

Sex and Circadian Periodicity of Cardiovascular Diseases

Are Women Sufficiently Represented in Chronobiological Studies?

Roberto Manfredini, MD^{a,*}, Raffaella Salmi, MD^b,
Rosaria Cappadona, MW^c, Fulvia Signani, PsyD^d,
Stefania Basili, MD^e, Niki Katsiki, MD^f

KEYWORDS

- Biological rhythms • Circadian rhythm • Sex • Clinical studies • Myocardial infarction
- Aortic aneurysm, rupture and dissection • Cerebrovascular disease • Stroke
- Sudden cardiac death

KEY POINTS

- Women are often excluded or underrepresented in clinical trials. Moreover, many studies do not report the number of men/women participants or provide analysis by sex.
- The onset of many life-threatening cardiovascular acute events respects a circadian (~24 hour) periodicity.
- Although 44% of the chronobiologic studies provided separate analysis by sex, these studies included 85% of total cases.
- Morning hours represent a critical time for the onset of acute cardiovascular diseases in men and women.

CLINICAL TRIALS AND SEX DISPARITIES

The problem of exclusion or underrepresentation of women in clinical trials has remained an open question over time. In his special report published in the *New England Journal of Medicine* more than 2 decades ago, Jean-Claude BenNET wrote that,

“although the inclusion of women and minorities in medical research is necessary for valid inferences about health and disease in these groups, both women and members of minority groups have been excluded from or underrepresented in many clinical trials.”¹ Over that time, the US Food and Drug Administration adopted specific

Disclosure Statement: N. Katsiki has given talks, attended conferences, and participated in trials sponsored by Amgen, Angelini, AstraZeneca, Boehringer Ingelheim, Galenica, MSD, Novartis, Novo Nordisk, Sanofi, and WinMedica. The other authors have nothing to disclose.

^a Department of Medical Sciences, School of Medicine, Pharmacy and Prevention, University of Ferrara, via L. Ariosto 35, I-41121 Ferrara, Italy; ^b Second Internal Medicine Unit, Azienda Ospedaliera-Universitaria ‘S. Anna’, Ferrara, Italy; ^c Department of Morphology, Surgery and Experimental Medicine, School of Medicine, Pharmacy and Prevention, University of Ferrara, Ferrara, Italy; ^d Azienda Sanitaria Locale, Ferrara, Italy; ^e Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy; ^f Second Department of Propaedeutical Internal Medicine, Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece

* Corresponding author. Department of Medical Sciences, School of Medicine, Pharmacy and Prevention, University of Ferrara, via L. Ariosto 35, I-41121 Ferrara, Italy.

E-mail address: roberto.manfredini@unife.it

Heart Failure Clin ■ (2017) ■–■

<http://dx.doi.org/10.1016/j.hfc.2017.05.008>

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measures aimed at improving and ensuring the representativeness of women participating in clinical trials. In detail, the National Institutes of Health Revitalization (1993) required that National Institutes of Health-funded clinical trials should include women and minorities. Later, in 1998, the US Food and Drug Administration issued the “demographic rule,” requiring drug manufacturers to report the age, sex, and race of clinical trial participants in their annual reports to the agency.² A study by Geller and colleagues³ aimed to determine the level of compliance with these guidelines for the inclusion, analysis, and reporting of sex and race/ethnicity in federally funded randomized controlled trials and to compare the current level of compliance with that from 2004. After a PubMed search, 86 articles were included in the analysis (30 were sex specific, and 56 included both men and women). The median enrollment of women in these latter studies was slightly more than one-third (37%), and 75% of the studies did not report any outcomes by sex. Compared with 2004, no significant changes in inclusion or reporting of sex or race/ethnicity were found. A cross-sectional study of 86 novel therapeutics approved by the US Food and Drug Administration (2011–2013) on the basis of 206 pivotal trials was recently done.⁴ A similar proportion of pivotal trial participants was found for males and females (mean 50.3% and 49.7%, respectively). Thus, progress has been made since the early 2000s, when the participation of women in clinical research was limited.⁴ Even if much has changed since the U.S. federal law mandating the inclusion of women as well as men in clinical trials and analyzing the results by sex, such progress is not considered sufficient by some authors.⁵

CIRCADIAN PERIODICITY OF CARDIOVASCULAR DISEASES

Chronobiology is the biomedical science aimed to study biological rhythms. According to the cycle length, such rhythms may be divided into 3 main types: (a) ultradian (<24 hours, eg, hours, minutes or even seconds), (b) circadian (approximately 24 hours), and (c) infradian (>24 hours, eg, days, weeks, months, or seasons).⁶ Circadian rhythms, driven by specific clocks, are the most commonly and widely studied biological rhythms; this topic is the subject of other articles in this special issue.^{7,8} In conditions of both health and disease, the cardiovascular system is organized in nature according to a oscillatory circadian order, and several pathophysiological factors, not so harmful if considered alone, are capable to trigger unfavorable, events if they present all together within

the same temporal window. This phenomenon opened up the new concept of ‘chronorisk.’⁹ As a consequence, since the early 1980s a series of studies demonstrated that the occurrence of cardiovascular events is not evenly distributed in time, but shows specific temporal patterns varying with the time of the day.^{10,11} In this special issue, specific articles are devoted to circadian and other temporal rhythmic oscillations (eg, weekly, seasonal) for several diseases of the cardiovascular system, such as ischemic heart disease, acute aortic syndromes, and venous thromboembolism.^{12–15}

Quoting Berlin and Ellenberg,¹⁶ we aimed to try to answer their questions. Do the results of chronobiological studies apply consistently and equally across all clinically meaningful subclasses of patients enrolled in the studies? In other words, are women sufficiently represented in the studies exploring the circadian periodicity of acute cardiovascular diseases? Can the results of these studies be extrapolated to sex subgroups of patients who did not participate sufficiently in the original research? Thus, a PubMed search was performed, investigating the papers published between 1996 and 2015, focusing on the circadian periodicity of acute myocardial infarction (AMI), sudden cardiac death (SCD) and cardiac arrest, rupture or dissection of aortic aneurysms, and cerebrovascular events (eg, stroke, ischemic and hemorrhagic, intracerebral and subarachnoid hemorrhage). For each of these diseases, data on published studies were collected, including authors, country and year of publication, as well as clinical trial characteristics, including number of patients, age, number of men and women, circadian peak time of occurrence, and analysis by sex (when performed) with respective peak times. Moreover, for each of these diseases a figure showed the weighted mean ratio between number of events per hour during the 24 hours of the day, roughly splitting the day in 2 parts (such as midnight to noon, and noon to midnight) both for men and women. In these figures, the diameter of each circle is proportional to the number of subjects analyzed in each study.

ACUTE MYOCARDIAL INFARCTION

Awareness of a clinical condition represents a crucial point. Although coronary heart disease (CHD) awareness among women has increased over the last decades, it is still suboptimal. In this context, the 2012 American Heart Association National Women’s Survey showed that only 56% of women respondents cited CHD as the leading cause of death in women, and only 48% of women

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