A medicine for tall, white, blond-haired and blue-eyed, middle-aged, physically active, rich males?

Gaia Cattadori[1], Chiara Segurini[1], Piergiuseppe Agostoni[2,3] and Susanna Sciomer[4]

It is known and acknowledged by researchers that the population studied in clinical trials is different from that seen in our hospital wards. As a consequence, trial results may not be perfectly reproduced in the general population, making therapeutic choices somehow ambiguous and undefined. This is an important limitation, because treatment guidelines are based on trials, and we are instructed to treat patients according to guidelines as much as possible. Notably, in the case of a litigation, guidelines are used as a reference.

For instance, in cardiac diseases, female subjects, the elderly and patients with comorbidities are still often underrepresented or even excluded from randomized clinical trials.

Indeed, women constitute over 50% of the heart failure population,[1] but only 20–30% of the decision-making trial populations are female (Table 1).[2–12] This also applies to registries and retrospective analyses. For instance, the MECKI score is based on a registry of cardiopulmonary-exercise-test data on top of a comprehensive evaluation of 6223 heart failure patients, at present, but only 1125 are female, that is, 18%.[13] Moreover, recent meta-analyses of clinical trials confirm an underrepresentation of females.[14,15] Altogether, these observations raise an important warning about research results superficially and erroneously applied to women.

The same applies to elderly people. Indeed, even though cardiovascular diseases are mainly present in elderly subjects, patients >75 years old are rarely included in trials, and most treatments have primarily been tested in middle-aged men.[16] In the year 2000, only 3.45% of 8945 patients randomized in clinical trials and 1.2% of patients used in 706 meta-analyses were over 65 years of age.[17] Similarly, heart failure mainly affects older people and is uncommon under the age of 60. Heart failure incidence and prevalence rise steeply with age in those aged over 60.[18] Its prevalence in community-dwelling people aged 25–49 years is 1.2%, and it is 0.7–1.3% in people aged 45–54 years.[19]

The most-often-mentioned prevalence estimate for the adult population aged 65 years and over is 5–9%, rising to ≥10% among people >70 years of age.[20] Unfortunately, the mean age of patients in the landmark trials of heart failure guidelines is 60–70 years (Table 1).

The presence of comorbidities makes the scenario of patient evaluation even more complicated. Indeed, in several studies on cardiovascular diseases, comorbidities are excluded, although they affect prognosis and although patients with multiple diseases are the most frequent in our hospital. In this regard, the respiratory literature has generated a concept that we believe is very important, the so-called *comorbidome*. The *comorbidome* is a graph built for patients with COPD, showing the likelihood of death in the middle, and the different comorbidities around it represented with circles whose size corresponds to the prevalence of the disease in COPD. Unfortunately, we do not have such a concept in cardiovascular medicine, but, using data from the Euro Observational Research programme as revised by van Deursen et al.,[21] we can draw the chronic heart failure *comorbidome* (Figure 1). Briefly, 3226 outpatients with chronic heart failure from all over Europe are described. On both axes, the hazard ratio of all-cause mortality for each heart failure comorbidity is reported with a value of 4 in the centre and 0 in the periphery (multivariate analysis). Each circle is a specific comorbidity with

[1]Multimedica, IRCCS, Milan, Italy
[2]Centro Cardiologico Monzino, IRCCS, Milan, Italy
[3]Dipartimento di Scienze Cardiovascolari, Università di Milano, Italy
[4]Dipartimento di Scienze Cardiovascolari, Respiratorie, Nefrologiche, Anestesiologiche e Geriatriche, 'Sapienza', Rome University, Italy

Corresponding author:
Piergiuseppe Agostoni, Cardiovascular Section, Department of Clinical Sciences and Community Health, Centro Cardiologico Monzino, University of Milan, Via Parea 4, 20138 Milan, Italy.
Email: piergiuseppe.agostoni@ccfm.it

Table 1. Mean age and percentage of women in landmark trials for heart failure patients.

