**Epidemiology of first cardiovascular disease manifestation according to age and sex in Catalonia, Spain**

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**Introduction**

Cardiovascular diseases (CVDs) are responsible of a large part of total deceases in Spain as well as in other European countries. These diseases are mostly consequence of the presence of large, or numerous, and/or complicated (hemorrhage, rupture, thrombosis, etc) atheroma plaques deposited in the arterial walls. Heart failure is also a relevant manifestation of cardiovascular disease. Longer survival in better health care systems is an important determinant of HF, one of the CV disease manifestation associated with greater healthcare expenditures. Although, coronary heart disease is a leading determinant of heart failure, obesity, diabetic cardiomyopathy, ageing, and high blood pressure are strong determinants of HF on their own.

There are varied manifestations of CVD according to the vascular location where atherosclerosis is more prominent or complications affect critically organ/system perfusion or function. Myocardial infarction, angina, ischemic or hemorrhagic stroke, transient ischemic attack, short distance intermittent claudication, or acute ischemia of the foot, are probably best known and referred as hard or classical manifestations of CVDs. However, advanced preclinical atherosclerosis (such as carotid stenosis), abdominal aortic aneurysm, renovascular hypertension, revascularization procedures (not always a direct consequence of an acute event), stable initial angina or undetermined ischemic heart disease, and silent lacunar infarction, among others, are also clinical manifestations of CVD that deserve clinical attention.

Although, classical, so called hard, manifestations of CVD have stronger clinical implications, and are the main outcome for randomized trials evaluating preventive therapies, other atherosclerotic manifestation of CVDs are also relevant in terms of lifestyle and treatment initiation, deeper cardiovascular evaluation (imaging test, lab work, ischemia testing, etc), hospital admission, and, most important changes in individuals quality of life or perception of health status. Furthermore, type of CVD manifestation and severity varied by age and sex, between and within populations (country’s wealth, genetic, cultural and ethnic backgrounds, access to health care and socioeconomic status, etc), and they can change overtime according to the health system (prevention programs, proactive treatment, cardiovascular checks, etc) and the prevalence and evolution of traditional and non-traditional risk factors.

In this study, we aimed, from a clinical population-data driven approach, to describe the first reported clinical manifestation of cardiovascular disease in Catalonia (Spain), and to evaluate differences by age group and sex.

**Methods**

**Study design, data sources and selection criteria**

The Catalonian Health System (CatSalut) is the public health provider in Catalonia, Spain, where national Health System competences are transferred to autonomous regions and are financed by general taxes under principles of universality, free access and equity. The Catalonian Health Institute (ICS) is the main provider of primary healthcare services in CatSalut, managing 286 primary care teams, including 74% of the total population. Primary care professionals from ICS (approximately 15,000) use the same computerized medical record program (e-CAP). The SIDIAP database was created in 2010 for research purposes and contains anonymous, longitudinal, patient information extracted from the e-CAP. CMBD database (data from hospitalization statistics and specialized out-patient care of the hospitals of the National Health System) and pharmacological treatments (from the pharmacy-invoicing data provided by the CatSalut) are automatically added to the SIDIAP. This makes SIDIAP a very comprehensive source of information to evaluate non-communicable diseases.

Our study population consisted of persons aged at least 18 years included in the SIDIAP dataset on January 1st, 2010 (n=4339045). We excluded individuals with prevalent cardiovascular events (n=221913, 5,1%), known type 1 diabetes (n= 15489, 0,36%), and/or known atrial fibrillation (n= 85953, 1,98%). The remaining were considered at risk individuals (n=4052987) and were followed until cardiovascular event, death, or end of study (December 2016). The study population was divided into 5 different age-groups according to baseline age and sex: < 35 years men and women (**young, Y**), 35-55/65 (men/women) (**early adulthood, EA**), 55-65/65-70 (**middle adulthood, MA**), 65-75/70-75 (**young old, YO**) y, and > 75 years men and women (**middle-to-very old, MVO**), respectively (Table 1). This age grouping is a pragmatic and convenient approach based on how clinical practice is conducted in our Public Health Care System considering the age range at which systematic cardiovascular risk evaluation is recommended (Framingham-REGICOR strategy 35-75 years), and the age limit to define premature events according to sex, i.e., < 55 y for men and < 65 for women (refe).

