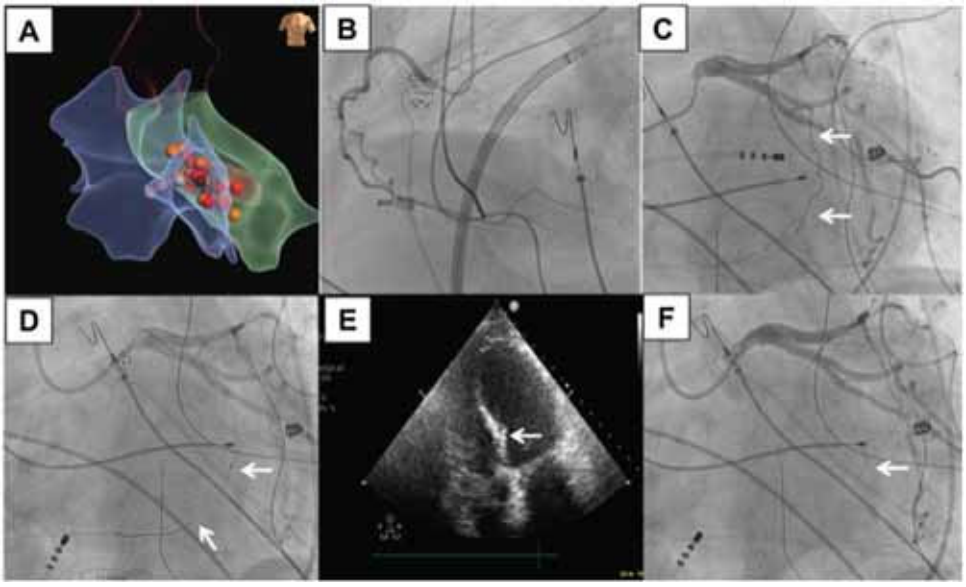

Figure 2. Coronary angiography and echocardiography from during the procedure. The arrows indicate, respectively, the atrioventricular nodal (AVN) artery and the area of the septum with contrast uptake. A: electroanatomical map (Ensite Precision, Abbott) showing the different radiofrequency applications from the right atrium, the coronary sinus, the right ventricle, and the left ventricle on an antero-posterior projection. B: right coronary artery on left anterior oblique (LAO) projection. C: left coronary artery (LAO projection; the arrow indicates the AVN artery). D: the arrow indicates the angioplasty guidewire and the coaxial balloon catheter in the AVN artery (LAO projection). E: echocardiography (apical view) during the selective infusion of echo contrast; the arrow indicates the area of the septum with uptake of echo contrast. F: left coronary artery after the selective injection of ethanol; the arrow indicates the amputated AVN artery (LAO projection).

cardiac silhouette, corresponding to the AVN artery. Use of echocardiography for guidance and to help locate the area of the myocardium to be ablated has refined the technique compared with that described in early publications, ensuring greater safety and efficacy.

In conclusion, alcohol ablation of the AVN artery is a classic technique that should still be considered when radiofrequency ablation fails.

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Three cases of psychosis after use of sacubitril/valsartan

Tres casos de psicosis tras la toma de sacubitrilo-valsartán

To the Editor,

Over recent years, sacubitril/valsartan has become an increasingly common treatment for patients with heart failure and reduced ejection fraction. Its use is supported by its excellent outcomes in terms of reduced mortality, improved symptoms, and preventing readmission, which has revolutionized the treatment of these patients.[1]

Sacubitril is a prodrug whose mechanism of action is inhibition of neprilysin, an enzyme that metabolizes atrial and brain natriuretic peptides. This inhibition is produced by an active metabolite of sacubitril (sacubitrilat).

Neprilysin has been implicated in the degradation of beta-amyloid protein (involved in the pathogenesis of neurodegenerative diseases). This has led to some authors raising concern about its possible effects on the brain and the possible association between sacubitril and cognitive decline. Although some clinical trials are underway on this topic, taking sacubitril has not consistently been associated with adverse cognitive effects.[2,3] Considering its involvement in brain function, it could be

