karlson et al, 2017).

Oral anticoagulants

New oral anticoagulant agents have recently become for patients an alternative option to conventional treatment in the therapy of venous thromboembolism (VTE). A review of available information on adverse events (Aes) of apixaban compared to conventional therapy (heparin or vitamin K antagonists) in randomized controlled trials (RCTs) on patients treated for VTE, was addressed especially to evaluatesex subgroups. Considering all subjects enrolled in the eleven RCTs as a whole, there was an events/subjects rate of 57.8% for Aes, 7.7% for serious Aes, 9.1% for bleeding events, and 3.2% for discontinuation of apixaban. The percentage of Aes was lower in subjects treated with apixaban than in those treated with conventional VTE therapy (53% vs. 56%, respectively). However, only one study provided data on separate analysis by sex of either efficacy or safety of apixaban. Even in this case, data with separate analyses by sex are extremely limited (Fabbian et al, 2016).

CHRONOBIOLOGY AND BIOLOGICAL RHYTHMS: A THIRTY-YEAR PERSONAL RESEARCH STORY

Chronobiology is a branch of biomedical sciences aimed at the study of biological rhythms. Biological rhythms exist at many levels in living organisms and, according to their cycle length, may be divided into: a) circadian (period of ~ 24 hours), b) ultradian (period < 24 hours), c) infradian (period > 24 hours). Circadian rhythms are the widely studied, and are driven by circadian clocks. Circadian clocks can be defined as a transcriptionally based molecular mechanism, based on both positive and negative feedback loops, with a free-running period of approximately 24 hours. The principal circadian clock or *master clock*, located in the suprachiasmatic nucleus (SCN), is entrained by light and is supposed to entrain peripheral clocks via neurohumoral modulation. However, circadian clocks have been identified within almost all mammalian cell types, including cardiomyocytes, vascular smooth muscle cells and endothelial cells. The principal role of cellular biological clocks is driving circadian rhythms to adapt the organism to further needs in an anticipatory manner, thus providing selective advantage.

Nearly four decades ago, Horne & Ostberg published their study on possible individual differences in circadian attitudes (Horne & Ostberg, 1976). They presented a self-assessment *Morningness-Eveningness* (M/E) questionnaire, evaluated against individual differences in the circadian variation of oral temperature. The questionnaire consisted in 19 items with a definite score each, identifying five categories: definitely *Evening* type (16-30), moderately *Evening* type (31-41), neither type (42-58), moderately *Morning* type (59-69), and definitely *Morning* type (70-86). M-types showed a significantly earlier body temperature peak time than E-types and tended to have a higher daytime temperature. I-type had temperatures between those of the other groups. M-types retired and arose significantly earlier than E-types, but the three types

did not show significant differences in sleep length (Horne & Ostberg, 1976). Such a circadian individual preference was defined 'chronotype'. Evening types are also defined al 'owls', and Morning type as 'larks', and chronotype may deeply impact on working activity (Lopez-Soto et al, 2018).

Light-dark alternation has always been the strongest external circadian "zeitgeber" for humans. Due to its growing technological preference and light abuse, our society is quickly transforming toward a progressive "eveningness", with consequences on individual chronotype, depending on gender as well. We reviewed the available evidence of possible relationships between chronotype and gender, with relevance on disturbances that could negatively impact general health, including daily life aspects. Electronic searches of the published literature were performed in the databases MEDLINE and Web of Science, by using the Medical Subject Heading (MeSH), when available, or other specific keywords. Results were grouped into four general areas, i.e. (a) "General and Cardiovascular Issues", (b) "Psychological and Psychopathological Issues", (c) "Sleep and Sleep-Related Issues" and (d) "School and School-Related Issues". (a) E was associated with unhealthy and dietary habits, smoking and alcohol drinking (in younger subjects) and, in adults, with diabetes and metabolic syndrome; (b) E was associated with impulsivity and anger, depression, anxiety disorders and nightmares (especially in women), risk taking behavior, use of alcohol, coffee and stimulants, psychopathology and personality traits; (c) E has been associated, especially in young subjects, with later bedtime and wake-up time, irregular sleep-wake schedule, subjective poor sleep, school performance and motivation, health-related quality of life; (d) E was associated with lowest mood and lower overall grade point average (especially for women) (Fabbian et al, 2016).

PERIODICITY OF ACUTE DISEASES

The symptom intensity and mortality of human diseases, conditions, and syndromes exhibit diurnal or 24 h patterning (Smolensky et al, 2015), and our group actively participated in demonstration of temporal windows for some of the, e.g., fever seizures (Manfredini R. et al, 2006), migraine (Manfredini R. et al, 2006), renal colic (Manfredini R. et al, 2002), epistaxis (Manfredini R. et al, 2000), febrile seizures (Manfredini R. et al, 2006) and migraine attacks in children (Soriani et al, 2006), psychiatric/behavioral and aggressive (Manfredini R. et al, 2001; 2018), parasuicide and suicide (Manfredini R. et al, 1994; Caracciolo et al, 1996; Gallerani et al, 1996), addictive heroin cravings and withdrawal phenomena (Manfredini R. et al, 1994; Gallerani et al, 2001), accidental falls (Manfredini R. et al, 2011, 2012; Lopez-Soto 2015, 2016). Again, many medical conditions, disorders, and syndromes exhibit predictable-in-time diurnal and 24 h patterning in the signs, symptoms, and grave nonfatal and fatal events (Smolensky et al, 2015), e.g., 3rd degree atrial-ventricular block (Manfredini R. et al, 2002), paroxysmal supraventricular tachycardia (Manfredini et al, 1995), acute (non-fatal and fatal) incidents of myocardial infarction (Muller et al, 1985; Manfredini R. et al, 2004), acute cardiogenic pulmonary edema (Manfredini R. et al, 2000); hypertensive crisis (Marchesi et al, 2013); abdominal, aortic, and thoracic dissections (Manfredini et al, 1999; Mehta et al, 2002; Manfredini R. et al, 2004), pulmonary thromboembolism (Gallerani et al, 1992), and cerebrovascular transient ischemic attack and hemorrhagic and ischemic stroke (Gallerani et al, 1993, 1994, 1996; Manfredini R. et al, 1997, 2005). In a few words, there is a time for every emergency (Manfredini R. et al, 2002). A close relationship between time and onset of certain acute diseases is extremely intriguing and fascinating. The CV system, and most CV

functions, are organized according to a specific circadian order. Since circadian pattern is rhythmic, predictable-in-time differences in the physiological status of the cardiovascular system give rise to rhythmic variations in the susceptibility of human beings to morbid and mortal events (Portaluppi et al, 1999). On the other hand, the pathological mechanisms of cardiovascular disease themselves exhibit temporal changes in both their manifestation and severity, leading to predictable-in-time differences in their ability to precipitate and graduate the overt expression of disease (Portaluppi et al, 1999). It is already well known that the occurrence of cardiovascular events is not evenly distributed in time, but shows peculiar temporal patterns that vary with time of the day, the day of the week, and the month of the year. Due to temporal variation in the (I) pathophysiological mechanisms that trigger cardiovascular events and (II) physiological changes in the body rhythms, it is possible that several factors, not harmful if taken alone, may trigger unfavorable events when presenting all together at the same time (chronorisk) (Portaluppi et al, 1999). In fact, when peak levels of critical physiologic variables, such as BP, heart rate (HR), sympathetic activation, and plasma levels of endogenous vasoconstricting substances, are aligned together at the same circadian time, the risk of acute events becomes significantly elevated such that even relatively minor and usually harmless physical and mental stress and environmental phenomena can precipitate dramatic life-threatening clinical manifestations (Manfredini R. et al, 2013).

There are close relationships between BP rhythms and temporal patterns of cardiovascular events (Manfredini R. el al, 1996). BP reaches peak values in the morning, although a secondary peak is usually present in the late afternoon or early evening. Although there is no consensus on whether the BP morning surge begins

during sleep or just before or after awakening, it is possible that there are two patterns. One pattern is a gradual increase in BP before awakening, especially common in younger persons, and the other pattern involves elevation of BP with initial physical activity, especially common in the elderly. HR shows a morning peak as well, and its circadian rhythmicity is well known. Plasma norepinephrine level and plasma renin activity are elevated in the morning; both hormones have potential to induce coronary vasoconstriction. A circadian rhythm in vascular basal tone is also demonstrated in relation to increased α-sympathetic vasoconstrictor activity in the morning. In addition, the circadian pattern of plasma cortisol secretion, characterized by a sharp morning rise, may contribute to increased sensitivity of arterial vessels to vasoconstrictor stimuli (Manfredini R. et al, 2004).

ACUTE MYOCARDIAL INFARCTION

Circadian (time of day)

Myocardial infarction exhibits highest frequency of onset during morning hours (6–12 AM). It has been estimated that the incidence rate of acute myocardial infarction (AMI) onset is 40% higher in the morning period than throughout the rest of the day, and nearly 28% of morning infarctions and 22% of sudden cardiac deaths (accounting for approximately 9% and 7% of all AMIs and sudden deaths, respectively), are attributable to the morning excess (Cohen et al, 1997). Moreover, it is possible that time-dependent differences in clinical outcome may be present as well. During 6 AM–noon period, a trend toward a higher frequency of fatal cases was also shown (41.5% *vs.* 35.2%), independent of age, infarct site, and peak levels of MB creatine-kinase (Manfredini R. et al, 2004). Moreover, a retrospective cohort study conducted in 1,946

consecutive acute coronary syndrome (ACS) admissions to assess presenting clinical variables in patients admitted on days *vs.* nights and WD *vs.* WE found that there were fewer ACS admissions than expected on nights and WE ($p<0.001$), but the proportion of patients with ACS presenting with ST-elevation myocardial infarction (STEMI) was 64% higher on WE ($p<0.001$) and 31% higher on nights (LaBounty et al, 2006). This could explain a higher severity and mortality during morning hours and WE *(Figure 1)*.

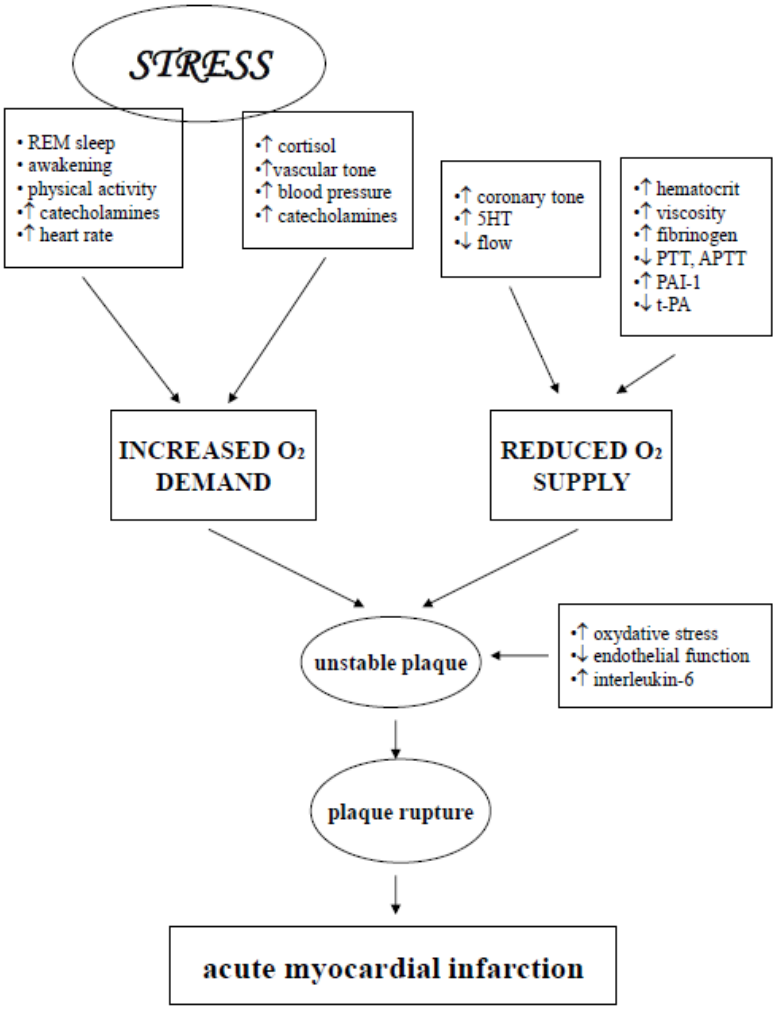

Figure 1. Schematic outline of the way in which several concurring risk factors might contribute to trigger the onset of acute myocardial infarction during morning hours. Abbreviations: REM, rapid eye movement; 5HT, 5-hydroxytryptamine; PTT, partial thromboplastin time; APTT, activated partial thromboplastin time; PAI-1, plasminogen activator inhibitor-1; t-PA, tissue plasminogen activator. (Manfredini R. et al, Encyclopedia of Stress, Second Edition, Fink G. (ed), Oxford: Academic Press, 2007).

Seasonal

Data from the U.S. Second National Registry of Myocardial Infarction reported 53% more cases in the winter than in the summer, and winter was characterized by the highest frequency of fatal cases (Ornato et al, 1996). The majority of studies have reported the lowest frequency of AMI onset in the summer and the highest frequency during winter (Manfredini R.et al, 2005). Similar pattern has been confirmed by our group in more than 64 000 consecutive cases of AMI hospitalized between 1998 and 2006 in the Emilia-Romagna region of Italy (Manfredini R. et al, 2009).

Circaseptan (weekly)

More than two decades ago, Willich et al (1994) in Germany, and Gnecchi-Ruscone et al (1994) in Italy, reported an increased risk of AMI on Monday. In particular, Willich et al. found that this weekly variation with a Monday peak was present only in the working but not in nonworking population. A couple of years after, Spielberg et al (1996), in Germany, confirmed the higher frequency of events on Monday, but with no differences between working or retired patients. A meta-analysis study aimed to quantify the excess risk associated with the Monday peak in cardiovascular mortality (Witte et al, 2005), found an increased pooled odds ratio of 1.19, without significant differences between subgroups by sex and age. Our group also confirmed the Monday excess (16.1%) with a lower rate on Sunday (11.8%) (Manfredini R. et al, 2009). A meta-analysis of 28 community-based studies (Barnett et al, 2005) confirmed a statistically significant excess in coronary events on Mondays in 20 out of 28 studies. The Monday excess in events was observed in both fatal and non-fatal events, in both sexes, and was greater in younger compared with older subjects.

However, this meta-analysis showed that, even if greater than zero, the Monday excess in coronary event was small (being calculated as less than 1 event in 100, with a relative increase of 1%), compared with the estimated excess in morning (+40%) and in winter (+45%). More recently, our group investigated the mortality records extracted in the Veneto region of Italy (years 2000-2013). Among 41,024 deaths from circulatory diseases registered in the study population, mortality rates on Monday were increased by 13% (CI 9-17%) with respect to Sunday and by 6% (CI 4-9%) with respect to the overall daily mean. The Monday peak was demonstrated in both genders and in all the analyzed disease categories, and was more pronounced in younger age classes (Capodaglio et al, 2016).

AORTIC ANEURYSMS

Circadian (time of day)

Although acute aortic rupture or dissection is relatively uncommon, it ranks in third position among necropsy-confirmed causes of out-of-hospital sudden death in the general population (Manfredini R. et al, 1996). Also for aortic aneurysms, abdominal or thoracic, several studies have found a circadian variation, characterized by an increased risk of rupture or dissection during early morning hours (Manfredini R. et al, 1999; Gallerani et al, 1997; Sumiyoshi et al, 2002). Analysis of the IRAD registry showed that this morning peak (around 8-9 am) was independent of gender, type A or B dissection, age $<$ or $\geq$ 70 years, and presence or absence of hypertension (Mehta et al, 2002). Such pattern coincides with the temporal variation in the pathophysiology mechanisms that trigger cardiovascular events and the physiologic changes in body rhythms (Manfredini R. et al, 2004) *(Figure 2)*.

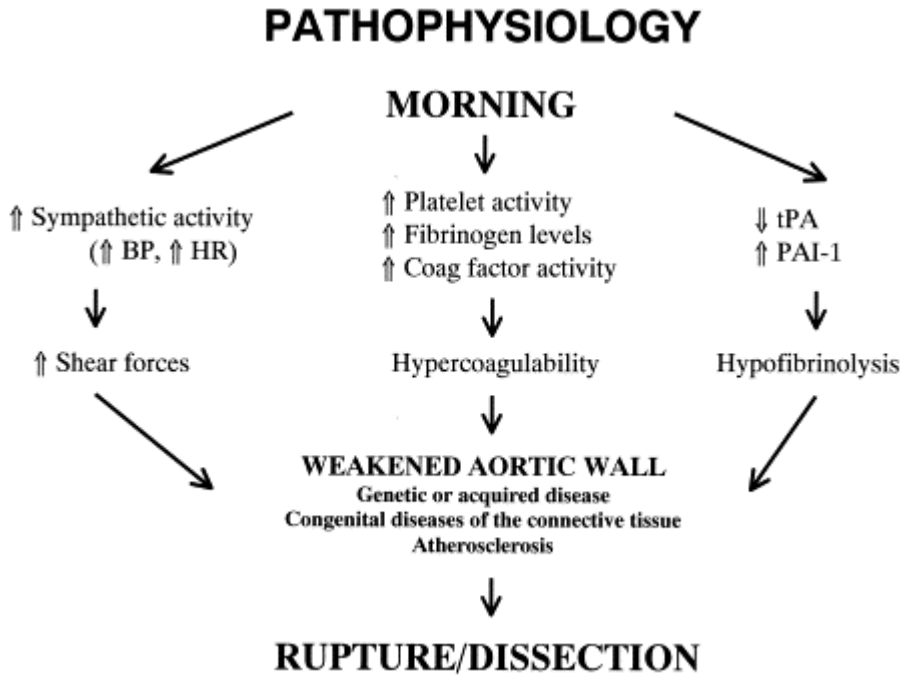

Figure 2. Concurrent pathophysiologic mechanisms underlying circadian variation of aortic rupture or dissection. BP, Blood pressure; HR, heart rate; tPA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor-1. (Manfredini R et al, J Vas Surg 2004).