This is a retrospective study using anonymous health data, thus, informed consent was not obtained from participants according to Spanish regulations on observational studies. The study was approved by the Ethics Committee of the Primary Healthcare University Research Institute (IDIAP) Jordi Gol (Barcelona, Spain).

**Baseline characterization and cardiovascular disease outcomes**

Baseline characteristics of the study population were collected on January 1st 2010, which was considered the inclusion date (index date). We collected from the SIDIAP database diagnoses based on ICD-9/ICD-10 codes (diabetes, hypertension, hyperlipidaemia, overweight/obesity, fatty liver, etc), cardiovascular and comorbid related medications) based on the Anatomical Therapeutic Chemical (ATC) classification system, values and concentrations of laboratory data available for each individual (lipids, creatinine, urinary albuminary excretion (UAE)), and blood pressure, and anthropometric data. Specific diagnosis codes can be found in online supplementary information (Table). Chronic kidney disease was based on the estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and the urine albumin-to-creatinine ratio (UACR). Microalbuminuria was defined as a UACR of 30 to 299 mg/g and macroalbuminuria was defined as a UACR ≥300 mg/g.

Cardiovascular outcomes involving 4 major conditions were recorded and are presented as coronary heart disease, cerebrovascular disease, peripheral artery diseases, and heart failure. Coronary heart disease was defined as fatal or non-fatal myocardial infarction, angina or unstable angina, undetermined ischemic heart disease, and coronary revascularization (coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI)). Cerebrovascular disease was defined as fatal or non-fatal ischemic or hemorrhagic stroke, transient ischemic attack (TIA), and intracerebral revascularization. Peripheral artery diseases were defined as intermittent claudication, extracerebral artery stenosis, and carotid or peripheral revascularization (endovascular, stenting, or surgical bypass). Heart failure included congestive/acute heart failure and other heart failure diagnoses (systolic and diastolic, chronic, or undetermined).. Specific diagnosis codes can be found in online supplementary information (TABLE).

**Results**

Between January 2010 and December 2016, 257926 (6.36%) individuals, from a total of 4052987 at risk, experienced a first cardiovascular event.

**Incidence of first cardiovascular events**

The study population was followed for a median of 7 years. During a total of 26,947,469 person-years of follow-up from a total of 4,052,966 at risk individuals (mean age 69 years, 46.7% women), 257905 (6.36%) developed a first CV event, with an annual incident rate of 0.96%. Incident rate per year was higher in men than in women, 1.06 vs. 0.86%, with a 7 year cumulative incidence of 7.04 and 5.74%, respectively (Table 4, Supplementary Figure 3). Cumulative incidence increased with age from 0.37 in Y to 2.71, 10.82, 17.66, 25.40% in EA, MA, YO, and MVO, respectively, and was higher in men (from Y 0.42 to MVO 28.35%) than in women (from Y 0.33 to MVO 23.81%) for all age group categories (table 4). Overall, men had a 24% higher risk (HR [95% CI] 1.24 [1.23;1.25], ) of new cardiovascular events compared with women, being this higher risk consistent at all age group categories: 1.29 [1.20;1.38], 1.32 [1.30;1.34], 1.19 [1.17;1.22], 1.32 [1.30;1.35], 1.28 [1.26;1.29], for Y, EA, MA, YO, and MVO, respectively, (Figure 3, supplementary table).

