Reduced Ventricular Proarrhythmic Potential of the Novel Combined Ion-Channel Blocker AZD1305 Versus Dofetilide in Dogs With Remodeled Hearts

Daniel M. Johnson, BSc; Monique M.J. de Jong, BSc; Harry J.G.M. Crijns, MD, PhD; Leif G. Carlsson, PhD; Paul G.A. Volders, MD, PhD

Background—AZD1305 is an investigational antiarrhythmic agent for management of atrial fibrillation. It blocks various cardiac ion currents at different potencies and has atrial-predominant electrophysiological effects. We investigated the electrophysiological and proarrhythmic effects of AZD1305 versus dofetilide in dogs with chronic complete atrioventricular block and myocardial hypertrophic remodeling.

Methods and Results—AZD1305 was administered to anesthetized mongrel dogs before and >2 weeks after the induction of atrioventricular block and ventricular and atrial electrophysiological parameters were assessed. In all dogs, the selective IKr blocker dofetilide was used to examine susceptibility to acquired torsades de pointes in chronic atrioventricular block and for comparison. At normal sinus rhythm, AZD1305 increased QT and RR intervals from 290±7 to 397±15 ms (+37%, P<0.0001) and from 603±22 to 778±32 ms (+29%, P=0.002), respectively. In the same animals at chronic atrioventricular block, AZD1305 increased the QT interval from 535±28 to 747±36 ms (+40%, P<0.0001), similar to the QT prolongation by dofetilide (511±22 to 703±45 ms [+38%, P<0.0001]). AZD1305 slightly slowed the idioventricular rhythm. Whereas all (n=14) chronic atrioventricular block animals exhibited torsades de pointes on dofetilide, the arrhythmia was induced in only 4 of 11 dogs after AZD1305. Beat-to-beat variability of left-ventricular monophasic-action-potential duration increased after dofetilide (2.3±0.2 to 6.3±0.7 ms; P<0.0001) but not after AZD1305 (2.8±0.3 to 3.7±0.3 ms; P=0.20) despite similar left-ventricular monophasic-action-potential duration prolongations.

Conclusions—Despite causing similar degrees of repolarization delay as the selective IKr blocker dofetilide, the combined ion-channel blocker AZD1305 induces less repolarization instability and has a lower ventricular proarrhythmic potential in the remodeled dog heart. (Circ Arrhythm Electrophysiol. 2012;5:201-209.)

Key Words: antiarrhythmic drugs ■ ion channels ■ remodeling ■ torsade de pointes

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the Western world with age-related prevalence reaching >10% in octogenarians. It has been predicted that >5.6 million patients in North America will be diagnosed with AF by 2050. This arrhythmia is a frequent complication of uncorrected hypertension, myocardial ischemia, or valvular disease. Moreover, familial AF or lone AF without apparent familial segregation is increasingly recognized.

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Currently, the pharmacological treatments aimed at maintaining sinus rhythm include Class I, II, and III antiarrhythmic agents. Termination of persistent AF may require any of these options (with variable effectiveness) or electric cardioversion. However, none of the aforementioned therapies are considered atrial-specific and cause effects on ventricular electric activation and repolarization, and some carry an inherent risk of ventricular proarrhythmia.

The proarrhythmic liability of anti-AF drugs could potentially be circumvented by designing compounds with composite actions on multiple ion channels. Vernakalant, a predominantly atrial-selective compound targeting IKur, IKr, ITO, and INa, was recently approved in Europe for the rapid conversion of recent (≤7 days) onset AF to sinus rhythm. Clinically, vernakalant has been shown to be effective in restoring sinus rhythm in patients with AF episodes lasting between 3 hours and 7 days with a low proarrhythmic risk. This compound has been shown to be less efficacious in patients with congestive heart failure. However, to date, no
results have been reported on patients with severe heart failure in whom cardiac remodeling could predispose to altered drug efficacy or adverse side effects. Dronedarone is another new agent for the management of AF with composite actions at multiple ion channels. Although this compound may have an improved safety profile compared with amiodarone, it is less efficacious in reducing AF recurrence rates.6