Seasonal

Most available studies indicate a greater occurrence of aortic rupture or dissection during the fall and winter months (Liapis et al, 1992; Manfredini R. et al, 1997, 1999; Kobza et al, 2002; Manfredini R. et al, 2008), although thus temporal pattern seems to be independent of climatic variables (Mehta et al, 2005). Moreover, mortality does not seem to be affected by seasonal (or circadian) patterns (Mehta et al, 2005). Cold exposure determines increased sympathetic activity, blood pressure, and arterial spasm, with increased platelet count and volume, red blood cell count, blood viscosity, lipid levels, and clotting activity. Further, fibrinogen levels demonstrate wide seasonal variation, increasing up to 23% during the colder months. Changes in the

hematologic properties such as viscosity and coagulation have been described in relation to air temperature. Even mild surface cooling increases hematocrit and platelet count, thereby favoring spontaneous thrombosis. Moreover, hypertensive effects of low temperatures are well known; a significant negative correlation between ambient temperature and blood pressure, and an increase in arterial pressure during mild surface cooling have been reported. During peripheral vasoconstriction, systolic blood pressure increases more than diastolic pressure does; thus, pulse amplitude is generally increased, although there is a little change in cardiac output or pulse rate. This enhances the forces that act to produce wall deformation, and increase friction and shear stress on the internal surface. The consequent vascular damage may progress, culminating in arterial dissection and rupture of the aorta. (Manfredini et R. al, 2004).

Genetic aneurysms

Marfan syndrome is an autosomal dominant connective tissue disease associated with acute aortic dissection (AAD). Based on data from two large registries, the International Registry of Acute Aortic Dissection (IRAD) and the Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) registry, AAD was more likely in the winter/spring season (November to April) than the other half of the year (57% vs 43%, $p = 0.05$). Dissections were significantly more likely to occur during the daytime hours, with 65% of dissections occurring from 6 a.m. to 6 p.m. ($p = 0.001$). Such circadian variation exhibited a gender difference, since men were more likely to dissect during the daytime hours (6 a.m. to 6 p.m.) than women (74% vs 51%, $p = 0.01$) (Siddiqi et al, 2017).

Circaseptan (weekly)

A few studies have investigated this temporal aspect. Sumiyoshi (2002) found a small peak on Monday and a trough on Thursday and Friday, but the distribution was homogenous as a whole. The IRAD Registry study (Mehta et al, 2002) did not find any significant weekly variation. A weekly pattern, characterized by a decreasing frequency from Monday to Sunday, was shown in over than 4 500 cases in the Emilia-Romagna region of Italy (Manfredini R. et al, 2008). Interestingly, fatal cases showed an opposite trend with a peak on Sunday. Moreover, mortality was found to be higher in cases admitted on weekends compared with weekdays both in the Emilia-Romagna region (Gallerani et al, 2012) and in Italy as a whole country (Gallerani et al, 2013).

Meta-analysis

Our group performed a meta-analysis study on time of aortic aneurysms rupture or dissection (AARD). Forty-two studies (more than 80 000 patients) were included. Results showed a significantly increased incidence of AARD in Winter (RR 1.17), in December (RR 1.14), on Monday (RR 1.21), and in the hours between 6 am and 12 pm (RR 1.59) (Vitale et al, 2015).

STROKE

Circadian (time of day)

Since the late 80's, a number of studies has indicated that the incidence of stroke shows a significant circadian rhythm, characterized by a higher frequency during morning hours (Marler et al, 1989; Marsh et al, 1990; Kelly-Hayes et al, 1996; Gallerani et al, 1996). A comprehensive meta-analysis of 31 separate studies found that

approximately 55% of ischemic strokes, 34% of hemorrhagic strokes, and 50% of TIAs occurred between 6 and 12 AM (Elliott, 1998). As for ischemic stroke, it has been found that the morning preference is independent of patients' age, sex, common risk factors, i.e., smoke, hypertension, diabetes, dyslipidemia, as well of type of stroke (Casetta et al, 2002). The interesting analogy of the temporal window of occurrence of either ischemic and hemorrhagic strokes (Gallerani et al, 1996; Casetta et al, 2002; Gallerani et al, 1994; Casetta et al, 2002), seems to suggest that probably a series of common risk factors are shared by the two entities (Manfredini R. et al, 2005) *(Figure 3)*.

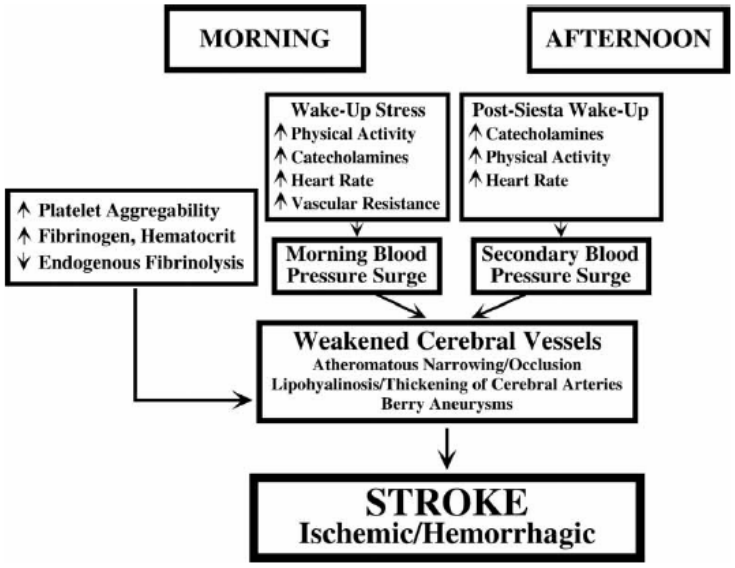

Figure 3. Circadian variation of onset of ischemic and hemorrhagic stroke: possible cluster of triggering or favoring factors. (Manfredini R et al, Chronobiol Int 2005).

Seasonal

Several studies have reported a seasonality in the occurrence of stroke, characterized by a winter and autumn peak for its occurrence (Haberman et al, 1981;

Ricci et al, 1992; Gallerani et al, 1993; Manfredini R. et al, 1997). Interestingly, also the complications of acute carotid surgery exhibit a similar pattern (Coen et al, 2010).

Circaseptan (weekly)

Several studies have indicated that Monday represents a critical day for onset of stroke (Manfredini R. et al, 2001), and this seems to be independent of the presence or not of most common risk factors (Manfredini R. et al, 2009). A recent study by our group on more than 56 000 ischemic strokes admitted to the hospitals of the Emilia-Romagna region of Italy, confirmed that admissions were most frequent on Monday (16.6%) and least frequent on Sunday (12.9%), also with no significant differences between fatal or nonfatal cases (manfredini et al, 2009). Interestingly. Such pattern was found to be exactly the same also for transient ischemic attacks (16.1% vs. 11.6%) (Manfredini R. et al, 2010).

PULMONARY EMBOLISM

Circadian (time of day)

Previous studies reported the existence of a circadian variation also in the occurrence of acute pulmonary embolism (Gallerani et al, 1992), characterized by the same main morning peak observed also for arterial embolism (Manfredini R. et al, 1998).

Seasonal

A seasonal pattern, characterized by an autumnal but especially a winter peak, has been reported both for venous thromboembolism (deep vein thrombosis and pulmonary embolism (Manfredini R. et al, 1994; Boulay et al, 2001; Bilora et al, 2002;

Gallerani et al, 2004; Gallerani et al, 2007; Manfredini R. et al, 2009), although some studies did not confirm this pattern (Stein et al, 2004). A recent metanalysis of the available literature (about 35 000 cases) confirmed the increased incidence of venous thromboembolism in winter, with a relative risk of 1.14 (1.19 in the month of January) (Dentali et al, 2011). Such pattern seems to be independent of risk factors and patients' comorbid conditions (Manfredini R. et al, 2004).

Circaseptan (weekly)

No reports are available dealing with weekly variation of pulmonary embolism, although a higher mortality has been found in patients hospitalized during weekends compared with weekdays (Gallerani et al, 2011, 2018).

VENOUS THROMBOEMBOLISM (VTE)

A systematic review and a meta-analysis, based on seventeen studies (35,000 patients) on VTE, twelve 78ospitali the seasonal variation and 10 studies the monthly variation was performed. Results showed a significantly increased incidence of VTE in winter (RR 1.14), and a significantly increased incidence of VTE in January (RR 1.19) (Dentali et al, 2011).

TAKOTSUBO SYNDROME

Takotsubo cardiomyopathy (TTC) is a unique acute syndrome characterized by transient left ventricular systolic dysfunction in the absence of significant coronary artery disease, occurring mostly in postmenopausal women after emotional and/or physical stress. Interestingly, women and men have distinct cardiovascular reactivity mechanisms for mental stress-induced myocardial ischemia (MSIMI). For women,

stress-induced peripheral vasoconstriction with mental stress, and not increased hemodynamic workload, is associated with MSIMI, whereas for men, it is the opposite (Sullivan et al, 2018).

Terminology of this cardiomyopathy derives from the shape of the left ventricle when imaged during systole, the octopus pot trap (*takotsubo*) of Japanese fishermen. Given the nonspecific symptoms and signs, a high clinical index of suspicion is necessary to detect the disease in different clinical settings and scenarios. Noninvasive multimodality imaging may be useful to distinguish this cardiomyopathy from other acute cardiac and thoracic diseases. Coronary angiography remains, however, mandatory to differentiate TTC from acute coronary syndromes. (Bossone et al, 2013). The clinical expert consensus document (part I) recently summarized the current state of knowledge on clinical presentation and characteristics of TTS and agrees on controversies surrounding TTS such as nomenclature, different TTS types, role of coronary artery disease, and etiology. Moreover, it has proposed new diagnostic criteria based on current knowledge to improve diagnostic accuracy. (Ghadri et al, 2018) In the last years, our group gave substantial contribution to the study of Takotsubo syndrome. On one hand, several studies yielded specific temporal patterns of onset, eg, circadian, seasonal, and weekly (Bossone et al, 2011, 2013; Citro et al, 2009; De Giorgi et al, 2014, 2015; Fabbian et al, 2015, Manfredini R. et al, 2009, 2010, 2011, 2013, 2014, 2018). On the other, chronobiology officially entered with a dedicated paragraph into the ESC Expert Document (Ghadri et al, 2018).

Circadian (time of day)

Two studies reported a morning preference for TTC onset (Kurisu et al, 2007; Citro et al, 2009), but another did not find significant variations (Abdulla et al, 2007). Kurisu et al (2007) in Japan, found a non-significant trend for TTC occurrence during the morning and afternoon 6-hour periods (6AM-noon and 12 PM-6 PM, respectively). However, when comparing daytime (6 AM – 6 PM) vs nighttime (6 PM – 6 AM), the distribution was statistically different (73% vs 27%, p=0.004). Citro et al (2009), in a series of patients in Italy, confirmed a higher frequency of events in the morning and fewest at night (40.5% vs. 10.2%, p=0.021). Abdulla et al (2007), did not find significant differences in the timing of onset of symptom in 35 subjects in Australia, by splitting the day into three 8-hour periods (morning 6 AM-2 PM, afternoon 2 PM-10 PM, night 10 PM-6AM). Sharkey et al (2012) reported for TTC a nonuniform distribution with a distinctive afternoon peak from 12 noon to 4 PM, and a nadir at 12 to 4 AM ($p<0.001$) *(Figure 4)*.

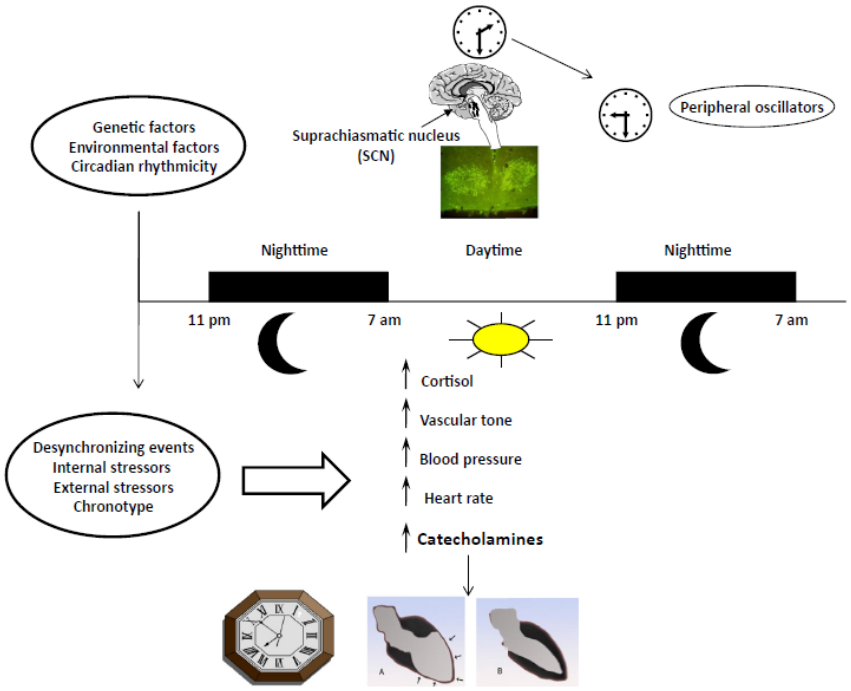

Figure 4. Morning preference for Takotsubo cardiomyopathy: hypothesis for a circadian model. (Manfredini R. et al, Stress: Fink G (ed) Neuroendocrinology and Neurobiology, Academic Press, 2017).

Seasonal

Abdulla et al (2007) found a slight, statistically not significant, summer preference. Hertting et al (2006), found that one half of patients had an event during summer months. A significant summer preference was confirmed also from studies in the United States, Rhode Island Registry (Regnante et al, 2010) and in a multicenter series in Italy (Manfredini R. et al, 2004). Different results were reported by Eshtehardi et al (2009) in Switzerland (peak in winter, p=0.03), Sharkey et al in the USA (2012) (peak in December), and Mansecal et al (2010) in France (peak in April). Other studies conducted in the United States (Summers et al, 2010), and in Italy (Parodi et al, 2011) did not confirm the preference of a temporal pattern (not significant peaks in August and January, and spring and summer, respectively). Results from the United States

Nationwide Inpatients Sample database confirmed a peak in July (and a trough in January) (Deshmukh et al, 2012).

Circaseptan (weekly)

Manfredini R. et al (2010) first reported a peak on Monday, later confirmed by Song et al (2013). On the other hand, Parodi et al (2011) did not found significant differences in their population. Sharkey et al (2012) found highest frequency of events on Tuesday and lowest on Sunday, but events were uniformly distributed throughout the week (p=0.18).

THE 'MISTERY' OF WEEKEND

A series of studies has reported a so called "weekend (WE) effect" for hospital admissions, referring to a higher risk for mortality for patients admitted on WE (Saturday to Sunday) than for those admitted on weekdays (WD) (Manfredini R. et al, 2017). More than fifteen years ago, Bell & Redelmeier reported an association between WE admissions and significantly higher in-hospital mortality (IHM) rates for some acute diseases (Bell & Redelmaier, 2001). Many factors contribute to this weekend effect (Fedeli et al, 2017), and several explanations have been put forward. They include:

Suboptimal standard and quality of care. Reduction in staffing and resources and presence of less experienced doctors and nurses (Bell et al, 2013). It has been reported that the risk of death for stroke was higher in the case of a low nurse/bed ratio, and independent of rounds by specialist physicians (Bray et al, 2014).

Different case-mix of diseases. More patients are admitted on WD than at WE, and a higher proportion of patients are admitted during WE through the ED, therefore patients admitted at WE could have increased illness severity and altered case mix (Mikulich et al, 2011). Nanchal et al. (2012) reported a 19% increased risk of death in patients admitted on WE for pulmonary embolism, and the hypothesis of a higher severity could be strengthened by the existence of several parameters of severity, such as need for mechanical ventilation, thrombolytic therapy use, and use of vasopressors (Manfredini et al, 2013).

Disease specific studies. WE effect seems to be related to mortality especially in conditions at high risk of death immediately following the onset of acute disease, in which timely interventions could significantly impact survival. For example, a nationwide US study reported a reduction over time of the WE effect for myocardial infarction, with a progressive reduction over time from years 2000–2002 (OR 1.10) and 2003–2005 (OR 1.11), and a disappearance in 2006–2008 (OR 1.02, not significant) (Kumar et al, 2015).

Walker and colleagues recently provided novel and interesting evidence with their study on 503,938 emergency admissions to four Oxford University National Health Service hospitals, UK 2006–2014, with a primary outcome of evaluating in- or out-of-hospital death within 30 days of admission (Walker et al, 2017). They designed several models, considering the effect of adjusting for 15 common haematology and biochemistry test results (haemoglobin, platelets, lymphocytes, neutrophils, eosinophils, monocytes, C-reactive protein, urea, bilirubin, creatinine, albumin, alanine aminotransferase, alkaline phosphatase, sodium, and potassium) using the closest result to admission time within two days before or after admission. Results showed that 4.7%

of WD and 5.1% of WE emergency admissions, respectively, died within 30 days (P<0.0001). Moreover, 9,347 patients underwent 9,707 emergency admissions on public holidays of whom 5.8% died within 30 days (P<0.0001 *vs.* weekday). The analyzed 15 routine haematology and biochemistry test results were highly prognostic for mortality, since adjustment for test results and standard patient features explained 33% of the excess mortality associated with emergency admission on Saturdays compared with Wednesdays, 52% on Sundays, and 87% on public holidays. Interestingly, despite previous suggestions of the responsibility role played by reduced staffing for excess mortality risk associated with WE admissions, this study did not find any association with mortality and staffing levels and service provision relative to each specific day of the week. Moreover, Walker and colleagues found that mortality risk differed significantly by admission hour, being lowest at 8–11 AM. Authors reported that circadian variation in mortality risk was as great as (if not greater than) differences in risk between WE and WD. Adding admission hour significantly improve both the statistical models used, and excess mortality risk associated with WE admissions was somewhat greater between 8 AM and midnight, particularly between 11 AM and 3 PM, and somewhat less for admissions from midnight to 8 AM (Walker et al, 2017). Myocardial infarction represents a disease in which the weekend effect is more clearly associated with factors acting after hospital admission. A systematic review found that weekend and off-hour presentations were associated with significantly increased short-term mortality (Sorita et al, 2014). Such increased risk paralleled longer door-to-balloon times among patients with ST-elevation myocardial infarction.

We assessed the association between weekday (WD) or weekend (WE) admission and mortality for 265 035 patients hospitalized with acute PE (Italian Health

Ministry database 2001 to 2014). Admissions for PE were more frequent on Mondays (15.8%) and less frequent on Saturdays (12.2%) and Sundays (12.3%). Patients admitted on WE were on average 1 year older, presented more frequently with respiratory failure, and had more common comorbidities. After adjustment for age, gender, comorbidities, and presence of respiratory failure, in-hospital mortality for patients admitted on WE was greater (OR 1.15; $p < 0.001$) (Gallerani et al, 2018).

GENDER PERSPECTIVES

Women are often excluded/underrepresented in clinical trials; sometimes, the number of men/women participants or separate analysis by sex are not reported. A robust body of evidence demonstrated that several life-threatening acute cardiovascular diseases, for example, acute myocardial infarction, sudden cardiac death, cardiac arrest, rupture or dissection of aortic aneurysms, and stroke, exhibit a circadian periodicity with a morning peak. An analysis of 20 years of chronobiologic studies (44% of them, accounting for 85% of total cases, with separate analysis by sex) confirmed that morning hours are a critical time of onset of acute cardiovascular diseases in men and women (Manfredini R. et al, 2017) *(Figure 5) (Table 3)*.

