Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The BRAKE-AF project is a promising undertaking, as the therapeutic armamentarium available for heart rate control in patients with permanent atrial fibrillation is scant and insufficient in a significant percentage of patients. In fact, beta-blockers, which are the most effective drugs in this context, do not achieve adequate heart rate control in 30% of patients.[6] Furthermore, calcium channel blockers are contraindicated in the presence of severe ventricular dysfunction, and digoxin has a narrow therapeutic margin and is associated with higher mortality.[7] As a result, some patients require pacemaker implantation and AV node ablation to achieve adequate heart rate control.[8] New drugs with negative chronotropic effects could add to current therapeutic options and may help minimize invasive treatment.

The project is based on a sound design with 2 differentiated arms: an experimental arm to analyze the effect of the drug on the action potential of the AV node and a noninferiority clinical trial. The aim of the clinical trial, which compares the efficacy of digoxin with ivabradine, is rational, as digoxin is less successful in controlling heart rate than beta-blockers or L-type calcium channel blockers. The trial has several limitations. In particular, it uses an unblinded approach, in view of the effects of digoxin on the surface electrocardiogram, and includes patients with and without ventricular dysfunction. Ivabradine could have a different effect in patients with ventricular dysfunction; therefore, based on the results of the trial, a second study could be undertaken in this subgroup.

We look forward to the publication of the results of the BRAKE-AF project to learn the therapeutic possibilities of ivabradine in this context.

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Do we have a new drug for heart rate control in patients with permanent atrial fibrillation? Response

¿Hay un nuevo fármaco disponible para el control de la frecuencia cardiaca de pacientes con fibrilación auricular permanente? Respuesta

To the Editor,

We thank Drs Rivas-Gándara and Francisco-Pascual for their interest shown in the BRAKE-AF project.[1]

There is indeed evidence to suggest that ivabradine could be effective for rate control in permanent atrial fibrillation (AF). Following publication of its efficacy in a patient with poorly-controlled AF,[2] we were aware that to "make this hypothesis a reality" we would need to conduct a clinical trial.[3]

Permanent AF is the most common form of AF yet, surprisingly, new drugs for rate control have not been developed in the past 30 years. The industrial development of antiarrhythmic drugs is increasingly uncommon, probably because it involves investment that is risky and/or with small profit margins; this means that clinicians must assess the antiarrhythmic effect of drugs that are marketed for other indications, as is the case with ranolazine.[4] We would like to point out that the BRAKE-AF project was undertaken with public funding only and thanks to the generous effort of independent investigators: cardiologists from several hospitals and pharmacologists from the *Universidad Complutense de Madrid.*

Our trial is currently in the recruitment phase, and bears the difficulties inherent to any clinical trial with the added impact of the recent COVID-19 outbreak. Like Rivas-Gándara and other authers,[5] we hope that the BRAKE-AF trial will answer the question of whether there is a new drug for rate control in AF. If so, the next question will be, "Could ivabradine improve prognosis in patients with permanent AF?"

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Competing risk largely explains the drop in admissions for acute cardiovascular disease during the COVID-19 pandemic

El riesgo competitivo puede explicar en gran medida la disminución de los ingresos por enfermedad cardiovascular aguda durante la pandemia de COVID-19

To the Editor:

The peak of the COVID-19 pandemic was accompanied by a widely observed drop in hospital admissions for acute myocardial infarction (AMI) and other cardiovascular disorders. In Spain, the number of percutaneous coronary interventions dropped by 40%,[1] and within Spain Catalonia saw a 50% decline in hospital admissions for AMI.[2] Reductions of around 40% in admissions for urgent cardiovascular conditions have also been reported in other countries affected by the pandemic.[3]

A number of feasible explanations have been proposed for this situation, including the avoidance of medical care due to social distancing concerns, underdiagnosis of ST-segment elevation myocardial infarction (STEMI), and competing risk with the acquisition and severity of COVID-19.[2] However, a view appears to have taken hold that the most likely cause of the drop in cardiovascular admissions is patient reluctance to seek medical help due to fears about the pandemic, and this view is reflected in campaigns reminding patients with these conditions of the importance of contacting emergency services.

With the currently available data, it is not possible to determine the relative contribution of avoidance of medical attention, underdiagnosis, and competing risk. However, a careful review or the data suggests that the main factor underlying the reduction in cardiovascular emergency admissions is competing risk, although there has obviously also been a slowdown in diagnosis, as we have reported.[4]

Competing risk can be defined as a "situation [that] happens when the occurrence of one type of event changes the ability to observe the event of interest."[5] This situation tends to arise when there are alternative outcomes, such that the occurrence of one event or outcome impedes the occurrence of the other, which might be the main focus of interest. Competing risk is a particular concern in long-term follow-up studies, especially studies of high-risk patients in whom the outcome measure is not death. The patients in these studies have a high risk of dying during the follow-up period from a variety of causes, and death obviously prevents a patient from later having the event of interest (AMI or stroke, for example). Studies of this type should therefore always report total mortality because this acts as a competing risk for the outcome measure.[6] With COVID-19, the deaths of large numbers of people from this disease will clearly have prevented the same individuals from having an AMI and attending hospital for its treatment.

An analysis of the data presented by Romaguera et al.[2] reveals that, during the peak of the pandemic between March 1 and April 19, 2020, there was a 50% reduction in the number of patients admitted for STEMI at Catalan hospitals compared with the same period in 2019 (524 in 2019 vs 395 in 2020). This was reflected in a drop in daily admissions over the 50-day period from 10.5 to 7.9 (incident rate ratio, 0.75; 95% confidence interval [95%CI], 0.66-0.86). Notably, compared with those treated in the same period in 2019, patients admitted during the pandemic peak tended to be younger (mean age, 63.4 ± 0.6 years in 2019 vs 61.9 ± 0.7 years in 2020; $P = .104$), and fewer of them were older than 80 years (70% in 2019 vs 37% in 2020: $P = .062$). Mortality due to COVID-19 is high among elderly patients, and it is precisely this age group that has not sought hospital treatment for AMI, probably because they were infected by and died from the coronavirus.

Delays have been reported in the care of patients who contacted the emergency services during the pandemic; however, medical care was not delayed for those who went directly to hospital, although these patients did experience an increase in door-to-balloon time. In other words, during the most intense phase of the pandemic, patients who directly seeking hospital care experienced no increase in time to first medical contact but, once admitted, waited longer before transfer to the catheterization lab, probably due to the high burden of care at hospitals during this period.

While a variety of factors may have contributed to the reduction in hospital admissions for AMI during the COVID-19 pandemic, the data indicate that this reduction was largely due to a situation of competing risk between COVID-19 mortality and acute cardiac ischemia. The pandemic has provided us with an *in vivo* experiment.

CONFLICTS OF INTEREST

M.Á. Arias is an associate editor at *Revista Española de Cardiología*; this manuscript has been handled in accordance with the editorial procedure established by the journal to ensure impartiality.

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