Quinidine, a life-saving medication for Brugada syndrome, is inaccessible in many countries.

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Abstract.

Background. Limited patient access to life-saving medications commonly results from the inability of healthcare resources to meet the high costs of expensive medications. Less well-recognized is the opposite situation, in which the lack of availability of important medications is governed by its *low price* and restricted indication for a low-prevalence disease, rendering unfavorable pharmaceutical market forces from the perspective of the industry. The latter setting is exemplified by the case of quinidine. Quinidine is the only oral medication consistently effective for arrhythmic storms related to Brugada syndrome or idiopathic ventricular fibrillation (VF), yet is not sold in many counties.

Methods. We conducted a world survey of quinidine availability by contacting arrhythmia specialists in as many countries as possible. Physicians were mailed a questionnaire requesting information concerning the quinidine preparation available at their hospital. We also requested information concerning cases of adverse arrhythmic events resulting from quinidine unavailability.

Results. A total of 139 physicians from 75 countries provided information regarding quinidine availability. According to these data, quinidine is readily available in only 16 (21%) countries. In contrast, this medication is not accessible in 46 (61%) countries and is available but only through specific regulatory processes that require 4-30 days for completion in 13 (17%) countries. We were able to gather information concerning 21 patients who had serious arrhythmias probably related (10 cases) or possibility related (11 cases) to the absence of quinidine, including 2 fatalities.

Conclusions. The lack of quinidine accessibility is a serious medical hazard at the international level.

E-mail received on June 8, 2012 (no editing was done):

Hi, I hope this finds you well!

I am sorry to trouble you, but I have no one else to ask! I have a patient who had an out-of-hospital cardiac arrest a couple of years ago, and had an ICD implanted. He returned last week with multiple shocks for VF, and a suspicious ECG for Brugada syndrome. He did not respond to beta-blocker therapy and I wanted to start quinidine for him - I recall having a few patients at Sunnybrook as a resident who were taking quinidine, and we ordered it without a problem. I tried to get quinidine for this patient via SAP with Health Canada, and it was declined - they stated they did not provide it for NEW patients, only patients already on the therapy. How are you managing your Brugada patients with multiple shocks or recurrent arrhythmias? This seems completely ridiculous!

With kind regards,

Signed by a Cardiology Fellow in Canada.

Limited patient access to curative or life-prolonging medications is a major problem worldwide. It is well-acknowledged that this problem commonly results from the inability of healthcare resources to meet the high costs of patented drugs or even that of generic substitutes (examples: anti-retroviral medications in Africa or heart failure therapy for the uninsured in the USA).[1,2] Less well-recognized is the opposite situation, in which the unavailability or inaccessibility of a life-saving medication is governed by its *low price* and restricted indication for a low prevalence disease, rendering unfavorable pharmaceutical market forces from the perspective of the industry. The latter setting is exemplified by the case of quinidine.[3-5]

Quinidine is the *only* oral medication that has consistently shown efficacy in terminating arrhythmic storms due to recurrent ventricular fibrillation (VF) in patients with Brugada syndrome,[6-14] idiopathic VF[15-20] and early repolarization syndrome.[21-23] Without appropriate drug therapy, such events can prove lethal even in patients with an implanted cardioverter defibrillator (ICD), who may receive dozens of ICD shocks per day, eventually leading to cardiogenic shock. Quinidine is also the only antiarrhythmic drug that normalizes the QT interval in patients with the congenital short QT syndrome.[24,25] Yet, ever since the unexpected cessation of quinidine production by its main manufacturer,[26] prescribing this valuable medication has become increasingly difficult in many countries. In fact, on several occasions during recent years the first author has had to mail emergency supplies of quinidine overseas to physicians treating patients in urgent need of this medication because of arrhythmic storms. In view of this emerging problem, we conducted a worldwide survey designed to estimate the magnitude of quinidine shortage and its clinical implications.

Methods.