AZD1305 (Figure 1A) is an investigational compound that has been under development for the management of persistent AF. Although AZD1305 predominantly blocks IKr, it also has major inhibitory effects on ICaL and INa (predominantly INa,Late) and minor effects on other K+ currents.7,8 In the normal canine heart, this compound exerts atrial-predominant electrophysiological effects both in vivo and in vitro.9 In the anesthetized methoxamine-sensitized rabbit model of torsades de pointes ventricular tachyarrhythmias (TdP), intravenous AZD1305 increased the QT interval without inducing ventricular extrasystoles or TdP.7 Beat-to-beat variability of repolarization duration (BVR of the QT interval) also remained unaltered. In contrast, the selective IKr blocker dofetilide prolonged the QT interval, increased BVR, and induced TdP in the majority of animals tested.7 AZD1305 has been shown to depress excitability and suppress delayed-afterdepolarization-induced triggered activity in canine pulmonary-vein sleeve preparations.10 Recent clinical data suggest that this compound has electrophysiological effects that may translate into antiarrhythmic efficacy in patients with AF and may have a reduced proarrhythmic potential as compared with selective IKr blockers.11,12

In the present study, we investigated the electrophysiological effects of AZD1305 in anesthetized dogs with remodeled hearts with our hypothesis being that due to the composite ion-channel blockade by AZD1305, less ventricular proarrhythmia will be seen when compared with IKr blockers (Figure 1A), which exerts torsadogenic actions in this animal model.

### Methods

#### General

Animal handling was in accordance with the Dutch Law on Animal Experimentation and the European Directive for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, European Community Directive 86/609/CEE, and under the regulations of the Committee for Experiments on Animals of Maastricht University, The Netherlands. Fourteen adult mongrel dogs (10 female and 4 male; body weight 20.1 ±0.8 kg; Marshall BioResources) were included in these experiments. After overnight fasting, animals were sedated with 0.5 mg/kg methadone, 0.5 mg/kg acepromazine, and 0.5 mg atropine intramuscularly. Anesthesia was induced with 25 mg/kg sodium pentobarbital intravenously and maintained by isoflurane (0.5%–1%). After intubation, the dogs were artificially ventilated with a mixture of oxygen and compressed air (2:1). Proper animal care was taken before, during, and after the experiments, including a thermal mattress to maintain body temperature, fluid administration to prevent volume depletion (0.9% NaCl), and administration of antibiotics (1000 mg ampicillin intramuscularly) and analgesics (0.015 mg/kg buprenorphine intramuscularly).

In all experiments, standard lead and precordial electrocardiographic registrations were combined with endocardial monophasic action potential recordings and continuously stored. Monophasic action potentials (Hugo Sachs Elektronik) were recorded from left ventricular (LV), right ventricular (RV), and right atrial (RA) endocardial sites. Monophasic action potential signals were accepted on the basis of amplitude, morphology, and stability. Monophasic action potential catheters were kept in the same position during drug infusions.

#### Experimental Design

The experimental protocol is shown in Figure 1B. AZD1305 was dissolved in an equimolar amount of 0.1 mol/L tartaric acid and then diluted in 0.9% saline. AZD1305 was infused at a rate of 36 μg/kg/min for a total of 30 minutes >1 week before creating AVB to investigate the effects of this compound in the normal unremodeled heart with sinus rhythm and in acute and chronic AVB. AVB was induced by radiofrequency catheter ablation of the His bundle as previously described.15 Dofetilide was dissolved in 0.9% saline and intravenously administered at a dose of 12.5 μg/kg/5 minutes to test for TdP inducibility 2 to 3 weeks after inducing AVB (chronic AVB) in all dogs. Three animals developed intractable ventricular fibrillation during TdP. To
investigate whether AZD1305 suppresses dofetilide-induced TdP, a bolus (870 μg/kg) of the compound was administered after the first episode of TdP in 4 dogs (Figure 1B). In 4 animals, 12.5 μg/kg/5 minutes dofetilide was also infused >1 week before AVB was created so a comparison of atrial effects of this compound could be made pre- and postremodeling and compared with AZD1305.

In a total of 11 dogs, AZD1305 (36 μg/kg/min for 30 minutes) was administered at 3±1 week after the induction of AVB (chronic AVB) to examine its electropharmacological effects in the remodeled heart. In 4 of these experiments, after the AZD1305 infusion, a dofetilide challenge was reapplied to investigate preventive effects of AZD1305 against dofetilide-induced TdP (Figure 1B).