**Baseline characteristics of individuals developing CV**

Baseline characteristics of subjects with incident CV events by age group (supplementary table 1) and age group and sex are shown at table 1. Overall, there was a higher percentage of men 53.3% (n=137341), especially in MA and YO (71.8% and 68.7%) groups, however, in the oldest MVO age category female sex was more prevalent (61%). Mean age of first cardiovascular event was 69.1 (SD= 13.8) years, and was higher in women (72.7 ± 13.2) than in men (65.9 ± 13.4)., The number and proportion of CV events was lowest at young age and highest in the oldest age group. However, while in men there were a steady increase in number of events (EA 29066 [21.16%]; MA 31897 [23.22%]; YO 34914 [25.43%]; MVO 39710 [28.91%]), in women, this number was particularly high in the oldest MVO (62118, representing 51.5% of their total first events) and EA group (28727 [23.8%]), compared with MA and YO (12547 [10.4%]; and 15884 [13.2%], respectively) (supplementary table 1, Table 1).

Cardiovascular risk factors (CVRF) differed by age group and sex (supplementary table 1 and Table 1). Hypertension (52.6% overall, 60% women, 46.1% men) and obesity (41.3% overall, 47.1% women, 35.5% men) were the most prevalent risk factors. Active smoking was particularly prevalent in Y individuals (55.3% overall, 44% women, 64.6% men) and decrease thereafter in both sexes. Besides smoking, Y individuals from both sexes had the lowest prevalence of classical and non-classical CVRF. The highest prevalence or concentrations of several classical and non-classical risk factors was observed in the EA (a few in MA) group including: total and LDL cholesterol, triglycerides and remnant cholesterol, atherogenic dyslipidemia, BMI and obesity, diastolic blood pressure, microalbuminuria, high-risk alcohol consumption, and higher deprivation index. On the other hand, anti-hypertensive treatment, type 2 diabetes, systolic blood pressure, and CKD (eGFR EPI < 60 ml/min) were highest in older YO and MVO groups. Statin and antiplatelet treatment also increased with age.

Differences by sex and sex-and-age group were varied (table 1). Women had higher total and LDL cholesterol (especially at older age groups), atherogenic dyslipidemia prevalence, BMI, and received more frequently hypotensive medications, but had lower CKD-EPI. Men, instead, had higher prevalence of smoking and microalbuminuria, higher concentrations of triglycerides and remnant cholesterol, and higher DBP, but lower HDL cholesterol. Although globally T2DM prevalence was not different in men and women, T2DM was more prevalent in EA and MA women (16.4 vs. 13.6%, and 27.8 vs. 22.5%, compared to men, respectively), and the opposite trend was observed for YO and MVO women (25.2 vs. 29.2%, and 22.5.8 vs. 25.1%, compared to men, respectively). Statin treatment was also more prevalent in EA and MA women (29.5 vs. 20.7%, and 40.3 vs. 35.0%, respectively).

**Age group, sex, and cardiovascular territory**

Table 2 and supplementary figure 1A show number of individuals from the overall at risk baseline population who suffered a first cardiovascular event during the study period and the vascular territory affected. Coronary heart disease represented 39 and 40.1% of total events in Y and EA individuals, respectively, and decreased progressively to 18.3% in individuals aged 75 and above. The opposite trend was observed for heart failure as the first manifestation of CVD, ranging from 45.5% of all incident events in the oldest MVO to 12.6% in the youngest Y group. Cerebrovascular disease followed a similar, although less evident, pattern to that observed in coronary heart disease, with higher proportion of cerebrovascular events in the Y (32.1%) and lowest (24.4%) in the MVO group. Finally, the proportion of peripheral artery disease events was similar in most of the age groups (16.3-21.9%) and lowest in the MVO (12%).

Some differences in the proportion of CV events by territory and age in men and women were apparent (supplementary table 2 and supplementary Figures 1B and 1C). In women, there was a sharper increase in the proportion of HF from the Y (12.3%) to the MVO group (50.3%). Similarly, but on the opposite direction, proportion of PAD events decreased from 18 to 8.94% in women, but in men increased until the age of 75y (from Y to YO groups, 15 to 24.4%, respectively), after which a lower proportion of PAD (16.8%) was observed. Cerebrovascular event proportion varied less in men (lowest in EA 21.3% and highest in Y 27.8%) than in women, in whom a progressive decrease from 37.8 to 24.6%, from youngest Y to oldest MVO group, respectively, was observed. Coronary event proportion by age group for men and women followed a similar trend to that described for the total population (supplementary table 2 and supplementary Figure 1B, 1C).

