DESIGN PAPER

Dronedarone vs class Ic agents for early AF: Protocol for the DRIVE-AF randomized clinical trial

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BACKGROUND Early rhythm control is crucial in atrial fibrillation (AF), yet clinical equipoise remains regarding the optimal initial antiarrhythmic drug (AAD). Although class Ic agents are widely used, their safety profile often necessitates complex coadministration with rate-control drugs, potentially limiting adherence. Dronedarone offers distinct safety advantages, but direct randomized comparisons with class Ic agents in early AF are lacking.

OBJECTIVE This study aimed to test the hypothesis that dronedarone is noninferior to class Ic AADs regarding efficacy (AF recurrence) and superior regarding safety (drug discontinuation owing to adverse events).

METHODS The Dronedarone Rhythm Intervention for Early Atrial Fibrillation trial is a prospective, multicenter, randomized, open-label trial to be conducted at 14 academic centers in Korea. The study will enroll 1898 patients diagnosed as having AF within 12 months who require AAD therapy. Participants will be randomized (1:1) to receive either dronedarone (400 mg twice daily) or standard-of-care class Ic agents (flecainide or propafenone) for 12 months.

RESULTS The dual primary endpoints are AF recurrence at 12 months (noninferiority) and drug discontinuation owing to adverse events (superiority). Secondary outcomes include AF-specific quality of life, medication adherence (proportion of days covered), and major adverse cardiovascular events. Analyses will be performed on both intention-to-treat and per-protocol bases.

CONCLUSION The Dronedarone Rhythm Intervention for Early Atrial Fibrillation trial is the first large-scale, randomized trial directly comparing the "safety-first" strategy of dronedarone with the traditional class Ic strategy. By establishing comparative efficacy and safety, this study aims to refine international standards for pharmacologic rhythm control in early AF.

TRIAL REGISTRATION ClinicalTrials.gov identifier: NCT07270848

KEYWORDS Atrial fibrillation; Dronedarone; Class Ic antiarrhythmic drugs; Flecainide; Propafenone; Early rhythm control; Randomized clinical trial; Noninferiority; Drug safety; Medication adherence

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Introduction

Atrial fibrillation (AF) is a major public health burden associated with increased risks of stroke and mortality.[1–6] Recent evidence from the EAST-AFNET 4 trial has fundamentally shifted the treatment paradigm, establishing early rhythm control (within 1 year of diagnosis) as a crucial strategy to improve cardiovascular outcomes.[7] However, the optimal pharmacologic approach to achieve this goal while minimizing adverse effects remains to be established.[8]

Traditional class Ic agents (flecainide and propafenone) are effective for maintaining sinus rhythm in patients without structural heart disease (SHD). However, to mitigate the risk of 1:1 atrioventricular (AV) conduction during atrial flutter—a well-recognized proarrhythmic concern—current clinical standards, including the 2023 American College of Cardiology/American Heart Association/American College of Clinical Pharmacy/Heart Rhythm Society guidelines, strongly recommend the concomitant use of AV nodal-blocking agents, such as beta-blockers.[9] Although class Ic agents are generally well tolerated as monotherapy, this mandatory combination therapy significantly increases the cumulative risk of symptomatic bradycardia and hypotension.

Indeed, large-scale registry data have shown that antiarrhythmic drug (AAD) therapy, particularly when combined with rate-lowering agents, is associated with a 2.5-fold increased risk of bradyarrhythmia-related events requiring pacing or hospitalization compared with rate control alone.[10] Such iatrogenic risks are primary drivers of treatment discontinuation and poor medication persistence in real-world practice.[11,12]

Conversely, dronedarone possesses integrated multichannel blocking properties, providing inherent rate-controlling effects. Although this effect is modest (approximately 10–15 beats/min reduction), it may simplify the treatment regimen by reducing the required dose or intensity of additional background rate-controlling agents, potentially improving overall treatment tolerability.[13,14] Despite these advantages, head-to-head comparisons between dronedarone and class Ic agents in the specific context of early rhythm control are lacking.