When TdP did not stop spontaneously within 10 to 20 seconds or when the arrhythmia deteriorated into ventricular fibrillation, the dog was electrically cardioverted. If TdP recurred in a period >10 minutes, magnesium sulfate (100 mg/kg for 2 minutes) was used to restore a regular rhythm.

After euthanasia, hearts were excised and weighed (n=11 dogs with chronic AVB). Average heart weights were 217±11 g. Heart-weight to body-weight ratios averaged 10.5±0.2 g/kg, similar to previous studies on chronic AVB and significantly higher than unremodeled dog hearts.13-15

### Plasma Analysis of AZD1305

Venous blood samples were obtained at baseline and then at 5, 10, 15, 30, 45, 60, 90, 120, and 150 minutes after the start of AZD1305 infusion. Samples were collected in K2-EDTA tubes, centrifuged for 10 minutes at 4000 rpm at 4°C, and the plasma stored at −80°C. The plasma concentration of AZD1305 was determined by online solid-phase extraction followed by tandem mass spectrometric detection. The lower limit of quantification was 0.0150 μmol/L.

### Data Analysis

RR, QRS, QT, PP, and PR intervals in electrocardiographic lead II, LV and RV monophasic action potential duration (LV and RV MAPD) at 90% repolarization (MAPD90), and RA MAPD at 50% repolarization (MAPD50) and 90% repolarization were measured off-line using a custom-made computer program (IDEEQ, IDEE; Maastricht University). QT intervals were corrected for heart rate changes according to Van de Water et al (QTcV=QT/0.87(RR−1000)). Most data were averaged from 30 consecutive beats measured at −5 and 0 minutes (baseline) and at 5, 10, 15, 30, 45, and 60 minutes after the start of AZD1305 or dofetilide infusion. If extrasystolic activity was seen, parameters were measured before the first extrasystole. BVR was quantified from LV MAPD90 of 30 consecutive beats as follows: BVR=(LV MAPD90−LV MAPD90, baseline)/30+(2). Electrophysiological parameters were compared using (repeated-measures) analysis of variance followed by Bonferroni test. Data are reported as mean±SEM. Countables such as TdP episode numbers were tested with a Mann-Whitney rank sum test and are reported as median (interquartile range). Differences were considered statistically significant if P<0.05.

### Results

#### Concentration-Dependent Prolongation of Ventricular Repolarization by AZD1305 in the Normal Dog Heart

In 14 normal anesthetized dogs, intravenous administration of AZD1305 resulted in a maximal plasma concentration of 1.57±0.05 μmol/L at 30 minutes (Figure 2). The QT and QTcV interval increased from 290±7 ms and 324±6 ms at baseline to 397±15 ms and 417±14 ms at 30 minutes AZD1305, respectively (+37% and +29%, P<0.0001) along with an increase in the RR interval (Figure 2; Table). Repolarization prolonged in a concentration-dependent manner with MAPD90 increasing more in the LV than in the RV (+48% versus +39%; Figure 2). LV and RV BVR did not change significantly. P-wave duration and the QRS interval change significantly. P-wave duration and the QRS interval were slightly but significantly increased by AZD1305 (Table). The compound did not induce ventricular or atrial arrhythmias in these normal hearts. After stopping infusion, AZD1305 plasma levels rapidly declined, reaching 0.57±0.05 μmol/L 30 minutes later.

#### Rate-Dependent Repolarization Effects of AZD1305 in the Normal, Acutely Overloaded and Chronically Remodeled Dog Heart

In 6 dogs, steady-state pacing was applied at a cycle length of 500 ms in the normal heart (RA pacing) and at 500 ms and 1000 ms just after AVB induction and at chronic AVB (RV-apex pacing). Figure 3 illustrates the rate-dependent effects of AZD1305 (versus baseline) on LV MAPD90. Effects during pacing are plotted next to those during sinus or idioventricular rhythm. At a pacing cycle length of 500 ms, AZD1305 led to a 20% increase of LV MAPD90 in the normal heart, a 30% increase at acute AVB, and 37% prolongation at chronic AVB at 3 weeks. Reverse use-dependent prolongation of LV and RV MAPD90 was most accentuated in the remodeled heart at chronic AVB.

