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Clinical Research

Adenosine Following Pulmonary Vein Isolation to Target Dormant Conduction Elimination (ADVICE): Methods and Rationale

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ABSTRACT

Background: Pulmonary vein (PV) isolation (PVI) has emerged as an effective therapy for paroxysmal atrial fibrillation (AF). However, AF recurs in up to 50% of patients, generally because of recovery of PV conduction. Adenosine given during the initial procedure may reveal dormant PV conduction, thereby identifying the need for additional ablation, leading to improved outcomes. The Adenosine Following Pulmonary Vein Isolation to Target Dormant Conduction Elimination

RÉSUMÉ

Introduction : L'isolation des veines pulmonaires (IVP) est un traitement reconnu de la fibrillation auriculaire (FA) paroxystique. Cependant, la FA réapparaît chez presque 50 % des patients, généralement en raison d'un rétablissement de la conduction dans les VP. L'adénosine administrée durant l'intervention initiale permet d'identifier des zones de conduction dormante dans les VP, justifiant une ablation supplémentaire susceptible d'améliorer

Atrial fibrillation (AF) is the most common cardiac arrhythmia.[1,2] Radiofrequency catheter ablation, generally involving pulmonary vein (PV) isolation (PVI), has emerged as an effective treatment option.[3,4] Controlled trials indicate superiority of PVI over antiarrhythmic drug therapy,[5-8] and current guidelines recommend ablation after the failure of a single antiarrhythmic agent.[9,10] Although the effectiveness of PVI for paroxysmal AF is established, a second intervention is required in 20% to 59% of patients.[4,6,11,12]

Considerable evidence supports the relationship between permanent electrical isolation of PVs and long-term success.[13-16] The appearance of PV-atrial conduction block during the initial procedure may be permanent or indicate dormant conduction,

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(ADVICE) study is a prospective multicentre randomized trial assessing the impact of adenosine-guided PVI in preventing AF recurrences.
Methods: Patients undergoing a first PVI procedure for paroxysmal AF will be recruited. After standard PVI is completed, all patients will receive intravenous adenosine in an attempt to unmask dormant conduction. If dormant conduction is elicited, patients will be randomized to no further ablation (control group) or additional adenosine-guided ablation until dormant conduction is abolished. If no dormant conduction is revealed, randomly selected patients will be followed in a registry. The primary outcome is time to first documented symptomatic AF recurrence. Assuming that dormant conduction is present in 50% of patients post PVI and symptomatic AF recurs in 45% of controls, 244 patients with dormant conduction will be required to obtain $>$ 90% power to detect a difference of 20%. Thus, a total of 488 patients will be enrolled and followed for 12 months.
Conclusion: The ADVICE trial will assess whether a PVI strategy incorporating elimination of dormant conduction unmasked by intravenous adenosine will decrease the rate of recurrent symptomatic AF compared with standard PVI.

l'efficacité du traitement. ADVICE (Adenosine Following Pulmonary Vein Isolation to Target Dormant Conduction Elimination) est une étude prospective multicentrique visant à évaluer l'efficacité de l'IVP guidée par l'adénosine pour le traitement de la FA.
Méthodes : L'étude portera sur des patients atteints de FA paroxystique, référés pour ablation par cathéter. À la suite d'une IVP standard, l'adénosine est administrée par voie intraveineuse pour identifier la présence de conduction dormante dans les VP. En présence de conduction dormante, le patient est assigné de manière aléatoire à l'un des 2 groupes suivants: aucune ablation supplémentaire (groupe témoin) ou ablation supplémentaire guidée par l'adénosine jusqu'à l'abolition de la conduction dormante. En l'absence de conduction dormante, un groupe est également constitué pour faire l'objet d'un suivi. Le critère d'évaluation principal est la récidive de FA symptomatique. En supposant une prévalence de conduction dormante de 50 % et la récidive de FA chez 45 % des patients du groupe témoin, 244 patients avec conduction dormante seront requis pour la validation statistique des résultats. L'étude devra donc inclure 488 patients et le suivi sera d'une durée de 12 mois.
Conclusion : L'étude ADVICE permettra de déterminer si la stratégie d'IVP guidée par l'adénosine est supérieure à l'IVP standard pour prévenir la récidive de FA.

which subsequently recovers. Injecting intravenous adenosine to restore conduction in viable but acutely nonconducting PVs may distinguish permanent block from dormant PV conduction, thereby allowing additional targeted ablation.[17,18] The primary hypothesis of the **Ad**enosine Following Pulmonary **V**ein **I**solation to Target Dormant **C**onduction **E**limination (ADVICE) trial is that a PV-ablation strategy incorporating elimination of dormant conduction unmasked by intravenous adenosine will result in fewer symptomatic AF recurrences compared with standard PVI.