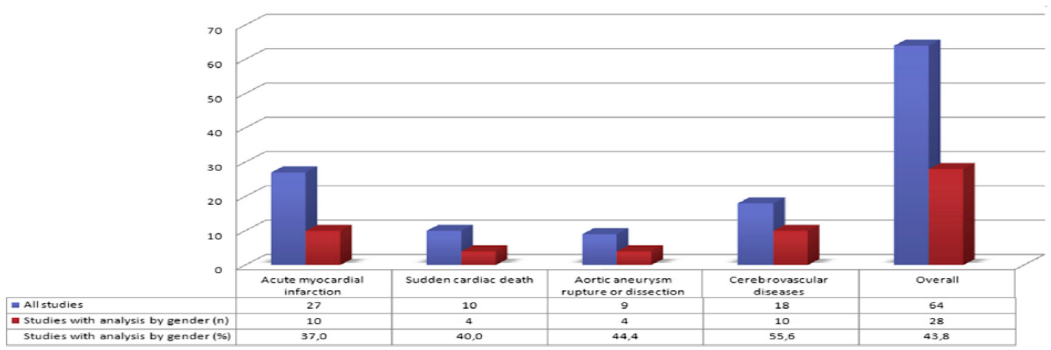

Figure 5. Comprehensive review of worldwide chronobiologic studies (1996-2015): overall studies and number (and percentage) of studies with separate analysys by sex. (Manfredini R. et al, Heart Fail Clin 2017).

Disease	Studies (n)	Cases (n)	M/W (n)	Studies with Analysis by Sex (n/%)	Cases in Studies with Analysis by Sex (n)	Percent of Cases in Studies with Analysis by Sex/Overall (%)	M/W in Studies with Analysis by Sex (n)	M/W in Studies with Analysis by Sex (%)
AMI	27	549,568	340,168/209,400	12/44.4	522,669	95.1	320,983/20,1093	61.4/38.6
SCD	10	71,094	40,502/30,592	4/40.0	6956	9.8	4921/2035	70.7/29.3
AARD	9	2328	1601/727	4/44.4	1367	58.7	978/389	71.5/28.5
CD	18	28,117	15,181/12,936	10/55.6	21,669	77.1	11,455/10,214	52.9/47.1
Overall	64	651,107	382,998/253,655	28/43.8	552,142	84.8	338,337/213,805	61.3/38.7

Abbreviations: AARD, aortic aneurysm rupture or dissection; AMI, acute myocardial infarction; CD, cerebrovascular diseases; M/W, men/women; SCD, sudden cardiac death.

Table 3. Studies on circadian periodicity of acute cardiovascular disease (1996-2015) and men/women distribution (overall) (Manfredini R. et al, Heart Fail Clin 2017)

PILLS OF CHRONOTHERAPY

It is possible that a given medication may be therapeutic and safe when administered at some biological time, but subtherapeutic or poorly tolerated at another time (Manfredini R. et al, 2013). CV disease has been a first laboratory for chronotherapy (Manfredini R. et al, 1994). Adequate evidence seems to support that at least ACE-inhibitors or angiotensin receptor blockers, simvastatin, corticosteroids (slow-release formulation) for arthritic patients, and ranitidine should preferably be administered in the evening. Morning dosing could be better for proton pump inhibitors, whereas time of administration is not crucial for asthma inhalation drugs (De Giorgi et al, 2013). Studies are available for other drugs, but not so strong enough to draw definite conclusions. For now, we need prospective intervention trials specifically designed to investigate the long-term effects of a temporal approach to medical therapy. However, since switching to morning-evening administration or vice versa is simple and inexpensive, in some cases it could be considered, remembering that, in any case, adherence remains the crucial point (Manfredini R. & Fabbian, 2017).

MARITAL STATUS

More than two decades ago, Gordon et al. (1995) observed that, in hospitalized subjects, marital status (MS) represented independent risk factor for some important

outcomes in hospitalized subjects. Admission severity of illness was higher in unmarried than married patients, and moderate or high severity was significantly different from unmarried and married patients (40 vs. 32%, respectively), Moreover, Kaplan et al (2006) showed that current marriage was associated with longer survival, and the death rate for unmarried subjects was significantly higher than for married subjects, independently of demographic and socioeconomic characteristics. Although the effect was significant for all categories of unmarried persons, it was greatest for those who had never married, and significantly stronger for men than for women (Kaplan et al, 2006). A comprehensive review and meta-analysis of 53 studies, including more than 250 000 subjects showed that the overall relative risk (RR) for married vs non-married individuals (including widowed, divorced/separated, and never married) was 0.88, independent of gender and geographical area (Manzoli et al, 2007). In particular, compared with married individuals, the widowed, divorced/separated and never married persons had increased RRs of death (1.11, 1.16, and 1.11, respectively) (Manzoli et al, 2007).

Recently, our group aimed to evaluate the available evidence in the literature on the association between MS and either cardiovascular (CV) diseases and CV risk factors (Manfredini R. et al, 2017). We performed search across the PubMed database of all papers including the term ‘marital status’ in their title. All papers were then manually checked for the presence of the following terms or topic: CV diseases, acute myocardial infarction, acute coronary syndrome, coronary artery disease, cardiac arrest, heart failure, heart diseases, and CV mortality. Moreover, other search terms were: CV risk factors, hypertension, cholesterol, obesity, smoking, alcohol, fitness and/or physical activity, and health. Systematic reviews, meta-analyses, controlled trials, cohort studies

and case-control studies were potentially considered pertinent for inclusion. Case-reports, comments, discussion letters, abstracts of scientific conferences, articles in other than English language, and conference abstracts or proceedings were excluded. In total, 817 references containing the title words "marital status" were found. After elimination of papers dealing with other topics, 70 records were considered pertinent. Twenty-two were further eliminated for several reasons, i.e., old papers, no abstract, full text unavailable, other than English language, comments, letters. Out of the remaining 48 papers, 13 were suitable for the discussion, and 35 (accounting for 1 245 967 subjects) were included *(Figure 6)*.

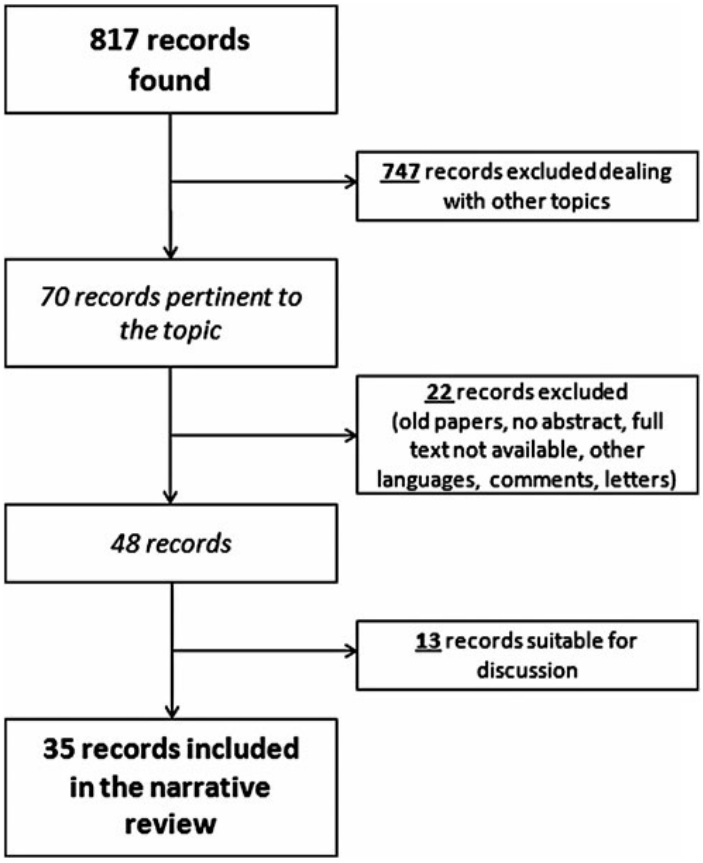

Figure 6. Flowchar of the inclusion procedure. Marital status, cardiovascular disease and cardiovascular risk factors (Manfredini R. et al, J Womens Health 2017)

The results confirmed the importance of MS for CV diseases and CV risk factors. Most studies showed better outcomes for married persons, and men who were single generally had the poorest results. It is possible that persons who are married may have lower mortality because of protective effects of marriage or even selection of healthy individuals into marriage. It is likely that people who have a spouse may exhibit higher compliance with medical controls, medications, and screening programs. Marital status could be associated also with biological, behavioral, and also psychological factors. Many factors could be related, in general, to being married vs loneliness: healthier meals, better sleep, less stress, financial benefits, better mood. The single individuals who never married deserve further studies on their right as they are a self-selected group likely with their own special needs.

PERIPHERAL ARTERIAL DISEASE & GENDER

Epidemiology

There are a wide series of sex differences for PAD, including epidemiology and risk profile, clinical presentation, management, and outcome (Srivaratharajah & Abramson, 2018).

Although peripheral arterial disease (PAD) is the third most common manifestation of CV disease, following coronary artery disease (CAD) and stroke, it remains underdiagnosed and under-treated in women (Jelani et al, 2018). Numbers are impressive. As of 2010, more than 200 million people worldwide are affected by PAD, and this represents a 29% increased prevalence in low-middle income countries and 13% increase in high income countries (Fowkes et al, 2013; Sampson et al, 2014). Around 20–30% of women aged 70 years or older are affected by PAD (Criqui et al,

1985), maybe due to the loss of the vascular protective effects of estrogen. However, diagnosis is not always easy, since the majority of PAD patients do not have typical claudication (Hirsch et al, 2001), and women have higher rates of asymptomatic/subclinical disease and the majority have atypical symptoms (McDermott et al, 2003). A recent French study on near 6,000 patients with PAD (mean age 70.8 years, 68.1% males), reported cumulative mortality rates of 13.2% at 1 year and 19.4% at 2 years (versus 3.2% and 6.5% in controls). Cumulative incidence rates of death and major cardiovascular events (AMI and ischemic stroke) were 15.7% at 1 year and 22.9% at 2 years vs 3.9% and 7.8% in controls ($p < 0.05$) (Bura Riviere et al, 2018).

Despite all these considerations, women continue to have very limited enrollment in studies on PAD. In their systematic review of cardiovascular trials, collecting more than 400,000 patients, Vyas et al (2013) found that women were only 27% of total population. The importance of this topic has been recognized by the American Heart Association, which published a "call to action" article on women with PAD (Hirsch et al, 2012).

Risk factors

The common risk factors for PAD are similar for men and women, and include age, smoking, hypertension, dyslipidemia, and diabetes mellitus. Diabetes, particularly in patients with comorbid risk factors, confers increased odds of PAD, even in the absence of coronary heart disease. Thus, patients with DM should be carefully screened for presence of PAD (Wilcox et al, 2018).

Abnormally high ABI represents risk factor. The results from a prospective population based cohort study of 6352 subjects, followed up for 6 years, found that an

abnormally high ABI (≥ 1.4) was independently associated with all-cause mortality (HR = 2.0) and CV mortality (HR = 3.1). In these subjects, female sex, together with age, diabetes, and lower diastolic BP, were independent related factors (Velescu et al, 2017).

Prognosis

PAD is associated with increased risk of CV disease mortality and morbidity, but women with PAD have a two- to fourfold increased risk of cardiovascular mortality and morbidity compared to women without PAD (Higgins & Higgins, 2003), and are more likely to be admitted for AMI, compared to men (Hussain et al, 2016).

Cardiovascular mortality of patients with combined PAD and CAD is twice as high as that in those with either disease alone. It is known that patients with PAD undergoing PCI have a higher incidence of adverse cardiac events such as myocardial infarction or target vessel revascularization. Bryniarski et al (2017) compared the detailed characteristics of culprit and nonculprit plaques between patients with and those without PAD. In culprit lesions, PAD patients had a higher prevalence of lipid-rich plaque, higher lipid index, calcification, macrophage accumulation, and cholesterol crystals. In nonculprit lesions, PAD patients had a higher prevalence of calcification, macrophage accumulation, and cholesterol crystals. Thus, PAD patients show greater coronary plaque vulnerability in both culprit and nonculprit lesions. Thus, a more aggressive risk management is suggested in patients with combined PAD and CAD (Bryniarski et al, 2017).

A secondary analysis of data from the German MONICA/KORA Myocardial Infarction Registry (4307 patients aged 28-74 years) showed that from patients with

PAD (8.9%), 7.3% died within 28-days post-AMI in contrast to 2.9% of patients without PAD. Long-term follow-up found significantly increased (32.4% versus 14.4%) cases of deaths among patients with and without PAD, respectively (Dinser et al, 2018).

Critical limb ischemia (CLI) is a frequent and major vascular problem and can lead to amputation and death despite surgical revascularization. Women have been shown to have 3 to 4% lower revascularization rates for CLI compared with men as well as inferior outcomes. A prospective cohort study on data from the Nationwide Inpatient Sample (2007-2010, 113,631 admissions, 47.8% women) found that revascularization rates were lower in women (31.6% vs. 35.1%, $p < 0.001$). In multivariable analysis, female gender (OR 0.87, $p < 0.001$) and very-low hospital volume (OR 0.21, $p < 0.001$) were both significantly associated with lower rates of revascularization. Women were more likely to be admitted to low-volume hospitals for treatment of CLI, so that they are less likely to undergo revascularization, but had lower rates of major amputation (Scaumeier et al, 2018). Moreover, women with PAD are at a higher risk of 12-month repeat intervention than men (Jeon-Slaughter et al, 2017).

Endovascular treatment for PAD. Data was obtained from National Inpatient Sample showed that females presented late with more comorbidities and underwent more emergent/urgent procedures. There was no difference in in-hospital mortality between males and females in matched cohorts (2.3% vs 2.4%). Acute renal failure, gangrene, infection, and composite of all complications were higher in males. Only blood transfusion was noted higher in females (Doshi et al, 2017). Again, Ramkumar et al (2018) reported that women presented at an older age (69 vs. 67 years), were less often current or former smokers (72% vs. 85%), more frequently underwent treatment for rest pain (11% in men vs. 16% in women), claudication (59% in men vs. 53% in

women) or tissue loss (28% in men vs. 27% in women). Treatment modality did not differ by sex but was associated with disease severity and lesion location (Ramkumar et al, 2018).

Lower extremity bypass (LEB). Marital status may affect outcomes through factors related to health risk behaviors, adherence, and access to care. Compared with unmarried patients, married patients were older at the time of their bypass procedure (67±11 years vs. 62 ± 11 years; $p = 0.05$). Married patients also had a lower prevalence of female gender (12% vs. 33%; $p = 0.02$). Twenty-four-month primary patency was 66% for married versus 38% for unmarried patients. In a multivariable proportional hazards model adjusting for proximal and distal graft inflow/outflow, medications, gender, age, race, smoking, diabetes, and minimum vein graft diameter, married status was associated with superior primary patency (HR = 0.33; $p = 0.05$) (Lagregren et al, 2017).

A recent study analyzed 40 studies to evaluate gender differences in post-intervention outcomes (Wang et al. 2017). Short-term outcomes: women had significantly increased risks of 30-day mortality (OR 1.31), amputation (OR 1.07), early graft thrombosis (OR 1.56), embolization (OR 1.64, incisional site complications (OR 1.56), cardiac events (OR 1.21), stroke (OR 1.35), and pulmonary complication (OR, 1.07). No significant differences were found between women and men for short-term reinterventions and renal complications. Long-term outcomes: no significant differences between women and men, with similar rates of cumulative survival, primary patency, secondary patency, and limb salvage. However, in the open surgery subgroup, women had significantly reduced survival compared with men (HR 1.21) (Wang et al. 2017).

Readmissions

Hospital readmissions are associated not only with increased mortality, morbidity, and costs. Moreover, with current health-care dispositions, readmissions are exposed to financial and administrative penalties, and females are more prone to readmissions (Fabbian et al, 2015; De Giorgi et al, 2016). In particular, vascular surgery patients may have higher than average readmission rates. Approximately 1 in 5 patients hospitalized for CLI and undergoing revascularization is readmitted within 30 days. The most common causes include infections (23.5%), persistent or recurrent manifestations of peripheral artery disease (22.2%), cardiac conditions (11.4%), procedural complications (11.0%), and endocrine issues (5.7%). Risk of readmission is influenced by CLI presentation, patient demographics, comorbidities, and in-hospital complications, but not by the mode of revascularization (Kolte et al, 2017). Based on data from the US Nationwide Readmission Database, a study on all patients admitted for claudication who underwent percutaneous transluminal angioplasty, peripheral bypass, or aortofemoral bypass (92,769 patients admitted for peripheral vascular disease, 33,055 with claudication and 59,714 with CLI) found that the 30-day readmission/any readmission rate was 8.97%/21.49% and 19.26%/40.36%, for claudication and CLI, respectively (Martinez et al, 2018). Significant differences were found for claudication and CLI, respectively, on initial cost of admission, readmission costs, LOS (4 days vs. 9 days, $p < 0.001$), days to readmission (73 days vs. 59 days, $p < 0.001$), mortality during initial admission (256 vs. 1,363, $p < 0.001$), and mortality during any admission (538 vs. 3,838, $p < 0.001$). Female sex, together with claudication, CLI, angioplasty, peripheral bypass, aortofemoral bypass, age >65,

Charlson Comorbidity Index, and LOS were significant predictors of 30-day and overall readmissions at varying degrees (Martinez et al, 2018).

Quality of life

PAD is associated with poor health status, including symptoms, functioning, and quality of life (QOL). The Patient-centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease: Investigating Trajectories (PORTRAIT) study has investigated patients with new or worsening PAD symptoms. As compared with men, women were less often Caucasian, married and employed, and more often lacking health insurance, living alone (36.2% vs 23.6%), had depression and avoided care due to cost (17.0% vs. 12.3%). Women and men were of a similar age and education level, and had similar ABI values (0.7 ± 0.2). Female sex was independently associated with lower scores of Peripheral Artery Questionnaire (PAQ) on all domains (physical functioning adjusted mean difference; social functioning adjusted mean difference; QOL adjusted mean difference). However, despite similar ABIs, women presenting with symptoms of PAD had poorer PAD-specific functioning as compared with men, impacting all major health status domains, independent of socio-economic and clinical characteristics (Roumia et al, 2017). Also, a study on PAD patients and intermittent claudication (IC) from the United States, the Netherlands and Australia showed that patient characteristics independently associated with poorer health status were female sex, age, not being married, economic burden, difficulty getting care, chronic lung disease, back pain, bilateral vs unilateral PAD, intermittent claudication severity, and lack of prior participation in an exercise program (Noyes et al, 2018).