### Repolarization Prolongation and Proarrhythmic Potential by AZD1305 and Dofetilide in the Chronic AVB Dog Heart

In chronic AVB, intravenous administration of AZD1305 resulted in a maximal plasma concentration of 1.77±0.29 μmol/L at 30 minutes (Figure 4) decreasing to 0.66±0.10 μmol/L 30 minutes after stop of infusion. Plasma concentrations at all time points were not significantly different compared with those seen in sinus rhythm. The QT and QTcV interval increased from 535±28 ms and 444±30 ms at baseline to 747±36 ms and 634±35 ms at 30 minutes.
AZD1305, respectively (+40% and +43%, P<0.0001; Table). A slowing of the idioventricular rate was noted (Table). The LV MAPD90 was prolonged from 431 ± 22 ms to 692 ± 34 ms (+61%, P<0.0001), whereas the LV BVR remained unaltered (2.8 ± 0.1 vs. 2.7 ± 0.3 ms, P=0.20). Similar results were obtained for the RV repolarization variables. Figure 5 illustrates changes in repolarization induced by AZD1305 infusion in the same dog both at normal sinus rhythm and chronic AVB.

In separate experiments, dofetilide was administered to test for Tdp inducibility. Similar to AZD1305, dofetilide prolonged the QT and QTCv interval by 38% and 41%, respectively (Table). The LV MAPD90 was prolonged by 51% (411 ± 17 ms to 625 ± 26 ms; P<0.0001) and was accompanied by an increase in BVR from 2.3 ± 0.2 ms to 6.3 ± 0.7 ms (P<0.0001).

Next, we examined the appearance of ventricular extrasystolic beats in the presence of AZD1305 and dofetilide. In the case of AZD1305, these were observed at 6.2 ± 0.3 minutes after the start of infusion in 6 of 11 dogs. Except for 2 dogs, no ventricular extrasystolic beats occurred beyond 8 ± 1 minutes during the remainder of the experiment in any of the animals. By contrast, during exposure to dofetilide, ventricular extrasystoles were induced in all dogs (P=0.009 versus AZD1305) on average at 4.1 ± 0.1 minutes. There were no repolarization differences in beats before, during, and after extrasystolic activity (Supplemental Figure I; http://circp.ahajournals.org).

BVR was significantly different during infusion of AZD1305 versus dofetilide. Figure 6 illustrates how both LVMAPD90 and BVR were altered in 2 chronic AVB animals after either AZD1305 or dofetilide infusion. Dofetilide

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**Table. Ventricular Electrophysiological and Proarrhythmic Effects of AZD1305 and the Reference Compound Dofetilide in the Normal and Remodeled Canine Heart**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>AZD1305</th>
<th>P</th>
<th>Control</th>
<th>Dofetilide</th>
<th>P</th>
<th>Control</th>
<th>AZD1305</th>
<th>P</th>
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<td>PP</td>
<td>611±24</td>
<td>780±34*</td>
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<td>591±18</td>
<td>733±19*</td>
<td>&lt;0.0001</td>
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<td>1863±95</td>
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<td>2044±217</td>
<td>2326±221</td>
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<td>QT</td>
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<td>397±15*</td>
<td>&lt;0.0001</td>
<td>511±22</td>
<td>703±45*</td>
<td>0.0009</td>
<td>535±28</td>
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<td>QTCv</td>
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<td>624±41*</td>
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<td>444±30</td>
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<tr>
<td>P wave duration</td>
<td>72±3</td>
<td>77±3*</td>
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<tr>
<td>RV MAPD90</td>
<td>229±5</td>
<td>319±9*</td>
<td>&lt;0.0001</td>
<td>332±34</td>
<td>472±22*</td>
<td>0.004</td>
<td>339±31</td>
<td>536±26*</td>
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<td>0.07</td>
<td>2.3±0.2</td>
<td></td>
<td>6.3±0.7*</td>
<td>&lt;0.0001</td>
<td>2.8±0.3</td>
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<td>RV BVR</td>
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<td>1.1±0.3</td>
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<td>2.9±0.8</td>
<td>5.6±1.7</td>
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<td>5.4±2.4</td>
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<td>Tdp inducible</td>
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<td>14 of 14</td>
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SR indicates sinus rhythm; CAVB, chronic complete atrioventricular block; LV, left ventricular; MAPD, monophasic-action-potential duration; RV, right ventricular; BVR, beat-to-beat variability of repolarization; Tdp, torsades de pointes.

