Drugs and Brugada syndrome patients: Review of the literature, recommendations, and an up-to-date website (www.brugadadrugs.org)

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BACKGROUND Worldwide, the Brugada syndrome has been recognized as an important cause of sudden cardiac death in individuals at a relatively young age. Importantly, many drugs have been reported to induce the characteristic Brugada syndrome-linked ECG abnormalities and/or (fatal) ventricular tachyarrhythmias.

OBJECTIVE The purpose of this study was to review the literature on the use of drugs in Brugada syndrome patients, to make recommendations based on the literature and on expert opinion regarding drug safety, and to ensure worldwide online and up-to-date availability of this information to all physicians who treat Brugada syndrome patients.

METHODS We performed an extensive review of the literature, formed an international expert panel to produce a consensus recommendation to each drug, and initiated a website *(www.brugadadrugs.org)*.

RESULTS The literature search yielded 506 reports for consideration. Drugs were categorized into one of four categories: (1) drugs to be avoided (n = 18); (2) drugs preferably avoided (n = 23); (3) antiarrhythmic drugs (n = 4); and (4) diagnostic drugs (n = 4). Level of evidence for most associations was C (only consensus opinion of experts, case studies, or standard-of-care) as there are no randomized studies and few nonrandomized studies in Brugada syndrome patients.

CONCLUSION Many drugs have been associated with adverse events in Brugada syndrome patients. We have initiated a website *(www.brugadadrugs.org)* to ensure worldwide availability of information on safe drug use in Brugada syndrome patients.

KEYWORDS Brugada syndrome; Drugs; Adverse effects; Proarrhythmia; Antiarrhythmic drug; Sudden cardiac death

ABBREVIATIONS **ACC** = American College of Cardiology; **AHA** = American Heart Association; **ECG** = electrocardiogram; **ESC** = European Society of Cardiology

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Introduction

Worldwide, the Brugada syndrome is recognized as an important cause of sudden cardiac death occurring in individuals at a relatively young age. Brugada syndrome is diagnosed in the presence of specific electrocardiographic (ECG) abnormalities (known as the type 1 Brugada syndrome ECG; Figure 1) seen in combination with an absence of gross structural abnormalities and several other criteria.[1,2] In addition, Brugada syndrome often shows familial aggregation.

The presence of the type 1 Brugada syndrome ECG in particular has been linked to an increased risk for ventricular tachyarrhythmias, cardiac arrest, and sudden death in patients with Brugada syndrome.[3] Importantly, many drugs have been reported to induce the type 1 Brugada syndrome ECG and/or (fatal) arrhythmias in patients with Brugada syndrome (Figure 2). Therefore, patients with Brugada syn-

