Globally, an estimated 71 million people have chronic hepatitis C virus (HCV) infection, which is a leading cause of morbidity and mortality. Approximately 399,000 persons die each year from HCV-related complications such as cirrhosis, hepatocellular carcinoma, and liver failure. In addition, clinical studies have shown that HCV infection increases the risks for not only liver disorders, but also many extrahepatic diseases, including cryoglobulinemia, renal disease, and cardiovascular disease (CVD), such as coronary artery disease, myocarditis, and cardiomyopathy (Figure). Consistent with these reports, other clinical studies have revealed that a higher prevalence of metabolic disorders, such as type 2 diabetes mellitus, insulin resistance, and steatosis, is observed in HCV-infected patients than in non-infected controls. This could be because the HCV infection interferes with glucose and lipid metabolism and thus develops atherogenic disorders.

Chronic infection with certain organisms is also thought to promote systemic inflammation and consequent atherosclerosis. Indeed, chronic HCV infection has been shown to induce pro-inflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, C-reactive protein, and fibrinogen, which affect not only the coronary arteries, resulting in CVD, but also the pulmonary vasculature, resulting in pulmonary hypertension, both of which conditions could lead to heart failure (HF). Portocardiac shunt-induced pulmonary hypertension is another cause of HF in patients with chronic HCV infection, especially in the advanced stage complicated by cirrhosis. The possibility of a direct association between HCV infection and myocardial injury, resulting in myocarditis or cardiomyopathy, has been reported by Matsumori et al, who found a higher prevalence of anti-HCV antibodies in patients with cardiomyopathies and myocarditis than in the general population and detected the minus strand of HCV-RNA from cardiac tissue suggesting replication of the virus, both of which indicate a direct association between HCV and cardiac...
injury through its proliferation.

Thus, these factors promote CVD and HF in patients with HCV infection. How does antiviral therapy affect HCV-related CVD and HF? Moreover, is it possible to reduce the risk of developing CVD or HF by administering antiviral therapy?

The standard care for HCV has been interferon (IFN)-based therapy (IBT). IFN is a cytokine broadly used to treat viral infections, malignancies, and disorders of the immune system. After the standard IFN monotherapy was introduced in the 1980s, the addition of polyethylene glycol (PEG) to IFN (PEG-IFN) enabled long-lasting effects, and the combined application of ribavirin and PEG-IFN improved the treatment efficacy. Thus, IBT is one of the most effective treatment strategies and has achieved an effective eradication of HCV. However, despite these advantages, IBT is accompanied by complications that affect various organs and systems. Giannini et al reported discontinuation of IFN in 17% of HCV-infected patients mainly because of cardiovascular complications. Cardio-myopathy, myocardial infarction, and myocarditis impairing the systolic function of both ventricles are other well-known cardiovascular side effects of IBT. Pulmonary complications (e.g., interstitial pneumonia, sarcoidosis, bronchiolitis obliterans organizing pneumonia, exacerba-
tion of asthma, acute respiratory distress syndrome, and pulmonary artery hypertension) are also reported, and these influence cardiac function.

Thus, the treatment of HCV infection with IBT is controversial because of its ambivalent (beneficial or harmful) influence on HF, and a large-scale study on the incidence of HF or cardiovascular events after IBT has not been well documented. In this issue of the Journal, Lin et al report that IBT for chronic HCV infection could have a protective effect against HF hospitalizations, critical vascular events, and cardiovascular death, based on their study using a large-data, national health insurance research database (NHIRD) in Taiwan. They evaluated the clinical outcomes of 16,824 patients with HCV infection who received IBT in comparison with the same number of propensity score-matched patients with HCV infection who did not receive IBT, with respect to HF hospitalizations, including those caused by acute myocardial infarction, ischemic stroke, and peripheral artery disease, all-cause death, and cardiovascular death. Patients who received IBT were less likely to be hospitalized for HF compared with untreated patients (incidence density [ID], 0.9 vs. 1.5 events per 1,000 person-years; hazard ratio [HR], 0.58; 95% confidence interval [CI], 0.42–0.79; P=0.001). The treated patients also had a significantly lower risk of composite vascular events (ID, 3.7 vs. 5.0 events per 1,000 person-years; P<0.001), all-cause death (ID, 5.6 vs. 17.2 events per 1,000 person-years; P<0.001), and cardiovascular death (ID, 0.2 vs. 0.6 events per 1,000 person-years; P=0.001).

Among the 20,366 patients who had IBT initiated, 1,345 (6.6%) who did not complete IBT, defined as an IBT course of <16 weeks, were excluded from the study. The early termination of IBT was because of either poor viral response within 12 weeks according to the national insurance guideline in Taiwan or the occurrence of adverse effects within 16 weeks. Accordingly, the beneficial effect on HF and cardiovascular events reported by Lin et al is based on the data of patients who received complete IBT without any adverse events in the first 2 weeks of IBT administration, although the details of the adverse events are not clear from this health insurance database-oriented study. The actual extent of sustained viral response is also unavailable from the NHIRD. Nevertheless, it can be said that IBT, if tolerated, could play a protective role in HF hospitalization, critical vascular events, and cardiovascular deaths in patients with chronic HCV infection.

Globally, the annual number of people being initiated with the more effective eradication therapy (i.e., direct-acting antiviral medicines: DAAs), to cure HCV has increased from around 1 million in 2015 to almost 3 million at the end of 2016. This increasing number of patients treated with DAAs will clarify in the near future whether a direct association exists between HCV eradication and a reduction in the incidence of CVD.

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