*P<0.05 versus baseline.

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**Figure 3.** Rate-dependent repolarization effects of AZD1305 at normal sinus rhythm and acute and chronic AVB. Depicted are the changes in LV MAPD90 before (open triangles) and after (closed triangles) treatment at different intrinsic (sinus/idioventricular) and paced rates ("P": right-atrial pacing in normal heart; RV pacing in acute and chronic AVB). *P<0.05 versus before treatment at the same cycle length (or sinus/idioventricular rate). AVB indicates atrioventricular block; LV, left ventricular; MAPD, monophasic action potential duration; RV, right ventricular.
Dofetilide caused a progressive and parallel increase in LV MAPD90 and BVR promoting extrasystolic activity and TdP. In contrast, AZD1305 infusion did not increase BVR despite significantly prolonging MAPD90 (see also the Table). Whereas dofetilide caused TdP in all dogs, this occurred in only 4 of 11 dogs after AZD1305 (P = 0.0007 versus dofetilide). Furthermore, dofetilide-induced TdP episodes occurred more frequently, lasted longer, and required electric cardioversion more often. The cycle lengths of AZD1305- versus dofetilide-induced TdP were similar (311 ± 18 ms versus 286 ± 27 ms, respectively, P = 0.10). Figure 7 illustrates an example of TdP during infusion of AZD1305, occurring at 6.5 minutes. Spontaneous conversion from TdP to idioventricular rhythm occurred twice in this animal.

Suppressive Effects of AZD1305 on Dofetilide-Induced TdP

In 4 chronic AVB dogs with confirmed TdP induction by dofetilide in separate experiments, dofetilide was infused again after the administration of AZD1305 (Figure 1B). Under these conditions, first extrasystolic activity was postponed, occurring at 13 ± 2.2 minutes after the start of dofetilide infusion (versus 3.8 ± 0.2 minutes after dofetilide without AZD1305 pretreatment; P = 0.002). LV MAPD90 prolonged from 412 ± 24 ms at baseline to 644 ± 40 ms during AZD1305 (P = 0.002 versus baseline) to 684 ± 49 ms after AZD1305 plus dofetilide (P = 0.02 versus AZD1305). In 2 of 4 animals, no TdP was seen at all despite previous TdP susceptibility to dofetilide alone. In the other 2 animals, dofetilide after AZD1305 caused significantly fewer TdPs than during its solo administration: 1 (0–2) versus 7 (3–11) episodes, respectively (P = 0.02).

As an alternative regimen (Figure 1B), AZD1305 was administered as a fast bolus infusion (870 ± 926 μg/kg) after the first dofetilide-induced TdP (n = 4). Under these conditions, the number of TdP episodes was decreased (2 [1–3] versus 7 [3–11]; P = 0.05) compared with dofetilide alone.

Atrial Effects of AZD1305 in the Normal and Remodeled Dog Heart

The atrial effects of AZD1305 are illustrated in Figure 8. In the normal unremodeled heart, RA MAPD50 (+31% from 137 ± 6 ms at baseline, P = 0.001) and MAPD90 (+33% from 228 ± 5 ms, P < 0.001) were significantly increased by AZD1305 as was the PP cycle length. These effects were very similar to those seen with dofetilide (Supplemental Figure II). After chronic AVB, baseline RA MAPD50, MAPD90, and PP intervals were similar as during sinus rhythm and atrial repolarization and PP cycle length was still significantly prolonged by AZD1305 (Figure 8). For example, RA MAPD90 was 223 ± 9 ms at baseline versus 270 ± 17 ms (P = 0.03, +21%) at the end of AZD1305 infusion.

Figure 4. Changes in QT interval, LV and RV MAPD90, and RR interval in relation to plasma concentration of AZD1305 (36 μg/kg/min intravenously for 30 minutes) in the remodeled canine heart with chronic AVB. LV indicates left ventricular; RV, right ventricular; MAPD, monophasic action potential duration; AVB, atrioventricular block.