Health expenditure

Adjusted for age, gender, and race, individuals with a diagnosis of PAD had significantly higher average annual health care-related expenditures compared with the US adult population as a whole. Average annual expenditures per individual for patients with PAD were $11,553 compared with only $4219 for those without. Expenditures were driven by increased prescription medication expenditures as well as by expenditures for inpatient care, outpatient hospital-based care, and outpatient office-based care. Individuals with PAD had significantly higher out-of-pocket (OOP) prescription medication expenditures ($386 vs $192, which varied by insurance type (Scully et al, 2018).

REHABILITATION FOR CARDIOVASCULAR DISEASES? A MISSED OPPORTUNITY FOR WOMEN?

Cardiac rehabilitation (CR) provides comprehensive secondary prevention services and improves outcomes among patients with CHD, systolic HF, and other cardiac indications. Worldwide, cardiac rehabilitation services are underutilized. Underutilization is more common among women than in men (Bittner, 2018).

Previous consolidated data state that if women are fortunate enough to be referred to CR, they do not fare as well as men. They typically have very low attendance rates, and report difficulty completing the recommended program due to their social roles of caregiver or of household employment responsibilities (McSweeney et al, 2001; Beckie et al, 2011; Colbert et al, 2014; Menezes et al, 2014; Beckie et al, 2014), Other barriers that may account for the disparity among women and minorities related to CR attendance and completion include lack of awareness among women about their IHD risk, low education level, psychological stress, financial and/or language barriers, cultural differences, geographic inaccessibility, lack of transportation, physical deconditioning, and lack of significant social support system (McSweeney et al, 2001; Beckie et al, 2011; Colbert et al, 2014; Menezes et al, 2014; Beckie et al, 2014). It is likely that people who have a spouse may exhibit higher compliance with medical controls, medications, and screening programs. For example, the attendance at outpatients CR programs was significantly higher for married/partnered subjects (OR=1.72) (Molloy et al, 2008). Completion rates for women are significantly lower than their male counterparts (50.1% vs 60.4%, $p<0.0001$) and minorities have decreased completion rates as compared to whites (Colbert et al, 2014; Menezes et al, 2014). Beckie et al (2014) compared younger women < 55 to older women > 55 enrolled in cardiac rehabilitation, and found that women who did not complete cardiac rehabilitation were significantly younger with more risk factors for IHD and increased

levels of anxiety and depression. Although there are mixed results regarding who benefits the most from completion of cardiac rehabilitation, all studies conclude that women benefit from attendance, regardless of age. For instance, one study found women who complete cardiac rehabilitation experienced the highest reduction in mortality (HR 0.36) with a relative benefit higher than men (HR 0.51) (Colbert 2014). Therefore, women with known IHD, regardless of age or race, benefit from referral to and completion of a cardiac rehabilitation program. Interventions need to be developed that address the social constraints that prevent many women from benefitting from cardiac rehabilitation.

Very recently, CR referrals of women has been more investigated. To determine whether there are gender differences in the factors that predict attendance at the initial CR baseline assessment (CR engagement) after referral, Galdas et al (2018) analysed 95638 patients referred to CR following a cardiovascular diagnosis/treatment. The authors investigated 18 factors considered important predictors of CR participation in previous research, grouped into four categories: sociodemographic factors, cardiac risk factors, patient medical status and service-level factors. There were no important differences in the factors that predict the likelihood of CR engagement in men and women, but the extremely important determinant of engagement in both men and women was receiving an invitation to attend an assessment session. From data on 48993 CAD patients from 365 hospitals across the United States, only 40% of eligible patients received CR referrals. CR referral was associated with 40% lower 3-year all-cause mortality. Females were 12% less likely to receive this procedure compared with males. Women who received CR referral at hospital discharge had significantly lower mortality compared with those who did not (OR 0.61) (Li et al, 2018). Evidence on gender-

specific, individually tailored secondary prevention by CR services for women with heart disease is very limited. As a matter of fact, women are less likely to participate in rehabilitation programs, so increasing their risk of further cardiac events. Rao et al (2018) reviewed the available evidence, and even after searching through four databases, identified only three RCTs including 725 women. Of these, one third (one study) reported significant improvements for outcomes, including also items of general and mental health, and quality of life. Kim et al (2018) investigated the existence of gender differences after 9 months of home-based CR program in post-PCI patients, and did not show significant difference in terms of dropout rate between men and women. However, there was an increase in HDL-C levels and an improvement in cardiorespiratory endurance, strength, and agility in men, whereas no significant difference in most risk factors and fitness variables was found in women. Low et al (2018) investigated whether a CV program tailored to the specific needs of women could lead to improved outcomes. They randomised 100 female patients to receive cardiology follow-up with the conventional sex-neutral cardiac programme (control), or the sex-tailored Women's Heart Health Programme (intervention). The primary outcome was CV risk factor improvement at 1 year. Secondary outcomes included CV event rates, quality of life scores, and self-reported improvement in knowledge, attitudes, intentions and practices. Patients in intervention group had better control of diabetes mellitus (lower HbA1c and BMI) at 1 year, but there was no significant difference in BP or lipid control. Overall, there was a trend towards better risk factor control, 31.6% of intervention group versus 26.5% of control group achieved improvement in at least 1 CV risk factor control to target range. There was no

significant difference in incidence of CV events, quality of life, or domains in knowledge, attitudes, intention and practices (Low et al, 2018).

VASCULAR REHABILITATION: A RIDE THROUGH FIFTEEN-YEARS STUDIES

Claudication is typical of second-stage PAD, which affects 6% of the US population aged 55 and older (Weitz et al, 1996). Intermittent claudication restricts activity and mobility considerably affecting the health-related quality of life (Dumville et al, 2004; McDermott et al, 2001), therefore the primary treatment goal in these patients is to improve their deambulatory function and quality of life (Lane et al, 2017).

The proven effectiveness of physical exercise in reducing this functional handicap (Leng et al, 2000; Dormandy & Rutherford, 2000; Stewart et al, 2002) has opened the way for developing efficacious tests and methods that can be used in designing optimal rehabilitation programs.

According to the TASC guidelines (Norgren et al, 2007), in patients with claudication, the clinical benefits of a supervised exercise program in improving exercise performance and community-based walking ability are supported by a considerable body of evidence. The Recommendation 14 dealing with exercise therapy in intermittent claudication, reports that:

● *Supervised exercise should be made available as part of the initial treatment for all patients with peripheral arterial disease [A - grade of recommendation according to US Agency for Health Care Policy and Research].*

● *The most effective programs employ treadmill or track walking that is of sufficient intensity to bring on claudication, followed by rest, over the course of a 30–60 minute session. Exercise sessions are typically conducted three times a week for 3 months [A - grade of recommendation according to US Agency for Health Care Policy and Research].*

A recent Cochrane (Lane et al, 2017) has confirmed the effectiveness of supervised programs versus home based programs, where exercise is provided under the supervision of physical therapist or other medically trained personnel. However, widespread implementation of supervised exercise programs is limited due to a combination of factors including an insufficient number of available facilities in the patients' area, issues of reimbursement, awareness, and motivation (Norgren et al, 2007; Lane et al, 2017) as well the presence of comorbidities which may contraindicate this type of intervention (Norgren et al, 2007).

If unstructured community- or home-based walking programs based on general recommendations to walk more are considered not efficacious (Gerhard-Herman et al, 2017), recent studies have provided strong evidence in support of the community- or home-based approach for patients with PAD (Gerhard-Herman et al, 2017), which may overcome these limitations.

An original approach to structured home-based exercise rehabilitation in PAD has been proposed around 20 years ago by Manfredini F and coworkers. The physiological approach to a precise training intensity to be performed at home by patients was based on a new testing protocol (Manfredini F et al, 2002).

For decades, assessment of arteriopathic patients has been performed using tests based on a predetermined time (Montgomery & Gardner, 1998) or on determination of the critical distance to pain, known as 'pain-free walking distance'. This parameter was obtained either through single-stage or progressive protocols on the treadmill. The progressive method appears to be more appropriate for evaluating arteriopathic patients, since it implies a gradual increase in metabolic demand (Gardner et al, 2008).

Fabio Manfredini et al. proposed a patient evaluation on the ground (Manfredini F et al, 2002), and then on a treadmill (Manfredini et al, 2004) based on small speed increments that would eventually cause the onset of the typical cramping pain. The authors aimed to define the functional handicap by a precise individual critical speed, called the pain threshold speed (PTS), rather than by a less specific distance to the onset of pain, attained by walking at a fixed speed. Painful cramping occurs at a walking speed that differs from patient to patient and seems to be related primarily to the degree of occlusive pathology and the functionality of the collateral circulation. Unlike other available methods, PTS may represent a useful tool for measuring the outcome of rehabilitation. The novel finding of this study was the demonstration that claudication can be evaluated by means of an individual critical speed at the onset of pain, rather than by distance covered at a predetermined speed. The new test offered a precise indication of the functional handicap of each patient, as PTS was always determined. The low initial walking speed and very small speed increments made it possible to synchronize the haemodynamic supply with the metabolic requirements of the patient, thereby preventing the early activation of anaerobic glycolysis. The new test was also shown to be repeatable and independent of protocol modifications. In patients who underwent two tests over a short period of time, the reported onset of claudication pain was repeatable. In fact, it occurred at the same walking speed and the same level of cardiovascular effort (as indicated by heart rate), independent of the degree of pathology. Thus, this test can be used both for assessing claudication and for monitoring functional improvements during rehabilitation (e.g., higher walking speeds attained). PTS and corresponding heart rates, when not modified by a specific pharmacological

therapy, can also be used for evaluating other exercise-induced cardiovascular adaptations, such as reduced heart rate at specific exercise intensities.

A second step was to verify the effectiveness of a 120-day home-based program guided by the pain threshold speed (PTS) (Manfredini F. et al, 2004). A group of patients with stable claudication were measured for ankle pressure (AP), ankle-brachial index (ABI), PTS, maximal speed (Smax) on treadmill. Then, they were prescribed daily walking sessions at a speed 20-30% below PTS, and determination of training speed was supervised and facilitated at home. The program included a daily record of exercise data and symptoms, an intermediate PTS re-evaluation to adjust the training speed, and the reassessment of all the parameters after 120 days. The final results showed dramatic improvements of functional parameters. Overall patients showed a reduction of systemic BP (151.3+/-14.3 to 147.6+/-18.3 mmHg; 77.1 +/-9.1 to 72.4+/-8, p=0.008) while AP did not. ABI increased from 0.65+/-0.13 to 0.71+/- 0.18 (p=0.01). PTS and Smax rose from 3.2+/-1.1 to 4.2+/-1.5 km/h (p=0.0001) and from 3.9+/-1.3 to 4.6+/-1.3 km/h (p=0.0001), respectively. According to their compliance, patients were subdivided into 3 groups: 1) trained (T): exercise at the prescribed speed, 2) free-walkers (FW): walking speed markedly below PTS and 3) untrained (U): incomplete program compliance. T group showed symptom reduction up to pain disappearance. The ABI change (0.72+/-0.09 to 0.82+/- 0.16, $p<0.02$) was correlated to AP increase ($r= 0.879$). PTS and Smax rose from 3.6+/-1.1 to 5.4+/-0.8 km/h ($p<0.02$) and from 4.7+/-1.2 to 5.7+/-0.7 ($p<0.02$), respectively. FW showed improvement of all parameters, and U a better walking efficiency (Manfredini F. et al, 2004).

A further step was to evaluate the effects on walking ability and hemodynamic parameters of a novel approach to home-based rehabilitation for PAD patients, the test

in –train out program (Ti-To), compared with the traditional home-based free walking exercise (Tr-E) (Manfredini F. et al, 2008). A total of 143 patients with claudication (117 men, average age 68+/-10 years), were included in a Ti-To (n=83) or Tr-E program (n=60). Evaluations, which were carried out upon entry and at 1, 2, 3, 4 and 6 months, included: self-reported claudication, walking ability (ie, absolute claudication distance, pain threshold speed), resting/exercise HR, systolic/diastolic brachial pressure (SBP/DBP), AP, and ABI. Ti-To involved 2 daily 10-min home walking sessions at maximal asymptomatic speed and the patient attending monthly check-ups at hospital. Tr-E involved 20-30 min of daily walking at self-selected speeds up to pain tolerance. A total of 126 patients (Ti-To, n=74; Tr-E, n=52) completed the program. Ti-To induced better relief from claudication ($p=0.001$). Functional parameters improved significantly for both groups ($p<0.0001$) with significant intergroup difference for Ti-To ($p<0.0001$). SBP and exercise HR decreased significantly in both groups, with Ti-To improving resting HR ($p=0.0002$), DBP ($p=0.003$), lowest AP worse limb ($p=0.004$) and ABI worse limb ($p=0.0002$). Thus, a Ti-To program had more positive effects on perceived claudication, and functional and hemodynamic parameters than did a Tr-E program (Manfredini F et al, 2008). The method was applied also in a group of dialysis patients. A 6-month exercise program prescribed at the hospital and performed at home improved physical capacity (6MWD: 308 -/+ 105 m, to 351 -/+ 118 m, $p=0.0007$), and HRQL, significantly for bodily pain, physical role and mental health ($p<0.05$), and decreased PDF and recovery time ($p<0.05$). Moreover, patients maintained an active lifestyle after discharge and showed a slow functional decline over a 2-year period (Manfredini F. et al, 2008). The study was the basis to plan and length a large multicenter randomized control trial in dialysis patients (Manfredini F et al, 2017). The group of Fabio

Manfredini (Malagoni et al, 2011) showed also that a Test-in/Train-out program provided favourable patient compliance, Quality of Life (QoL) impact and cost-effectiveness. At discharge, in fact, both SF-36 domains and walking performance significantly increased ($P < 0.0001$). A total of 1,839 in-hospital check-ups (7.36 /patient) were performed. Direct and indirect costs represented 93% and 7% of the total costs, respectively. The average costs of a visit and of a therapy cycle were euro 68.93 and euro 507.20, respectively, and the cost to walk an additional meter before stopping was euro 9.22 (Malagoni et al, 2011)

Nicola Lamberti and Fabio Manfredini (2016) compared the effects of the original structured home-based exercise program and revascularization in elderly patients with PAD over a 4-month period (Manfredini F et al, 2016). Participants, affected by moderate to severe claudication were randomized into (1) a test in-train out group (Ti-To) that performed a home-based walking program prescribed and controlled at the hospital or (2) a revascularization group (Rev) that underwent an endovascular and/or surgical procedure. The primary end-point was quality of life as evaluated by the physical component summary (PCS) score of the Medical Outcomes Study Short Form 36 questionnaire. Secondary outcome measures included initial claudication distance (ICD) and absolute claudication distance (ACD), 6-minute walk distance (6MWD) and pain-free walk distance (PFWD), ankle-brachial index (ABI), and cost per walking meter gained. The PCS score significantly increased for both treatments at follow-up without a significant intergroup difference, as did ICD, ACD, and PFWD. The 6MWD and ABI significantly improved in the Rev group, and the Ti-To group exhibited a markedly lower cost per meter gained. The comparable effects of the 2 treatments need to be confirmed in a larger, randomized controlled trial.

Moreover, active mobilization of endothelial progenitor cells (EPCs) was found to be related to the degree of exercise capacity (Manfredini F. et al, 2007). It is known that mobilization of circulating endothelial progenitor cells (EPCs) is increased after acute exercise and training. In a group of hemodialysis patients, multivariate analysis indicated 6 MWD as the most significant independent factor associated with EPC level. EPC percentage value was significantly lower ($p=0.0087$) in the worse (6 MWD < 300 m) than in the better performing group (6 MWD > 300 m) (Manfredini F. et al, 2007). On one hand, haemodialysis patients have few (EPCs and an unfavourable CV outcome. On the other, even a moderate-intensity exercise is capable to selectively increase the number of e-CFU, and the change in e-CFU was directly and significantly correlated to patient-reported training load (Manfredini F. et al, 2008).

Near-infrared spectroscopy

The physiological approach to exercise training in PAD proposed by Manfredini F and colleagues was improved in the last 10 years by the use of the Near-infrared spectroscopy (NIRS). NIRS allows an objective study of muscle metabolism at rest and under dynamic and post-exercise conditions (Mancini et al, 1994; Quaresima et al, 2003; Ferrari et al, 2004), revealing different patterns in early O_2 desaturation or low muscle O_2 extraction in low-performing populations (Wilson et al, 1989; Boushel et al, 2001; Grassi et al, 2007). For PAD patients, whose performance depends on both oxygen availability and its use, NIRS measurements have been proposed (Komiyama et al, 1994; McCully et al, 1994; Egun et al, 2002; Comerota et al, 2003). However, despite the potential usefulness, its routine use remains limited for PAD assessment (Vardi & Nini, 2008). Fabio Manfredini et al. (2009) conducted a study on a group of 76 consecutive patients affected by Fontaine's second-stage PAD with stable

claudication or walking impairment, to determine whether calf deoxygenation detected by NIRS during a progressive level test was quantifiable in a predetermined range of walking speed, whether the score would differ in legs with PAD according to the severity of the disease, and whether the presence of PAD might be recognised among the legs under study. O_2Hb_{AUC}, HHb_{AUC} and dHb_{AUC} differed between diseased and non-diseased legs ($P < 0.0001$) and exhibited different patterns related to PAD severity according to the ABI value. A compensatory heart rate increase was observed in PAD patients. Compared with the ECD positivity for occlusions/stenoses or multiple plaques, only the receiver-operating characteristic (ROC) analysis of dHb_{AUC} (area = 0.932, $P < 0.0001$) showed a sensitivity/specificity of 87.6/93.4 for values ≤−197 (LR + LR−: 13.36/0.13). In conclusion, the dynamic NIRS-based test, quantifying muscle metabolic response according to presence and degree of PAD, allows the evaluation of patients with walking disabilities (Manfredini F. et al, 2009).

The assessment of NIRS parameters, that were found stable without training in healthy and modified in PAD only following structured training, are useful to outline the local exercise-induced adaptations (Manfredini F. et al, 2012). Moreover, it has been successfully utilized also in chronic diseases, such as diabetes (Manfredini F. et al, 2015), multiple sclerosis (Malagoni et al, 2013), and end stage renal disease (Manfredini F. et al, 2015).

