OPINION

The emerging role of amiodarone and dronedarone in Chagas disease

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Abstract | Chagas disease has emerged as an important health problem in the Americas and, with globalization, in other parts of the world. Drug therapy for this parasitic infection has remained largely ineffective, especially in chronic stages of the disease. However, developments in experimental therapy might signal an important advance for the management of patients with Chagas disease. Herein, we review studies on the potential use of the benzofuran derivatives amiodarone and dronedarone in patients with Chagas disease. These agents have a dual role, not only as primary antiarrhythmic drugs, but also as antiparasitic agents. We believe that this 'kill two birds with one stone' approach represents a new tactic for the treatment of Chagas disease using currently approved drugs.

Benaim, G. & Paniz Mondolfi, A. E. *Nat. Rev. Cardiol.* **9**, 605–609 (2012); published online 7 August 2012; doi:10.1038/nrcardio.2012.108

A worldwide menace

More than a century after its discovery by the Brazilian physician and parasitologist Carlos Chagas, American Trypanosomiasis (Chagas disease) continues to be among the most neglected of all tropical diseases, affecting millions of people and posing a serious health and economic setback for most Latin American countries.[1,2] Furthermore, as a consequence of increased migration, both domestically (from rural to urban areas) and internationally, Chagas disease has spread from Latin America to become a worldwide menace.[2,3] Estimates from the World Health Organization and the Centers for Disease Control and Prevention indicate that between 8 and 11 million people are infected, and at least 100 million are at risk of infection, by the disease-causing parasite *Trypanosoma cruzi*.[4,5] Central and South American countries such as Argentina, Bolivia, Brazil, and Venezuela continue to have the highest prevalence of this disease,[4,6] but cases have been described in Australia, Canada, and Europe,[3] and at least 300,000 individuals residing in the USA are estimated to have this condition.[7]

Competing interests
The authors declare no competing interests.

Pathophysiology

After infection by the protozoan parasite *T. cruzi*, the disease undergoes an acute and then a chronic phase.[8] During the acute phase, a wide variety of parenchymal cells become parasitized, including those of the gastrointestinal tract (colon and esophagus), brain and, especially, the heart.[8] Chronic cardiomyopathy is the most frequent and serious manifestation in late-stage disease, affecting up to 40% of individuals, and can occur years or decades after initial infection.[6,8] The pathophysiology of myocardial damage is based on the direct injury caused by the intracellular forms of the parasite (amastigotes; Figure 1), which provokes the host inflammatory response, resulting in a chronic, focal-to-multifocal, fibrosing myocarditis and consequent impairment of myocardial contractile function.[6,8,9] This diffuse pattern of panmyocarditis serves as the anatomical substrate for the electrocardiographic patterns of intraventricular conduction disturbances and the atrial and ventricular arrhythmias seen in advanced forms of chagasic cardiomyopathy.[6,9]

Although several studies in the past have suggested an autoimmune component in the pathogenesis of this disease, multiple studies have shown a positive correlation between tissue parasitism and the extent of cardiac dysfunction.[10,11] Tarleton *et al.* have demonstrated that heterotopic neonatal heart transplants to syngeneic mice with chronic experimental Chagas disease and severe cardiomyopathy do not elicit autoimmune-type rejection or are targets of inflammatory responses from the host.[12] Rejection occurred only when the hearts were directly injected with live parasites, leading to a dramatic inflammatory response and cessation of contractile activity.[12] In addition, effective antiparasitic treatment leads to regression of the inflammatory heart lesions and fibrosis in experimental animals and also stops progression of disease in humans, supporting the notion that the presence of the parasite is necessary and sufficient for chagasic cardiomyopathy to develop.[10]

Treatment options

To date, there are only two commonly available drugs to treat Chagas disease, the nitroheterocyclic compound nifurtimox and the nitroimidazole derivative benznidazole.[9] Large, multicenter, randomized trials of these drugs, including the BENEFIT trial,[13] are currently underway. However, neither nifurtimox nor benznidazole is ideal to treat the chronic phase of Chagas disease because of their limited efficacy, the presence of naturally resistant strains of the parasite, and substantial toxic adverse effects.[14]

Paradoxically, and despite the wide spectrum of atrial and ventricular arrhythmias and conduction disturbances frequently observed in patients with chagasic cardiomyopathy, drug therapy with conventional antiarrhythmics in this setting is also frequently ineffective.[6,8,9] Several studies have demonstrated the efficacy of implantable cardioverter–defibrillators in treating malignant arrhythmias in patients with Chagas cardiomyopathy;[15] however, this alternative is not readily available for low-income populations such as those affected by this disease.