Figure 5. Effects of AZD1305 on ventricular repolarization in the same dog before and after cardiac remodeling by chronic AVB. Representative recordings of ECG Lead II and LV monophasic action potentials (MAPs) before (baseline) and at the end of the 30-minute infusion of AZD1305. MAPD (ms) is indicated below the LV MAP signals. RR and QT intervals (ms) are shown below and above the ECGs, respectively. Vertical calibration bars depict 1 and 10 mV for ECG and MAP recordings, respectively. AVB indicates atrioventricular block; ECG, electrocardiogram; LV, left ventricular; MAPD90, monophasic action potential duration.
Interestingly, even after remodeling, dofetilide still led to significantly prolonged atrial repolarization (Supplemental Figure II).

**Discussion**

In this study, we used the dog model with chronic AVB to compare in vivo cardiac electrophysiological effects and any pro- and antiarrhythmic actions of the novel investigational agent AZD1305 with dofetilide in the remodeled heart. Chemically, dofetilide is a methanesulphonamide derivative and thus a member of the same family of specific IKr-blocking antiarrhythmic agents such as ibutilide and d-sotalol (Figure 1A). AZD1305, on the other hand, is a disubstituted 9 oxabispidine compound structurally related to its congener AZD7009 (Figure 1A). Interestingly, the minor structural differences in AZD1305 versus AZD7009 introduce potent ICaL activity to the IKr- and INa-blocking characteristics described for both agents.7,8,17 Hence, with its combined ion channel-blocking profile, AZD1305 has been proposed as an antiarrhythmic agent against AF with a lower proarrhythmic potential than other antiarrhythmic drugs. AZD1305 has been demonstrated to cause atrial-predominant effects in the

![Figure 6. 1, Baseline. 2, AZD1305. BVR is not increased in this animal after AZD1305. No arrhythmias were seen in this animal. 3, Baseline. 4, Dofetilide. BVR increased by dofetilide and TdP ensued after this. Right panels, LV MAPD90s (ms) are shown below signals. Vertical calibration bars, 10 mV. Horizontal calibration bars, 1 second. BVR indicates beat-to-beat variability of repolarization; TdP, torsades de pointes; LV, left ventricular; MAPD, monophasic action potential duration.](http://circep.ahajournals.org/)

![Figure 7. Self-terminating TdP after AZD1305 infusion in a chronic AVB dog. Left, ECG Lead II, LV and RV monophasic action potential (MAP) at baseline. Next panels, 5.5 minutes after the start of AZD1305 infusion, the first ventricular extrasystole occurred. At that moment, LV MAPD90 had prolonged to 567 ms compared with 320 ms at baseline. At 6.5 minutes of AZD1305, after 3 additional extrasystoles, an episode of self-terminating TdP occurred (total TdP duration 16 seconds). Right, at 10 minutes of AZD1305, all extrasystolic activity had stopped despite further repolarization prolongation (LV MAPD90 685 ms). Numbers above ECG Lead II indicate QT time (ms). Below, idioventricular cycle length (ms). Below LV and RV MAPs, MAPD90 (ms). Vertical calibration bars depict 1 and 10 mV for ECG and MAP recordings, respectively. TdP indicates torsades de pointes; AVB, atrioventricular block; ECG, electrocardiogram; LV, left ventricular; RV, right ventricular; MAPD, monophasic action potential duration.](http://circep.ahajournals.org/)

healthy dog heart and attenuates ventricular repolarization-related instability caused by sudden rate changes during selective Ikr blockade. In fact, AZD1305 was devoid of proarrhythmia in anesthetized methoxamine-sensitized rabbits, whereas other selective Ik blockers proved very torsadogenic in this animal model. In our experiments on anesthetized dogs with normal hearts, AZD1305 caused ventricular and atrial repolarization prolongation but no repolarization instability or proarrhythmias. In chronic AVB dogs with remodeled hearts and a high susceptibility to disordered atrial-predominant blockade of INa (particularly tonic inhibition), which is suggested to translate into high antiarrhythmic efficacy.9 Previously, the predecessor to AZD1305, AZD7009, was shown to restore sinus rhythm in up to 82% of patients with AF episodes lasting up to 30 days and with minimal proarrhythmic side effects.29,30