HYPOTHESIS AND OBJECTIVES

HYPOTHESIS

Peripheral artery disease, rehabilitation and gender, what do we know now? There is evidence of a well-established benefit following a typical 12-week exercise training program (Hiatt et al, 1990, 1994), although patients with PAD experience a profound limitation in exercise performance, but women have greater lower extremity functional impairment (McDermott et al, 2003), with shorter treadmill distance to intermittent claudication, and shorter maximal treadmill walking distance (McDermott et al, 2003; Gardner, 2002). Lower extremity exercise training has been shown to increase time to claudication, increase distance before claudication, and increase overall walking distance (Parmenter et al, 2011). Several studies found that women with PAD could be less responsive to exercise rehabilitation programs (Gardner et al, 2014), particularly diabetic women. This may partly be due to a greater impairment in calf muscle oxygen saturation during and following exercise (Gardner et al, 2009).

Gardner et al. reported that improvements in absolute walking distance were significantly less for women than men after 1 year of standard exercise therapy. Women also reported less subjective improvement on walking impairment questionnaire domains (Gommans et al, 2015). These differences have been attributed to lower hemoglobin saturation during ambulation (Gardner et al, 2009), poorer leg strength (Gardner et al, 2010), higher inflammation, higher level of oxidative stress, and insulin resistance (Gardner et al, 2009).

OBJETIVES

General objective:

To describe epidemiological, chronobiological and gender-oriented aspect of medical disease

Specific objectives:

- To determine chronobiological and gender differences in cardiovascular disease, considering therapy, intervention procedures and clinical outcomes
- To evaluate gender-related differences in a novel rehabilitation program performed by peripheral arterial disease patients.

DESCRIPTIVE, INFERENTIAL AND GENDER-ORIENTED STUDY

Cardiovascular disease (CVD) remains the primary cause of death in women, with an estimated 44 million women either living with or at risk for heart disease in the United States (Raeisi-Giglou et al, 2018). Resistant hypertension (Smith et al, 2016), poor lipid control due to either lack of social support (Goldstein et al, 2017) or higher discontinuation of lipid-lowering treatment (Rodriguez et al, 2016), and even mild-to-moderate reduced kidney function (Pary et al, 2017) are all novel pieces of the complex puzzle of the gender gap in CVD. Among the wide spectrum of CVD, peripheral artery disease (PAD) is a highly prevalent pathology in the elderly; it is responsible for disability and reduced quality of life (QoL) at the intermediate stages (Norgren et al, 2017). However, the burden of PAD is increasingly striking in young adults (Sampson et al, 2014) and women. Due to the increased disability and mortality associated with PAD in the last 20 years (Sampson et al, 2014), the prevalence in women is equal to that in men (Sampson et al, 2014; Hirsch et al, 2014; Barochiner et al, 2014). Although women with PAD may be more frequently asymptomatic or report atypical symptoms (Barochiner et al, 2014) in the presence of claudication, compared to men, they show lower functioning even with similar hemodynamic severity (Roumia et al, 2017), a higher prevalence of mood disturbance, and bodily pain (Oka et al, 2003).

In terms of treatment, the female **sex** also represents a risk factor that negatively affects vascular intervention outcomes, with a differential impact according to race and intervention type (Vouvouka et al, 2017; Arnaoutakis et al, 2017; Jain et al, 2014; Jackson et al, 2014; Bechter-Hugl et al, 2014; Wang et al, 2017). For the abovementioned reasons, exercise therapy and primary treatment of claudication symptoms (Norgren et al, 2007) might be crucial for the management of walking disabilities among women. Unfortunately, a lower response or adherence to

rehabilitation has been reported in women with various chronic diseases (Arthur et al, 2013; Foy et al, 2001; Anjo et al, 2014) as well as with PAD, possibly due to interest, comorbidities or rehabilitation strategies (Dorenkamp et al, 2016; Gardner et al, 2014; Gommans et al, 2015).

An alternative model of unsupervised rehabilitation based on a structured, home-based, personalized symptom-free prescription of exercise with only a monthly check-up at the hospital (Test in-Train out, Ti-To) has been developed for PAD (Manfredini F. et al, 2008; Malagoni et al, 2011). The model, which aimed to overcome many barriers to exercise, has also been successfully tested in several selected populations, e.g., dialysis patients (Manfredini F. et al, 2017; Torino et al, 2014) and stroke survivors (Malagoni et al, 2016; Lamberti et al, 2017), and obtained significant functional and clinical improvements.

Since this model has sustainable and feasible features such as setting, intensity, and low impact that could be suitable for women, we hypothesized that equal improvements in functional outcomes are attainable after rehabilitation in both women and men. The aim of this study was to evaluate whether sex-based differences in PAD patients with claudication are observable at discharge from the program.

MATERIAL AND METHODS

STUDY DESIGN AND SETTING

This single-center, retrospective cohort study was carried out at the Department of Rehabilitation Medicine of the Azienda Ospedaliero-Universitaria of Ferrara between 2003 and 2016. The study was developed during usual care practice for PAD patients at this hospital. The local Ethics Committee of the University of Ferrara approved the study; no written informed consent was obtained from the patients because they no longer attended the program. This article was written according to the Strengthening the Reporting of Observation Studies in Epidemiology (STROBE) checklist for cohort studies (Vandenbroucke et al, 2007).

PARTICIPANTS

A total of 1164 PAD patients who had attended the Vascular Rehabilitation Program were analyzed for possible inclusion in the study. PAD was previously diagnosed at the Vascular Surgery Unit of the Hospital of Ferrara by clinical and Echo-Color-Doppler examination (Aboyans et al, 2018).

Patients of all ages and sexes were included in the study based on the presence of PAD at stage II of the Leriche-Fontaine classification, with stable claudication for at least 3 months. Patients with conditions contraindicating safe training execution at home (e.g., unstable angina, severe heart failure, major amputation or clinical conditions limiting treadmill testing) were excluded from the analysis. Finally, patients who did not complete the exercise program for any reason were not included in this analysis.

VARIABLES AND COMORBIDITIES AT ENTRY

During the first session of the program, information regarding clinical status and functional impairment was collected by consulting patient medical documents by means of physician examination or by specific tests. Particularly, scholar qualification, cardiovascular risk factors, comorbidities adjunct to PAD (with the Charlson comorbidity index calculation) (Charlson et al, 1994), and location of endovascular lesions were identified. Patients' reported claudication distance was also noted.

OUTCOME MEASURES

Hemodynamic and functional measurements were performed at entry and discharge from the rehabilitation program. All outcome measures were carried out in a temperature-controlled environment in the morning between 8:00 AM and 12:00 PM.

Hemodynamic assessment: After five minutes of rest, patients underwent ankle-brachial index (ABI) measurements according to a standard procedure (Aboyans et al, 2018) using Doppler ultrasound (Stereodop 448.S; Ultrasomed, Milan, Italy) with a 9.3 MHz transducer and a standard blood pressure cuff. The leg with the lowest ABI value was considered the worst leg. The vessels were considered "not compressible" for ABI measurements > 1.31 or for a procedure that had been interrupted due to painful symptoms at a cuff pressure of 300 mmHg with a Doppler signal still present.

FUNCTIONAL MEASUREMENTS

An incremental treadmill test based on level walking (Manfredini F. et al, 2004) was performed by each patient. Participants were familiarized with the motorized treadmill (Technogym RunRace, Cesena, Italy) by walking on it at low speed for one

minute. Use of the handrail to maintain balance was permitted. The testing procedure was explained to the patients who were asked to immediately report the onset, intensity and location of symptoms. After the warm up, the test started at a speed of 1.5 kmh^{-1}, which was progressively increased by 0.1 kmh^{-1} every 10 meters. The speed at the onset of pain (pain threshold speed, PTS), as reported by the patient, was noted. The test finished when the patient was unable to maintain the walking speed imposed for any reason (fatigue, dyspnea and claudication); this walking speed was recorded as the maximal walking speed (Smax).

After a 10-minute resting period, the 6-minute walking test was performed according to the published standard (Montgomery et al, 1998). Patients were instructed to walk back and forth along a 22-m corridor alone at their own pace with the aim of covering as much distance as possible in 6 minutes. The total distance walked (6-minute walking distance, 6MWD) and the pain-free walking distance (PFWD) were recorded.

EXERCISE PROGRAM

The Ti-To structured home-based exercise program (Manfredini F. et al, 2008) was prescribed to all patients. The Ti-To program encompasses a center-based phase and home-based phase with walking exercises. The first phase included circa-monthly visits at the hospital for clinical assessment, ABI and PTS/PFWD measurements, an updated prescription of the home-based walking program, and evaluation of patient adherence to the program. The home-based phase included the execution of exercise at home, preferably indoors (e.g., hallway or heated room). The program was based on two 10-minute walking sessions per day (six days per week) of intermittent walking (1-minute work and 1-minute seated rest) at a prescribed speed. The training speed was

converted into walking cadence (steps/minute) to be maintained at home by a metronome by patients who were specifically educated to walk in rhythm with it. The exercise program was increased weekly from 60 to 84-100 steps/min according to the severity of claudication at baseline. Progressively, the length of each bout was amplified with a work:rest ratio from 1:1 to 2:1 and 3:1, while the entire duration of each session remained constant. Patients were also asked to fill out a daily training log, indicating completion of the exercise, which was certified by a caregiver when possible. The exercise program ended when the patients reached a PFWD normal for their sex and age or when no more improvements in functional parameters were registered in two consecutive tests. Additional details on the exercise program are reported elsewhere (Manfredini et al, 2008; Malagoni et al, 2011).

EVALUATION OF PATIENT ADHERENCE

At discharge, rehabilitation team members evaluated the training diaries of each patient to determine the adherence score (Malagoni et al, 2011). The arbitrary score ranged from 1 (lowest adherence) to 4 (highest) and was calculated by summing the percentage of certified exercise sessions completed ($\geq$ 75% = 3 points; $\geq$ 50% and < 75% = 2 points; $\geq$ 25% and < 50% = 1 point; and < 25% = 0 points) and with respect to the prescribed training speed (yes = 1 point; no = 0 points).

At discharge, the total duration of the program and number of hospital visits were also recorded.

STUDY GROUP DEFINITION AND BIAS MANAGEMENT

The whole population at baseline was divided by sex into WomenPAD (W_{PAD}) and MenPAD (M_{PAD}).

Several potential biases in the interpretation of the study results were foreseeable and mainly related to significant changes in patient clinical status. Nonetheless, considering the hemodynamic and functional outcome measures examined, the main confounding issue was endovascular or surgical lower limb revascularization procedures that have a potential impact on study outcomes. Therefore, all patients who underwent a revascularization procedure during the exercise program were excluded from this analysis.

SAMPLE SIZE CALCULATION

Based on the starting hypothesis, we calculated the power for an equivalence trial. Sample size calculations indicated that 264 participants were required to be 95% certain that the 90% confidence interval (CI) excluded a difference in the change in PFWD greater than the equivalence limit of 20 m, corresponding to the minimal clinically important difference established in this population (Bohannon et al, 2017).

STATISTICAL ANALYSIS

Data are expressed as the mean ± standard deviation or median and 95% Cis (according to the data distribution) or as the percentage frequency (categorical data). Comparisons between W_{PAD} and M_{PAD} patients were made by independent t-test (normally distributed data), the Mann–Whitney test (nonnormally distributed data), or the chi-squared test (categorical data), as appropriate.

Within-group comparisons were performed by paired t-test (normally distributed data) or Wilcoxon rank test (nonnormally distributed data), as appropriate. The between-group comparison was performed with one-way analysis of variance. Within- and between-group differences are expressed as the mean changes and 95% Cis.

A propensity score model was estimated using the 23 variables described in *Table 4.*

	Women (n=*264*)	*Men* (n=*747*)	p
Age (years)	71±10	70±9	0.12
Education, *n* (%)			
Elementary school	195 (74)	538 (72)	0.56
Middle or secondary school	48 (18)	168 (22)	0.09
Degree	21 (8)	41 (6)	0.13
Risk factors, *n* (%)			
Smoking	178 (67)	692 (93)	**<0.001**
Hypertension	196 (74)	572 (77)	0.41
Hyperlipidemia	179 (68)	457 (61)	0.06
Diabetes	79 (30)	273 (37)	**0.049**
Family history for CVD	49 (18)	128 (17)	0.61
Comorbidities, *n* (%)			
Coronary heart disease	73 (28)	335 (45)	**<0.001**
Cerebrovascular disease	18 (7)	96 (13)	**0.007**
Osteoarticular disease	102 (39)	206 (28)	**<0.001**
Rheumatic diseases	30 (11)	26 (4)	**<0.001**
Charlson comorbidity index	6±2	6±2	0.21
Peripheral arterial disease			
Disease duration (years)	5±5	6±7	0.14
Lower limb revascularization	72 (27)	207 (28)	0.87
Self-reported claudication distance (m)	178±144	205±162	0.23
ABI, more affected limb	0.62±0.19	0.62±0.18	0.74
ABI, less affected limb	0.83±0.22	0.85±0.20	1.00
PTS (km/h)	2.3±0.9	3.0±1.1	**<0.001**
Smax (km/h)	2.8±1.1	3.5±1.1	**<0.001**
PFWD (m)	132±95	215±115	**<0.001**
6-minute walking distance (m)	279±73	340±88	**<0.001**

Statistically significant values have been indicated in bold.
ABI, ankle-brachial index; CVD, cardiovascular disease; PFWD, pain-free walking distance; PTS, pain threshold speed; Smax, maximal speed.

Table 4. Baseline characteristics of the patients included in the study

To estimate the propensity score, we used a logistic regression model in which gender (M_{PAD} vs. W_{PAD}) was regressed on the baseline characteristics listed in *Table 4*. Patients were then pooled and sorted in ascending order according to their propensity score. The selection process began from the cases with the lowest score. If patients were M_{PAD} and W_{PAD}, both were selected as a matched pair according to 1:1, 2:2, 3:3, or 4:4 blocks. A patient who did not have a suitable match within the acceptable rank range was excluded.

Statistical analyses were performed with MedCalc Statistical Software version 18.5 (MedCalc Software bvba, Ostend, Belgium).

RESULTS

A total of 1164 PAD patients were considered eligible; 153 were not included in the final analysis because they did not complete the rehabilitation program or because of biases potentially affecting data interpretation. The reasons for exclusion are reported in *Figure 7*. Within the excluded sample of patients, the same proportions of W_{PAD} and M_{PAD} were maintained (W_{PAD} n = 40). Thus, the final study population comprised 1011 PAD patients divided into 264 W_{PAD} and 747 M_{PAD}.

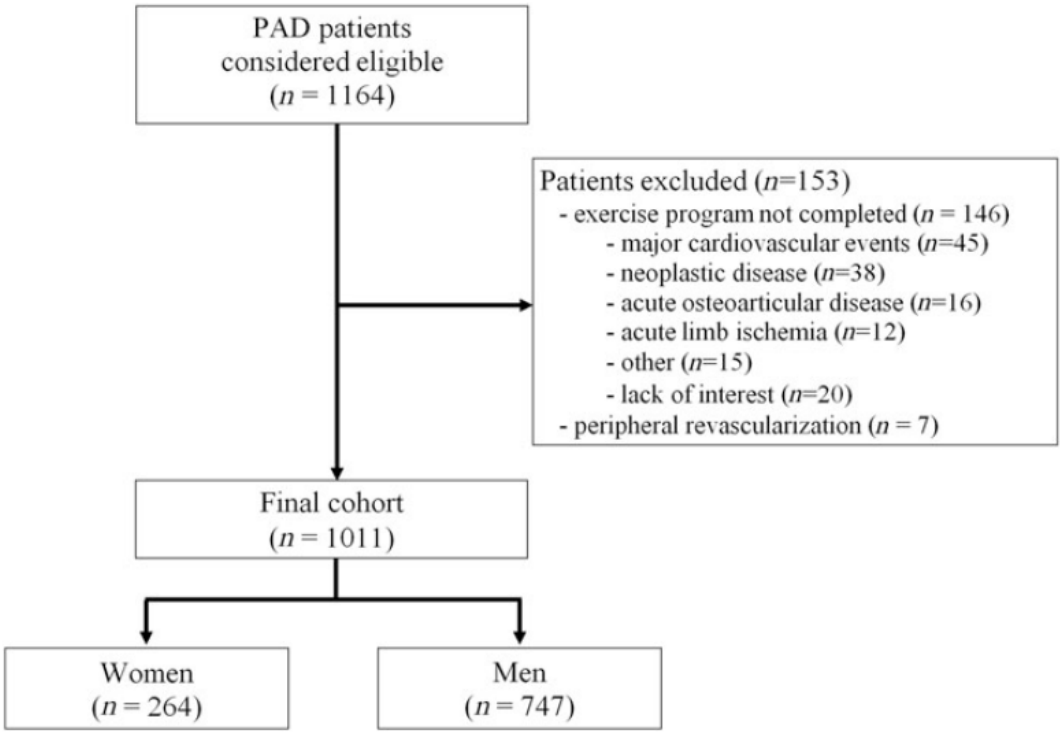

Figure 7. Study flow diagram. Pain-free exercise, peripheral arterial disease and gender

BASELINE GROUP COMPARISON

At baseline, the two groups did not differ in age or educational level. Considering cardiovascular risk factors, a smoking habit (93% vs 67%; $p < 0.001$) and diabetes (37% vs 30%; $p = 0.049$) were more prevalent among M_{PAD}, whereas W_{PAD} were more affected by hyperlipidemia (68% vs 61%; $p = 0.059$) but not significantly.

No differences were observed for hypertension and family history for cardiovascular diseases.

In terms of comorbidities, M_{PAD} presented a higher incidence of coronary heart diseases (45% vs 28%; $p < 0.001$) and cerebrovascular diseases (12% vs 7%; $p = 0.007$). In contrast, W_{PAD} showed more osteoarticular (39% vs 28%; $p < 0.001$) and rheumatic diseases (11% vs 4%; $p < 0.001$). Despite these differences, the Charlson comorbidity index was equal in both groups (6±2; p = n.s.).

Finally, both groups reported a similar duration of claudication symptoms (W_{PAD}: 5±5; M_{PAD}: 6±7; p = n.s.), as well as similar self-reported claudication distances (W_{PAD}: 178±144 m; M_{PAD}: 205±162 m; p = n.s.) (*Table 4*).

OUTCOME MEASURES AT BASELINE

At entry, the two groups did not differ in PAD severity for the more affected limb (ABI: W_{PAD}: 0.62±0.19; M_{PAD} 0.62±0.18; p = n.s.) and the less affected one (ABI: W_{PAD}: 0.83±0.22; M_{PAD} 0.85±0.20; p = n.s.).

The W_{PAD} group presented a significantly lower functional capacity in the incremental treadmill test and the 6-minute walking test. In detail, W_{PAD} exhibited a lower PTS (2.3±0.9 kmh^{-1} vs 3.0±1.1 kmh^{-1}; $p < 0.001$) and Smax (2.8±1.1 kmh^{-1} vs 3.5±1.1 kmh^{-1}; $p < 0.001$), as well as a lower PFWD (132±95 m vs 215±115 m; $p < 0.001$) and 6MWD (279±73 m vs 340±88 m; $p < 0.001$) (*Table 4*).

