heparin activity was not superior to the tryptase level as a diagnostic marker in patients with systemic mastocytosis. Although the study showed an increase in the tryptase level in patients with the mast-cell activation syndrome, the criteria used for the diagnosis of this syndrome have not been widely accepted and the data require confirmation.

Finally, we agree that heparin is capable of contributing to osteoporosis in the bone microenvironment, though such an association requires confirmation in a study with appropriate statistical power. However, both heparin and chondroitin sulfate, which are stored in mast-cell secretory granules, have been shown to inhibit mast-cell activation.[4,5]

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Bradyarrhythmias Associated with Sofosbuvir Treatment

TO THE EDITOR: Treatment with sofosbuvir-based regimens is associated with a sustained virologic response in more than 90% of patients with chronic hepatitis C virus (HCV) infection, with a rate of serious adverse events of less than 5%.[1] Here, we report three cases of severe bradyarrhythmia that occurred during treatment with sofosbuvir plus daclatasvir, simeprevir, or ribavirin among 415 patients treated in our unit from January 2 to December 31, 2014.

The characteristics of the patients at baseline are provided in Table 1, and electrocardiograms for Patients 1 and 3 are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org. Symptomatic bradycardia, with syncope in two cases (Patients 2 and 3), occurred within the first 10 days of treatment with sofosbuvir. The bradycardia was due to sinus-node dysfunction in Patients 1 and 2 and to intermittent third-degree atrioventricular block in Patient 3. In Patient 1, sinus-node dysfunction persisted after treatment with propranolol was discontinued. In Patient 2, sinus-node dysfunction resolved after discontinuation of treatment with sofosbuvir, simeprevir, and amiodarone. However, the reintroduction of sofosbuvir (with ribavirin), 46 days later, was followed by recurrence of the conduction abnormality at day 6. Pacemakers were implanted in all three patients. In Patient 1, interrogation of the pacemaker (performed by a cardiologist who was unaware of the patient's identity) during sofosbuvir treatment revealed atrial pacing during 26% of the exposure time. Three months after the discontinuation of sofosbuvir treatment, atrial pacing was observed for 4% of the exposure time.

Common causes of bradyarrhythmia (electrolyte disorders, renal insufficiency, thyroid dysfunction, and cardiac ischemia) were ruled out. In Patient 2, a known drug interaction between amiodarone and simeprevir could have been a factor in the initial occurrence of bradyarrhythmia. Simeprevir could not have contributed to the recurrence 46 days later. Given the long half-life of amiodarone, we cannot exclude the possibility that residual levels of this agent contributed to the recurrence when sofosbuvir treatment was reintroduced.

In January 2015, after four arrhythmias in 1337 patients were found in a safety investigation of the compassionate use of daclatasvir given with sofosbuvir in France, the French National Agency

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Patient 1	Patient 2	Patient 3
Sex	Male	Female	Male
Age (yr)	52	75	58
HCV genotype	1a	1b	1b
Severity of liver disease	Cirrhosis (Child–Pugh class C); MELD score of 23; large, grade III nonhemorrhagic esophageal varices	Cirrhosis (Child–Pugh class A); small esophageal varices	Cirrhosis (Child–Pugh class A)
Medical history and coexisting conditions	Coagulation factor XI deficiency	Rheumatoid polyarthritis; paroxysmal atrial flutter (diagnosed in 2011), with sinus rhythm for 3 yr; hypertension	HIV coinfection; tobacco smoking
Other medications	Propranolol (40 mg/day), furosemide (40 mg/day), spironolactone (75 mg/day), esomeprazole (20 mg/day)	Etanercept (50 mg/10 days), prednisone (5 mg/day), fluindione (10 mg/day), amiodarone (200 mg/day), levothyroxine (100 μg/day), bromazepam (3 mg/day), cholecalciferol (400 IU/day), spironolactone (50 mg/day), omeprazole (20 mg/day)	Efavirenz (600 mg/day), emtricitabine (200 mg/day), tenofovir (245 mg/day)
Antiviral agents	Sofosbuvir (400 mg/day) and daclatasvir (60 mg/day)	Sofosbuvir (400 mg/day) and simeprevir (150 mg/day), followed by sofosbuvir (400 mg/day) and ribavirin (1000 mg/day)	Sofosbuvir (400 mg/day) and daclatasvir (90 mg/day)
Rhythm abnormality	Sinus-node dysfunction with a junctional escape rhythm (ventricular rate, 30 beats/min) without resolution after discontinuation of propranolol treatment	Sinus bradycardia with syncope, with spontaneous resolution after discontinuation of the antiviral treatment and recurrence during the second course of treatment	Intermittent third-degree atrioventricular block with syncope
Interval between day 1 and the adverse effect	10 Days	1 Day during the first course of treatment; 6 days during the second course of treatment	6 Days
Timing of pacemaker implantation	4 Days after onset of the bradyarrhythmia	6 Days after recurrence of the bradyarrhythmia	1 Day after onset of the bradyarrhythmia
Virologic response	Sustained virologic response, with improvement of liver function (MELD score of 13 and Child–Pugh class A6)	Sustained virologic response	Sustained virologic response