Over the past 10 years, several novel approaches using new and old drugs have emerged on the basis of an increasing understanding of biochemical, physiological, and metabolic aspects of the parasite.[14,16] Among the most-promising candidates are specific drugs that have proven efficacy and have been extensively used for other clinical conditions, including the bisphosphonate risendronate[17]

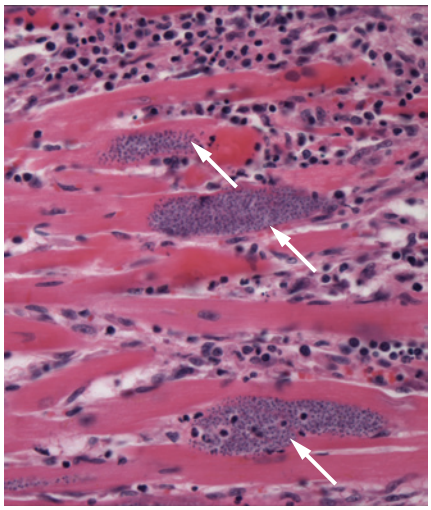

Figure 1 | Myocardium stained with hematoxylin and eosin, revealing severe inflammatory reaction composed primarily of lymphocytic cell infiltrate (small, round, dark blue cells), and nests of tightly packed amastigotes (white arrows) within muscle cells.