Historically, the clinical benefit of rhythm control has been a subject of intense debate. Although the ATHENA trial demonstrated that dronedarone significantly reduced cardiovascular hospitalizations and mortality, a post hoc analysis of the AFFIRM trial by Saksena et al[15] reported that AAD-based rhythm control was associated with higher rates of cardiovascular hospitalization and death. This conflict likely arose from the use of older class I and class III agents in an era with less stringent exclusion of SHD. Although contemporary trials such as CHANGE-AF are evaluating the real-world effectiveness of dronedarone, there remains a lack of randomized, head-to-head evidence specifically comparing dronedarone with class Ic agents in a strictly screened, non-SHD population.[16]

To address this gap, we designed the Dronedarone Rhythm Intervention for Early Atrial Fibrillation (DRIVE-AF) trial. This multicenter, randomized trial aims to compare the efficacy, safety, and quality of life impact of dronedarone with those of class Ic agents. We hypothesize that dronedarone will be noninferior regarding AF recurrence while demonstrating superiority in safety outcomes, particularly regarding drug discontinuation.

Methods

This prospective, multicenter, randomized, open-label, parallel-group trial will be conducted at 14 academic medical centers in the Republic of Korea. The study is designed to evaluate dronedarone vs class Ic AADs using a noninferiority framework for the primary efficacy endpoint (AF recurrence) and a superiority framework for the primary safety endpoint (drug withdrawal owing to adverse events). The DRIVE-AF trial was designed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials 2013 statement. The overall study design is presented in Figure 1.

To maintain scientific rigor while ensuring practical feasibility, we adopted a blinded endpoint (prospective randomized open-label blinded endpoint [PROBE]) design. A double-blind design was considered but deemed impractical for this 12-month pragmatic trial. Given that a double-blind, double-dummy setup would have imposed an excessive pill burden on participants, this approach was chosen to optimize treatment adherence and reflect real-world clinical practice, with all clinical outcomes adjudicated by independent assessors blinded to treatment assignment.[17]

Study procedures, including screening, randomization, and treatment initiation, will primarily take place in outpatient cardiology clinics; however, eligible inpatients may also be enrolled. Participants will be randomized in a 1:1 allocation ratio using a permuted block randomization method (SAS version 9.4) generated by an independent statistician, stratified by center. Patient and public were not involved in the design, conduct, or reporting of this study.

Eligibility criteria

Eligible participants are adults aged 19 years or older who have been diagnosed as having AF within the previous year and have an indication for AAD therapy. Candidates are required to have a life expectancy of at least 1 year and provide a voluntary written informed consent.

To ensure the cohort accurately represents early-stage AF, we exclude patients with permanent AF or long-standing persistent AF (defined as a continuous AF duration of >12 months at the time of enrollment), given that the pathophysiological changes and response to AADs in these patients may differ from the intended early AF population.

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KEY FINDINGS

- Establishing optimal strategy: the Dronedarone Rhythm Intervention for Early Atrial Fibrillation trial is the first large-scale, randomized clinical trial directly comparing the safety and efficacy of dronedarone with class Ic antiarrhythmic drugs in patients with early atrial fibrillation.
- Safety-first approach: this study tests the hypothesis that dronedarone is superior to class Ic agents in terms of safety, specifically by reducing treatment discontinuation rates owing to adverse events such as symptomatic bradycardia.
- Clinical real-world relevance: by reflecting real-world clinical practice in South Korea and using a pragmatic prospective randomized open-label blinded endpoint design, the results will provide actionable evidence for choosing initial rhythm-control therapy in nonstructural heart disease populations.
- Comprehensive assessment: beyond simple electrocardiogram recurrence, the trial evaluates patient-centered outcomes, including atrial fibrillation burden and quality of life, to provide a holistic view of treatment success in early rhythm control.

In addition, patients with a history of previous AAD failure are excluded. For participant safety, especially for those assigned to class Ic agents, we strictly exclude patients with a history of myocardial infarction or confirmed severe SHD (eg, left ventricular ejection fraction ≤40%, moderate or severe mitral stenosis, mechanical valve replacement, or dilated cardiomyopathy). Patients with severe renal or hepatic impairment, or those with specific contraindications to dronedarone or class Ic agents, are also excluded. The full list of inclusion and exclusion criteria is presented in the Supplemental Table 1.