Table 1
Baseline characteristics of patients and summary of the adverse events

	Case 1	Case 2	Case 3
Age, y	56	55	33
Sex	Male	Male	Male
Type of cardiomyopathy	Arrhythmogenic	Ischemic	Dilated idiopathic
Left ventricular ejection fraction	15%	29%	33%
New York Heart Association functional class	III	II	II
Past psychiatric history	No	No	Amphetamine-induced psychosis
Treatment modification	Started	Started	Dose increase
Symptom onset after treatment modification, d	2	6	5
Sacubitril/valsartan dose at which symptoms began, mg	24 + 26	49 + 51	24 + 26
Symptom duration, d	7	25	15
Sacubitril/valsartan stopped/reduced	Stopped	Stopped	Reduction to 12 + 13 mg/12 h
Time from stopping drug/reducing dose to symptom remission, d	7	5	15
Antipsychotic treatment	Yes	No	Yes
Hospitalized	Yes	No	No
Follow-up after the adverse event, mo	24	7	3
Recurrence of psychiatric symptoms	No	No	No

postulated as potentially being involved in the onset of psychiatric symptoms. However, there have been very few reports.[4]

We present a series of 3 cases of psychiatric symptoms after starting or increasing the dose of sacubitril/valsartan. In the 3 cases there was a clear temporal association between starting or increasing the dose of the drug and symptom onset, and improvement after stopping it or lowering the dose. The characteristics of each patient and the chronology of the adverse effects are shown in table 1. Here we present the psychiatric symptoms of each case.

The first case was a 56-year-old man with no psychiatric history. Two days after starting sacubitril/valsartan treatment (dose, 24 + 26 mg/12 h), symptoms began, consistent with verbosity, dysphoria, and irritability, along with mixed delusional ideation (grandiose and mystic) with suspiciousness, self-reference, and generalized paranoia. He had psychomotor agitation and resistant insomnia. He had no hallucinatory symptoms. He required admission as a psychiatric inpatient, sacubitril/valsartan was stopped, and treatment with haloperidol was started. The symptoms resolved after 7 days, and he was discharged. He had partial amnesia for the episode. Treatment with haloperidol was continued and then switched to aripiprazole for 4 months. Eventually, he received a heart transplant, and the antipsychotic medication was stopped. He is currently followed-up by cardiology and psychiatry and has not had a recurrence of the psychiatric symptoms.

The second case was a 56-year-old man with no past psychiatric history. Six days after starting sacubitril/valsartan (dose, 49 + 51 mg/12 h), he developed symptoms of irritability toward his family members, motivated by delusional ideation of harm with severe behavioral effects (aggression toward family members and temporarily leaving home). These symptoms were associated with psychomotor agitation and persistent general insomnia. He had no hallucinatory symptoms. The symptoms lasted a total of 25 days, during which the patient did not seek medical attention. His family members reported these symptoms to his cardiologist, who decided to stop the drug. Five days after stopping, the symptoms gradually resolved, with partial amnesia for the episode. The patient received no antipsychotic treatment. Mental state assessment was performed 2 months after the drug was stopped, confirming complete symptom resolution. Currently he is stable and under follow-up by cardiology and psychiatry.

The third case was a 33-year-old man, with history of amphetamine-induced psychosis 10 years prior, requiring short-term treatment with amisulpride; at the time of symptom onset he was not using any substances. The patient had been on treatment with sacubitril/valsartan at a subtherapeutic dose of 12 + 13 mg/12 h (due to hypotension) for 4 months. The dose was increased to 24 + 26 mg/12 h and 5 days later the patient started having delusional ideation similar to his first episode, with agitation and insomnia. When this was reported to his cardiologist, it was decided to reduce the dose to 12 + 13 mg/12 h again (which has been continued at follow-up). The patient was assessed by the psychiatrist, who already knew him, and was started on antipsychotic treatment with amisulpride. This was followed by substantial symptom improvement.

In the 3 cases presented here, psychotic symptoms (mainly delusional) began shortly after exposure to or an increase in dose of a drug: sacubitril/valsartan. Consequently, these episodes would correspond to the diagnosis of "substance or medication induced psychotic disorder" (DSM 5 292.9; ICD 10 F19.959)[5]. The 3 cases involved serious adverse effects with significant clinical repercussions for the patients and their families.

Although there are limitations to the conclusions that can be drawn from these cases, we cannot ignore the timing of symptom onset in relation to starting or increasing the dose of the drug and their resolution after stopping or reducing the dose (in 1 of the cases, spontaneously, without antipsychotic treatment). This could mean that psychotic symptoms may be an uncommon adverse effect of sacubitril/valsartan. When we reviewed our patient population on treatment with sacubitril/valsartan, we found no more cases with such a direct association between taking the drug and psychiatric symptoms.

The mechanisms by which neprilysin inhibition may produce psychiatric symptoms, as well as their true incidence, remain unknown. The hypothetical accumulation of beta-amyloid protein appears unlikely, since these episodes had an acute onset and resolution. Given the lack of available evidence, further studies would be beneficial.