REHABILITATION OUTCOMES

Data concerning the duration, participation and adherence to the exercise program were similar between the groups except for total rehabilitation days. These data are reported in *Table 5*.

	Women (n = *264*)	*Men* (n = *747*)	p
Program duration (days)[a]	376 (343–404)	330 (318–350)	**0.011**
Hospital visits (*n*)[b]	7.7 (7.3–8.1)	7.4 (7.2–7.7)	0.25
Walking speed (steps/min)[a]	84 (60–94)	90 (62–104)	0.19
Exercise sessions completed (%)[a]	84 (66–100)	86 (69–100)	0.64
Adherence (arbitrary score)[b]	3.0 (2.9–3.1)	3.1 (3.1–3.2)	0.64

Statistically significant values have been indicated in bold.
[a]Median (95% confidence interval); [b]mean (95% confidence interval).

Table 5. Features of the program in terms of duration and adherence in the two groups

Both groups showed significant improvements in hemodynamic measurements and functional capacity from baseline to the end of the program.

The W_{PAD} group exhibited a significant improvement in the ABI in both limbs (more diseased; $p < 0.001$; less diseased; $p = 0.001$). Additionally, all exercise capacity parameters showed a significant enhancement, particularly for PTS (+40%; $p < 0.001$) and PFWD (+108%; $p < 0.001$).

Similar outcomes were observed for the M_{PAD} group, with significant ABI variations in both limbs ($p < 0.001$) as well as improvements in all four functional parameters (particularly evident for PTS +35%, $p < 0.001$; PFWD +71%, $p < 0.001$). Similarly, the mean claudication onset time improved in both groups (W_{PAD} from 166 to 253 seconds; M_{PAD} from 207 to 298 seconds). Data are reported in *Table 6*.

The subsequent between-group comparison showed superimposable variations, without any statistically significant difference for PTS (W_{PAD}: 0.8±0.9 kmh^{-1}; M_{PAD}:

0.8±0.9 kmh^{-1}; p = n.s.), Smax (W_{PAD}: 0.4±0.8 kmh^{-1}; M_{PAD}: 0.4±0.7 kmh^{-1}; p = n.s.), PFWD (W_{PAD}: 95±100 m; M_{PAD}: 86±103 m; p = n.s.) and 6MWD (W_{PAD}: 33±58 m; M_{PAD}: 32±65 m; p = n.s.). Similarly, no differences were observed for ABI variations in both limbs (*Table 6*).

	Women (n = *264*)				*Men* (n = *747*)					
	Baseline	*End*	Δ	p *within-group*	*Baseline*	*End*	Δ	p *within-group*	*Between-group* Δ *in changes*	p *between-group*
ABI worst limb	0.62 (0.59–0.64)	0.69 (0.66–0.71)	0.07 (0.06–0.09)	**<0.001**	0.62 (0.61–0.63)	0.68 (0.66–0.69)	0.06 (0.05–0.07)	**<0.001**	0.00 (–0.01 to 0.02)	0.68
ABI best limb	0.83 (0.80–0.86)	0.88 (0.85–0.90)	0.05 (0.03–0.07)	**0.001**	0.85 (0.83–0.86)	0.89 (0.88–0.90)	0.04 (0.02–0.05)	**<0.001**	0.01 (–0.02 to 0.02)	0.54
PTS (km/h)	2.3 (2.2–2.4)	3.1 (2.9–3.2)	0.8 (0.7–0.9)	**<0.001**	2.9 (2.8–3.0)	3.7 (3.6–3.8)	0.8 (0.7–0.9)	**<0.001**	0.0 (–0.1 to 0.1)	0.70
Smax (km/h)	2.8 (2.7–2.9)	3.2 (3.1–3.3)	0.4 (0.4–0.5)	**<0.001**	3.5 (3.5–3.6)	3.9 (3.9–4.0)	0.4 (0.4–0.5)	**<0.001**	0.0 (–0.1 to 0.1)	0.61
PFWD (m)	132 (120–143)	223 (209–237)	95 (83–108)	**<0.001**	215 (206–223)	300 (291–309)	86 (77–94)	**<0.001**	9 (–5 to 24)	0.24
6MWD (m)	279 (270–287)	312 (303–322)	33 (28–39)	**<0.001**	339 (333–346)	371 (364–377)	32 (27–36)	**<0.001**	1 (–6 to 10)	0.44

Statistically significant values have been indicated in bold.
Data are expressed as mean and 95% confidence interval.
ABI, ankle-brachial index; 6MWD, 6-minute walking distance; PTS, pain threshold speed; Smax, maximal speed..

Table 6. Within- and between-group differences in rehabilitation outcomes

PROPENSITY SCORE ANALYSIS

After propensity score matching, two independent groups comprising 188 patients each without baseline covariate differences were identified (*Table 7*). In addition, the program duration (W_{PAD}: 402±245 vs. M_{PAD}: 356±202 days; p = 0.07), number of visits (W_{PAD}: 7.4±3.3 vs. M_{PAD}: 7.3±3.3; p = 0.57) and adherence (W_{PAD}: 3.1±0.8 vs. M_{PAD}: 3.2±0.8; p = 0.24) were measured at the end of the program and were balanced between the groups.

	Women (n = *188*)	*Men* (n = *188*)	p
Age (years)	71 ± 10	70 ± 10	0.40
Education, *n* (%)			
Elementary school	139 (74)	135 (72)	0.64
Middle or secondary school	35 (19)	44 (23)	0.25
Degree	14 (7)	9 (5)	0.28
Risk factors, *n* (%)			
Smoking	155 (82)	150 (80)	0.51
Hypertension	142 (76)	144 (77)	0.81
Hyperlipidemia	125 (67)	122 (65)	0.74
Diabetes	53 (28)	67 (36)	0.13
Family history for CVD	34 (18)	36 (19)	0.79
Comorbidities, *n* (%)			
Coronary heart disease	56 (30)	53 (28)	0.73
Cerebrovascular disease	16 (8)	12 (6)	0.43
Osteoarticular disease	71 (37)	56 (30)	0.11
Rheumatic diseases	12 (6)	12 (6)	1.00
Charlson comorbidity index	5.7 ± 1.7	5.7 ± 1.6	0.90
Peripheral arterial disease			
Disease duration (years)	6 ± 6	6 ± 7	0.85
Lower limb revascularization	52 (28)	63 (33)	0.22
Self-reported claudication distance (m)	198 ± 132	201 ± 151	0.48
ABI, more affected limb	0.63 ± 0.19	0.63 ± 0.18	0.78
ABI, less affected limb	0.84 ± 0.20	0.84 ± 0.21	0.99
PTS (km/h)	2.4 ± 0.9	2.5 ± 1.0	0.29
Smax (km/h)	3.0 ± 1.0	3.1 ± 1.1	0.25
PFWD (m)	151 ± 101	162 ± 95	0.25
6MWD (m)	294 ± 71	304 ± 89	0.20

6MWD, 6-minute walking distance; ABI, ankle-brachial index; CVD, cardiovascular disease; PFWD, pain-free walking distance; Smax, maximal speed.

Table 7. Baseline characteristics of the patients included in the study after the propensity analysis

The within-group analysis in the reduced samples confirmed the significant improvements for all hemodynamic and functional parameters for both groups. The between-group comparison also showed similar variations, without any significant difference for any hemodynamic and functional parameters (*Table 8*).

	Women (n = *188*)				*Men* (n = *188*)					
	Baseline	*End*	Δ	p *within-group*	*Baseline*	*End*	Δ	p *within-group*	*Between-group* Δ *in changes*	p *between-group*
ABI worst limb	0.63 (0.60–0.65)	0.70 (0.67–0.73)	0.07 (0.05–0.09)	**<0.001**	0.63 (0.60–0.66)	0.70 (0.67–0.73)	0.07 (0.05–0.08)	**<0.001**	0.00 (−0.02 to 0.01)	0.46
ABI best limb	0.84 (0.81–0.87)	0.89 (0.86–0.92)	0.05 (0.03–0.07)	**<0.001**	0.84 (0.81–0.87)	0.89 (0.88–0.90)	0.05 (0.03–0.06)	**<0.001**	0.00 (−0.02 to 0.02)	0.67
PTS (km/h)	2.4 (2.3–2.6)	3.3 (3.1–3.5)	0.9 (0.8–1.0)	**<0.001**	2.5 (2.4–2.7)	3.5 (3.3–3.7)	0.9 (0.8–1.1)	**<0.001**	0.1 (−0.1 to 0.2)	0.35
Smax (km/h)	3.0 (2.8–3.1)	3.5 (3.2–3.7)	0.5 (0.4–0.6)	**<0.001**	3.1 (2.9–3.3)	3.7 (3.6–3.9)	0.6 (0.5–0.7)	**<0.001**	0.1 (−0.1 to 0.2)	0.24
PFWD (m)	151 (136–165)	247 (221–264)	96 (83–108)	**<0.001**	162 (148–176)	278 (261–295)	115 (89–128)	**<0.001**	19 (−5 to 43)	0.34
6MWD (m)	294 (283–304)	334 (322–345)	40 (29–51)	**<0.001**	304 (291–317)	352 (339–365)	48 (34–59)	**<0.001**	8 (−4 to 20)	0.28

Statistically significant values have been indicated in bold.
Data are expressed as mean and 95% confidence interval.
6MWD, 6-minute walking distance; ABI, ankle-brachial index; PFWD, pain-free walking distance; PTS, speed at onset of claudication; Smax, maximal speed.

Table 8. Within- and between-group differences in rehabilitation outcomes in the propensity score-matched groups

DISCUSSION

In this study, compared to men, women with PAD and claudication following a structured low-intensity program obtained the same benefit in terms of reduction of walking disability as well as a similar degree of adherence. This observation was also confirmed after propensity analysis, which balanced the two groups in baseline characteristics and proved that no differences in rehabilitation outcomes exist between sexes.

To the best of our knowledge, the available literature on the response of women to rehabilitation in PAD is poor, and the present results represents a novel report. The only confirmation of previous data (Roumia et al, 2017; Lozano et al, 2014) is the low walking performance of women compared to that of men in absolute terms. The functional capacity at the entrance to the program measured with both treadmill and ground walking tests was lower in the female population with the same hemodynamic condition. This aspect may refer to the lower aerobic efficiency typical of the female sex or the lower biomechanical efficiency aggravated by deconditioning, possibly related to the presence of comorbidities (Lozano et al, 2014; Lamberti et al, 2018). In daily activities, women move at a slower rate than men and present a different ambulatory pattern[39]. However, after rehabilitation, the same degree of functional improvement, which was the main focus of our study, was observed in the two subpopulations, with an average variation in exercise capacity between 20% and 110% for patients of both sexes.

Different outcomes following rehabilitation programs in chronic pathologies were reported in women compared to those in men (Dorenkamp et al, 2016; Gardner et al, 2014; Gommans et al, 2015), with problematic issues related to interest/motivation,

adherence to physical activity or effects achieved (Arthur et al, 2017; Dorenkam et al, 2016; Gardner et al, 2014).

Various reasons were hypothesized to explain these results, such as the presence of comorbidities (Gardner et al, 2014; Lozano et al, 2014) or the type of intervention. According to the authors, programs for the rehabilitation of cardiovascular patients should not be based on exercise alone (Foy et al, 2001; Gardner et al, 2014); these programs may also benefit from the presence of staff members providing support (Moore, 1996). In general, the necessity of sex-based claudication treatment strategies should be considered (Gommans et al, 2015).

Therefore, we hypothesize that the novel results observed in the present study were derived from the rehabilitation program proposed and successfully tested in frail subjects (Manfredini F. et al, 2008; Malagoni et al, 2011; Manfredini F. et al, 2017; Malagoni et al, 2008; Torino et al, 2014; Malagoni et al, 2016; Lamberti et al, 2017) where the type of exercise and organizational model could have favored equal adherence and outcomes in both sexes.

Normally, the exercise recommended for the rehabilitation of patients with chronic PAD is under supervision in specialized facilities. This exercise is based on repeated walking sessions at a level of pain that increases patient tolerance and thus improves tolerance to exercise, thereby obtaining progressively longer gradual sessions (Gerhard-Herman et al, 2017). Considering the lower attitude of women toward exercise (Arthur et al, 2013) and the sex difference in the perception of pain (Oka et al, 2003), a different approach might be favorable in this subgroup, based on a progressively higher pain-free walking cadence supported by the aerobic adaptations obtained during the

program at controlled speed (Manfredini et al, 2004; Manfredini et al, 2012). A faster ambulatory cadence during a step-monitored home-based exercise program predicted greater walking improvements in women following a 3-month intermittent walking to mild-to-moderate claudication pain home exercise program (Gardner et al, 2015).

Walking without pain with rest breaks within each exercise session was well tolerated and often performed with pleasure. A significant improvement in physical functioning (Manfredini et al, 2004) and QoL was observed at discharge from the pain-free program in a sample of 90 subjects with a 50% increase in the bodily pain domain (Malagoni et al, 2011).

Notably, other authors reported that the low-intensity treadmill program without pain was as effective for subjects with PAD (Barak et al, 2009), with similar benefits in women compared to those in men (Dipmarine et al, 2016).

Moreover, the proposed program based on individualized, low-dose and interval exercise allows the enrollment of patients with severe PAD, important comorbidities and gait problems who are often excluded from traditional rehabilitation programs due to the exercise intensity used (Gerhard-Herman et al, 2017; Stewart et al, 2002); moreover, these patients obtain more benefits from the Ti-To program. Among barriers to physical activity, low energy levels related to the presence of diabetes, a low ABI and a low walking capacity for leg pain have been reported (Cavalcante et al, 2015). Additionally, comorbidities did not influence the outcomes in the study. In the female study population, every rehabilitation outcome parameter is favorably increased with or without diabetes or osteoarticular diseases (Lamberti et al, 2018).

However, the program in this study aimed to overcome other barriers to exercise through its organizational model.

In recent years, home-based programs have been considered feasible and effective for improving walking ability in PAD patients (Gerhard-Herman et al, 2017; McDermott et al, 2018; McDermott et al, 2016), and recent trials have provided support for this therapeutic option (McDermott et al, 2013; McDermott et al, 2018). In the present program, the modality of exercise allows the possibility to comfortably carry out all the exercises at home without giving up the surveillance of the family or the management of the house, which are typical duties of most elderly women in our region (personal observation).

The daily low dose of exercise required for an acceptable and fixed working time, which was inserted into daily life, gives women the possibility to manage housework and grandchildren.

Moreover, different from the supervised program, which requires the need to travel daily or three times a week to facilities for exercise execution (McDermott et al, 2016), the present model calls for few visits to the hospital, with low costs and a negligible or sustainable commitment on the part of the family. Finally, the program is offered to patients without cost, which is possible because of the low organizational costs of the procedures (Malagoni et al, 2011; Lamberti et al, 2016).

As a further result, in the study, we observed significant changes in the ABI value. This result, which is not usually reported following the recommended traditional programs but confirms previous observations and vascular adaptations following the same rehabilitation program (Manfredini F. et al, 2008; Malagoni et al, 2011; Malagoni

et al, 2012; Lamberti et al, 2016; Manfredini F. et al, 2009), was similar in the two groups.

We are aware that our study has several limitations, such as its single-center retrospective design and the lack of a control group. However, being a single-center study performed by the same operators over the entire study period represents an evident strength due to the operator-dependent limitations in the evaluation of the outcome measures.

The percentage of women was approximately 26%, which is far from the values reported by some authors but consistent with other papers and representative of the whole population sent to rehabilitation. However, an analysis that considers a different percentage has also been carried out. Finally, data analysis was not performed in a blinded fashion.

CONCLUSIONS

The inclusion of gender represents an important opportunity to discover differences in the relationship between exposure and outcomes for men and women, and arrange strategies for intervention. Our results, also based on the scientific experience of our research group, show that women are under-represented in research on medical disease, especially in CV disease.

Despite the high prevalence of PAD, mainly in elderly population, evidence show that it remains underdiagnosed and under-treated in women. Considering that claudication is typical of second-stage PAD, an original approach to structured home-based exercise rehabilitation in PAD was carried out to improve the deambulatory function and quality of life of such patients.

In this regard, a moderate intensity pain-free rehabilitation program in PAD patients was equally effective in men and women in terms of functional and hemodynamic improvements and adherence. Of course, further confirmation by a prospective study is needed. However, the implementation of effective organizational models tailored to the female population for the setting, exercise intensity, time of execution requested, tolerability and costs warrants further research efforts.

On the other hand, a robust body of evidence demonstrated that several life-threatening acute cardiovascular diseases exhibit diurnal or 24 h patterning, concretely, acute myocardial infarction, sudden cardiac death, cardiac arrest, rupture or dissection of aortic aneurysms, and stroke, exhibit a circadian periodicity with a morning peak.

In this regard, an analysis performed by my group, which I am responsible, of 20 years of chronobiologic studies all over the world confirmed that morning hours are a critical time of onset of acute cardiovascular diseases in men and women.