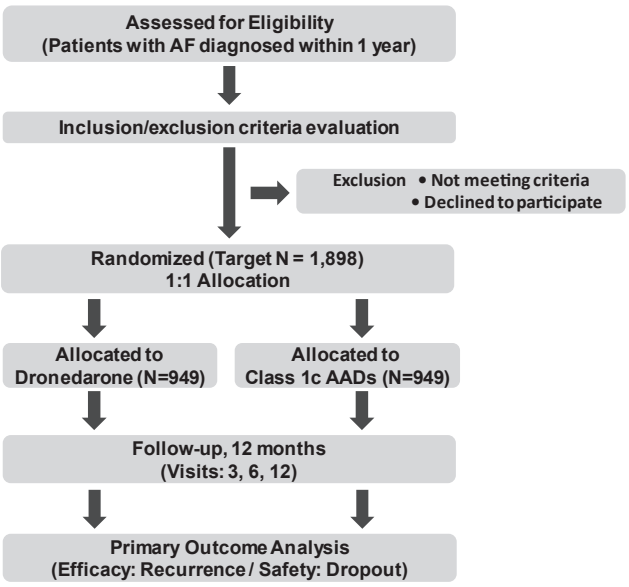


Figure 1 Study design flowchart of the Dronedarone Rhythm Intervention for Early Atrial Fibrillation trial. The diagram summarizes the participant flow from screening and randomization to the 12-month follow-up. AAD = antiarrhythmic drug; AF = atrial fibrillation.

Intervention and comparator

Participants will be randomized to receive either dronedarone or a class Ic AAD. In the intervention group, dronedarone will be administered at a standard fixed dose of 400 mg twice daily. Although this is the mandated protocol dose, temporary dose interruption is permitted at the investigator's discretion based on objective safety and tolerability parameters (eg, corrected QT interval prolongation or bradycardia), as outlined in the standardized safety protocol (Supplemental Table 2).

In the comparator group, the choice and dosage of class Ic agents (flecainide or propafenone) follow local labeling and standard clinical guidelines. Although the sustained-release formulation of propafenone (twice daily dosing) is the predominant standard of care in South Korea, the protocol also permits the use of the immediate-release formulation at the investigator's discretion to fully reflect the pragmatic nature of the trial. Specific dosing ranges and formulations are presented in Supplemental Table 3. The actual usage proportions of immediate-release and sustained-release formulations of propafenone will be recorded throughout the study period and reported descriptively in the final analysis to provide transparency regarding the treatment regimens. All study medications will be self-administered by participants.

Study treatment will be temporarily or permanently discontinued in the event of significant safety concerns. Key discontinuation criteria include corrected QT interval prolongation (>500 ms), symptomatic bradycardia (<50 beats/min), or development of severe hepatic or renal impairment. Recurrence of AF does not mandate discontinuation unless the investigator deems the treatment ineffective and a change in therapeutic strategy (eg, catheter ablation) is clinically necessary. Specific criteria for dose modification and discontinuation are presented in Supplemental Table 2.

Medication adherence will be assessed at 6 and 12 months using the proportion of days covered (PDC) method, calculated based on prescription and electronic medical records; a PDC of ≥80% will be defined as adherent.[18] Regarding concomitant care, oral anticoagulation is strongly recommended for all eligible participants.[1,9] Rate-control agents (beta-blockers, calcium channel blockers) are permitted, whereas the use of other class I or III AADs and potent CYP3A4 inhibitors (for the dronedarone group) is prohibited. Furthermore, potential drug-drug interactions with dronedarone will be strictly managed according to standard prescribing information. For patients receiving digoxin, the dose will be reduced by approximately 50% upon initiation of dronedarone, with mandatory serum level monitoring. For statins metabolized by CYP3A4 (eg, simvastatin or atorvastatin), dose restrictions—such as limiting simvastatin to 10 mg/d—or switching to non-CYP3A4-metabolized statins

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(eg, rosuvastatin or pravastatin) will be implemented. In addition, for moderate CYP3A4 inhibitors used for rate control, such as diltiazem or verapamil, investigators are advised to use the lowest effective dose or consider dose reduction when coadministered with dronedarone to mitigate the risk of excessive bradycardia and increased drug exposure.

