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Do we need sex-specific guidelines?

Our medical guidelines are primarily based on prospective randomized trials, secondarily on meta-analysis evaluations, post-hoc analyses from large clinical trials and thirdly on results of large registry data with retrospective evaluation. Guideline expert committees prove the consistency of data from all available studies and provide us with "traffic-light" graded recommendations, comments with 30–40 -or even more- text pages, numerous tables and hundreds of references. Some time after each renewal of societies' guidelines follow "Consensus statements" or "Systematic Reviews", which try to evaluate and interpret what has been accumulated thereafter in new trials and reports. Although guidelines and expert consensus statements claim translating scientific evidence into clinical practice to assist the practicing physician with daily decision making or clinical judgement, we need "real world" registries to confirm what the scientific sages have assembled in the guidelines. Nation-wide registries are most suitable to make visible how trial results are implemented into daily practice. Large landmark trials have shown the benefit of defibrillator therapy for secondary- and primary prevention of sudden arrhythmic death, and with this a decrease of overall mortality. Sub-studies of these trials have further assessed the impact of defibrillator therapy on patient subgroups, various underlying diseases and co-morbidities.

Today, our focus is directed to potential sex differences of defibrillator benefit and outcomes for both secondary - and primary prevention indication. However, we must admit having overlooked or accepted that in all these guideline-forming trials the percentage of women enrolled were not more than 25%, mostly even lower. Nonetheless appropriate statistical analyses provided useful and valuable information on specific questions and topics, such as women outcomes. But we did not raise the question- or found an answer why there were always such significant sex enrollment differences. May it be more difficult convincing women being enrolled into randomized trial arms with potential device implantation, is there reluctance of female patient referring to trial centers, or a screening bias within trial centers? Do we have a true sex difference of disease development and prevalence, an imbalance of device provision for women, a real "undertreatment" or even prejudice for women enrollment? Why did we neglect or even ignore this disparity for a long time? Perhaps, we will encounter a solution to these questions by setting up large nation-or region-wide long-term registries? What about having the courage of designing specific "women trials" or registries?

In this current issue, S. Ingelaere and R. Willems provide an important contribution related to our questions. Within a large nation-wide registry of all newly implanted defibrillators (ICDs) between 2010 and 2019 only 21% of the total patient cohort receiving ICDs for either primary prevention (68%) or secondary prevention was females [1]. Male patients had a preponderance of coronary artery disease (54% versus 28% females), women's underlying disease were more frequently non-ischemic cardiomyopathies (68% versus 44% men); enrolled women were slightly younger, but had a tendency of more severe heart failure (NYHA II/III), a somewhat higher left ventricular ejection fraction (LVEF) (37% versus 34% in men), but less co-morbidities. Female patients had a wider QRS-complex and they underwent more often cardiac resynchronization therapy (CRT-D). During an average follow-up of almost four years women had a lower overall mortality (12.5% versus 17.1% in men) with no significant difference between primary- or secondary prevention indication. After adjustment for covariates sex category did not remain a predictor of mortality. The reported results from this registry are quite interesting; they match results from randomized prospective trials. ICD receiving women seem to have a different disease profile but benefit similarly- or even more from ICD implantation then men. Unfortunately, the registry is unable to provide information on occurrence of ICD shock delivery or VT/VF events. It would be challenging comparing real-world shock events with the recently published sub-study of all four MADIT-trials [2]. With only 24% females enrolled in this study, women had more non-ischemic cardiomyopathies (NICM), had significantly lower risk of sustained VT/VF events and less appropriate ICD shocks than men during a 3-year follow-up period. The lower risk of VT/VF events was more pronounced in women with non-ischemic cardiomyopathies. Does this really mean that women in general- and particularly with NICM have a lower risk of life-threatening arrhythmic events? These study results request better sex-specific risk assessment with "guideline-derived" ICD implantation before we accuse ICD "undertreatment" of women. Will all female patients who are candidates for ICD devices get the proper treatment, or indeed do fewer women require ICD implantation? As correctly pointed out in the herewith reported Belgian nation-wide registry the denominator of all potential ICD candidates is missing. We need reliable epidemiologic data of the true need for ICDs particularly in women. Interesting information is provided by a recent publication that reports data of the proportion of women enrolled in clinical trials submitted for Food and Drug Administration (FDA) approval studying drug- or device efficacy [3]. Of a total of 1433 to FDA- submitted trials, 263 trials were cardiovascular (CV) disease trials. Of these, 76% were industry-funded trials, 15% were government sponsored trials and 9% were funded by both industry and government organizations. Female patients were underrepresented (41% females) compared with a calculated 49% female proportion of the disease population in CV diseases. A similar disparity between calculated disease proportion and female study enrollment was noted in cancer- or psychiatric disease trials. Trials that investigated medical devices had the lowest rates of female study participation. A remarkable observation was that submitted industry-

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funded trials contained a higher female proportion than government funded trials. The authors request that efforts are needed to better align female participants in trials with the demographics of the disease affected population. A few years ago, another study evaluated women participation in CV-drug trials submitted for FDA approval between 2005 and 2015 [4]. The study assessed the percentage of women among trial participants divided by the percentage of women in the disease population ("participation to prevalence ratio", called PPR). A PPR range between 0.8. and 1.2 was interpreted as "desired representation" of women in trials. Overall, 36 drug trials were evaluated. A desirable range of women participation was noticed in drug studies for atrial fibrillation (PPR 0.8–1.2), hypertension (PPR 0.9) and pulmonary arterial hypertension (PPR 1.4). Heart failure drug trials (PPR 0.5–0.6), coronary artery disease studies (PPR 0.6) and Acute coronary syndrome trials (PPR 0.6) showed significantly lower PPR values. Under-representation of women in trials was mostly related to pre-trial screening of their potential study participants. In summary, data from this study teach us that a disease prevalence-corrected estimation of necessary women participation in trials is crucial to assess potential sex differences in trial outcomes.

Data from large and complete nation-wide registries, such as the presented Belgian registry are of eminent importance for detection of potential shortcomings and problems that may not have been recognized with the initial cornerstone trials [5]. Such a problem is the inequality between women and men with ICD implantation for primary- or secondary prevention indication. It seems odd that international ICD guidelines or consensus statements so far have ignored the obvious disparity of women enrollment in evaluated trials when it comes to translation of scientific evidence into clinical practice. We have assessments of patients' age, co-morbidities, underlying disease and heart failure differences, but a potential difference of ICD benefit or outcomes in women were not discussed, or at least are not published anywhere in the guidelines. The term of required female participation divided by the percentage of women in the disease population (PPR) has not yet entered a broad discussion when planning prospective trials. However, the FDA constantly requests a higher rate of women participation, at least of more than 25%.

Therefore, one may ask if we need specific guidelines for women? This seems cloistered, but with increasing attention to the demonstrated women disparity in trials, it may be worth considering. If this will be feasible, or studies will be doable enrolling only women, is another question. Overall, sex disparity is a multifactorial problem, containing epidemiologic, social, cultural and ethnic aspects. It needs to be tackled immediately to find satisfying answers. Until then, the term "undertreatment" of women with ICDs, just because women's under-representation in trials, should not be used, before we have a deeper insight into this complex problem.

Conflict of interest

The author of this invited Editorial comment declares that he has no conflict of interest to declare.

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