Bundle Branch Block and Benefit from Cardiac Resynchronization Therapy

Introduction

Through its pre-market review process, usually in the form of clinical trials, the U.S. Food and Drug Administration (FDA) makes every effort to assure that high-risk medical devices are effective and associated risks have been minimized before they are approved to enter the market. However, women have historically been underrepresented in many clinical trials, as is also true for other patient subgroups. This especially pertains to clinical trials investigating certain cardiovascular devices, many of which often carry a high risk to patients and have the potential to save or sustain life.

Certain differences between women and men, including physiology and anatomy, can result in medical devices performing better or worse. When participants in clinical trials reflect a diverse, real-world population (females and males, young and old, various racial and ethnic backgrounds, and patients with differing comorbid diseases and conditions), and when subgroup data from clinical trials and other data sources are appropriately analyzed, much more information can be known about the product and more relevant clinical data can be reported. However, an information gap exists on the safety and effectiveness of medical devices when not enough women are included in clinical trials, making it difficult to detect potential sex-specific outcomes.

To ensure that regulatory decisions are based on science, it is one of FDA's missions to conduct regulatory science. Regulatory science is defined as: "developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products".[1,2] In this report, we utilize regulatory science research to evaluate cardiac resynchronization therapy (CRT), a device-based therapy for patients with heart failure, as an example to describe significant differences in device safety and efficacy between women and men. Furthermore, we refer to how these sex-specific results can potentially be detected and reported.

Cardiac Resynchronization Therapy for Heart Failure in Women

More than 800,000 patients in the U.S. develop heart failure each year.[3] The mortality associated with heart failure is significant making it an important public health issue. Furthermore, heart failure mortality has been shown to be higher in women than in men.[3] Therefore, appropriate, and perhaps sex-specific, therapy is of vital importance. CRT is such a therapy for patients with heart failure and has been shown to significantly improve heart failure symptoms, decrease hospitalizations and reduce mortality.

In clinical trials for CRT, women only represented approximately 20% of patients. The effects of CRT are therefore primarily based on the results in men, as well as the current clinical guidelines for the implantation of CRT devices.[4] The regulatory research studies we conducted that are described in this report were aimed at assessing potential differences in CRT efficacy between sexes. We used various data sources including analysis of CRT clinical trial data and data from patients included in a national registry for implantable defibrillators.

For the analysis of pre-market clinical trials we combined individual patient data from three CRT trials. The trials were submitted to FDA as part of pre-market approval applications (PMAs) for CRT. By performing such an individual-patient data meta-analysis the FDA found that women have a significantly lower mortality after receiving CRT than men.[5] Patients of both sexes with a left bundle branch block (LBBB), an electrical conduction disorder in the heart, benefited most. However, women did so at a shorter QRS

duration (time to complete electrical activation of the heart) than men. In patients with a LBBB and shorter QRS duration, women had a 76% reduction in heart failure or death while men did not derive any benefit. With LBBB and longer QRS duration, both sexes benefited equally from CRT.[5]

A second and third FDA analysis used data from real-world CRT recipients included in a national implantable defibrillator registry (the National Cardiovascular Data Registry [NCDR] ICD Registry operated by the American College of Cardiology).[6,7] In these two studies, it was shown that women had a lower mortality risk with CRT compared to men, and that this difference between sexes increased in the presence of a LBBB, similar as in the meta-analysis. However, as opposed to the meta-analysis there was no difference by QRS duration between women and men. Both sexes benefited at shorter as well as longer QRS durations.[6]

That women benefit more from CRT compared to men is important since women are less likely than men to receive CRT treatment. This also indicates that this device may be underused in women. One of the reasons why women have greater benefit with CRT is that they have smaller hearts and may therefore more often have a LBBB than men.[8] This, however, does not only pertain to CRT. There may be multiple reasons why women and men respond differently to medical device therapy, both in terms of safety and efficacy. These may be attributable to intrinsic factors (e.g. genetics, hormones, body size, sex-specific physiology), extrinsic factors (e.g. diet, sociocultural issues, environment) or even interactions between these factors.[9] This regulatory research highlights the importance of combining clinical trial data and using multiple data sources for the detection of potential sex- and other subgroup differences in medical device clinical studies.

This deficiency of sex-specific information creates difficulties in assessing the safety and effectiveness of devices in CRT therapy as well as interpreting data from device trials in general. The regulatory science performed by the FDA demonstrates that there can be important differences in device performance between women and men, both in pre-market trials as well as in real-world use. Therefore FDA recommends that in general, study enrollment should be based on representative proportions of women and men (consistent with, for example, disease prevalence) and that data from both pre-market and post-market medical device studies are appropriately analyzed for potential sex-specific results.

Developments and Recommendations to Enhance Participation of Women

There can be multiple reasons why women may be underrepresented in clinical trials for medical devices. These may include a lack of understanding about main obstacles to female participation or about sex-differences in disease etiology and pathophysiology, fear of potential fetal consequences, avoidance of female patients due to the perception that it takes more time and money to recruit them, there may be family responsibilities limiting a woman's ability to participate, or clinical study in- and exclusion criteria may simply unintentionally exclude women.[9] As a result, the FDA has recently been looking at ways to encourage greater inclusion of women and other demographic subgroups in medical device clinical trials and how to appropriately analyze the clinical data for potential sex-specific results.

FDA published an Action Plan – mandated by Congress - for the implementation of Section 907 of the FDA Safety and Innovation Act (FDASIA), the section concerning the demographic subgroup data from clinical trials.[10] This Action Plan contains

recommendations for improving the quality, transparency, and diversity of available data on women, as well as other demographic subgroup populations. It also references the regulatory science research discussed in this report as an example of how this can be achieved.[10] In addition, FDA published a Sex-Gender Guidance document that provides a clear framework for how to analyze and communicate data on women in medical device clinical trials.[9] The final guidance includes recommendations on encouraging appropriate representation by sex in clinical studies of devices and explains that data from such studies should be appropriately analyzed by sex. Both the complete Action Plan and final guidance can be accessed through the FDA website (Action Plan: http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/UCM410474.pdf and final guidance: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM283707.pdf)).

Raising Awareness and Stakeholder Input

The research community needs to become more aware of the historical underrepresentation of women and other demographic subgroups in certain clinical trials where study outcomes can differ between sexes, races and ages. The regulatory research studies on CRT treatment for heart failure presented in this report can serve as an example of how such studies can be conducted and reported. Next to increasing awareness, this will hopefully also translate into the inclusion of more diverse populations in future clinical trials.

The FDA and sponsors of medical products cannot complete this effort alone. There is a need for stakeholder input to achieve the goal of including a more diverse patient population in clinical trials and appropriate analysis of data for potential sex-specific results. FDA plans to continue its interactions with all interested groups to achieve this important goal and improve the public health.

Conclusions

There can be important differences in medical device performance between patients from different demographic subgroups (e.g. women) sometimes underrepresented in certain clinical trials, leading to an important information gap regarding the safety and efficacy of these devices. By continuous multi-stakeholder input, barriers to clinical trial enrollment for demographic subgroups can be addressed and diverse participation encouraged. The implementation of the 907 FDASIA Action Plan will provide a first step towards achieving this goal.

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