Outcomes

The primary efficacy outcome is the recurrence of AF, defined as the first documented episode of AF, atrial flutter, or atrial tachycardia lasting ≥30 seconds. To ensure consistent documentation and mitigate monitoring bias, all participants follow a standardized monitoring schedule: a 12-lead electrocardiogram (ECG) at every clinic visit (months 3, 6, 9, and 12) and a mandatory 24-hour Holter or long-term wearable ECG (W-ECG) monitoring at 6 and 12 months.

In accordance with real-world clinical practice and national insurance reimbursement criteria in South Korea—which permit catheter ablation only after a minimum of 6 weeks of documented AAD failure—investigators may perform additional rhythm monitoring at any time based on clinical symptoms. Any AF recurrence documented through these clinically indicated tests (eg, during the early 2–3-month stabilization period) will be adjudicated as a primary endpoint event.

Secondary outcomes include the change in quality of life, assessed using the total score of the Atrial Fibrillation Quality of Life questionnaire from baseline to 12 months. Medication adherence will be evaluated at 6 and 12 months using the PDC. AF burden is also assessed as a key secondary via prolonged rhythm monitoring, including 24-hour Holter or long-term W-ECG (ranging from 48 hours up to 14 days), at the 12-month follow-up. To reflect the pragmatic nature of the trial, the duration of W-ECG (ranging from 48 hours up to 14 days) is determined by the investigator in consultation with the patient, consistent with Korean reimbursement tiers. AF burden will be calculated as the total duration of AF episodes (each lasting ≥30 seconds) divided by the total analyzable monitoring duration, expressed as a percentage. To ensure a consistent and rigorous assessment of all arrhythmic outcomes, the burden of other atrial arrhythmias (eg, atrial tachycardia) will be calculated using the same methodology as AF burden.

For maintaining monitoring consistency across this multicenter framework, each site follows its established institutional protocol for all patients. Any potential detection bias is mitigated through stratified randomization by center, ensuring a balanced distribution of monitoring devices between the treatment arms within each site.

Participant timeline

Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants are presented in Table 1.

Sample size

The target sample size was determined to ensure sufficient statistical power for both the primary efficacy and safety endpoints. Given that the study aims to demonstrate either noninferiority in efficacy or superiority in safety, sample sizes were calculated independently for each endpoint, and the larger of the 2 estimates was adopted as the final target sample size. To control the overall family-wise type I error rate at a 1-sided 0.025, a Bonferroni correction was applied, setting the significance level (α) at 0.0125 for each endpoint.

For the efficacy assessment (noninferiority regarding AF recurrence), we performed a meta-analysis using data extracted from the systematic review by Valembois et al[19] to calculate the risk difference (RD). Based on a common placebo event rate ($P_{placebo} = 72.1\%$) and the derived RDs, the expected recurrence rate for the control group (class Ic agents) was estimated at approximately 47.4%–47.5%, assuming a weighted usage ratio of flecainide to propafenone ranging from 9:1 to 7:3. The noninferiority margin was defined using the fixed-margin method, conservatively preserving 50% of the lower bound of the 95% confidence interval of the effect of propafenone over placebo (−0.299), consistent with regulatory guidance. Consequently, the noninferiority margin was set at 14.9% (0.149). Using a 1-sided Z-test (pooled) with $\alpha = 0.0125$ and a power of >99%, the required sample size was calculated to be 1174 participants (587 per group), accounting for a 20% dropout rate.

For the safety assessment (superiority regarding drug discontinuation owing to adverse events), discontinuation rates were also derived from the meta-analysis of randomized trials included in Valembois et al's[19] study. The discontinuation rate for the dronedarone group was estimated at 11.9%. For the class Ic group, a weighted average discontinuation rate ranging from 17.5% to 18.8% was assumed, reflecting the real-world usage patterns of flecainide and propafenone. To detect this difference with 80% power at a 1-sided $\alpha = 0.0125$, the required sample size was calculated to be 1898 participants (949 per group), assuming a 20% dropout rate.