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Association between myocardial injury and prognosis of COVID-19 hospitalized patients, with or without heart disease. CARDIOVID registry

Asociación entre el daño miocárdico y el pronóstico de pacientes hospitalizados por COVID-19, con y sin cardiopatía. Registro CARDIOVID

To the Editor,

In December 2019, a cluster of cases of severe acute respiratory syndromes was first reported in Wuhan (China). A novel coronavirus was isolated and was named SARS-CoV-2.[1] By April 1, 2020, the disease caused by SARS-CoV-2, known as COVID-19 (Coronavirus disease 2019), was declared a global pandemic by the World Health Organization.[2]

Although the main clinical manifestation of this new virus occurs in the respiratory system, other organs such as the heart can also be affected. There are several mechanisms by which SARS-CoV-2 could cause myocardial damage. The presence of angiotensin-converting enzyme-2 receptors (used by this virus to invade the pneumocyte) in cardiomyocytes could be associated with the development of myocarditis, which can cause systolic dysfunction and heart failure (HF).[3] Another mechanism of cardiac damage could be the high degree of inflammatory activity. COVID-19 precipitates a cytokine storm with increased levels of interleukin (mainly 2, 7 and 10) and other proinflammatory cytokines, such as granulocyte-colony stimulating factor and tumor necrosis factor, among other mediators of the systemic and local inflammatory response. This proinflammatory storm can reduce flow to the coronary arteries, as well as destabilize coronary atherosclerosis plaques, associated with a hypercoagulable state that precipitates the microvascular thrombosis responsible for myocardial damage and the consequent elevation of troponin (Tn).[4,5]

In situations of hypoxemia or sustained hypotension, type 2 acute myocardial infarction may also occur. Finally, stress cardiomyopathy or tachycardias due to adrenergic discharge, either endogenous or exogenous, are other forms of myocardial damage related to this virus.[6]

This work was conducted to evaluate the impact on mortality, HF and on both combined of TnI elevation in COVID-19, both in patients with and without previous heart disease (HD), defined as a history of ischemic heart disease, at least moderate heart valve disease, or left ventricular dysfunction (ventricular ejection fraction $< 40\%$).

From March 10 to April 6, 2020, we included all patients with confirmed SARS-CoV-2 infection in our health area who were admitted to hospital (n = 245). Of these, 33 (14.1%) required intensive critical care. A total of 27 deaths were recorded (11%), and 35 (14.3% patients) developed HF. A total of 42 patients (17.1%) had HD. Of these, 15 (35.7%) had elevated Tn compared with 13.3% of patients without HD.

Table 1 summarizes the baseline characteristics of COVID-19 patients and provides a comparison of the cohorts with normal and elevated TnI values, as well as the results of the univariate analysis for the association of death and HF for all hospitalized patients, respectively.

Figure 1A represents the clinical complications observed in patients with high or normal TnI, based on the prior presence of HD. In all groups, TnI elevation identified a group of patients with a worse prognosis, but the rate of events in patients with elevated TnI compared with those with normal TnI was higher in patients without HD than in those with HD.

In the adjusted and nonadjusted analyses of the association between TnI and the clinical complications observed during hospitalization, TnI elevation was associated with higher mortality (odds ratio [OR] 334; 95% confidence interval [95%CI] 4.91-2285.10; $P = .025$), but not with a higher risk of developing HF (OR, 3.12; 95%CI, 0.72-13.63; $P = .130$). The combined outcome of mortality and HF was more frequent (OR, 5.58; 95%CI, 1.24-25-12, $P = .025$) in the group with elevated TnI.

On multivariate analysis of the association between TnI and clinical complications, both in patients with and without previous HD, TnI elevation was related to higher mortality (OR, 4.93; 95%CI, 1.24-19.52; $P = .023$), HF (OR, 4.28; 95%CI, 1.30-14.07; $P = .017$), and with the combined outcome of mortality or HF (OR, 7.09; 95%CI, 2.28-22.03; $P = .001$) in patients without HD, but not in patients with previous HD ($P = .561$, $P = .337$ and $P = .992$, respectively).

Figure 1B describes the relationship between TnI and the predicted probability of death or HF. As Tn rose, there was an increase in the risk of developing adverse outcomes. This relationship was more robust in patients without previous HD.

Tn elevation in patients without HD could indicate more severe infection and respiratory distress, which could determine the prognosis of COVID-19. In contrast, in patients with previous HD, Tn elevation may not only be related to the infectious process, but also to their underlying disease, so that, by itself, it does not identify the severity of COVID-19.

These findings could have relevant clinical implications. Tn elevation allows easy and rapid identification of a group of patients