We conducted a world survey of quinidine availability by contacting professional societies of cardiology, national working groups on arrhythmia and electrophysiology and arrhythmia specialists in as many countries as possible through electronic mail. We emailed all our relevant contacts and took advantage of dedicated email networks (e.g., FORO IBEROAMERICANO DE ARRITMIAS EN INTERNET, with >700 subscribers at http://listserv.rediris.es/cgi-bin/wa?A0=ARRITMIAS) and the Chinese forum http://www.cv-research-symposium.org). Additional email addresses were obtained via a literature search for articles published on Brugada syndrome, idiopathic VF and early repolarization syndromes. All recipients were emailed a simple questionnaire requesting information concerning the quinidine preparation available at their hospital (including commercial name and manufacturer). Also requested was information pertaining to the actual time required for quinidine to be supplied for use as well as the regulatory processes involved. In addition, we specifically requested information about the number of patients in each center treated with quinidine due to Brugada syndrome, idiopathic VF or early repolarization syndromes. Corroborating evidence was sought from at least one other physician, pharmacist and all searchable public and regulatory bodies to validate physician reports. Finally, we requested information concerning cases of serious adverse arrhythmic events (specifically, recurrent symptomatic ventricular arrhythmias or ICD shocks) resulting from quinidine unavailability. All contacted physicians were also requested to forward the study-questionnaire to as many contacts of their own. Therefore, only the number of responders is known, the number of physicians who declined to respond is not. The entire e-mail survey was conducted in June-August 2012.

Arrhythmic events were defined as related to quinidine unavailability when the following criteria were met: 1) Occurrence of arrhythmias known to respond to quinidine (i.e., polymorphic VT or VF) in an appropriate clinical setting (i.e., a definite diagnosis of the Brugada syndrome or idiopathic VF with or without early repolarization); 2) inability to administer quinidine at the time of its prescription; 3) further ventricular tachyarrhythmias requiring defibrillation occurring from the time of quinidine prescription to the time of its actual administration. Events associated with quinidine unavailability were further classified as "probably resulting" from the absence of the medication in cases where arrhythmia resolution was ultimately achieved by quinidine administration. All cases in which quinidine was never administered were classified as "possibly resulting" from quinidine unavailability.

Results.

We collected information concerning quinidine availability in 100 countries (Figure 1). Missing data almost exclusively to African countries. Discordant information arrived from only 7 countries

(Argentina, China, Canada, the Czech Republic, Norway and Sweden) mostly due to discordant responses of "not available" and "available with restrictions."

Quinidine is readily and immediately available in only 17 (17%) countries. In contrast, this medication is not accessible in 70 (70%) countries and is available but only through specific regulatory processes that require 4-90 days for completion in 13 (13%) countries (Figure 1). Sixty nine (33%) physicians responded having at least one patient in need for quinidine therapy because of idiopathic VF or Brugada syndrome. Importantly, 28 (14% of physicians responding to our survey and 41% of physicians treating patients with Brugada syndrome or idiopathic VF reported having one or more patients who developed arrhythmic events related to inaccessibility to quinidine when prescribed. *Within a short period of time we were able to gather detail information concerning 22 patients who had serious arrhythmias probably related (10 cases) or possibly related (11 cases) to the absence of quinidine, including 2 patients who possibly died due to lack of quinidine therapy* (Table 1).

Discussion.

Quinidine was the most commonly used medication for the prevention of ventricular and atrial arrhythmias only 16 years ago.[27,28] However, several events led to a gradual decrease in the use of this drug: First, the potential for QT-prolongation and torsade-de-pointes provocation by quinidine became clearly evident in the 1980s;[29-31] then, in 1989 the Cardiac arrhythmia Suppression Trial (CAST) revealed that the use of class I antiarrhythmic drugs for the prevention of sudden death in patients with asymptomatic ventricular arrhythmias and impaired left ventricular function actually resulted in increased mortality.[32] Finally, in 1990 an extensively quoted meta-analysis suggested that quinidine use is associated with increased mortality even in the setting of atrial fibrillation therapy.[33] The decline in quinidine use was perpetuated by the introduction of new antiarrhythmic drugs, considered safe at the time. Thus, by 2006, marketing of quinidine was no longer considered profitable and AstraZeneca, the main manufacturer of quinidine, discontinued its production.[3,26,34] The discontinuation of quinidine due to financial considerations might be accepted as inevitable given modern pharmaceutical market forces, though it was clearly problematic from the ethical point of view since the unique effectiveness of quinidine for VF prevention[15-18] and for controlling arrhythmic storms in patients with idiopathic VF[19,20] had been known for more than two decades at that time. Moreover, the laboratory[35] and clinical evidence[6-8] establishing the high efficacy of quinidine in the management of the Brugada syndrome, particularly for arrhythmic storms,[9-13] were well known at the time quinidine production was discontinued.