Consequently, the larger estimate driven by the safety endpoint was adopted, resulting in a final target sample size of 1898 participants. Therefore, a total of 1898 participants will be enrolled. All calculations were performed using PASS 2024 software (NCSS, LLC).

Recruitment

Recruitment will take place at 14 high-volume academic medical centers in the Republic of Korea. Potential participants will be identified primarily through systematic screening of daily patient lists and electronic health records in outpatient cardiology clinics, as well as via inpatient consultation networks. To expedite the process, a competitive enrollment strategy will be used across all sites; there is no fixed cap on enrollment per institution, allowing sites with faster recruitment rates to enroll patients until the total target sample size of 1898 is reached.

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Table 1 Schedule of enrollment, interventions, and assessments (SPIRIT figure)

Study period	Enrollment	Allocation	Postallocation (follow-up)			
Timepoint (visit window)	Baseline (d 0)	Baseline (d 0)	Month 3 (±1 mo)	Month 6 (±1 mo)	Month 9 (±1 mo)	Month 12 (±1 mo)
Visit number	V1	V1	V2	V3	V4	V5
Enrollment and allocation						
Informed consent	X					
Eligibility screening	X					
Medical history and demographics	X					
Randomization		X				
Interventions						
Study drug prescription*		X	X	X	X	X
Assessments						
Physical examination and vital signs	X		X	X	X	X
12-lead ECG	X		X	X	X	X
Holter/wearable ECG†				X		X
Transthoracic echocardiogram‡	X					(X)
Laboratory tests§	X					X
Adverse event monitoring			X	X	X	X
Concomitant medications	X		X	X	X	X
Patient-reported outcomes						
AF-QoL questionnaire	X					X
Medication adherence (PDC)				X		X

AF-QoL = Atrial Fibrillation Quality of Life; ECG = electrocardiogram; PDC = proportion of days covered; SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials.

*Participants are randomized to either dronedarone or class Ic antiarrhythmic drugs.

†24-hour Holter or Food and Drug Administration–/Korea Food and Drug Administration–approved wearable ECG monitoring. Additional symptom-driven monitoring may be performed at unscheduled visits if clinically indicated.

‡Historical echocardiogram data within 3 years before baseline may be used. Follow-up echocardiogram is optional based on clinical judgment.

§Includes complete blood count, liver function tests (aspartate aminotransferase, alanine aminotransferase, bilirubin), renal function tests (blood urea nitrogen/creatinine), and electrolytes.

To ensure recruitment quality and targets are met, the steering committee will monitor enrollment rates on a monthly basis. Regular feedback and training sessions will be provided to subinvestigators and research coordinators to ensure strict adherence to eligibility criteria and the informed consent process.

Randomization

Participants will be randomized in a 1:1 ratio to receive either dronedarone or a class Ic AAD. The randomization sequence has been generated by an independent statistician using a permuted block method (SAS version 9.4, SAS Institute Inc) with stratification by center.

The randomization schedule will be distributed to each of the 14 participating sites before enrollment. Upon obtaining a written informed consent, participants will be assigned a screening number. Once eligibility is confirmed based on inclusion and exclusion criteria, investigators will assign the next available sequential randomization number from the site-specific Excel-based randomization log to allocate the treatment. The study will use a competitive enrollment strategy across all institutions.

Blinding and adjudication

This study uses an open-label design (PROBE); thus, participants and site investigators will be aware of the treatment allocation.[17] However, to minimize detection bias, outcome adjudication and statistical analyses will be performed in a blinded manner.

In particular, for the assessment of the primary efficacy endpoint (AF recurrence), all ECG and Holter monitoring data will be deidentified and coded before review. Independent assessors will adjudicate these tracings without access to treatment group information. To mitigate potential physician bias inherent in an open-label design regarding study drug discontinuation, standardized discontinuation criteria based on objective clinical parameters (detailed in Supplemental Table 2) were implemented. In particular, the study protocol mandates the immediate discontinuation of study medications if a participant develops new-onset myocardial infarction or heart failure characterized by a reduced left ventricular ejection fraction (<40%) or New York Heart Association class III/IV symptoms during the follow-up period.[17]

Data management and quality assurance

Data collection and management will be conducted using a validated, Web-based Electronic Data Capture system (eg, iMedidata) that complies with 21 CFR Part 11[20] and Korean Good Clinical Practice guidelines.[21] The system will maintain a complete, time-stamped audit trail of all entries and modifications. To ensure data quality, the Electronic Data Capture

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system uses automated logical and range checks to prevent erroneous entry. Discrepant or missing data will be resolved through electronic queries issued by the data management team or monitors. For standardization, adverse events will be coded using the Medical Dictionary for Regulatory Activities, and concomitant medications will be coded using the World Health Organization Drug Global Dictionary.

