Case Study: Bucindolol

Key lessons learned

- The safety profile of a medication may differ among different subpopulations of participants and the possibility of differences in adverse events—and efficacy—is good reason to include participants of diverse backgrounds in clinical trials and post- marketing research studies.
- Prior experience and data arguably inform future trials.
- Efficacy of beta-blockers, specifically bucindolol, appeared to differ between White and Black patients, a finding that was in part revealed by sufficient representation of the populations to permit *post hoc* subgroup analysis.
- Genetic polymorphisms, and the different background rates of the polymorphism in different race and ethnic populations, may have contributed to different efficacies in response.
- Often the biological basis of any difference in safety or efficacy based on demographics is poorly understood.

Disease background

Heart failure, also known as congestive heart failure, occurs when the heart either fails to fill with enough blood (right sided heart failure) and/or is unable to pump enough blood to support other organs in the body (left sided heart failure).[1] Heart failure affects 26 million people worldwide[2] and despite significant advances in therapies and preventions, people still suffer from complications and treatment challenges.

Drug development and clinical findings

A combination of different therapies and medications are used in the treatment of heart failure. Beta-blockers are one class of drugs used to control the symptoms of heart failure caused by activity of certain hormones.[3] Bucindolol is a beta-blocker that was tested in clinical trials for heart failure.[4]

[1] National Heart, Lung and Blood Institute. Heart Failure [Internet]. National Institutes of Health. Available online: https://www.nhlbi.nih.gov/health-topics/heart-failure [Accessed 15 April 2020].
[2] Savarese G, Lund LH. Global public health burden of heart failure. Cardiac failure review. 2017 Apr;3(1):7.
[3] National Heart, Lung and Blood Institute. Heart Failure [Internet]. National Institutes of Health. Available online: https://www.nhlbi.nih.gov/health-topics/heart-failure [Accessed 15 April 2020].
[4] Givertz MM, Cohn JN. Pharmacologic management of heart failure in the ambulatory setting. In Cardiovascular Therapeutics: A Companion to Braunwald's Heart Disease 2007 Dec 1 (pp. 331-362). Elsevier Inc.

In the BEST (Beta-Blocker Evaluation Survival Trial) clinical trial, bucindolol was given as an additional therapy at the same time as two other drugs to see if it provided any added benefit.[5] The trial specifically recruited selected subgroups (e.g., women, ethnic and racial minority populations) as it was known that Black patients have a higher rate of death from heart failure in the United States.[6,7] Treatment groups were divided not only by the severity of their heart failure symptoms, but also by sex and self-reported race.

Findings from trials initially suggested good effect: death from cardiovascular causes was significantly lower in the bucindolol group; and bucindolol reduced the average number of hospitalizations and average number of inpatient days per patient.[8] However, while the addition of bucindolol to treatment for heart failure reduced the number of times patients had to go to the hospital, it did not appear to change the risk of death from heart failure.

Careful study of the results and further subgroup analysis, however, showed that "non-black" patients—that is, patients other than those who described themselves as Black—did better on bucindolol than without it. And that advantage was seen in each way bucindolol was first thought as being beneficial—the rate of death from heart disease, the number of times that patients had to go back into the hospital for heart problems and how long they stayed, and overall outcomes. Black patients, however, did not experience the same level of survival benefit. [9]

The reason that Black patients did not benefit—and that non-black patients did benefit—was further studied. Different forms of one gene change whether or not a person responds to the drug, and one form of that gene is more common (but certainly not always present) in Black patients than non-black patients.[10,11] The drug response does not relate to *race*—it relates to the fact that one form of the gene is more common in one population than another. However, given the lack of impact on overall mortality in the Black population, and the general availability of effective beta-blockers and other therapies, the development of bucindolol in the United States was abandoned. Whether genetic testing would be helpful to drive the choice of therapy has not yet been examined.

[5] BEST Steering Committee. Design of the beta-blocker evaluation survival trial (BEST). The American Journal of Cardiology. 1995 Jun 15;75(17):1220-3.
[6] Gillum RF. Epidemiology of heart failure in the United States. Am Heart J 1993;126:1042-1047
[7] Dries DL, Exner DV, Gersh BJ, Cooper HA, Carson PE, Domanski MJ. Racial differences in the outcome of left ventricular dysfunction. New England Journal of Medicine. 1999 Feb 25;340(8):609-16.
[8] Torp-Pedersen C, Køber L, Ball S, Hall A, Brendorp B, Ottesen MM, Berning J, Jensen G, Hampton J, Zilles P, Eberle S. The incomplete bucindolol evaluation in acute myocardial infarction Trial (BEAT). European journal of heart failure. 2002 Aug;4(4):495-9.
[9] Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. New England Journal of Medicine. 2001 May 31;344(22):1659-67.
[10] Bristow MR, Murphy GA, Krause-Steinrauf H, Anderson JL, Carlquist JF, Thaneemit-Chen S, Krishnan V, Abraham WT, Lowes BD, Port JD, Davis GW. An a2C-adrenergic receptor polymorphism alters the norepinephrine-lowering effects and therapeutic response of the β-Blocker bucindolol in chronic heart failure. Circulation: Heart Failure. 2010Jan 1;3(1):21-8.
[11] Liggett SB, Mialet-Perez J, Thaneemit-Chen S, Weber SA, Greene SM, Hodne D, Nelson B, Morrison J, Domanski MJ, Wagoner LE, Abraham WT. A polymorphism within a conserved β1-adrenergic receptor motif alters cardiac function and β-blocker response in human heart failure. Proceedings of the National Academy of Sciences. 2006 Jul 25;103(30):11288-93.