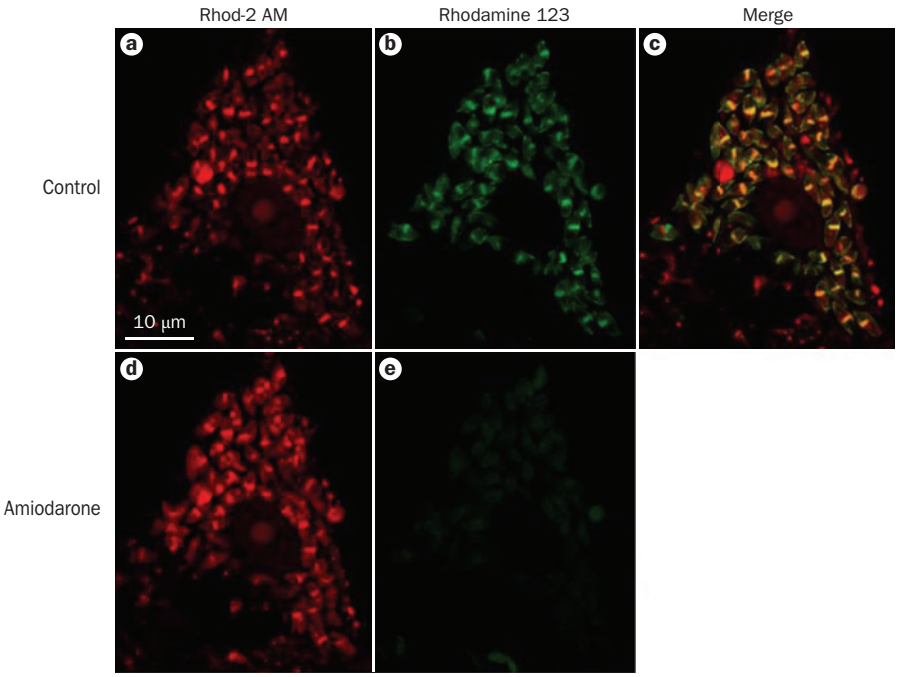

Figure 2 | Amiodarone disrupts intracellular Ca^{2+} homeostasis in *T. cruzi*. Vero cells heavily infected with *T. cruzi* amastigotes were incubated simultaneously with cell-permeant Rhod-2 AM (to show Ca^{2+} distribution; red) and Rhodamine 123 (to show mitochondrial membrane electrochemical potential; green). **a** | Under control conditions, the red fluorescence of Rhod-2 came mainly from intracellular Ca^{2+}-rich compartments—primarily mitochondria—because the low affinity of Rhod-2 for Ca^{2+} limits its fluorescence in the Ca^{2+}-poor cytoplasm of the amastigotes or Vero cells. **b** | Also under control conditions, the green fluorescence of Rhodamine 123 was distributed across the inner mitochondrial membrane showing its membrane potential. **c** | A merge of parts a and b shows co-localization of these fluorescent stains. **d** | When the individual Vero cell (infected with *T. cruzi* amastigotes) was treated with amiodarone (12.5 μmol/l), Ca^{2+} was released from the parasites' mitochondria and a concomitant increase in the parasites' cytoplasmic Ca^{2+} concentration was observed. However, no effects were seen on the cytoplasmic Ca^{2+} levels in the host Vero cell. **e** | The amiodarone-induced change in Ca^{2+} localization within the parasite (shown in part d) was associated with a collapse of the mitochondrial membrane potential, as depicted by decreased green fluorescence compared with that seen in part b. Reprinted with permission from Benaim, G. *et al.* Amiodarone has intrinsic anti-*Trypanosoma cruzi* activity and acts synergistically with posaconazole. *J. Med. Chem.* **49**, 892–899 (2006). Copyright 2006 American Chemical Society.

and several azole-based antifungals, such as itraconazole[16] and posaconazole.[14,18] However, the option that has become more tempting, because of its dual mechanism of action, is the antiarrhythmic agent and benzofuran-derivative amiodarone.

A dual mechanism of action

Amiodarone

Frequently prescribed to patients with complex arrhythmias as a consequence of their baseline chagasic cardiomyopathy,[16] amiodarone is primarily considered a class III antiarrhythmic agent, but shares at least some of the properties of other electrophysiological classes of antiarrhythmic drugs.[16,19] Actions of amiodarone include inhibition of Na^+ channels, L-type Ca^{2+} channels, K^+ channels, and the Na^+/Ca^{2+} exchanger, as well as noncompetitive blockade of α and β adrenergic receptors.[19] Although no specific agent has yet been demonstrated to prolong survival in patients with Chagas disease in randomized trials,[9] two studies have shown that amiodarone is the most-effective antiarrhythmic agent in patients with this condition.[20,21] Indeed, ambulatory electrocardiographic monitoring over a 26-month period revealed only a few minor arrhythmic events in patients with chronic chagasic myocarditis and malignant ventricular arrhythmias who had been treated with amiodarone.[22] These observations suggest that nonelectrophysiological mechanisms of action might have a role in the superior efficacy of amiodarone in this setting.

In 2006, amiodarone was reported to have specific anti-*T. cruzi* effects in addition to its antiarrhythmic activity.[17] The direct anti-*T. cruzi* activity of amiodarone, as well as its potent synergistic effect when coupled with the ergosterol biosynthesis inhibitor posaconazole, was demonstrated *in vitro* and in infected mice.[17] Amiodarone disrupts Ca^{2+} homeostasis in *T. cruzi* by inducing the release of this ion from intracellular stores (Figure 2), specifically from the single giant mitochondrion present in the parasite[17] as well as from the acidocalcisomes (acidic organelles containing high concentrations of pyrophosphate and Ca^{2+}).[23,24] Interestingly, this action seems to be parasite-specific, since it was not observed in the mammalian host cells (Figure 2), which grew normally under the amiodarone levels that led to loss of parasite viability within 24 h. Additionally, amiodarone was found to block sterol biosynthesis in *T. cruzi* by inhibition at the level of oxidosqualene cyclase, an effect also potentiated by posaconazole.[17] The combined effects of these two mutually reinforcing molecular mechanisms, the disruption of the parasite's Ca^{2+} homeostasis and the blockade of *de novo* ergosterol biosynthesis, contribute to the antiproliferative and synergistic effects of amiodarone against this parasite.[17] Electron microscopy studies have confirmed that these drugs, when used individually or in combination, induce parasite death, as shown ultrastructurally by intense wrinkling of the protozoan surface, shedding of plasma membrane vesicles, vesicle formation in the flagellar pocket, swelling of the parasite's mitochondrion, accumulation of lipid inclusions in the cytoplasm, disorganization of the Golgi complex, and formation of autophagic vacuoles (Figure 3).[25,26] This direct activity