Methods

Study design

The ADVICE study (ClinicalTrials.gov #NCT01058980) is a multicentre prospective randomized clinical trial. The study will be conducted at 19 clinical centres in North America, Europe, and Australia. Patients with symptomatic paroxysmal AF referred for PVI will be enrolled. Dormant conduction will be assessed with intravenous adenosine (Fig. 1). If dormant conduction is present, patients will be randomized to group 1 (no additional ablation) or group 2 (additional targeted ablation until elimination of dormant conduction). Patients will be assigned in a 1:1 ratio to either treatment arm using permuted block randomization stratified by site. If dormant conduction is not elicited, patients will be randomly selected for inclusion in a registry (Fig. 2), in which they will be followed in a manner identical to adenosine-positive patients. The registry group will allow for further assessment of the role of dormant conduction as a predictor of AF recurrence. Patients will be blinded to their randomization assignment. An independent adjudicating committee blinded to treatment allocation will classify all outcomes. Written informed consent will be obtained prior to study inclusion. The study protocol will receive approval by each centre's institutional review board prior to enrollment.

Patient population

Inclusion and exclusion criteria are detailed in Table 1. Patients undergoing first ablation for symptomatic paroxysmal AF that is refractory to at least 1 antiarrhythmic drug will be included. At least 1 episode of AF must be documented on 12-lead electrocardiogram (ECG) or Holter monitor within 12 months of randomization. Paroxysmal AF is defined according to American Heart Association, American College of Cardiology, and European Society of Cardiology practice guidelines as AF in which the majority of episodes are self-terminating within 7 days of recognized onset.[1] An episode $\geq$ 30 seconds in duration will be considered an AF episode.[9] Symptoms may include palpitations, dizziness, weakness, chest discomfort, and breathlessness.

Catheter ablation procedure

Standard PVI. Effective anticoagulation with oral vitamin K antagonists (international normalized ratio 2-3), dabigatran, or fractionated subcutaneous heparin for at least 1 month or the exclusion of a left atrium (LA) thrombus by a recent transesophageal echocardiogram is mandated prior to ablation.[9] Antiarrhythmic drugs will be discontinued before the procedure, allowing a washout period of 5 half-lives (except for amiodarone). Interventions will be performed on patients in the fasting state under conscious sedation or general anesthesia, per local practice.

PVI will be performed according to standard clinical practice.[9] A multipolar catheter will be placed in the coronary sinus via central venous access. After transseptal LA access is obtained, intravenous heparin will be administered as a bolus, with a continuous infusion to maintain an activated clotting time $>$ 300 seconds. Through 1 transseptal access, a decapolar, circular catheter will be advanced into the LA. An irrigated-tip ablation catheter will be placed in the LA through a second access site. If available, a 3-dimensional, nonfluoroscopic mapping system may be used for anatomic reconstruction. The circular catheter will be sequentially placed within each PV to record electrical activity. Circumferential ablation lesions will be placed via the ablation catheter 1 to 2 cm from the PV ostia to electrically isolate the PVs. Circumferential lesions will be