Trial	Year	Drug class	Mean age (years)	Women (%)
CONSENSUS[2]	1987	ACE-I	P: 71 T: 71	P: 29 T: 30
SOLVD Treatment[10]	1991	ACE-I	P: 61 T: 61	P: 19 T: 20
SOLVD Prevention[11]	1992	ACE-I	P: 59 T: 59	P: 11 T: 11
Val-HeFT[4]	2001	ARB	P: 63 T: 62	P: 20 T: 20
RALES[9]	1999	MR antagonist	P: 65 T: 65	P: 27 T: 27
EMPHASIS-HF[12]	2011	MR antagonist	P: 69 T: 69	P: 22 T: 23
US Carvedilol HF Study[7]	1996	Beta-blocker	P: 58 T: 58	P: 24 T: 23
COPERNICUS[8]	2001	Beta-blocker	P: 63 T: 63	P: 20 T: 21
SCD-HeFT[3]	2005	ICD	P: 60 T: 60	P: 23 T: 23
MADIT-CRT[5]	2009	CRT	ICD: 64 CRT: 65	P: 24 T: 25
PARADIGM[6]	2014	ARNI	ICD: 64 CRT: 65	P: 24 T: 25

ACE-I: angiotensin-converting enzyme inhibitor; P: placebo; T: treatment; ARB: angiotensin receptor blocker; MR: mineralcorticoid receptor; ICD: implantable cardioverter defibrillator; CRT: cardiac resynchronization therapy; ARNI: angiotensin receptor neprilysin inhibitor.

a different width based on its specific prevalence. We reported the following comorbidities: chronic kidney disease, anaemia, diabetes, hypothyroidism, hyperthyroidism, sleep apnoea, stroke, and COPD. Clearly, there are several more comorbidities that can influence heart failure prognosis, but comparable data were not available.

Finally, the prognosis of cardiovascular diseases changes with time, and it has fortunately improved. However, prognosis also varies according to the place where the patient lives depending on country economic status, health care availability, climate, attention to fitness and dietary habits. This is among the reasons why pharmaceutical companies always extend large-population studies worldwide including low-income countries where clinically relevant 'events' are more likely to happen. However, studies performed in high-income and in low-income countries provide different results.[22,23] Accordingly, trials' results should be, but are not, applied to populations similar to those studied, including for a cultural and socio-economical environment.

The paper by Gronhoj et al.[24] in the present issue of the *European Journal of Preventive Cardiology* reaffirms and overcomes these concepts, underscoring another aspect of uncertainty: who are the patients who refuse to participate in a multicentre-population-based observational study? The results are astonishing: subjects who decline participation have higher comorbidities and lower socio-economic status. Therefore, the main question is: by using the trial-based results, are we providing the best treatment to all our patients or are we generating a medicine for tall, white, blond-haired and blue-eyed, middle-aged, rich males who are physically active and know about risk factors? We are probably generating an unfair medicine: we need to recognize it and to do our best to overcome this structural limitation. Accordingly, Gronhoj et al. should be congratulated for underscoring this population bias present in one of the most advanced European countries.

In conclusion, research trials and guidelines must be applied when considering the general population, but they must be followed with caution in daily-life medical judgment. Indeed, analysing the single patient, personal and specific characteristics must also be taken into account while making the doctor's personal judgment central. Medical decisions cannot be totally left to a computer.
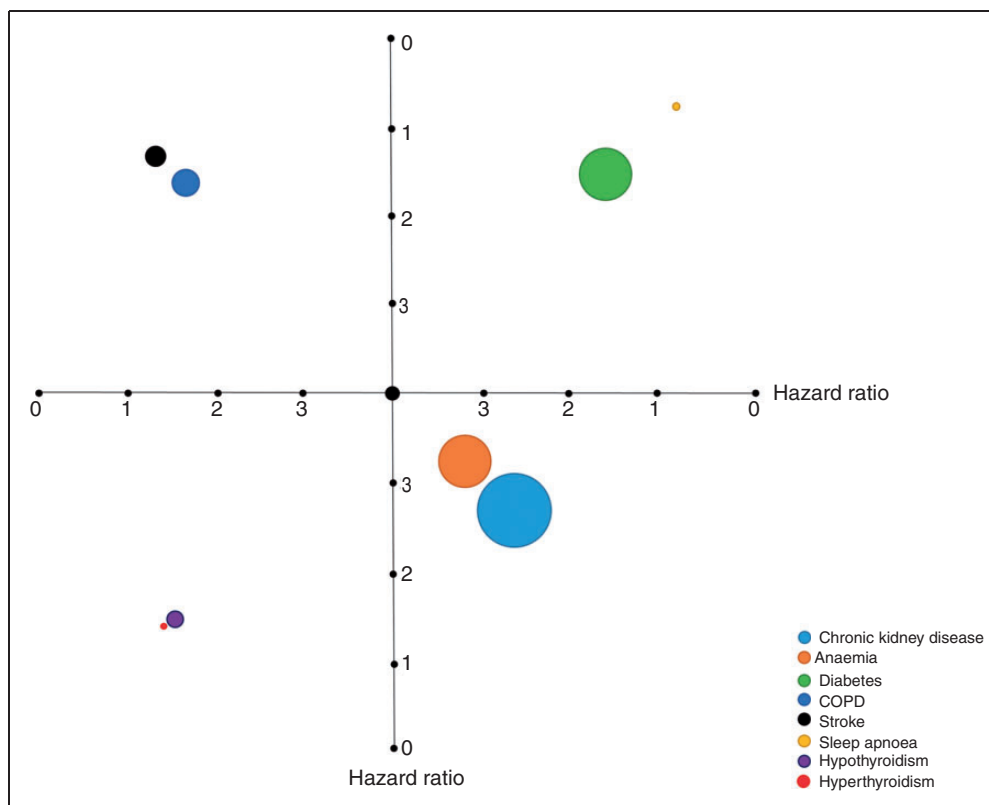
Figure 1. Chronic heart failure *comorbidome*. Data are derived from the Euro Observational Research programme as revised by van Deursen et al.[21] The hazard ratio of all causes mortality for each heart failure comorbidity is reported on both axes with a value of 4 in the centre and 0 in the periphery. Each circle is a specific comorbidity with a different width based on its prevalence. The following comorbidities are reported: chronic kidney disease, anaemia, diabetes, hypothyroidism, hyperthyroidism, sleep apnoea, stroke, and chronic obstructive pulmonary disease (COPD).