* Child–Pugh classes A, B, and C indicate the severity of liver disease, with C indicating the most severe disease. Model for End-Stage Liver Disease (MELD) scores, which are used in the allocation of liver grafts, range from 6 to 40, with higher scores indicting more severe disease. HCV denotes hepatitis C virus, and HIV human immunodeficiency virus.

for Medicines and Health Products Safety published an online warning.[2] In March 2015, the Food and Drug Administration warned that serious slowing of the heart rate can occur when HCV treatments, including sofosbuvir plus another antiviral drug, are taken together with amiodarone.[3]

The pathophysiological mechanism underlying this potential adverse event is not clear. However, the potential cardiac toxicity of sofosbuvir-containing regimens suggests the need for caution with the use of such regimens, including review of other medications, consideration of risk factors for bradyarrhythmias, and possibly monitoring of cardiac rhythm during the initiation of therapy.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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3. Food and Drug Administration. FDA drug safety communication: FDA warns of serious slowing of the heart rate when antiarrhythmic drug amiodarone is used with hepatitis C treatments containing sofosbuvir (Harvoni) or Sovaldi in combination with another direct acting antiviral drug. March 24, 2015 (http://www.fda.gov/Drugs/DrugSafety/ucm439484.htm).

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GILEAD SCIENCES, THE MANUFACTURER OF SOFOSBUVIR, REPLIES: The three cases of bradyarrhythmia described by Fontaine and colleagues, in addition to other cases, were promptly reported by Gilead Sciences to the Food and Drug Administration and to the European Pharmacovigilance Risk Assessment Committee as we became aware of them earlier this year. To date, according to data on file at Gilead Sciences, more than 13,000 clinical trial participants have received a sofosbuvir-containing regimen, and more than 470,000 patients have been treated with sofosbuvir or ledipasvir–sofosbuvir since their approvals in 2013 and 2014, respectively. To put this in a broader context, postmarketing pharmacovigilance identified nine cases of symptomatic bradycardia worldwide in patients who were taking amiodarone and sofosbuvir, in combination with another direct-acting antiviral agent. These cases resulted in "Dear Health Care Provider" letters and label updates to sofosbuvir, ledipasvir–sofosbuvir, simeprevir, and daclatasvir. Efforts are under way to elucidate the potential mechanism of the interaction with amiodarone and the combination of direct-acting antivirals. Symptomatic bradycardia has not previously been associated with sofosbuvir treatment in the absence of amiodarone and another direct-acting antiviral (e.g., sofosbuvir with ribavirin or pegylated interferon and ribavirin).

In their case report, Patient 2 was receiving amiodarone. Although treatment with amiodarone was discontinued, its mean plasma half-life of 58 days[1] suggests that substantial drug levels may have been present at the time HCV treatment was reintroduced, 46 days later.

The report also suggests that the reduction in atrial pacing from 26% during HCV treatment to 4% at 3 months after treatment suggests a causal relationship between treatment and a requirement for pacing in Patient 1. This patient had decompensated cirrhosis (Child–Pugh class C with a MELD [Model for End-Stage Liver Disease] score of 23, on a scale from 6 to 40, with higher scores indicating more severe disease) at the time of treatment, and after sustained virologic response, the patient had substantial clinical improvement, with a reduction in MELD score to 13. This clinical improvement could also potentially account for the change in the need for atrial pacing, given the well-described effects of end-stage liver disease on cardiac function, including bradyarrhythmias.[2,3]

According to data on file at the Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET), amiodarone use is uncommon among HCV-infected patients who are treated with sofosbuvir in combination with another direct-acting antiviral agent. Per the recent label updates, cardiac monitoring is recommended in the rare instance in which coadministration of amiodarone and sofosbuvir with another direct-acting antiviral is necessary to avoid these rare events. However, making generalized recommendations on the basis of these isolated case reports — such as routine monitoring of cardiac rhythm during the initiation of sofosbuvir therapy, as suggested by Fontaine et al. — seems premature.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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