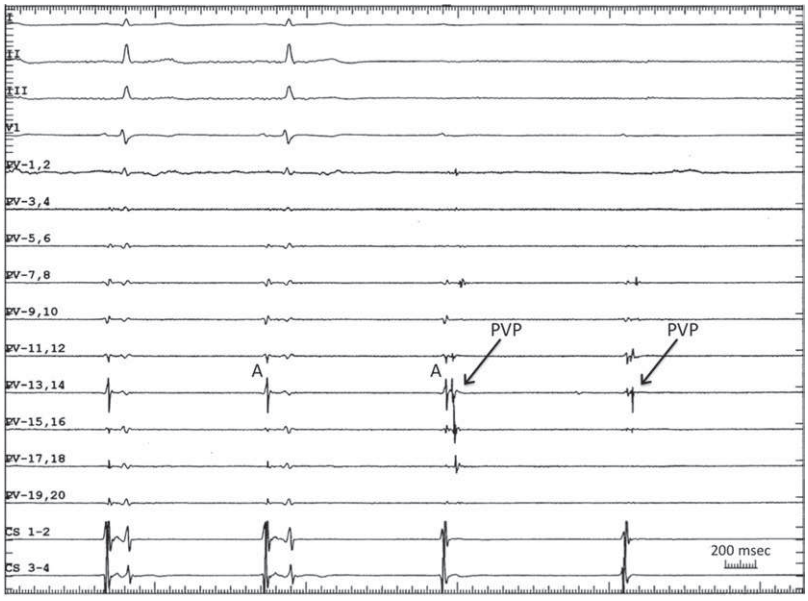

Figure 1. Evaluation of dormant conduction after pulmonary vein (PV) isolation. After catheter ablation to isolate the left superior PV, no PV potentials (PVPs) are observed during the first 2 beats, with the circular mapping catheter (PV 1,2 to PV 19,20) recording only atrial far-field signals (A). Adenosine administration (12-mg intravenous rapid bolus) results in atrioventricular block with transient recovery of PV conduction. The atrial far-field signal (A) is recorded first, followed by PVP. CS 1-4: coronary sinus recordings.

considered complete when PV spikes are no longer recorded by the circular catheter. Radiofrequency energy will be delivered with an irrigated-tip catheter at a target temperature of 50°C and 25 to 35 W. Patients remaining in AF at the end of the procedure will be electrically or chemically cardioverted back to sinus rhythm. Remapping of all PVs post cardioversion will be performed to confirm PVI. Focal triggers identified outside PVs will also be targeted, if possible.[9] No AF induction testing by burst pacing, prophylactic linear ablation lesions, or ablation of complex fractionated atrial electrograms will be performed. Following isolation of all PVs, a 20-minute observation period will be used to assess spontaneous recovery of conduction; if spontaneous reconnection occurs, reconnected PVs will be reisolated. In order to avoid excessive prolongation of the PVI procedure, the observation period will not be reset in the event of additional ablation.

Evaluation of dormant conduction. Dormant conduction will be assessed with the use of a circular catheter in each PV by intravenous injection of 12 mg or more of adenosine to obtain at least 1 blocked P wave or a pause $\geq$ 3 seconds. Dormant conduction will be defined by reappearance of PV conduction for $\geq$ 1 beat. If there is no dormant conduction in any PV, the patient will be randomized to either a registry (registry group) or usual medical care without further trial follow-up. If dormant conduction is elicited, the patient will be randomized to no additional ablation (group 1) or to additional targeted ab-

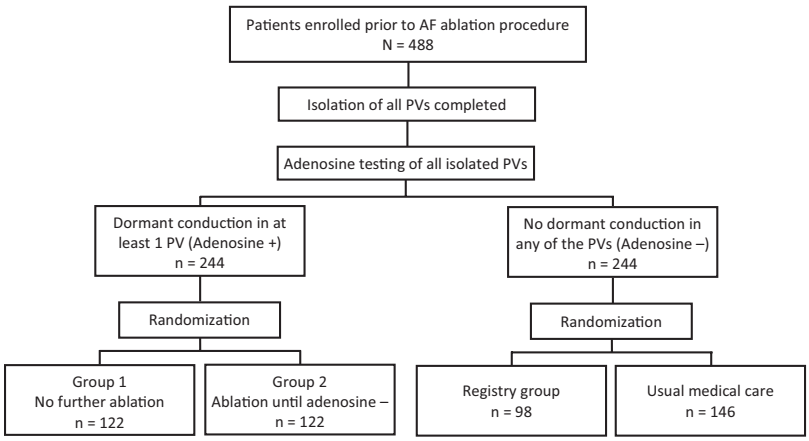

Figure 2. Randomization scheme for Adenosine Following Pulmonary Vein Isolation to Target Dormant Conduction Elimination (ADVICE) study. AF, atrial fibrillation; PV, pulmonary vein.