and TdP during early AZD1305 infusion was due to initial proarrhythmic Ik inhibition followed by antiarrhythmic Ica suppression on mounting levels of the compound. Inhibition of either I Na or Ica has previously been shown to be effective in suppressing Ik block-induced TdP in various experimental models. For example, I Na block by lidocaine attenuated the incidence of TdP by almokalant in rabbits without influencing the almokalant-induced QT prolongation. Similar effects have been shown in the chronic AVB dog after dofetilide-induced TdP both with lidocaine and the novel I Na-Late blocker ranolazine, although in the latter study multiple ventricular ectopic beats were not completely abolished. In the same animal model, Oros et al showed a robust antiarrhythmic effect of both flunarizine and verapamil against dofetilide-induced TdP. To our knowledge, AZD1305 is the first compound, with the exception of amidarone and dronedarone, with effects on Ik together with ancillary dual I Na and Ica-blocking effects that has been investigated in this proarrhythmic model, and our results suggest that compounds with this profile could be devoid of proarrhythmic side effects if the ion-channel-blocking potencies are balanced (more so than for AZD1305), leaving no Ik block unattended.

Repolarization Lability and Proarrhythmia Liability

Various research groups have investigated the value of BVR parameters to predict imminent arrhythmia under conditions of repolarization lability. In the chronic AVB dog, increases of beat-to-beat variability of MAPD have been shown to predict drug-induced TdP. Compounds increasing MAPD per se, but not BVR, are generally not torsadogenic in this experimental model. Beat-to-beat variability of the QT interval also has proven useful in heralding arrhythmia in other TdP models. In the clinical setting, increased BVR of the QT interval characterized patients with drug-induced proarrhythmia, even in the absence of QTc prolongation. Likewise, this parameter identified latent repolarization disorders in patients with congenital long QT syndrome. BVR of the QT interval was also found to be increased in patients with dilated cardiomyopathy and heart failure, probably reflecting acquired repolarization disturbances and an increased susceptibility to sudden arrhythmic death. In the present study, we have demonstrated that the combined inhibition of Ica and I Na together with Ik blockade does not significantly increase BVR in dogs with chronic AVB despite causing marked repolarization prolongation. These data reinforce the notion that BVR is a robust predictor of TdP, more so than repolarization duration per se, at least under these experimental conditions.

Atrial Effects of AZD1305 in the Remodeled Heart

AZD1305 has been shown to be an effective antiarrhythmic agent in various animal models of AF. It causes an atrial-predominant blockade of I Na (particularly tonic inhibition), which is suggested to translate into high antiarrhythmic efficacy.9 Previously, the predecessor to AZD1305, AZD7009, was shown to restore sinus rhythm in up to 82% of patients with AF episodes lasting up to 30 days and with minimal proarrhythmic side effects. AZD7009 was less

Figure 8. Atrial effects of AZD1305 in the normal and remodeled canine heart. Upper panels, Representative right-atrial monophasic action potentials (MAPs) at baseline and at the end of a 30-minute infusion of AZD1305 in the same dog before (sinus rhythm) and 3 weeks after AVB induction (chronic AVB). Above the signals, cycle length (ms). Below, MAPD90s (ms). Lower panels, Average values for right atrial MAPD50 and MAPD90 and PP intervals from 11 dogs. Vertical calibration bars, 10 mV.
effective in patients with AF durations >1 month. A recent clinical study showed that AZD1305 was effective in converting AF to SR with a conversion rate of 50% within 90 minutes in the highest dose group despite AF episode durations of up to 3 months.\textsuperscript{12} In the present study, AZD1305 led to significant increases in RA MAPD50 and MAPD90 in both the normal and the AMB-remodeled dog heart (Figure 8). The mechanisms and consequences of atrial remodeling during chronic AVB are still incompletely understood.\textsuperscript{31} In an early study in dogs, RA pressures were increased during acute and chronic overload,\textsuperscript{31} thus promoting dilatation and hypertrophy. In goats, progressive atrial dilatation has been demonstrated in chronic AVB along with atrial hypertrophy, prolongation of induced AF paroxysms, and local conduction delays.\textsuperscript{32} Importantly, atria undergoing remodeling due to electrically induced AF were less responsive to IKr blockers given as solo administration.\textsuperscript{33} The additional blockade of IKur, I\textsubscript{TO}, and I\textsubscript{K,appl}, which prolonged the early atrial repolarization, led to restoration of the antiarrhythmic Class III action of the IKr blocker in this goat model.\textsuperscript{32} In other dog models, the myocardial substrate of AF in congestive heart failure is likely due to differential affinities of the drug for various ion channels, resulting in a window of preferential proarrhythmic potential than the selective IKr blocker in this goat model.\textsuperscript{32} Collectively, these data illustrate the impact of the type of remodeling on atrial drug responsiveness.