Our study shows that quinidine is entirely unavailable or available only with delay in 83% of all countries providing data. Interestingly, quinidine is produced in France by a large manufacturer (Sanofi-Aventis), but is not readily available in neighboring countries such as Germany. Lack of fiscal incentives, driven by low pricing and the low prevalence of the conditions for which the drug is indicated, is the likely explanation for the variations in quinidine availability noted between countries. Ironically, one of the quinidine brands available in the U.S. is made in India but not marketed in that country. As a consequence of this absurdity, a 10-year old girl with Brugada syndrome presenting with arrhythmic storm well-controlled by quinidine, is forced to receive these Indian-made medication shipped from the U.S., and this is through collaboration between colleagues in these two countries (Table 1). The lack of quinidine in South East Asian countries like Thailand and the Philippines is intolerable because Brugada syndrome is highly prevalent in that region.[36]

Through our survey, we identified 22 patients who suffered from serious adverse events (mainly recurrent ICD shocks for VF) that were attributed to quinidine inaccessibility, including two fatalities possibly due to this problem. The fact that 10% of physicians responding to our inquest could provide detail evaluation concerning patients in urgent need of quinidine therapy could represent selection bias; in other words, it is possible that physicians with patients in need for quinidine were more likely to respond to our survey and were therefore over-represented. Nevertheless, the fact that within a very short period we were able to collect data for so many adverse events, in some many countries, suggest that the lack of quinidine accessibility is a serious medical hazard at the international level.

Our study has important clinical implications: 1) Professional medical organizations, in particular the Heart Rhythm Society, the European Heart Rhythm Association and the Asian Pacific Heart Rhythm Society, must work in unison with national healthcare authorities to insure expedited access and reduce the price of the processes required to make quinidine legally available in all countries. 2) Until that happens, arrhythmia centers (at least in referral hospitals) should ensure an adequate supply of quinidine for immediate access in medical emergencies. 3) Drug manufacturers must assume responsibility for adequate and continuous supply of irreplaceable medications proven valuable even when their marketing is no longer profitable. Legislative measures to prevent independent and unilateral discontinuation of crucial drug production by manufacturers, pending the availability of efficacious substitutes, should be considered at the national level.

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Table 1. Reported Serious Adverse Events (SAE) Related to Immediate Inaccessibility to Quinidine.

Country *City* Hospital	**Case description.**
Germany *Hannover*	**Recurrent ICD shocks probably due to quinidine inaccessibility.** A 39-year old male patient with Brugada syndrome had multiple ICD shocks for VF and responded well to quinidine therapy. When the marketing of quinidine was discontinued in Germany, the patient suffered from recurrent appropriate shocks again due to spontaneous VF. Eventually, hydroquinidine was imported from France and the patient remained arrhythmia free.
Thailand *Bangkok.* Bhumibol Adulyadej Hospital	**Death from VF storm possibly related to quinidine (and isoproterenol) inaccessibility.** A 67 year old man hospitalized with VF storm. He had diabetes, hypertension, and presented with chest pain, but had no significant coronary artery disease during emergency catheterization. He went into incessant VF within 30 minutes. He failed to respond to antiarrhythmic therapy, including intravenous amiodarone. The diagnosis of "idiopathic VF" was considered and therapy with intravenous isoproterenol and oral quinidine was prescribed. *However, neither of these medications was available.* After multiple DC shocks, cardiogenic shock developed and an intra-aortic balloon pump was placed. The patient ultimately died of cardiogenic shock.
Mexico *Mexico City.* Instituto Nacional de Cardiologia Ignacio Chavez,	**Recurrent ICD shocks probably due to quinidine inaccessibility.** A 37 year old patient with Brugada syndrome and VF-storm that responded to quinidine therapy. He received quinidine for 14 months without arrhythmic events until quinidine marketing was discontinued in Mexico. Shortly thereafter, he received two appropriate ICD shocks for VF. It took 8 days to get quinidine supplies. Once quinidine administration was ensured, he remained free of arrhythmias for the remaining follow-up period, >7 years. **Recurrent ICD shocks probably due to quinidine inaccessibility.** A 30 year old patient with Brugada syndrome presented with VF storm that responded immediately to quinidine therapy. He received quinidine for more than 5 years without events until quinidine marketing was discontinued in Mexico. Shortly thereafter he received one appropriate ICD shock for VF. It took 8 days to get quinidine supplies. Once quinidine administration was ensured, he remained free of arrhythmias for the remaining follow-up period (6 months).