Table 1. ADVICE study inclusion and exclusion criteria

Inclusion criteria
● Age ≥ 18 years
● Paroxysmal AF ≥ 6 months with ≥ 3 symptomatic episodes during the previous 6 months
● Candidates for AF ablation based on AF that is symptomatic and refractory to ≥ 1 class I or III antiarrhythmic drugs
● Documentation of at least 1 AF episode on 12-lead ECG, Holter monitor, transtelephonic monitor, or telemetry strip within 12 months of randomization
● Continuous anticoagulation for > 4 weeks prior to the ablation; or a transesophageal ECG (< 48 hours before ablation) that excludes left atrial thrombus
● Written informed consent
Exclusion criteria
● Contraindication to oral anticoagulants
● History of any previous ablation for AF
● Intracardiac thrombus
● AF due to reversible cause (eg, hyperthyroidism)
● LA size > 55 mm or significant mitral valve disease (moderate or severe mitral stenosis or regurgitation)
● Pregnancy
● Asthma, history of bronchospasm, or known adverse reaction to adenosine

ADVICE, Adenosine Following Pulmonary Vein Isolation to Target Dormant Conduction Elimination; AF, atrial fibrillation; ECG, electrocardiogram; LA, left atrium.

lation (group 2). In patients randomized to further ablation, additional radiofrequency energy will be delivered at sites of reconduction in each affected PV. Immediately after additional targeted ablation, abolition of dormant conduction will be assessed by repeated intravenous injections of 12 mg or more of adenosine to obtain at least 1 blocked P wave or a pause ≥ 3 seconds. Ablation will be performed until adenosine fails to induce reconnection in any PV.

Postablation follow-up

Barring complications, patients will be discharged within 1 to 4 days after ablation. All patients will remain anticoagulated for ≥ 2 months, and repeat procedures will be deferred for > 3 months if possible, in accordance with the Heart Rhythm Society guidelines.[9]

Patients randomized to group 1, group 2, and registry group. Antiarrhythmic drugs (except amiodarone) may be used in the first 3 months to treat early recurrences post ablation. They will be discontinued 5 half-lives before the end of the 3-month blanking period.[9] Scheduled visits will occur at 3, 6, and 12 months from the first ablation procedure (2-week margin). A 24-hour Holter and 12-lead ECG will be performed at 3, 6, and 12 months. A transtelephonic monitor will be provided to each patient after the ablation procedure. Patients will routinely record an ECG rhythm strip weekly and will transmit recordings in the event of symptoms. Rhythm strips from implanted devices will also qualify.

Patients randomized to usual medical care. Clinical follow-up will be performed by the treating physician in accordance with the Heart Rhythm Society guidelines.[9] Demographic data will be compared with those of patients randomized to group 1, group 2, and the registry.

Study end points

Primary end point. The primary outcome is time to first recurrence of symptomatic electrocardiographically documented AF, atrial flutter, or atrial tachycardia between days 91 and 365 after ablation, or repeat ablation procedure during the first 90 days. AF or atrial flutter/tachycardia will qualify as an arrhythmia recurrence after ablation if it lasts 30 seconds or longer and is documented by 12-lead ECG, surface ECG rhythm strips, or transtelephonic monitor recordings.[9] All documented episodes will be adjudicated by a blinded committee. Time 0 will be defined as day 91 post ablation, with follow-up extending 365 days after ablation. The primary end point and the 3-month blanking period adhere to the Heart Rhythm Society recommendations for reporting outcomes in AF ablation trials.[9]

Secondary end points. (1) Time to first recurrence of any electrocardiographically documented AF, atrial flutter, or atrial tachycardia (symptomatic or asymptomatic) between days 91 and 365 after ablation. (2) Repeat ablation procedure for documented recurrence of symptomatic AF, atrial flutter, or atrial tachycardia. (3) Emergency visits or hospitalizations. (4) Antiarrhythmic drug use because of documented recurrence of symptomatic AF, atrial flutter, or atrial tachycardia. (5) Proportion of patients with AF, atrial flutter, or atrial tachycardia occurring during the first 90 days post ablation. (6) Major peri-procedural complications including stroke, PV stenosis, cardiac perforation, atrio-esophageal fistulae, and death. (7) Generic and disease-specific quality of life (assessed by the Canadian Cardiovascular Society Severity of AF scale and 36-Item Short Form Health Survey questionnaire at baseline and at 3, 6, and 12 months post randomization).