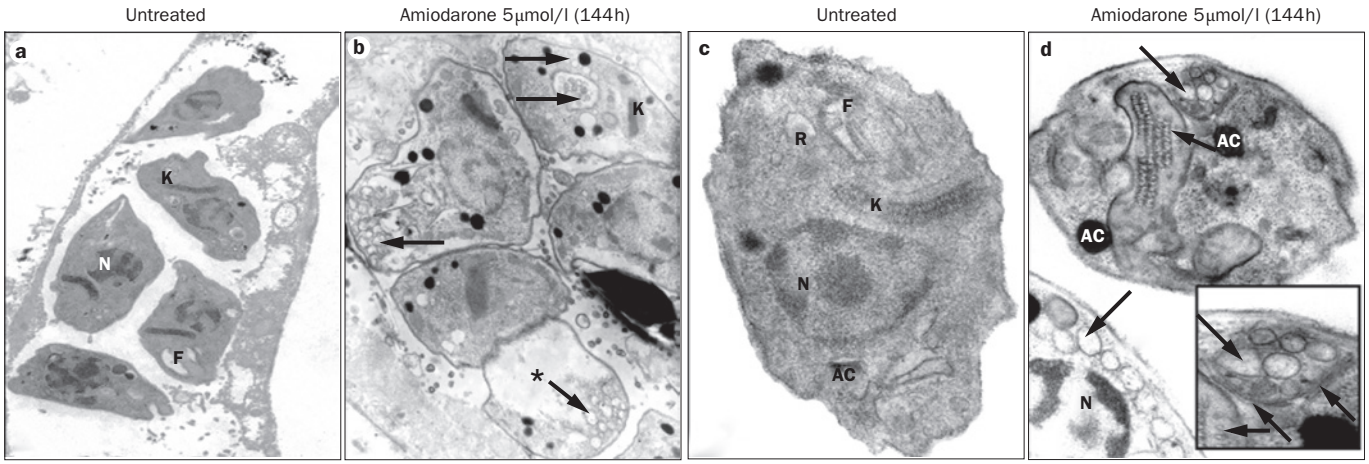

Figure 3 | Effects of amiodarone on the ultrastructure of intracellular *T. cruzi* (Y strain) amastigotes. **a** | Untreated heart muscle cells, after 192 h of infection with *T. cruzi*, displaying severe intracellular damage and intact amastigote forms each with a bar-shaped kinetoplast (K), nucleus (N), and flagellum (F). **b** | Infected cell cultures treated with 5 μmol/l amiodarone for 144 h showed parasites with membrane blebs (arrows), loss of intracellular material (star), and kinetoplast (K) alterations. **c** | Released parasites from untreated cell cultures displayed acidocalcisomes (AC) and a bar-shaped kinetoplast (K), nucleus (N), reservosome (R), and flagellum (F), as expected. **d** | Parasites obtained from cell cultures treated with 5 μmol/l amiodarone (144 h) showed important alterations in the kinetoplast and Golgi apparatus (arrows). The acidocalcisomes (AC) and nucleus (N) are labelled. Reproduced with permission from the American Society for Microbiology © Adesse, D. *et al.* Amiodarone inhibits *Trypanosoma cruzi* infection and promotes cardiac cell recovery with gap junction and cytoskeleton reassembly *in vitro*. *Antimicrob. Agents Chemother.* **55**, 203–210 (2011), doi:10.1128/AAC.01129-10.

of amiodarone against *T. cruzi* has also been clearly demonstrated *in vivo* in murine models of Chagas disease.[17] Compared with several other therapies, treatment of infected animals with amiodarone alone reduced parasitemia and increased survival by 60 days and, when given in combination with posaconazole, also delayed the development of parasitemia.[17]

