Although evaluation and treatment of classic cardiovascular risk factors (ie, high blood pressure, smoking, hyperlipidemia and diabetes) play a central role in preventing cardiovascular disorders, measurement of biomarkers, such as C-reactive protein (CRP), B-type natriuretic peptide (BNP), and growth differentiation factor 15 (GDF15) can provide additional information that helps estimate cardiovascular risk.\(^1\)\(^2\)

Brown, et al first reported that GDF15, a divergent member of the transforming growth factor-β (TGF-β) superfamily, is associated with cardiovascular risk.\(^3\)\(^4\) They demonstrated that serum GDF15 levels were higher in women who subsequently experienced cardiovascular events during a 4-year follow-up period than those in women free of cardiovascular events. This finding remained significant even after the classic risk factors were adjusted between the two groups, suggesting that GDF15 levels reflect an independent element that is not influenced by established risk factors. Since this original study was published, extensive research in the field has focused on whether serum GDF15 levels can act as an independent predictor of various cardiovascular disorders, including chronic ischemic heart disease, acute coronary syndrome, heart failure, atrial fibrillation, and cardiomyopathy.\(^5\)\(^6\)

In this issue, Minamisawa, et al report that GDF15 levels serve as an independent predictor of major cardiovascular events in Japanese patients with acute myocardial infarction (AMI).\(^7\) Their study enrolled 430 Japanese AMI patients, all of whom were prospectively followed in the outpatient clinic for 3 years. Serum levels of biomarkers, including GDF15 and BNP, were measured one month after disease onset. Consistent with previous studies from other groups, higher levels of GDF15 were associated with a worse prognosis. Furthermore, for identifying patients with a high risk, a combined analysis of both GDF15 and BNP was found to be more useful than analyzing either one of the two biomarkers alone. Because chronic inflammation is critically involved in the progression of several cardiovascular disorders, serum levels of inflammatory biomarkers, such as CRP and ST2 (a soluble member of the interleukin-1 receptor family), were measured concurrently. In contrast to the previous reports suggesting that CRP and ST2 act as reliable predictors of cardiovascular risk, the authors found in this study that these two biomarkers were not associated with major cardiovascular events.

Based on numerous clinical studies including the one published in this issue, GDF15 is currently considered a reliable biomarker. However, controversy persists regarding whether GDF15 actually contributes to the pathogenesis of cardiovascular disorders or is just a biomarker (Figure). Although GDF15 can easily be detected in the systemic circulation, GDF15 is abundantly expressed only in placenta and prostate in human tissues under physiological conditions.\(^8\)\(^9\) Importantly, however, GDF15 expression can be induced in various tissues by stressors, such as hypoxia, inflammation, and acute tissue damage. In agreement with this finding, GDF15 is not produced from normal cardiomyocytes, but cardiac GDF15 expression is induced after myocardial infarction in mice and humans. To study the physiological relevance of this GDF15 induction in vivo, Gdf-15 null mice were subjected to myocardial infarction and ischemia/reperfusion (I/R) injury. Gdf-15 null mice exhibited enhanced cardiomyocyte apoptosis and polymorphonuclear leukocyte (PMN) recruitment, resulting in larger infarct size and an increased incidence of cardiac rupture when compared with wild type littermates.\(^10\)\(^11\) \(^12\) This indicates that induction of endogenous GDF15 in the heart plays a protective role in limiting myocardial tissue damage. In contrast to this protective role of cardiac GDF15, de Jager, et al have recently reported that induction of GDF15 expression in macrophages promoted atherosclerosis.\(^13\)\(^14\) Consistent with the hypothesis that chronic inflammation plays a critical role in atherosclerosis and induces GDF15 expression, macrophages that reside in atherosclerotic lesions expressed GDF15 during atherosclerosis progression. Interestingly, GDF15 in macrophages exerted detrimental effects both in the early and late phases of atherosclerosis by enhancing apoptotic cell death, necrotic core formation, and CCR2-mediated macrophage chemotaxis. Hence, these two significant examples (ie, GDF15 in cardiomyocytes and macrophages) clearly demonstrate that the biological effects of GDF15 are context-dependent.

Although molecular mechanisms underlying GDF15 actions have been partially resolved in several pathophysiological conditions, the receptor complex for GDF15 has yet to be identified. The TGF-β superfamily comprises more than 30...
ligands including GDF15, and these ligands can be categorized into two major subfamilies: the TGF-β subfamily and the bone morphogenetic protein (BMP)/GDF subfamily. The signaling mechanisms for most of these ligands are similar. Each of the ligands needs two types of serine/threonine kinase receptors, named type I and type II receptors, to activate downstream signaling pathways. Ligand binding mediates the formation of the type I-type II receptor complex, resulting in the phosphorylation and activation of SMAD transcription factors. Since GDF15 is a member of the TGF-β superfamily, previous studies have reported that some of the GDF15 actions were dependent on the TGF-β type II receptor and SMAD proteins. However, the type I receptor or co-receptor that forms a receptor complex with the type II receptor for GDF15 signaling is still unclear. Lack of unequivocal knowledge of the receptors involved may thus explain why the signaling mechanisms of GDF15 remain unknown. Only when these signaling mechanisms that drive the biological actions of GDF15 are fully understood, will it be possible to utilize recombinant GDF15 or anti-GDF15 antibodies as a therapeutic agent. Indeed, no clinical trial for recombinant GDF15 or anti-GDF15 antibodies has been reported. Although GDF15 has been established as a reliable biomarker for cardiovascular risk assessment, further studies will be required to elucidate its pathophysiological roles in various cardiovascular disorders prior to the development of drugs that specifically target GDF15.

**REFERENCES**