Conclusions
Despite causing a similar degree of repolarization delay, the combined ion-channel blocker AZD1305 induces less ventricular repolarization instability, reflected in LV BVR, and has a lower proarrhythmic potential than the selective IKr blocker dofetilide in the chronic AVB-remodeled dog heart. AZD1305 can still lead to TdP in the remodeled heart, although in a minority of animals, during an infusion phase when plasma levels of the compound are still increasing. This is likely due to differential affinities of the drug for various ion channels, resulting in a window of preferential proarrhythmic IKr block. Further development of safer combined ion-channel blockers as antiarrhythmics could take this information into account.

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**CLINICAL PERSPECTIVE**

Antiarrhythmic drug treatment of atrial fibrillation is still not optimal, both from mechanistic and safety standpoints. Most available drugs are not atrial-specific and carry an inherent risk of ventricular proarrhythmia, including drug-induced torsades de pointes. The novel ion-channel blocker AZD1305 has composite actions on both inward ($I_{CaL}$ and $I_{Na}$) and outward ($I_{Kr}$ and $I_{Ks}$) currents involved in cardiac depolarization and repolarization. Its blockade of $I_{Na}$ is atrial-predominant. In the present study, we measured ventricular and atrial effects of AZD1305 administered intravenously in dogs, serially at normal sinus rhythm, and during chronic complete atrioventricular block (causing proarrhythmia). Effects of AZD1305 were compared with those of the pure $I_{Kr}$ blocker dofetilide. Whereas both compounds led to similar ventricular repolarization prolongation, AZD1305 caused less beat-to-beat variability of repolarization duration in remodeled hearts and had a lower proarrhythmic potential than dofetilide. In a minority of dogs with chronic atrioventricular block, AZD1305 still led to torsades de pointes during the initial infusion phase when plasma levels of the compound were rising. AZD1305 and dofetilide prolonged right atrial repolarization duration to an equal degree. Our results in normal and remodeled dog hearts suggest that antiarrhythmic compounds with composite actions could be devoid of proarrhythmic side effects if their ion channel-blocking potencies are balanced, leaving no $I_{Kr}$ block unattended. This information is relevant for the development of safer antiarrhythmics in the future.
Reduced Ventricular Proarrhythmic Potential of the Novel Combined Ion-Channel Blocker AZD1305 Versus Dofetilide in Dogs With Remodeled Hearts

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Supplemental Figure 1. Repolarization duration of ventricular extrasystolic and postextrasystolic beats after AZD1305 and dofetilide in the chronic-AVB dog. A, Representative examples of ECGs and LV MAPs. QT intervals and MAPD90 values (ms) are indicated below the traces. Vertical calibration bars depict 1 and 10 mV for ECG and MAP recordings, respectively. B, Average values for LV MAPD90 as a function of RR CL for the last beat of the idioventricular rhythm, the ventricular extrasystole and the postextrasystolic beat, respectively. Data are from all 4 dogs that exhibited ventricular extrasystoles during AZD1305. *, $P<0.05$ versus baseline beat; †, $P<0.05$ versus extrasystole.
**Supplemental Figure 2.** Atrial effects of dofetilide in the normal and remodeled canine heart.

Upper panels, Representative right-atrial MAPs at baseline and at the end of a 30-min infusion of AZD1305 in the same dog before (Sinus rhythm) and 3 weeks after AVB induction (Chronic AVB). Above the signals, cycle length (ms). Below, MAPD90s (ms). Lower panels, Average values for right-atrial MAPD50 and MAPD90, and PP intervals from 4 dogs. Vertical calibration bars, 1 mV. *, \( P < 0.05 \) versus baseline.