Consequently, we decided to explore whether antiarrhythmic treatment with amiodarone would also have an effect on parasite load in humans, or enhance the efficacy of other specific antiparasitic agents. The preliminary results have been very encouraging. In a case report, we showed that amiodarone treatment resulted not only in adequate control of arrhythmia, but also in a considerable reduction in parasite load in a 62-year-old man diagnosed with severe chagasic cardiomyopathy.[16] Surprisingly, 1 month after initiating amiodarone and obtaining clinical stabilization, circulating specific 'lytic' antibodies (anti-rTc24) against *T. cruzi* dropped dramatically.[16] Itraconazole was added to his regimen and, after an additional 6 months of combination treatment, specific anti-rTc24 antibodies reached levels below the cutoff point for detection. Moreover, our patient's clinical condition improved considerably, with his ejection fraction increasing from 25% to 32%, revealing an enhancement of myocardial function.[16] How, then, did amiodarone contribute to recovery of cardiac function in this patient?

The answer to this question came early in 2011, with the elucidation of the mechanism by which amiodarone promotes cardiac cell recovery at the same time as it inhibits *T. cruzi* infection.[26] Parasite proliferation is associated with progressive reduction of cardiomyocyte contractility. Because *T. cruzi* is known to disrupt gap junctional communication through reduction of the essential gap protein connexin 43 (also known as gap junction alpha-1 protein), Adesse *et al.* evaluated expression of connexin 43 and its interactions with actin filaments after amiodarone treatment of cell cultures infected with *T. cruzi*.[26] Notably, reassembly of these cytoskeleton elements was accompanied by recovery of spontaneous contractility of cardiac myocytes and, after several hours, the number of spontaneous beats was at a level comparable to that of uninfected cardiomyocyte cultures.[26] We believe that these results reflect, at a cellular level, the sequence of clinical events that led to the improvement of our patient with amiodarone treatment.

Unfortunately, amiodarone's adverse effects (including thyroid, pulmonary, and gastrointestinal toxicity) and potential phototoxic reactions represent a major challenge to use of this drug in certain clinical scenarios, such as interstitial lung disease, hyperthyroidism, hypothyroidism, or hepatic or renal dysfunction. These undesirable features have prompted consideration of a new candidate drug, a noniodinated benzofuran derivative of amiodarone, dronedarone.

Dronedarone

Like amiodarone, dronedarone is considered mainly a class III agent, but exerts multichannel-blocking properties by inhibiting multiple Na^+ channels, K^+ currents, L-type and T-type Ca^{2+} channels, as well as demonstrating substantial α-blocking and β-blocking properties.[19,27] Structurally, the iodine moieties of amiodarone are not present in dronedarone, and a methylsulfonamide group has been added to decrease lipophilicity (Figure 4a), thus reducing the possibility of neurotoxic and other adverse effects.[19,27]

To date, no experience of dronedarone use in patients with Chagas disease has been reported, and overall long-term clinical experience with this drug is limited (the largest trial of its use, the ATHENA study,[28] lasted for only approximately 21 months).[27] However, several randomized, placebo-controlled trials have demonstrated the efficacy of dronedarone for the maintenance of sinus rhythm and ventricular rate control in patients treated for atrial fibrillation or atrial flutter.[19,27,29] On a clinical basis, therefore, we believe that dronedarone is a good candidate for the treatment of chagasic cardiomyopathy in patients with associated arrhythmia, but what about its antiparasitic action?

Results obtained in our laboratory have shown that dronedarone effectively de-energizes the parasite mitochondrion (Figure 4b), and induces the release of Ca^{2+} from *T. cruzi* acidocalcisomes in a similar