India *New Delhi.* All India Institute of Medical Sciences.	**Recurrent ICD shocks probably due to quinidine inaccessibility in a child.** A 10-year old girl with Brugada syndrome who presented with VF storm. Originally treated with the intravenous antimalarial quinine because quinidine was not available.[37] Over the years, she was treated with oral quinidine. Although quinidine is produced in India, it is not marketed here. Consequently, physician colleagues in the U.S. periodically mail us quinidine supplies (made in India!) back to our country for the treatment of this child. Over the years, she has received ICD shocks definitively linked to temporary lack of quinidine availability.
Saudi Arabia *Jeddah.*	**1. Recurrent ICD shocks probably due to quinidine inaccessibility.** A young male with Brugada syndrome had frequent ICD shocks (every two months on average) despite amiodarone and beta-blocker therapy. Quinidine was prescribed but it took two months to import it from Egypt. During this 2-month period, the patient received additional ICD shocks. He has been free of arrhythmias ever since quinidine supplies were ensured.[38] **2. Recurrent VF possibly due to quinidine inaccessibility.** A second patient with Brugada syndrome admitted with recurrent VF refractory to antiarrhythmic drugs, including amiodarone. His family eventually brought quinidine from Egypt but only after 4 days and during this period he required repeated DC shocks. The Saudi patient has been arrhythmia free for years on quinidine therapy purchased in Egypt.
Mexico *Mexico City* UMAE Hospital de La Raza IMSS.	**ICD implantation and ICD shock probably due to quinidine inaccessibility** A 38-year-old man with Brugada syndrome received empiric quinidine therapy because of presyncope and spontaneous type I Brugada pattern plus early repolarization in the inferior leads. He remained completely asymptomatic for 2 years. One month after quinidine was withdrawn from the market in Mexico, the patient presented with recurrent presyncope and spontaneous non-sustained polymorphic ventricular tachycardia was recorded. Because of the inaccessibility of quinidine, he underwent ICD implantation. One month later he received an appropriate ICD shock for spontaneous VF.

Uruguay *Montevideo* Centro Cardiovascular Casa de Galicia	**1. Recurrent ICD shocks probably due to quinidine inaccessibility.** Recurrent ICD shocks probably due to quinidine inaccessibility. A 58 year-old male with Brugada Syndrome presented with appropriate ICD shocks for recurrent VF initially triggered by fever. During that period the patient received 15 ICD shocks despite amiodarone and lidocaine. He responded to isoproterenol and this drug infusion was maintained until we received quinidine directly mailed to us from Israel, but it took 6 days for the emergency pack to arrive. The patient has been arrhythmia free on quinidine (purchased from Argentina or France) for a 1-year period.
Canada: *London, Ontario* London Health Science Centre	**1. Recurrent ICD shocks possibly due to quinidine inaccessibility**. A 32 year-old female with idiopathic VF. Presented with VF storm leading to 10 ICD shocks. She eventually responded to intravenous isoproterenol and waited 5 days on continuous isoproterenol until we received hydroquinidine mailed to us from Israel. (http://www.theheart.org/article/1197113.do). The patient has remained free of arrhythmias while receiving quinidine purchased through a special access program. **2. Recurrent ICD shocks possibly due to quinidine inaccessibility**. A 54 year old woman with idiopathic VF. ICD implanted in 2006 after cardiac arrest. Developed a VF storm in 2010, with recurrent ICD shocks until quinidine was somehow obtained. She has remained arrhythmia-free for 2 years on quinidine
Uruguay *Montevideo* Instituto de Cardiología Infantil Mucam.	**Arrhythmic death possibly related to quinidine inaccessibility**. A 50 year old male with implanted ICD for idiopathic VF received recurrent appropriate ICD shocks for VF despite amiodarone therapy. Quinidine therapy was recommended but was not available. He was treated with sotalol and died suddenly sometime thereafter. The ICD was not interrogated thus arrhythmic death was not confirmed, albeit strongly suspected.
Denmark *Aarhus* Aarhus University Hospital	**VF storm (with 70 ICD shocks!) probably related to quinidine inaccessibility.** A 28 year-old male with idiopathic VF and early repolarization had recurrent ICD shocks for VF despite amiodarone, sotalol, metoprolol or flecainide. Quinidine was prescribed but not available. Radiofrequency ablation of the triggering extrasystoles was attempted but was not successful. VF was eventually controlled, first with isoproterenol and then with quinidine, but only after receiving 70 ICD shocks for VF. He has remained asymptomatic and arrhythmia-free ever since quinidine was started (follow-up 9 months).