Participant confidentiality will be protected through pseudonymization, where individuals will be identified solely by a unique study code. Access to the database will be strictly controlled via role-based permissions, and data will be stored on secure servers with SSL encryption. All study documents and data will be retained for at least 3 years after study completion, in accordance with local regulations.

Statistical methods

Efficacy analyses will be primarily performed on the per-protocol set, which includes all randomized participants who complete the study without major protocol violations. An intention-to-treat analysis (defined as all randomized participants who received at least 1 dose) will be performed as a supportive analysis to confirm the consistency of results. Safety analyses will be performed on the safety set, consisting of all participants who received at least 1 dose of the study medication, analyzed according to the treatment actually received.

For the primary efficacy endpoint (AF recurrence at 12 months), the RD between the dronedarone group (P_D) and the class Ic group (P_C) will be estimated. Noninferiority will be declared if the upper limit of the 2-sided 95% confidence interval for the RD ($P_D - P_C$) is less than the prespecified margin of 14.9% (0.149). For the primary safety endpoint (drug discontinuation owing to adverse events), a superiority test will be performed using a 2-sided χ^2 test. Superiority will be concluded if the discontinuation rate is significantly lower in the dronedarone group with $P < .025$ (corresponding to the 1-sided $\alpha = 0.0125$ used for sample size calculation).

Continuous variables will be presented as means ± standard deviations or medians with interquartile ranges and compared using the Student *t* test or Mann-Whitney U test, as appropriate. Categorical variables will be presented as frequencies and percentages and compared using the χ^2 test or Fisher's exact test. Time-to-event data, including AF recurrence and major adverse cardiovascular events (MACEs), will be estimated using the Kaplan-Meier method and compared using the log-rank test. To control for potential confounders, Cox proportional hazards models will be used. In these models, the type of monitoring device (24-hour Holter vs W-ECG) will be included as a covariate to account for potential differences in detection sensitivity. In addition, a sensitivity analysis will be performed to evaluate the robustness of the efficacy results across different monitoring methods.

The primary analysis will use complete case analysis. Sensitivity analyses will be performed to assess the impact of missing data where appropriate. For the secondary analysis of AF burden, a sensitivity analysis adjusting for the total W-ECG recording duration as a covariate will be performed to account for potential variability in monitoring intensity across participants. All statistical tests (except for the primary safety endpoint) will be 2 sided with a significance level of $P < .05$. Statistical analyses will be performed using commercially available software packages, such as SAS version 9.4 (SAS Institute Inc, Cary, NC), Stata, or SPSS.

Study oversight and monitoring

Given the open-label design and the use of standard-of-care agents with well-established safety profiles, a formal independent data monitoring committee was not appointed. Instead, safety oversight will be conducted by an internal safety management team comprising the principal investigator and designated coinvestigators. This team will continuously review safety data and report to the institutional review board (IRB) of Inha University Hospital, which provides independent ethical oversight. No formal interim analysis for efficacy is planned. However, the study may be terminated early by the principal investigator in consultation with the IRB if significant new safety risks emerge, if mandated by regulatory authorities, or if recruitment is insufficient to complete the study.

Trial conduct will be monitored by qualified clinical research associates appointed by the sponsor-investigator. Monitoring visits will occur at site initiation, annually during the study (interim monitoring visits), and at study closure. The monitoring process will follow a risk-based monitoring approach.[22] Source document verification will be performed to ensure data accuracy, with 100% verification required for critical data points including informed consent forms, eligibility criteria, primary efficacy endpoints (AF recurrence), and serious adverse events. Random sample verification (10%–20%) will be performed for routine data. Monitors will also verify regulatory compliance and drug accountability.