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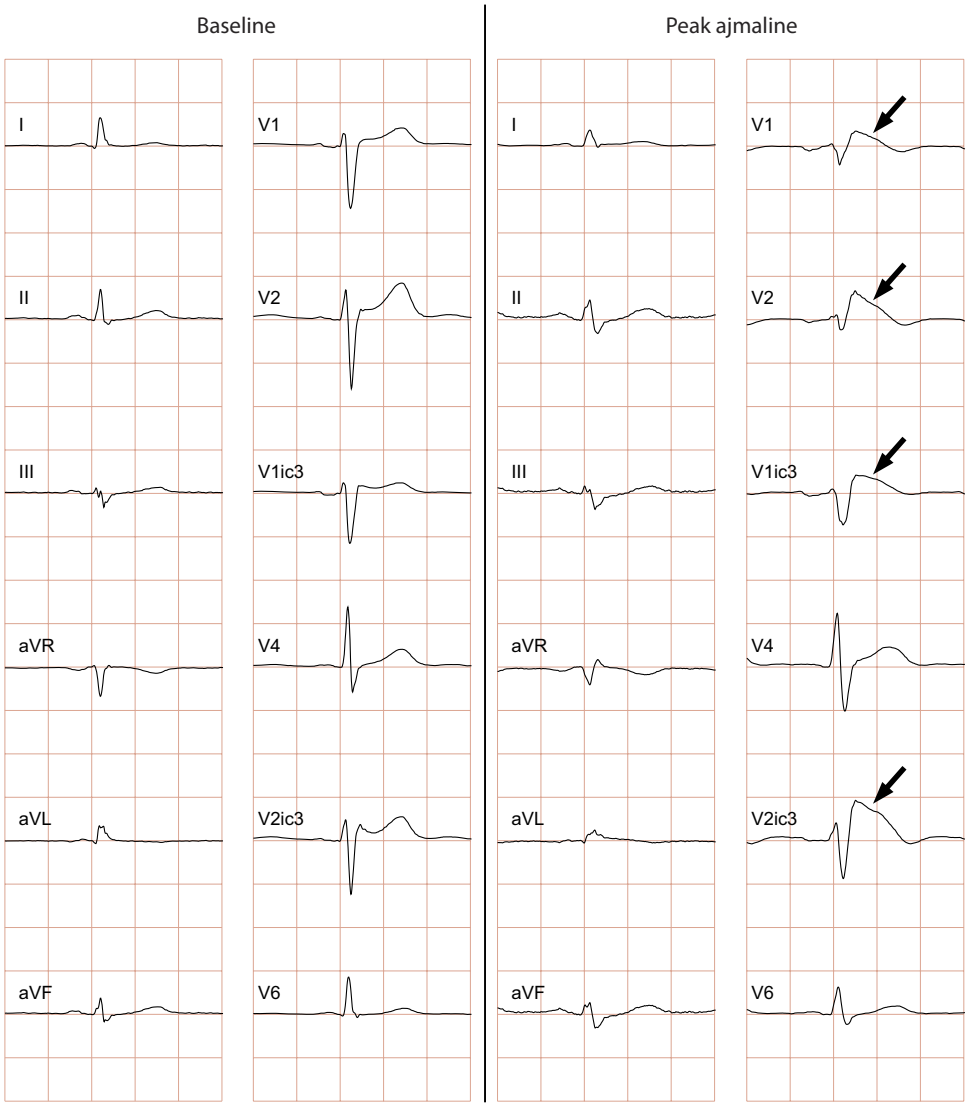

Figure 1 Conversion of a normal ECG to a type 1 Brugada syndrome ECG during ajmaline challenge. Note the coved-type ST segments *(arrows)* in the right precordial ECG leads at peak ajmaline (note that V_3 is placed in the third intercostal space above V_1 [V_{1ic3}], and V_5 is placed in the third intercostal space above V_2 [V_{2ic3}]).

drome should be advised not to use these drugs or to use them only under controlled conditions.

Although the most appropriate treatment of Brugada syndrome is under discussion,[4,5] avoidance of potentially proarrhythmic drugs and treatment of fever (which is a well-known trigger of cardiac events in Brugada syndrome)[6,7] are generally accepted to be an important part of (prophylactic) treatment. However, some patients may (only) be appropriately treated with an implantable cardioverter-defibrillator. Some drugs may have an antiarrhythmic effect and thus may be used favorably in the acute or chronic setting.[8–10] Because Brugada syndrome has a rather low prevalence (estimated at 1:2,000, varying in different regions around the world),[1] these and other critical characteristics of Brugada syndrome may not be common knowledge for many physicians.[11]

With the aim of aiding all physicians who treat patients with Brugada syndrome, we discussed the interaction between drugs and Brugada syndrome, performed an extensive review of the literature, formed an international expert panel to produce a consensus recommendation for each drug, and initiated a website *(www.brugadadrugs.org;* Figure 3) to ensure worldwide online and up-to-date availability of this knowledge base.

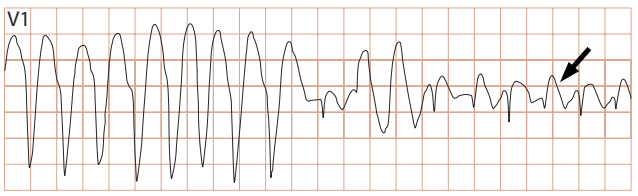

Figure 2 Nonsustained ventricular tachycardia in a patient who was given flecainide for paroxysmal atrial fibrillation. Note the coved-type ST segments *(arrow).* The patient was diagnosed with Brugada syndrome during an ajmaline provocation test.