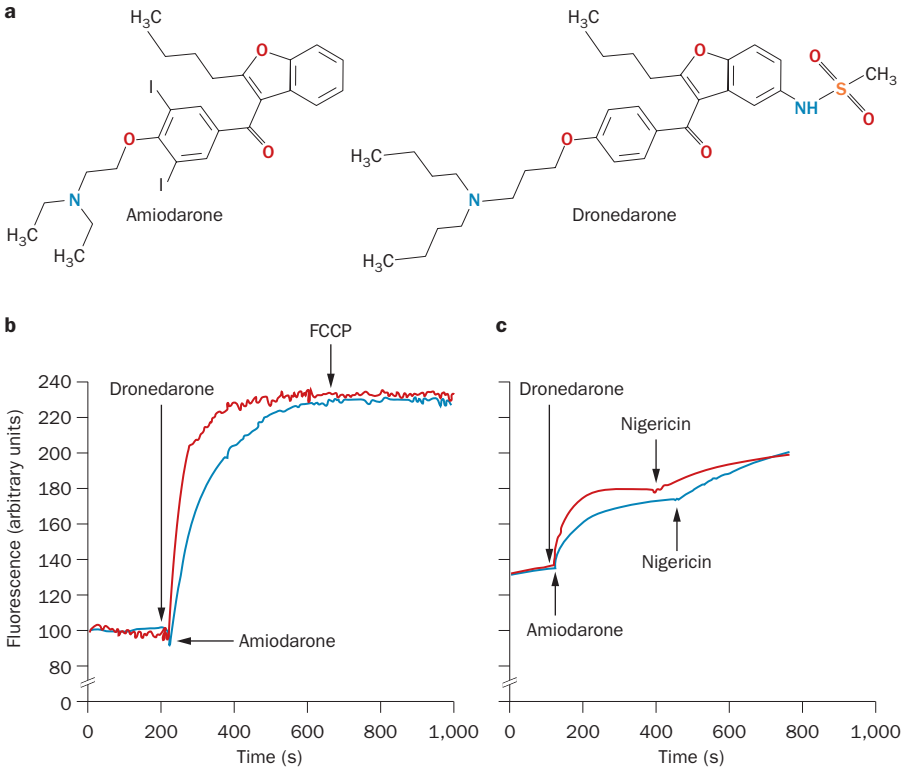

Figure 4 | Comparison of amiodarone and dronedarone structure and function. **a** | Molecular structures of amiodarone and dronedarone. The iodine (I) moieties in amiodarone are not present in the dronedarone molecule. Another difference between the two drugs is that dronedarone has a methanesulfonyl group attached to the benzofuran ring. **b** | Effects of amiodarone and dronedarone on the mitochondrial membrane potential in *T. cruzi*. Dronedarone induced a rapid release of Rhodamine 123, which was faster than that seen with amiodarone. The Rhodamine 123 release was not enhanced by the addition of the uncoupler protonophore FCCP, indicating that both amiodarone and dronedarone induced a total collapse of the electrochemical potential. **c** | Effects of amiodarone and dronedarone on the alkalinization of the parasite acidocalcisomes. Nigericin (an electroneutral K^+/H^+ exchanger that alkalinizes the parasite acidocalcisomes) was used as a control for alkalinization. As seen for the collapse in mitochondrial membrane potential in part b, dronedarone induced faster alkalinization than amiodarone, which possibly results in dronedarone's lower 50% inhibitory concentration. Abbreviation: FCCP, carbonyl cyanide 4-(trifluoromethoxy)phenylhydrazone. Adapted and reproduced with permission, Copyright © American Society for Microbiology, Benaim, G. *et al. In vitro* anti-*Trypanosoma cruzi* activity of dronedarone, a novel amiodarone derivative with an improved safety profile. *Antimicrob. Agents Chemother.* **56**, 3720–3725 (2012), doi:10.1128/AAC.00207-12.

fashion to amiodarone (Figure 4c),[23] thus effectively killing the parasites in both its extracellular form (epimastigotes) and its intracellular, and clinically relevant, form (amastigotes). As with amiodarone, the targeting of acidocalcisomes is critical, owing to the important role of these organelles in maintaining an adequate pH and osmoregulation within the parasites. Additionally, as a reservoir of polyphosphates, the fundamental function of acidocalcisomes in the bioenergetics of the parasite is crucial because pyrophosphate is an alternative energy source to ATP for these parasites and is more abundant.[24]