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ANNEXES

APPENDIX I: Tables 1 & 2

Doctoral student: Roberto Manfredini

Table 1. Publications that the doctoral student has carried out in the year 2018 (1/7)

N°	Authors	Title	Journal, year	Rank Quartile (Q) Decile (D) ISI Branch	Impact factor ISI 2017
1	Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, **Manfredini R,** Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, Y-Hassan S, Migliore F, Horowitz JD, Shimokawa H, Lüscher TF, Templin C.	*International Expert Consensus Document on Takotsubo Syndrome – PART I: Clinical characteristics, diagnostic criteria, and pathophysiology.*	Eur Heart J. 2018;39(22):2032-2046.	1/128 Q1 D1 CARDIAC & CARDIOVASCULAR SYSTEM	23.425
2	Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, **Manfredini R,** Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, Y-Hassan S, Migliore F, Horowitz JD, Shimokawa H, Lüscher TF, Templin C.	*International Expert Consensus Document on Takotsubo Syndrome – PART II: Diagnostic workup, outcome, and management.*	Eur Heart J. 2018;39(22):2047-2062.	1/128 Q1 D1 CARDIAC & CARDIOVASCULAR SYSTEM	23.425
3	Lopez Soto PJ, Fabbian F, Cappadona R, Zucchi B, Manfredini F, Garcia Arcos A, Carmona Torres JM, **Manfredini R**, Rodriguez Borrego MA.	*Chronotype, nursing activity and gender: a systematic review.*	J Adv Nurs. Oct 11. Doi: 10.1111/jan.13876. [Epub ahead of print]	7/118 Q1 D1 NURSING	2.267

Table 1. Publications that the doctoral student has carried out in the year 2018 (2/7)

N°	Authors	Title	Journal, year	Rank Quartile (Q) Decile (D) ISI Branch	Impact factor ISI 2017
4	**Manfredini R**, Lamberti N, Manfredini F, Straudi S, Fabbian F, Basaglia N, Rodriguez Borrego MA, Carmona Torres JM, Lopez Soto PJ.	*Gender differences in outcomes following a pain-free, home-based exercise program for claudication*.	J Womens Health (Larchmt). 2018 Sep 15. Doi: 10.1089/jwh.2018.7113 [Epub ahead of print]	4/42 Q1 D1 WOMENS STUDIES	2.097
5	Basili S, Raparelli V, Napoleone L, Talerico G, Corazza GR, Perticone F, Sacerdoti D, Andriulli A, Licata A, Pietrangelo A, Picardi A, Raimondo G, Violi F, PRO-LIVER Collaborators (**Manfredini R**).	*Platelet count does not predict bleeding in cirrhotic patients: results from the PRO-LIVER Study*.	Am J Gastroenterol. 2018;113:368-375.	6/80 Q1 D1 GASTROENTEROLOGY & HEPATOLOGY	10.231
6	**Manfredini R**, De Giorgio R, Fabbian F.	*Off-hours and in-hospital mortality: lower resources or higher severity?*	J Am Coll Cardiol. 2018;71(21):2492.	2/126 Q1 D1 CARDIAC & CARDIOVASCULAR SYSTEM	19.896
7	Ursini F, Russo E, Pallino G, D'Angelo S, Chiaravalloti A, De Sarro G, **Manfredini R**, De Giorgio R.	*Metformin and autoimmunity: a 'New Deal' of an old drug.*	Front Immunol. 2018;9:1236.	30/155 Q1 IMMUNOLOGY	5.511

Table 1. Publications that the doctoral student has carried out in the year 2018 (3/7)

N°	Authors	Title	Journal, year	Rank Quartile (Q) Decile (D) ISI Branch	Impact factor ISI 2017
8	Proietti M, Antoniazzi S, Monzani V, Santalucia P, Franchi C; SIM-AF Investigators, Fenoglio LM, Melchio R, Fabris F, Sartori MT, **Manfredini R**, De Giorgi A, Fabbian F, Biolo G, Zanetti M, Altamura N, Sabbà C, Suppressa P, Bandiera F, Usai C, Murialdo G, Fezza F, Marra A, Castelli F, Cattaneo F, Beccati V, di Minno G, Tufano A, Contaldi P, Lupattelli G, Bianconi V, Cappellini D, Hu C, Minonzio F, Fargion S, Burdick L, Francione P, Peyvandi F, Rossio R, Colombo G, Monzani V, Ceriani G, Lucchi T, Brignolo B, Manfellotto D, Caridi I, Corazza GR, Miceli E, Padula D, Fraternale G, Guasti L, Squizzato A, Maresca A, Liberato NL, Tognin T, Rozzini R, Bellucci FB, Muscaritoli M, Molfino A, Petrillo E, Dore M, Mete F, Gino M, Franceschi F, Gabrielli M, Perticone F, Perticone M, Bertolotti M, Mussi C, Borghi C, Strocchi E, Durazzo M, Fornengo P, Dallegri F, Ottonello LC, Salam K, Caserza L, Barbagallo M, Di Bella G, Annoni G, Bruni AA, Odetti P, Nencioni A, Monacelli F, Napolitano A, Brucato A, Valenti A, Castellino P, Zanoli L, Mazzeo M.	*Use of anticoagulant drugs in older patients with atrial fibrillation in internal medicine wards.*	Eur J Int Med. 2018;52:e12-e14.	27/154 Q1 MEDICINE, GENERAL & INTERNAL	3.282
9	Corrao S, Argano C, Natoli G, Nobili A, Corazza GR, Mannucci PM, Perticone F, REPOSI Investigators (**Manfredini R**).	*Disability, and not diabetes, is a strong predictor of mortality in oldest old patients hospitalized with pneumonia.*	Eur J Int Med. 2018;54:53-59.	27/154 Q1 MEDICINE, GENERAL & INTERNAL	3.282
10	Gallo P, De Vincentis A, Pedone C, Nobili A, Tettamanti M, Gentilucci UV, Picardi A, Mannucci PM, Incalzi RA, REPOSI Investigators (**Manfredini R**).	*Prognostic relevance of glomerular filtration rate estimation obtained through different equations in hospitalized elderly patients.*	Eur J Int Med. 2018;54:60-64.	27/154 Q1 MEDICINE, GENERAL & INTERNAL	3.282

Table 1. Publications that the doctoral student has carried out in the year 2018 (4/7)

N°	Authors	Title	Journal, year	Rank Quartile (Q) Decile (D) ISI Branch	Impact factor ISI 2017
11	Corsi N, Roberto A, Cortesi L, Nobili A, Mannucci PM, Corli O, REPOSI Investigators (**Manfredini R**).	*Prevalence, characteristics and treatment of chronic pain in elderly patients hospitalized in internal medicine wards.*	Eur J Int Med. 2018;55:35-39.	27/154 Q1 MEDICINE, GENERAL & INTERNAL	3.282
12	Cesari M, Franchi C, Cortesi L, Nobili A, Ardoino I, Mannucci PM, REPOSI Investigators (**Manfredini R**).	*Implementation of the Frailty Index in hospitalized older patients: results from the REPOSI register.*	Eur J Int Med. 2018;56:11-18.	27/154 Q1 MEDICINE, GENERAL & INTERNAL	3.282
13	Franchi C, Antoniazzi S, Proietti M, Nobili A, Mannucci PM, SIM-AF Investigators (**Manfredini R**).	*Appropriateness of oral anticoagulant therapy prescription and its associated factors in hospitalized older people with atrial fibrillation.*	Brit J Clin Pharmacol**.** 2018;84(9):2010-2019.	47/261 Q1 PHARMACOLOGY & PHARMACY	3.688
14	Agosti P, Tettamanti M, Vella FS, Suppressa P, Pasina L, Franchi C, Nobili A, Mannucci PM, Sabbà C, REPOSI Investigators (**Manfredini R**).	*Living alone as an independent predictor of prolonged length of hospital stay and non-home discharge in older patients.*	Eur J Intern Med. 2018 Nov;57:25-31. Doi: 10.1016/j.ejim.2018.06.014. Epub 2018 Jun 19.	27/154 Q1 MEDICINE, GENERAL & INTERNAL	3.282
15	Gallerani M, Fedeli U, Pala M, De Giorgi A, Fabbian F, **Manfredini R**.	*Weekend versus weekday admission and in-hospital mortality for pulmonary embolism: a 14-year retrospective study on the National Hospital Database of Italy*.	Angiology. 2018;69(3):236-241.	25/65 Q2 PERIPHERAL VASCULAR DISEASE	3.022
16	**Manfredini R**, Fabbian F, Cappadona R, Zucchi B, Lopez-Soto PJ, Rodriguez-Borrego MA.	*Attempted suicide as a trigger of Takotsubo syndrome: a minireview of available case reports*.	Intern Emerg Med. 2018;13(4):629-631.	41/154 Q2 MEDICINE, GENERAL & INTERNAL	2.453

Table 1. Publications that the doctoral student has carried out in the year 2018 (5/7)

N°	Authors	Title	Journal, year	Rank Quartile (Q) Decile (D) ISI Branch	Impact factor ISI 2017
17	**Manfredini R**, Fabbian F, Cappadona R, Modesti PA.	*Daylight Saving Time, circadian rhythms and cardiovascular health.*	Intern Emerg Med. 2018;13(5):641-646.	41/154 Q2 MEDICINE, GENERAL & INTERNAL	2.453
18	Raparelli V, Pastori D, Pignataro SF, Vestri AR, Pignatelli P, Cangemi R, Proietti M, Davì G, Hiatt WR, Lip GYH, Corazza GR, Perticone F, Violi F, Basili S, ARAPACIS Study Collaborators (**Manfredini R**).	*Major adverse cardiovascular events in non-valvular atrial fibrillation with chronic obstructive pulmonary disease: the ARAPACIS study.*	Intern Emerg Med. 2018;13(5):651-660.	41/154 Q2 MEDICINE, GENERAL & INTERNAL	2.453
19	Bossone E, Arcopinto M, Iacoviello M, Triggiani V, Cacciatore F, Maiello C, Limongelli G, Masarone D, Perticone F, Sciacqua A, Perrone-Filardi P, Mancini A, Volterrani M, Vriz O, Castello R, Passantino A, Campo M, Modesti PA, De Giorgi A, Monte I, Puzzo A, Ballotta A, Caliendo L, D'Assante R, Marra AM, Salzano A, Suzuki T, Cittadini A, TOSCA Investigators (**Manfredini R**).	*Multiple hormonal and metabolic deficiency syndrome in chronic heart failure: rationale, design, and demographic characteristics of the T.O.S.CA. Registry.*	Intern Emerg Med. 2018;13(5):661-671.	41/154 Q2 MEDICINE, GENERAL & INTERNAL	2.453
20	Mannucci PM, Nobili A, Pasina L; REPOSI Collaborators (REPOSI is the acronym of Registro Politerapie SIMI, Società Italiana di Medicina Interna) (**Manfredini R**)	*Polypharmacy in older people: lessons from 10 years of experience with the REPOSI register.*	Intern Emerg Med. 2018 Aug 31. Doi: 10.1007/s11739-018-1941-8. [Epub ahead of print]	41/154 Q2 MEDICINE, GENERAL & INTERNAL	2.453
21	Fabbian F, De Giorgi A, Boari B, Misurati E, Gallerani M, Cappadona R, Cultrera R, Rodriguez Borrego MA, **Manfredini R**, Lopez Soto PJ.	*Infections and internal medicine patients: could a comorbidity score predict in-hospital mortality?*	Medicine (Baltimore). 2018;97:42(e12818).	56/154 Q2 MEDICINE, GENERAL & INTERNAL	2.028
22	Lopez-Soto PJ, Garcia-Arcos A, Fabbian F, **Manfredini R**, Rodriguez-Borrego MA.	*Falls suffered by elderly people, from the perspective of health-care personnel.*	Clin Nurs Res. 2018;27(6):675-691.	39/118 Q2 NURSING	1.466

Table 1. Publications that the doctoral student has carried out in the year 2018 (6/7)

N°	Authors	Title	Journal, year	Rank Quartile (Q) Decile (D) ISI Branch	Impact factor ISI 2017
23	**Manfredini R**, Fabbian F, Cappadona R, De Giorgio R, Grassi L.	*A time of day for aggressive behavior? Possible insights for ED personnel.*	Am J Emerg Med. 2018 May 10. Pii: S0735-6757(18)30377-2. Doi: 10.1016/j.ajem.2018.05.014. [Epub ahead of print]	11/24 Q2 EMERGENCY MEDICINE	1.494
24	**Manfredini R**, Fabbian F, De Giorgi A, Zucchi B, Cappadona R, Signani F, Katsiki N, Mikhailidis DP.	*Daylight saving time and myocardial infarction: should we be worried? A review of the evidence.*	Eur Rev Med Pharmacol Sci. 2018;22(3):750-755.	137/261 Q3 PHARMACOLOGY & PHARMACY	2.387
25	Fabbian F, De Giorgi A, Tiseo R, Cappadona R, Zucchi B, Rubbini M, Signani F, Storari A, De Giorgio R, La Manna G, **Manfredini R**.	*Neoplasms and renal transplantation: impact of gender, comorbidity and age on in-hospital mortality. A retrospective study in the region Emilia-Romagna of Italy*.	Eur Rev Med Pharmacol Sci. 2018;22(8):2266-2272.	137/261 Q3 PHARMACOLOGY & PHARMACY	2.387
26	Pasina L, Cortesi L, Tiraboschi M, Nobili A, Lanzo G, Tettamanti M, Franchi C, Mannucci PM, Ghidoni A, Assolari A, Brucato A, REPOSI Investigators (**Manfredini R**).	*Risk factors for three-month mortality after discharge in a cohort of non-oncologic hospitalized elderly patients: results from the REPOSI study.*	Arch Gerontol Ger. 2018;74:169-173.	34/53 Q3 GERIATRICS & GERONTOLOGY	2.241
27	Paciullo F, Proietti M, Bianconi V, Nobili A, Pirro M, Mannucci PM, Lip GYH, Lupattelli G, REPOSI Investigators (**Manfredini R**).	*Choice and outcomes of rate control versus rhythm control in elderly patients with atrial fibrillation: a report from the REPOSI Study.*	Drugs Aging. 2018;35(4):365-373.	31/53 Q3 GERIATRICS & GERONTOLOGY	2.381

Table 1. Publications that the doctoral student has carried out in the year 2018 (7/7)

N°	**Authors**	**Title**	**Journal, year**	**Rank** **Quartile (Q) Decile (D)** **ISI Branch**	**Impact factor ISI 2017**
28	Lamberti N, Straudi S, Lissia E, Cavazzini L, Buja S, **Manfredini R**, Basaglia N, Manfredini F.	*Home-based exercise in elderly patients with intermittent claudication limited by osteoarticular disorders – feasibility and effectiveness of a low-intensity program.*	VASA. 2018;47(3):227-234.	53/57 Q4 PERIPHERAL VASCULAR DISEASE	1.210
29	**Manfredini R**, Fabbian F, De Giorgi A, Cappadona R, Zucchi B, Storari A, Rodriguez Borrego MA, Carmona Torres JM, Lopez Soto PJ.	*Takotsubo syndrome and dialysis: an uncommon association?*	J Int Med Res. 2018;46(11):4399-4406.	116/133 Q4 MEDICINE, RESEARCH & EXPERIMENTAL	1.023
Total					**142.136**

Table 2. Conference presentations that the doctoral student has carried out in the year 2018 (1/2)

N°	Authors	Conference, City, Date	Type	Title
1	**Manfredini R**.	Annual Meeting of the Assembly of National Sleep Societies (ANSS), European Sleep Research Society Parma (ITA), 5 May 2018	Invited lecture	Circadian Nobel Prize: Insights on chronobiology
2	**Manfredini R**.	23th World Congress on Heart Disease Boston (USA), 27-29 July 2018	Invited lecture	Daylight Saving Time and acute myocardial infarction: does a gender-oriented difference exist? (*) Selected for the International Academy of Cardiology Memorial Awards
3	**Manfredini R**.	24th World Cardiology Conference Hong Kong (CHI),17-18 September 2018	Keynote lecture	Women and circadian onset of cardiovascular diseases: 'Time is a gentleman'
4	**Manfredini R**.	24th World Cardiology Conference Hong Kong (CHI), 17-18 September 2018	Invited lecture	Daylight Saving Time, circadian rhythms and cardiovascular health
5	Cappadona R, Rizzati M, Fabbian F, De Giorgi A, Tiseo R, Lopez-Soto PJ, Rodriguez-Borrego MA, **Manfredini R**.	Nursing World Conference Roma (ITA), 17-19 September 2018	Poster	Takotsubo cardiomyopathy and attempted suicide: a review of the evidence.
6	Cappadona R, Rizzati M, Fabbian F, De Giorgi A, Tiseo R, Lopez-Soto PJ, Rodriguez-Borrego MA, **Manfredini R**.	Nursing World Conference Roma (ITA), 17-19 September 2018	Poster	Takotsubo cardiomyopathy and cesarean delivery: a review of the evidence.

Table 2. Conference presentations that the doctoral student has carried out in the year 2018 (2/2)

N°	Authors	Conference, City, Date	Type	Title
7	Fabbian F, De Giorgi A, Gozzi D, Pasin M, Storari A, Gallerani M, **Manfredini R**.	59° Congresso Nazionale Società Italiana di Nefrologia Rimini (ITA), 3-6 October 2018	Oral	Risk factors for in-hospital mortality in elderly patients admitted because of acute renal failure: a nationwide retrospective study.
8	Spampinato MD, Polito J, Ricciardelli MA, Strada A, Manfredini R, De Giorgio R.	119° Congresso Nazionale Società Italiana di Medicina Interna Roma (ITA), 26-28 October 2018	Oral	Transient ischemic attack and ABCD2 score in Ferrara's district: the provincial healthcare pathway results. (*) Best Communication Award
9	De Giorgi A, Fabbian F, Guarino M, Bagnaresi I, Salmi R, Gallerani M, De Giorgio R, **Manfredini R**.	119° Congresso Nazionale Società Italiana di Medicina Interna Roma (ITA), 26-28 October 2018	Oral	In-hospital mortality in elderly patients admitted for acute renal failure: does a weekend effect exist? A nationwide retrospective study.
10	Spampinato MD, Migliano MT, Ricciardelli MA, Polito J, Strada A, De Giorgi A, **Manfredini R**, De Giorgio R.	119° Congresso Nazionale Società Italiana di Medicina Interna Roma (ITA), 26-28 October 2018	Poster	Mechanical thrombolysis in patients with stroke: does gender impact on outcome? A narrative review of the literature.
11	De Giorgi A, Bonazzi S, Fabbian F, Guarino M, Leonardo A, Salmi R, De Giorgio R, **Manfredini R**.	119° Congresso Nazionale Società Italiana di Medicina Interna Roma (ITA), 26-28 October 2018	Poster	Spindle cell tumor of the liver: an uncommon case of an uncommon tumor in elderly.
12	Guarino M, De Giorgi A, Fabbian F, Spampinato MD, Gallerani M, Salmi R, De Giorgio R, **Manfredini R**.	119° Congresso Nazionale Società Italiana di Medicina Interna Roma (ITA), 26-28 October 2018	Poster	Acute esophageal variceal bleeding and in-hospital mortality: does gender matter? A retrospective study in Italy.
13	De Giorgi A, Fabbian F, Pasin M, Tonelli L, Guarino M, Bagnaresi I, De Giorgio R, **Manfredini R**.	119° Congresso Nazionale Società Italiana di Medicina Interna Roma (ITA), 26-28 October 2018	Poster	Ambulatory blood pressure monitoring during pregnancy: a single center Italian experience.