Bahrain (Riffa, Adel Khalifa Sultan Hamad.)	**Recurrent ICD shocks possibly due to quinidine inaccessibility.** A 20 year old male with Brugada syndrome who experienced recurrent ICD shocks. Quinidine was recommended but was not available and he was treated with amiodarone. However, he continued to suffer from appropriate ICD shocks for VF. He eventually moved to a different country and was lost to follow-up.
Canada *Toronto*. University Health Network	**Multiple ICD shocks possibly due to quinidine inaccessibility.** A male with suspected Brugada syndrome and ICD implanted for cardiac arrest. Presented with VF storm leading to multiple appropriate ICD shocks refractory to conventional antiarrhythmic drugs. Quinidine prescribed but not yet accessible.
Spain (Unidad de Arritmias, Hospital Puerta de Hierro, Madrid)	**Recurrent ICD shocks possibly due to quinidine inaccessibility.** A 47-year old male patient with Brugada syndrome admitted with appropriate ICD shocks. Isoproterenol was initiated but quinidine was not available. He received 5 ICD shocks for VF prior to isoproterenol therapy and two more shocks while waiting for quinidine supplies despite isoproterenol. He has been arrhythmia free since the initiation of quinidine therapy (follow-up 2 months).
Oman *Muscat* Royal Hospital, Muscat, Oman	**ICD shocks possibly due to quinidine inaccessibility. A** 20 year old cardiac arrest survivor likely due to idiopathic VF; had recurrent VF episodes not responding to conventional antiarrhythmic drugs.
Spain (Madrid, Dr. Peinado)	**ICD shock possibly due to quinidine inaccessibility.** A patient with idiopathic VF who presented with VF storm. Radiofrequency ablation was attempted but failed. Intravenous isoproterenol was initiated as quinidine was not immediately available. He received intravenous isoproterenol for 4 days until quinidine supplies arrived and during that period the patient received one shock. Remains asymptomatic on quinidine.
Iran (Tehran, ZE)	**ICD shocks possibly due to quinidine inaccessibility**. Two patients with Brugada syndrome who were reported in the literature as cases of arrhythmic storm who responded to quinidine[10,39] developed VF again once quinidine disappeared from Iran.

South Africa: Sunninghill Hospital, Gauteng.	**ICD shocks possibly due to quinidine inaccessibility**. A __ year old female patient with idiopathic VF presented with VF storm refractory to beta-blockers, verapamil, amiodarone. She underwent two attempts of radiofrequency ablation. Rapid atrial pacing decreased the frequency of ICD shocks. Quinidine was prescribed but was not available. It took 7 days to import quinidine and during that period she received 14 additional ICD shocks. Except for one shock shortly after the first does of quinidine, she has remained arrhythmia free on quinidine therapy.

Figure legends.

Figure 1. World map of quinidine availability. Countries where quinidine is readily available are shown in green, countries where quinidine is not available, or is available with restrictions are shown in red and yellow, respectively (see methods).