Declaration of conflicting interests

Funding

References

1. Shin JJ, Hamad E, Murthy S, et al. Heart failure in women. *Clin Cardiol* 2012; 35: 172–177.
2. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987; 316: 1429–1435.
3. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; 352: 225–237.
4. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991; 325: 303–310.
5. Goldenberg I, Kutyifa V, Klein HU, et al. Survival with cardiac-resynchronization therapy in mild heart failure. *N Engl J Med* 2014; 370: 1694–1701.
6. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; 371: 993–1004.
7. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996; 334: 1349–1355.
8. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001; 344: 1651–1658.
9. Pitt B, Zannad F, Remme WJ, et al. for the Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; 341: 709–717.
10. Yusuf S, Pitt B, Davis CE, et al. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991; 325: 293–302.

11. Yusuf S, Pitt B, Davis CE, et al. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992; 327: 685–691.

12. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; 364: 11–21.

13. Agostoni P, Corra U, Cattadori G, et al. Metabolic exercise test data combined with cardiac and kidney indexes, the MECKI score: a multiparametric approach to heart failure prognosis. *Int J Cardiol* 2013; 167: 2710–2718.

14. Cherubini A, Del Signore S, Ouslander J, et al. Fighting against age discrimination in clinical trials. *J Am Geriatr Soc* 2010; 58: 1791–1796.

15. Heiat A, Gross CP and Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med* 2002; 162: 1682–1688.

16. Rosano GM, Lewis B, Agewall S, et al. Gender differences in the effect of cardiovascular drugs: A position document of the Working Group on Pharmacology and Drug Therapy of the ESC. *Eur Heart J* 2015; 36: 2677–2680.

17. Nair BR. Evidence based medicine for older people: available, accessible, acceptable, adaptable? *Australas J Ageing* 2002; 21: 58–60.

18. Mosterd A and Hoes AW. Clinical epidemiology of heart failure. *Heart* 2007; 93: 1137–1146.

19. Ceia F, Fonseca C, Mota T, et al. Prevalence of chronic heart failure in Southwestern Europe: The EPICA study. *Eur J Heart Fail* 2002; 4: 531–539.

20. Van Riet EE, Hoes AW, Wagenaar KP, et al. Epidemiology of heart failure: The prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. *Eur J Heart Fail* 2016; 18: 242–252.

21. Van Deursen VM, Urso R, Laroche C, et al. Co-morbidities in patients with heart failure: An analysis of the European Heart Failure Pilot Survey. *Eur J Heart Fail* 2014; 16: 103–111.

22. Khatib R, McKee M, Shannon H, et al. Availability and affordability of cardiovascular disease medicines and their effect on use in high-income, middle-income, and low-income countries: An analysis of the PURE study data. *Lancet* 2016; 387: 61–69.

23. Helis E, Augustincic L, Steiner S, et al. Time trends in cardiovascular and all-cause mortality in the 'old' and 'new' European Union countries. *Eur J Cardiovasc Prev Rehabil* 2011; 18: 347–359.

24. Gronhoj MH, Gerke O, Mickley H, et al. External validity of a cardiovascular screening including a coronary artery calcium examination in middle-aged individuals from the general population. *Eur J Prev Cardiol*. Epub ahead of print 2018. DOI: https://doi.org/10.1177/2047487318774850