A potential drawback to the use of dronedarone in combination with other antiparasitic drugs is its extensive liver metabolism by cytochrome P450.[30,31] In contrast to amiodarone, which exerts a strong synergistic antiparasitic effect with itraconazole or posaconazole *in vitro* and *in vivo*, the use of dronedarone in combination with cytochrome P450 3A inhibitors, such as itraconazole, ketoconazole, and voriconazole, is reported to potentially result in a significant increase of dronedarone concentration and toxicity.[30,31] On the other hand, an increase in the plasma concentration of dronedarone (when concomitantly used with azoles) might increase exposure of the parasites to the drug. Nevertheless, the use of dronedarone in patients with severe heart failure is still controversial, with conflicting results from two of the most-important trials, the ANDROMEDA and ATHENA trials.[28,29,32] Although the former study revealed a higher mortality among patients with decompensated heart failure receiving dronedarone,[32] the latter indicated a positive outcome when considering time of first hospitalization or death as end points.[28]

Despite these potential drawbacks, we believe that dronedarone has emerged as a strong candidate for the treatment of chagasic cardiomyopathy in patients who have arrhythmia in light of its antiarrhythmic and antiparasitic efficacies, as well as its better overall safety profile compared with amiodarone. We strongly suggest that until more information is collected regarding the safety profile of dronedarone in patients with advanced heart failure, its use should be restricted to chagasic patients with arrhythmia and mild-to-moderated heart failure. At the moment, amiodarone remains the preferred of these two drugs, primarily because of its potential for use in combination with azole-derivatives. However, the more-potent antiparasitic effect of dronedarone places this drug as a better single-therapy candidate. Additionally, because of its powerful effect on killing parasites, we suggest that the duration of dronedarone treatment in combination with azoles could potentially be shortened or tailored to avoid potential adverse effects.

Conclusions

In Latin America, major efforts to control Chagas disease have included the implementation of housing improvement, case management, and vector-control campaigns.[33] However, important and successful programs such as the Southern Cone Initiative (INCOSUR) have clearly emphasized that current prevention strategies are not sufficient to control disease burden, and that diagnosis and treatment of every individual with Chagas disease is a key to success.[33] The organization Médecins Sans Frontières has demonstrated the feasibility of implementing Chagas disease diagnosis and treatment protocols in highly affected populations in the Andes and in Central American countries, as well as the need for more-effective drugs with improved safety profiles.[34]

The dual role of benzofuran-derivatives—not only as primary antiarrhythmic drugs, but also as proven antiparasitic agents—represents a clear example of the 'kill two birds with one stone' approach in therapeutics. Combination schemes including benzofuran derivatives with azole drugs could improve treatment efficacy, reduce dosage, treatment duration, and toxicity, and might prevent the potential development of resistant parasite

strains. Also, their complementary use with other therapeutical interventions (such as implantable cardioverter-defibrillators[15]) or other drugs with proven efficacy for this condition (for example, β-blockers[35]) might improve the overall survival of patients with Chagas disease.

Despite the World Heath Organization's most-recent efforts to eliminate Chagas disease (launched in 2007),[36] little has been accomplished. Chagas disease continues to impair human development by producing substantial morbidity, premature death, and disability,[33,37] with an estimated annual cost of 667,000 disability-adjusted life-years lost.[37,38] This condition thus severely affects the productivity and progress of an entire continent, and the lack of investment in, or solid commitment to, discovery and development of new antitrypanosomal drugs paints a forlorn picture. Therefore, the potential use of drugs already approved for treatment of other conditions in humans is emerging as a hope in the fight against this disease.

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Acknowledgments
This work was supported by grant 2011000884 from the Consejo Nacional de Investigaciones Científicas y Tecnológicas (FONACIT), Venezuela (to G. Benaim), grant PI 03-00-7380-2008/2 from the Consejo de Desarrollo Científico y Humanístico from the Universidad Central de Venezuela (C.D.C.H.-U.C.V), Venezuela (to G. Benaim), and grant IVSS-430-06-14/05/2007 from the Instituto Venezolano de los Seguros Sociales, Venezuela (to A. E. Paniz Mondolfi). The authors would like to thank Dr Emilia Mia Sordillo (Senior Attending Physician, Division of Infectious Diseases and Epidemiology, Department of Medicine, St. Luke's-Roosevelt Hospital Center, New York, NY, USA) for critically reviewing the manuscript.

Author contributions
The authors contributed equally to researching data, discussion of content, writing, and reviewing and editing the manuscript.