Sample size

Assumptions include a primary outcome rate of 55% in adenosine-positive patients not randomized to further targeted ablation. Considering that all patients will be followed for 12 months, a minimum of 236 patients with dormant conduction should be recruited, in a 1:1 ratio, to obtain > 90% power (log rank test) to detect a 20% difference in the primary outcome, with a 2-tailed α of 0.05. Factoring in a 3% loss to follow-up, 244 patients are required for randomization to groups 1 or 2. Considering that prior studies have documented the presence of dormant conduction in approximately 50% of patients after PVI,[19-21] 488 patients should be enrolled to meet the objective. To further assess the role of dormant conduction as a predictor of AF recurrence, 98 of 244 patients with no dormant conduction will be randomly selected for inclusion in the registry group. A sample size ranging from 95 to 98 patients would yield 86% power to detect a 20% reduction in the primary outcome between group 1 and the registry group. Power cal-

culations are based on the log-rank test for equality of survival curves (nQuery, version 6.01), using simulated data.

Statistical analyses

The primary efficacy analysis will be based on the intention-to-treat principle according to the initial allocated strategy. A secondary efficacy analysis will exclude patients with major protocol deviations. Survival curves will be estimated by the Kaplan-Meier method and compared by the log rank test, provided that event probabilities are constant over time. If this assumption fails, a χ^2 test will be used instead. A Cox proportional hazards model will be used to test the consistency of the groups while accounting for the effects of clinically important baseline characteristics. The hazard ratio will be presented for the treatment effect with 95% confidence intervals. Important baseline characteristics will include, but are not limited to, site, age, gender, race, weight, LA size, structural heart disease, AF duration, and antiarrhythmic drugs used in the past. The proportional hazard assumption will be assessed by visual inspection of the log-negative-log plot and through a formal test of the interaction term "group $\times$ time" at $\alpha = 0.05$. Should this assumption fail, a stratified Cox model will be fitted in order to correct for nonproportional hazards if possible, or if that technique is ineffective, time-dependent variables will be introduced. Should these corrective techniques fail, logistic regression will be used instead. To further assess the role of dormant conduction as a predictor of AF recurrence, a comparison of the primary end point will be performed between patients without dormant conduction (registry group) and groups 1 and 2 separately. All the above-mentioned secondary end points will be analyzed using Kaplan-Meier survival curves and a log rank test if appropriate. For all dichotomous qualitative variables, a Cochran-Mantel-Haenszel test will be performed to assess group differences while adjusting for possible site effects. Continuous variables, such as procedure and fluoroscopy times, will be analyzed with an analysis of variance while possible site effects are adjusted for. If the data are not normally distributed, the nonparametric Wilcoxon signed rank test will be used. Health-related quality-of-life scores will be compared by analysis of covariance, adjusting for baseline values to reduce the error mean squares. In the event of missing data, a multiple imputation approach using SAS procedures PROC MI and PROC MIANALYZE will be employed, if necessary. All tests will be conducted at an α level of 0.05.

Discussion

Possible mechanisms by which adenosine restores conduction to dormant PVs

PV myocardial sleeves have a complex structure that increases the likelihood of conduction block between PVs and the LA.[22] PV myocardial sleeves have less negative resting potentials than LA cells, resulting in functional inactivation of the Na^+ current (I_{Na}) responsible for conduction.[23] When PVs are ablated, irreversible injury leads to permanent loss of conduction. However, reversible injury can lead to loss of PV-LA conduction immediately post ablation, with subsequent recovery of conduction leading to AF recurrence. Cardiac conduction requires sufficient "source" current from activated cells to depolarize and fire cells in the downstream "sink." Source-sink mismatch, often a cause of functional conduction block, is particularly likely when small tissue strands with abrupt orientation changes, such as the PVs, connect to a larger mass of tissue such as the LA. When conduction is viable but acutely suppressed, it can be restored by increasing source current. Adenosine activates outward K^+ currents and leads to cellular hyperpolarization, especially in atrial cells.[24] This hyperpolarization increases I_{Na} by removing voltage-dependent inactivation, revealing dormant conduction in viable PVs.[25]