Coronary events were more prevalent at all age groups in men (ranging from 44.4 to 21.6% in MVO) than in women. On the contrary, women had higher proportion of cerebrovascular events at all age groups, in particular at younger groups Y and EA (37.8, 31.6%) as compared to men (27.8, 21.3%), respectively. Proportion of HF was also consistently higher in women, with the exception of the youngest group (women 12.3 vs. men 12.8%). Finally, peripheral CVD was more prevalent in men as compared to women, especially in the oldest (MA, YO, MVO) age groups (supplementary table 2 and Figure 1A 1B).

**Age group, sex, and type of cardiovascular manifestation**

Specific manifestation of first reported CV event by age and sex are presented in table 3 and represented in supplementary figure 2. In women, heart failure was the most prevalent manifestation with the exception of the youngest and EA group in whom TIA/ ischemic stroke (12-16% each), and unspecified ischemic heart disease (12-16%), were more frequently reported (Table 3, supplementary figure 2). Again, ischemic stroke was the leading manifestation, after heart failure, in MA/YO/MVO (13-14%). In men, PAD (17.4%) and MI (13.9%) were the most prevalent first manifestations overall. Myocardial infarction was the most frequent in Y (22.6 %) and EA (25.1%), peripheral artery disease in MA (20.9%) and YO (19.3%), and overall heart failure in MVO.

**Discussion**

In this retrospective study we show the contemporary incidence and type of first reported manifestation of cardiovascular disease in adult individuals in Catalonia, Spain, during a median 7 year follow-up. 0.96% of individuals at primary cardiovascular prevention experienced annually a CV event, and this incidence rate was higher in men than in women irrespective of age.

From a physiopathological perspective CV risk associated with age is a continuum. However, our age-grouping is a pragmatic approach on how cardiovascular prevention should be standardized in clinical practice. First, CV risk evaluation is not generally recommended in individuals younger than 35-40 y (Systematic Coronary Risk Evaluation (1) and our local Framingham-REGICOR approach(2). Second, prevention of premature CV events is an urgent need (refe WHO). Third, CV prevention should be individualized in individuals older than 75 years as per physician understanding, some clinical recommendations, and patient situation. Finally, reducing global and regional risk of premature non-communicable disease death, being CVD the largest contributor, by 25% by 2025 is a key target set by United Nations in 2011 (3).

We have observed large differences in the first clinical manifestation of cardiovascular disease by age, with coronary heart disease being more prevalent at younger, and heart failure at older, age groups. This data should prompt to evaluate how an ongoing prevention strategy could be partially swift or balanced from a mainly lipid-centric, an outstanding contributor of CHD, to a more adipo/diabetocentric and blood pressure approach, relevant determinants of heart failure. Thus, we believed this data should be useful to modulate current strategies, in a European Mediterranean country with low CVD mortality compared with north European ones.

Puntos:

1. Ofrecer comparaciones con estudios previos europeos sobre todo. Creo que hemos de ir a una revista europea de cardiología.
2. Large differences in first manifestation of cardiovascular disease by age and sex
3. Predictive equations based on data not incorporating cerebrovascular disease outcomes may underestimate risk in women since they are more prompt to cerebrovascular disease. On the other hand, prevention of atherosclerotic events (more focus in lipid prevention) in older women would promote cardiovascular medications (statins) that may not prevent heart failure, more close to body weight reduction and blood pressure control.
4. Data based on clinical diagnosis from treating physicians, they may not be as specific or objective as those specified in clinical trials but they imply medical treatment, consultant to other specialist to further study, treatmen optimization, further testing (imaging or lab tests), etc
5. Heart failure arose as the first manifestation in women.

Limitations

Double diagnosis at the same date

Infraregistro de eventos y comorbilidades