APPENDIX II: Cardiovascular disease. Sex differences

Acute coronary syndromes: drugs

Disease	Procedure	Objective	Sample	Results Main conclusions	Author, year
ACS	DAPT	Post-discharge bleeding	N=13727 W=23%	Administration of NAA compared to clopidogrel: 2-fold greater bleeding rate in W (7.3 vs 3.5%, p=0.004), but not in M (2.6 vs 2.7%, p=0.887) Multivariate analysis: NAA independent risk factor for bleeding only in W (HR 2.78, p<0.001). Female sex is not an independent risk factor of bleeding	Grodecki, 2018
ACS	AT	Primary end point: MACCEs, a composite of death, MI, stroke, or target vessel revascular iz. Coprimary end point: NACE (MACCE + MB)	N=840 W 26%	PCI and DES more often used in M (PCI: 87 vs 80%, p=0.02; DES: 76 vs 66%, p=0.01) M more often treated with DAPT; 94 vs 88%, p=0.01). Ticagrelor most prevalent strategy, regardless of gender (47 vs 49%, p=0.68); clopidogrel preferred in W (42 vs 33%, p=0.04); prasugrel preferred in M (11 vs 17%, p=0.04). Multivariate analysis: MACCE and NACE similar between genders	Cirillo, 2018

Acute coronary syndromes: interventive procedures (1/2)

Disease	**Procedure**	***Objective***	***Sample***	**Results** **Main conclusions**	**Author, year**
ACS	CABG and PCI	Outcomes: composite of all-cause death, MI, or stroke at 3 years	N=1905 23.1% W	Multivariate analysis: sex not independently associated with primary endpoint (HR 1.10) or all-cause death (HR 1.39) at 3 years. At 30 days, all-cause death, MI, or stroke occurred, respectively, in 8.9% and 3.6% of W and M with PCI; and in 6.2% and 8.4% of W and M treated CABG ($p<0.005$). The 3-year rate of the composite primary endpoint was, respectively, 19.7% and 13.8% in W and M with PCI; and 14.6% and 14.7% in W and M with CABG ($p=0.06$). Sex is not an independent predictor of adverse outcomes after revascularization. However, W with PCI had a trend toward worse outcomes, due to associated comorbidities and increased periprocedural complications	Serruys, 2018
ACS	PCI	Outcomes with Xience V stent	N=1938	Compared to M, W had ↑ MACE (14.1% vs 9.8% $p<0.01$, RR 1.4) and all-cause mortality (10% vs 6.2% $p<0.01$, RR 1.61) at 1 year, no difference in device specific outcomes. Multivariable analysis: MB strongest predictor of MACE (OR 10.51, $p<0.0001$), MI (OR 4.26, $p=0.012$), all-cause death (OR 5.3, $p<0.0001$). W with AMI and PCI with XIENCE ↑ higher all-cause mortality at 1 year compared to M	Gul, 2018

Acute coronary syndromes: interventive procedures (2/2)

Disease	**Procedure**	***Objective***	***Sample***	**Results** **Main conclusions**	**Author, year**
ACS	PCI: TRA vs TFA	30-day coprimary outcomes: MACCE: death, MI, or stroke, and NACE (MACCE or MB)	N=8404 W 26.6%	MACCE and NACE not significantly different between M and W, but W had ↑ risk of access site bleeding (M vs W RR 0.64; p<0.0016), severe bleeding (RR 0.17; p=0.0012), transfusion (RR 0.56; p<0.001). TRA vs TFA: no significant interaction for MACCE and NACE stratified by sex, for both coprimary endpoints. TRA benefit relatively greater in W (RR 0.73; p=0.019; and RR 0.73; p=0.012, respectively). No interaction between M and W for the individual endpoints of all-cause death, MI, stroke, and bleeding. W: ↑ risk of severe bleeding and access site complications. TRA was effective method to reduce complications and composite ischemic or bleeding endpoints	Gargiulo, 2018
ACS	PCI	Primary outcome: a composite of cardiac mortality, MI or stroke at 3 years of follow-up	N=18334 W 25.8%	Primary outcome: 15.2% W, 11.6% M, HR 1.35; p<0.001). W ↑ risk of all-cause mortality (15.4% vs 12.3%; p<0.001), cardiac mortality (10.2% vs 7.6%; p<0.001), stroke (2.6% vs 1.4%; p<0.001) than M. In matched patients, primary outcome occurred in 13.4% W vs 11.6% M, HR 1.18, p=0.033. W ↑ risk of MI (4.2% vs 3.1%; p=0.044) but not cardiac (8.7% vs 8.2%; p=0.306), all-cause death (12.5% vs 12.9%; p=0.991), stroke (1.9% vs 1.6%; p=0.550) than M. W ↑ risk of a composite of cardiac mortality, MI or stroke up to 3 years after PCI than M	Ndrepepa, 2018

Myocardial infarction: clinical

Disease	Procedure	Objective	Sample	Results Main conclusions	Author, year
MI	Clinical outcomes	Discharge disposition, DtB), TIS, LOS, IHM rates		Multivariate regression: D2B and TIS significantly ↑ in W compared to M (D2B 58 vs 54 min; TIS 206 vs 178 min; both p<0.001). LOS 0.45 median days longer. W much less likely to survive at discharge than M OR 0.63. W much less likely to be discharged to home than M (88% vs 92%, p<0.001). Sex-based disparities persist for both CV outcomes and discharge disposition, even in a modern system of care	Langabee, 2018
MI	Guideline-recommended statins for secondary prevention	Prescription fills for high-intensity statin therapy on discharge following MI	N=16898 W26% W adults <65 years	Filled high-intensity statin for MI: 56% M, 47% W. Adjusted risk ratios for filling a high-intensity statin comparing W with M were 0.91 in the total population, 0.91 among those with no prior statin use, and 0.87 and 0.98 for those taking low/moderate-intensity and high-intensity statins prior to their MI, respectively. W were less likely than M to fill high-intensity statins within all subgroups, and the disparity was largest in the youngest and oldest adults and for those without prevalent comorbid conditions.	Peters, 2018

Myocardial infarction: interventional procedures (1/2)

Disease	Procedure	Objective	Sample	Results Main conclusions	Author, year
MI	PCI	Gender differences in PCI outcomes	N=4776	PCI success similar in M and W (97.8% vs 97.7%, p=0.76). No significant gender difference in the number of vessels attempted (1.14 vs 1.12, p=0.25), mean number of lesions treated (1.34 vs 1.32, p=0.21) or mean number of stents used (1.32 vs 1.30, p=0.31). Equivalent use of drug eluting stents (38.2% vs 38.3%, p=0.94). W with STEMI: longer median symptom-to-door time (111 vs 90 min, p=0.0411) but no gender difference in DtB time or symptom-to-balloon time. No significant difference in percentages of W and M <75years treated with prasugrel or ticagrelor (11.1% vs 13.4%, p=0.092). Multivariate analysis: female sex is not a predictor of death. No significant gender difference in the overall incidence of unadjusted 1-year MACE (11.6% vs 10.8%, p=0.434).	Josiah, 2018
MI	PCI	Risk of 30-day mortality after STEMI. Role of age, drugs, and primary PCI	N=8834 W 30.1%	30-day mortality significantly ↑ W than M (11.6% vs 6.0%, p<0.001); with primary PCI: 7.1% vs 3.3%, p <0.001. After multivariable adjustment, W<60 had ↑ early mortality risk than M of the same age (OR, 1.88; p=0.02). The risk in the subgroups aged 60-74 and >75 years was not significantly different between sexes (OR, 1.28; p=0.19 and OR, 1.17; p=0.40; respectively). After adjustment, the relationship among sex, age category, and 30-day mortality was similar (OR, 1.56,1.49 and 1.21, respectively	Cenko, 2018
MI	PCI	Rates of all-cause mortality	N=32127 W 29.7%	W were older (69.4±12 vs 64.8±11.7 years; p<0.001), with more comorbidities (Charlson index 2.1±2.1 vs 1.9±2.1; p<0.001). Both sexes had a decline in cardiac deaths at 5 years (26% relative decrease in W, 17% in M, trend p<0.001 for each). Only a minority of deaths were cardiac (33.8% in W, 38.0% in M). After adjustment, no evidence for a sex-specific excess of risk for cardiac or noncardiac mortality	Raphael, 2018

Myocardial infarction: interventional procedures (2/2)

Disease	**Procedure**	**Objective**	**Sample**	**Results** **Main conclusions**	**Author, year**
MI	PCI	Timeliness of reperfusion in young patients with STEMI	N=1359 W 61.4%	W were more likely to exceed reperfusion time guidelines than M (42.4% vs 31.5%; p<0.01). In multivariable analyses, female sex persisted as an important factor in exceeding reperfusion guidelines after adjusting for ECG characteristics (OR 1.57). Positive voltage criteria for LV hypertrophy and absence of a prehospital ECG were positive predictors of reperfusion delay; and ST elevation in lateral leads was an inverse predictor of reperfusion delay.	Gupta, 2018

Atrial fibrillation: medical (1/2)

Disease	Procedure	Objective	Sample	Results Main conclusions	Author, year
AF	OA for stroke prevention	Gender differences	N=15092 45.5% W	Between-gender differences in OA use (↓ use in W compared with M by decreasing order of magnitude of the difference) were found for CHA_2DS_2-VASc score = 1; $CHADS_2$ score = 0; previous bleeding; age <65 years; no history of hypertension; MI; CAD; North America region; and specialist office setting. The prevalence of OA use is similar in W and M. The decision to use OA depends mainly on guideline-related differences in stroke risk stratification rather than on gender	Mazurek, 2018
AF	Patients newly diagnosed with AF and prescribed OA	Clinical outcomes	N= 9806 W 49.3%	Compared with warfarin, DOAC use was associated with a ↓ risk of ICH (HR 0.16) and all-cause mortality (HR 0.55) in W but not in M. The treatment by sex interaction was significant for ICH only, and a significantly ↓ risk of ICH remained in the DOAC group when compared with warfarin users with good anticoagulation control (HR 0.13) among W only. The risks of ischemic stroke or systemic embolism and GI with DOACs vs warfarin were comparable in both sexes. DOACs were associated with a ↓ risk of ICH and all-cause mortality in W only, where the association of lower ICH risk remained when compared with warfarin users with good anticoagulation control.	Law, 2018
AF	Warfarin therapy	Risk of stroke, bleeding events, and mortality	N=54568	Risk of stroke: no differences between genders (HR 0.97, p=0.304); CV mortality: ↓ in W (HR 0.82, p<0.001); All-cause mortality: ↓ in W (HR 0.79, p<0.001); Bleeding events: less frequent in W (HR 0.52, p<0.001) Female gender is not a risk marker for adverse outcomes in AF patients with proper warfarin therapy	Perittila, 2018

Atrial fibrillation: medical (2/2)

Disease	**Procedure**	**Objective**	**Sample**	**Results** **Main conclusions**	**Author, year**
AF	Management	Observational	N=6274 W 27%	W underwent ↓electric cardioversion (12.3% vs 19.6%, p<0.001), ↓radiofrequency ablation (12.4% vs 17.9%, p<0.001), and ↓antiarrhythmic drug therapy (44.7% vs 49.5%, p<0.001), despite having more severe symptoms (class III or IV, 45.8% vs 37.5%, p<0.001). NOAC use was more prevalent in W than M (70.4% vs 62.3%, p<0.001). Insufficient NOAC dosing was more common in W than M (61.5% vs 56.3%, p<0.001). W with AF were treated more conservatively and rhythm control strategies were used ↓ frequently than in M, even though W with AF had more severe symptoms.	Lee, 2018

Atrial fibrillation: interventive procedures

Disease	Procedure	Objective	Sample	Results Main conclusions	Author, year
AF	CA	Complication rates and outcomes	N=85,977 W 32.4%	Overall complications: more frequent among W vs M (12.4% vs 9.0%; p<0.001) Major complications: more frequent among W vs M (4.7% vs 2.7%; p<0.001) No difference in mortality (0.3% vs 0.2%) After adjustments, W were more likely than M to have major complication (OR 1.48; p<0.001).	Elayi, 2018
AF	CA	Clinical end points: 1) atrial arrhythmia recurrence, 2) CV rehospitalization, 3) RA	N=750	Female sex (HR 1.37; p=0.010) and prior direct current cardioversion (HR 1.40; p=0.013) were independently associated with AF recurrence. Female sex (HR 1.36; p=0.035) and HT (HR 1.48; p=0.013) independently predicted CV rehospitalization. A longer history of AF (HR 1.03; p=0.039) ↑ the rate of RA Female sex was associated with a 40% ↑ in the risks of primary efficacy failure and CV rehospitalization. History of AF was the only predictor of RA	Kuck, 2018
AF	CSI	Long-term clinical outcomes	N=1450	The cumulative 3-year incidence of all-cause death was significantly ↑ in W than in M (26.5% vs 17.2%, p<0.001), although after adjustments the excess mortality risk of W relative to M was no longer significant (HR 1.12, p=0.42). No significant differences in the adjusted 3-year risks for MI or stroke between M and W (HR 1.25, p=0.52, and HR: 1.15, p=0.52, respectively). However, both the cumulative 3-year incidence of and adjusted risk for MB were significantly ↑ in W than in M (17.0% vs 11.3%, p=0.002, and HR 1.47, p=0.03). No significant differences in the adjusted 3-year risks for all-cause death, MI, and stroke between M and W. However, Was compared with M were associated with excess adjusted risk for MB	Matsumura-Nakano, 2018

Cardio-surgical procedures (1/2)

Disease	**Object**	**Objective**	**Sample**	**Results** **Main conclusions**	**Author, year**
TAVR	Consecutive patients treated with TAVR	Primary endpoint: all-cause 3-year mortality	N=1818	M with DM: substantially ↑ 3-year mortality [39.8% compared to M without DM 29.7%, p<0.01]. M with DM: significantly ↑ 3-year mortality in comparison to W with (p<0.01) or without DM (p<0.01). No difference in 3-year mortality for W with (29.0%) and without DM (27.3%), p =0.70]. This ↑ in mortality in M DM was triggered by both CV and non-CV mortality DM: independent predictor of 3-year mortality after TAVR only in M. Interaction between M and DM was independent predictor of 3-year mortality [HR 1.88; p<0.01]. DM did not affect 30-day mortality for the overall cohort and for M	Linke, 2018
TAVR	Severe symptomatic aortic stenosis treat ed with TAVR	Sex-specific outcomes of patients undergoing TAVR with newer generation valves	N=1661 583 high risk W 42% 1078 intermediate risk W 38.2%	In both cohorts, W were more likely than M to be frail (22% vs 13%; p<0.001), but less likely to have comorbid conditions. W were more likely to receive ≤23-mm valves (74.1% vs 11.1%; p<0.001) and less likely to receive 29-mm valves (1.4% vs 35.1%; p<0.001). In combined cohorts, no difference in mortality for W compared with M at 30 days (2.0% vs 1.2%; p=0.20) or 1 year (9.3% vs 10.2%; p=0.59). No differences in disabling stroke or any stroke at 30 days or 1 year; however, W had an ↑ rate of minor stroke at 30 days (2.1% vs 0.7%; p=0.01). Female sex was associated with ↑ major vascular complications (7.9% vs 4.4%; p=0.003), but not with moderate or severe paravalvular regurgitation. No apparent sex-specific differences in survival or stroke.	Szerlip, 2018

Cardio-surgical procedures (2/2)

Disease	Object	Objective	Sample	Results Main conclusions	Author, year
TAVR	Exclusive all women treated with TAVR	Safety and performance of contemporary TAVR	N=1019 intermediate to high-risk W 100%	The primary VARC-2 efficacy composite endpoint occurred in 10.9% patients beyond 30 days and in 16.5% at 1 year. The incidence of 1-year death or stroke was 13.9%. Death occurred in 12.5% patients and stroke in 2.2%. Prior coronary revascularization (HR 1.72; p=0.006) and EuroSCORE I (HR 1.02; p=0.027) were independent predictors of the VARC-2 efficacy endpoint. Similarly, EuroSCORE I (HR 1.02; p=0.013), baseline AF (HR 1.58; p=0.022), and prior PCI (HR 1.50; p=0.035) were independent predictors of 1-year death or stroke.	Chieffo, 2018
TVD	Isolated TV surgery	Acute in-hospital outcomes	N=5005 W 58%	IHM (7.9% vs 7.7%; p=0.99) and median LOS (11 vs 11 days; P=0.99) were similar between M and W. However, median hospital charges were ↑ for M ($166000 vs $155000; p=0.04). In-hospital mortality was similar between M and W, but markedly high for both sexes in comparison to left-sided isolated valve surgery	Chandrashekar, 2018

Meta-analysis studies (1/2)

Disease	**Procedure**	**Objective**	**Sample**	**Results** **Main conclusions**	**Author, year**
ACS	Antiplatelet therapy	Beneficial effect of P2Y12 inhibitors in addition to aspirin	9 RCT, n=107126	Compared to aspirin alone, clopidogrel ↓ MACE in M (RR 0.79; p=0.003), but was not statistically significant in W (RR 0.88). Clopidogrel therapy significantly ↑ bleeding in W but not M. Compared to clopidogrel, prasugrel was beneficial in M (RR 0.84; p=0.02) but not statistically significant in W (RR 0.94; p=0.30); ticagrelor ↓ MACE in both M (RR, 0.85; p=0.001) and W (RR 0.84; p=0.02). Indirect comparison demonstrated no significant difference between ticagrelor and prasugrel in either sex. In comparison to aspirin alone, P2Y12 inhibitors ↓ MACE in W and M. Ticagrelor was superior to clopidogrel in both sexes. Prasugrel showed a significant benefit only in M. Indirect comparison did not demonstrate superiority of ticagrelor over prasugrel in W.	Brown, 2018
CAD	PCI	Clinical outcomes	49 studies, N=1032828 W 25%	In-hospital mortality (OR 0.58, p<0.001), 30-day mortality (OR 0.64, p=0.04), 1-year mortality (OR 0.67, p<0.001), and at least 2-years mortality (OR 0.71, p=0.005) were significantly ↓ in M than in W. The MACE was significantly ↓ in M compared with W in <1-year or at least 1-year (OR 0.67, p<0.001 and OR 0.84, p<0.001). M vs W: ↑ rate of revascularization for at least 1-year (OR 1.17, p<0.001), and ↓ rate of revascularization for < 1-year (OR 0.93, p<0.001).	Guo, 2018
AF	Anticoagulant therapy	Efficacy and safety DOACs	5 trials, N=66389 W 37.8%	W treated with DOACs were at ↑ risk of stroke and systemic embolism compared with M (RR 1.19) but there was a significantly ↓ risk of MB in W compared with M (RR 0.86). Meta-analyses suggested differences between various DOACs in M and W W treated with DOACs had a ↓ rate of MB and ↑ rate of stroke and systemic emboli compared with M	Raccah, 2018

Meta-analysis studies (2/2)

Disease	Procedure	Objective	Sample	Results Main conclusions	Author, year
AF	Outcomes in AF patients	Occurrence of stroke and TE	44 studies, N=993603 W 48.9%	↑ risk of stroke for W vs. M (HR 1.24). Overall, TE risk was not different between W and M. No sex differences were found for MB, CV death and all-cause death. Significant relationship between ↑ age and difference in stroke risk between W and M (HR: 1.01 for each year of age increase), is most evident at age > 65 years. W with AF are at ↑ risk of stroke compared to M.	Marzona, 2018