Animal data supporting the role of adenosine to reveal dormant conduction

The mechanisms of dormant conduction were recently addressed by recording action potentials from canine PV and LA cells with fine-tipped microelectrodes.[25] Adenosine selectively hyperpolarized PV resting membrane potential and increased PV maximum phase 0 depolarization rate, a reflection of I_{Na}. Dormant PV conduction was induced by applying radiofrequency ablation lesions to PVs: adenosine restored excitability and PV-LA conduction by hyperpolarizing PV cardiomyocytes. The basic mechanisms underlying differential PV sensitivity were addressed by measuring adenosine-induced K^+ current (by which adenosine hyperpolarizes atrial action potentials): there was significantly larger adenosine-induced K^+ current in PV vs LA cells. This result agrees with other observations of differential G protein–coupled inward rectifier K^+-current function in PV vs LA cardiomyocytes.[26]

Clinical data supporting the role of adenosine during PVI

A few observational studies evaluated the use of adenosine to identify and eliminate dormant PV conduction.[17-21,27-29] Arentz et al. first described PV dormant conduction revealed by adenosine and a possible association with AF recurrence.[17] After successful PVI in 29 patients, transient reconnection was observed in 25% of PVs with adenosine. In 14 patients (48%), a second ablation was needed for recurrent AF. PV conduction had recovered in 71% of adenosine-positive PVs and 35% of adenosine-negative PVs. In a study of 29 patients, Tritto et al. also found that adenosine could re-establish LA-PV conduction after apparently successful PV isolation in 35% of PVs.[18] They also demonstrated that adenosine-induced PV reconnection could be abolished by additional ablation. Hachiya et al. administered adenosine after successful PVI in 82 AF patients.[19] Adenosine revealed transient PV reconnection in 92 PVs in 34 patients (41%) after apparently successful PVI. Further ablation was performed at the site of PV reconnection. During a 6.1 $\pm$ 3.3-month follow-up, freedom from AF was achieved in 60 of 82 patients (73%) in the adenosine group compared with 102 of 170 (60%) of historical controls (170 patients with PVI without adenosine, $P = 0.04$). No complication attributed to an adenosine strategy was reported. Matsuo et al. performed standard PVI in 94 patients.[20] Elimination of adenosine-induced dormant conduction by additional radiofrequency ablation was performed in addition to standard PVI in 54 other patients. Transient PV reconnection with adenosine was observed in 56% (30/54) of patients after PVI. Elimination of dormant conduction was achieved in 95%, in whom a significant reduction in AF recurrence was observed during a mean follow-up of 20 months (20% vs 40%, $P < 0.05$). Recently, Gula et al. evaluated clinical AF recurrence

and recovery of PV conduction in 72 PVI patients with and without dormant conduction revealed by adenosine.[21] No further ablation was performed to eliminate dormant conduction. The presence of dormant PV conduction had a positive predictive value of 90% for later recovery of PV conduction.

Overall, the literature suggests that an adenosine-guided PVI approach is superior to standard PVI in improving freedom from recurrent AF. These encouraging findings, combined with supportive mechanistic studies demonstrating a biologically plausible link, provide solid justification to definitely address this critical question.

Alternative trial designs contemplated

Alternative clinical trial designs were considered with, for example, randomization of patients prior to the AF ablation procedure into 2 groups: adenosine-guided PVI approach vs standard PVI. However, such a design was deemed less efficient, considering that dormant conduction is present in only 50% of patients after PVI.[19,20] Only roughly half of the patients assigned to adenosine-guided PVI ablation would have received active adenosine-guided ablation. Moreover, outcomes in the control group would be diluted by the proportion of patients that would have been adenosine-negative if tested. In addition, such a design would not allow a distinction between benefits from additional ablation vs elimination of dormant conduction. Our proposed trial design most directly addresses the question of whether acting on adenosine-positive results bears clinical relevance.

Anticipated impact

Catheter ablation for AF has evolved from a niche procedure to a widely performed intervention. A major limitation of PVI is the high AF recurrence rate. If adenosine-guided ablation is demonstrated to improve success, it will become a routine component of PVI procedures. Improving the success of PVI procedures would reduce the need for emergency department visits and hospitalizations and prevent a significant number of repeat procedures, with important heath care and health cost implications.

Conclusion

The ADVICE trial is the first prospective randomized study designed to assess whether a PVI strategy incorporating elimination of dormant conduction unmasked by intravenous adenosine will improve arrhythmia-free survival.

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Disclosures

The authors have no potential conflicts of interest.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at doi:10.1016/j.cjca.2011.10.008.