

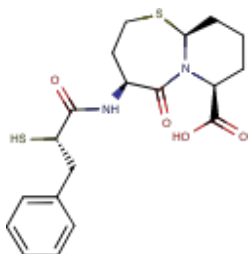
Case Study: Omapatrilat

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.
- Safety of a drug must be measured with regard to benefit, both which may vary by subpopulation.
- Often the biological basis of any difference in safety or efficacy based on demographics is poorly understood.

Disease background

High blood pressure, also known as hypertension, is a common condition whereby the blood that flows through veins or arteries is at a higher than normal pressure.¹ An estimated 1.13 billion people worldwide have hypertension, the majority of which live in low- and middle- income countries.² Having high blood pressure puts one at risk for heart disease and stroke. In 2017, nearly half a million deaths in the United States listed hypertension as a primary or contributing cause.³ Furthermore, rates of high blood pressure vary by sex, race, ethnicity and geography,⁴ all variables that may complicate treatment and medication management.



Drug development and clinical findings

Treatment for high blood pressure involves a combination of different therapies, lifestyle changes and medications. One of the more common anti-hypertensive drug class used to treat hypertension is angiotensin- converting enzyme (ACE) inhibitors. ACE inhibitors work by blocking the hormone (angiotensin II) responsible for narrowing blood vessels. Other drug classes control levels of proteins in the blood to help high blood pressure. Omapatrilat, a drug developed by Bristol-Myers Squibb, was initially heralded as a far more effective anti-

¹ National Heart, Lung, and Blood Institute. High Blood Pressure [Internet]. National Institutes of Health. Available online: <https://www.nhlbi.nih.gov/health-topics/high-blood-pressure> [Accessed April 15, 2020].

² World Health Organization. Hypertension [Internet]. World Health Organization. Sept 13, 2019. Available online: <https://www.who.int/news-room/fact-sheets/detail/hypertension> [Accessed April 15, 2020].

³ Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death, 1999–2018. CDC WONDER Online Database. Atlanta, GA: Centers for Disease Control and Prevention; 2018. Available online: <https://wonder.cdc.gov> [Accessed April 15, 2020].

⁴ Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death, 1999–2018. CDC WONDER Online Database. Atlanta, GA: Centers for Disease Control and Prevention; 2018. Available online: <https://wonder.cdc.gov> [Accessed April 15, 2020].

hypertensive treatment because it lowered blood pressure in two ways -- by inhibiting the hormones that cause blood vessels to constrict and also by changing proteins levels in the blood.

Clinical trials with omapatrilat were promising. They showed that omapatrilat was much more effective in lowering blood pressure than another common, marketed drugs.^{5,6,7} However, these studies also showed an increase in a side effect called angioedema – a condition where there is localized swelling of the skin particularly on the face, lips, mouth, and throat.⁸

Studies pursued the use of omapatrilat to control high blood pressure;⁹ the *OCTAVE* (Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril) study¹⁰ was a multicenter, randomized, double-blind, active-controlled trial that aimed to enroll approximately 25,000 patients to better characterize the risk–benefit relationship of omapatrilat compared with another ACE inhibitor. Findings showed that omapatrilat significantly reduced blood pressure as compared to the other drug and those who received omapatrilat did not require as much antihypertensive therapy overall. This was true for all subgroups analyzed (e.g., age, sex, ethnicity, race, type of and severity of hypertension, comorbidity).

The incidence of adverse events, however, was imbalanced as rate of angioedema was increased approximately threefold in Black patients as compared to others.¹¹ Smokers also had an increased risk for angioedema. Notably, given the risk of serious cardiovascular disease, the calculated reduction in potential cardiovascular events by treatment with omapatrilat would outweigh the risk of clinically significant angioedema in all patient groups, although the increased risk in Black patients and smokers would need to be considered prior to prescribing the drug.

Bristol-Myers Squibb (BMS), the developer of omapatrilat, voluntarily halted drug development in the United States in 2000 following the early reports regarding the risk of angioedema.

Clinical development proceeded elsewhere; however, in 2002, results from the *OCTAVE* study led to a non-approval vote by a U.S. FDA advisory committee and clinical development was stopped completely. To date, the biological cause of angioedema remains unexplained and the pathophysiological explanation for the increased risk in Black patients remains elusive.

⁵ Asmar R, Fredebohm W, Senftleber I, Chang PI, Gressin V, Saini RK. A085: Omapatrilat compared with lisinopril in treatment of hypertension as assessed by ambulatory blood pressure monitoring. *American Journal of Hypertension*. 2000 Apr 1;13(S2):143A.

⁶ Campese VM, Lasseret KC, Ferrario CM, Smith WB, Ruddy MC, Grim CE, Smith RD, Vargas R, Habashy MF, Vesterqvist O, Delaney CL. Omapatrilat versus lisinopril: efficacy and neurohormonal profile in salt-sensitive hypertensive patients. *Hypertension*. 2001 Dec 1;38(6):1342-8.

⁷ Neutel J, Shepherd A, Pool J, Levy E, Saini R, Chang PI. D054: Antihypertensive efficacy of Omapatrilat, a vasopeptidase inhibitor, compared with lisinopril. *American Journal of Hypertension*. 1999 Apr 1;12(S4):124A.

⁸ Gang C, Lindsell CJ, Moellman J, Sublett W, Hart K, Collins S, Bernstein JA. Factors associated with hospitalization of patients with angiotensin-converting enzyme inhibitor–induced angioedema. In *Allergy and asthma proceedings*. 2013 May (Vol. 34, No. 3, p. 267). OceanSide Publications.

⁹ Coats AJS. Omapatrilat—the story of Overture and Octave. *International Journal of Cardiology*. 2002; 86: 1-4.

¹⁰ Kostis JB, Packer M, Black HR, Schmieder R, Henry D, Levy E. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (*OCTAVE*) trial. *American Journal of Hypertension*. 2004 Feb 1;17(2):103-11.

¹¹ Coats AJS. Omapatrilat—the story of Overture and Octave. *International Journal of Cardiology*. 2002; 86: 1-4.