Ethical considerations

The study protocol and informed consent forms have been reviewed and approved by the IRB of Inha University Hospital (coordinating IRB; approval no. 2025-06-013) and by the local IRBs of all participating centers. The study will be conducted in full accordance with the Declaration of Helsinki and Korean Good Clinical Practice guidelines.[21,23] Any significant protocol amendments will be submitted to and approved by the IRB before implementation.

A written informed consent will be obtained from all participants by the investigators before enrollment. Participation is voluntary, and participants will be informed of their right to withdraw at any time. To protect confidentiality, all data will be pseudonymized using unique study identification codes. The master list linking codes to personal identities will be stored securely at each site, accessible only to authorized personnel.

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The sponsor (Inha University Hospital) has subscribed to Clinical Trial Liability Insurance to provide compensation for any study-related injuries. Post-trial care will follow standard clinical practice, with medications prescribed according to national health insurance coverage.

Discussion

The DRIVE-AF trial is the first large-scale, randomized investigation designed to directly compare the efficacy and safety of dronedarone with those of standard class Ic agents for early rhythm control. Following the paradigm shift supported by the EAST-AFNET 4 trial, selecting the optimal first-line AAD has become a critical clinical question.[7] This study aims to validate whether prioritizing the safety and tolerability of dronedarone offers a superior alternative to the traditional class Ic–based strategy.

Our study design specifically addresses the safety concerns raised by the analysis of Saksena et al,[15] which observed unfavorable outcomes with class I agents. Unlike older trials, the DRIVE-AF trial implements contemporary screening protocols, including mandatory echocardiography, to ensure a true non-SHD population. By mitigating the proarrhythmic risks historically associated with class I agents, this study aims to bridge the gap between the landmark findings of ATHENA[13] and earlier retrospective observations, reflecting modern clinical practice. This approach is consistent with recent real-world observations[16] and aims to reduce potential prescription biases held by physicians.

Although class Ic agents are effective, their long-term use may be constrained by concerns about proarrhythmic risk and treatment-related adverse events. Large-scale registry data have shown that the combination of rhythm-control AADs with AV nodal-blocking drugs is associated with a significantly increased risk of bradyarrhythmia and the need for permanent pacemaker implantation.[10] Given that class Ic agents are typically coprescribed with AV nodal blockers, these data support the clinical concern that symptomatic bradycardia or hypotension may lead to dose reduction or drug discontinuation, which may indirectly compromise long-term adherence to rhythm-control therapy.[11] Furthermore, treatment persistence with dronedarone has been characterized in both randomized trials and real-world registries. In the ATHENA trial,[13] long-term dronedarone therapy demonstrated an acceptable safety profile and a reduction in cardiovascular outcomes. In addition, observational cohort data, such as the EFFECT-AF study[24] and the Magdeburg Dronedarone Registry,[25] have described real-world patterns of long-term use and discontinuation of dronedarone in routine practice, providing more direct evidence regarding its feasibility and persistence as a rhythm-control option.

The DRIVE-AF trial has several distinctive strengths. First, the dual primary endpoint design (noninferiority for efficacy and superiority for safety) reflects the clinical reality that tolerability is as important as potency for long-term management. Second, the inclusion criteria target patients within 1 year of diagnosis, aligning with the population that benefits most from early intervention.[7] Third, the robust assessment of patient-centered outcomes, including quality of life (Atrial Fibrillation Quality of Life questionnaire) and medication adherence (PDC), provides comprehensive data beyond simple ECG recurrence. Finally, the PROBE design minimizes detection bias for efficacy endpoints while allowing for the practical administration of different dosing regimens.

Limitations

Our study has several limitations. First, the open-label design allows participants and investigators to be aware of treatment allocation, which could introduce performance or reporting bias, particularly regarding subjective adverse events. To mitigate this, we use blinded adjudication for the primary efficacy endpoint and objective criteria for safety discontinuation. Second, the study is being conducted exclusively in academic medical centers in South Korea, which may limit the generalizability of the findings to other ethnic groups or health care systems. Third, although we newly incorporated AF burden as a secondary outcome measured via prolonged ECG monitoring (ranging from 24 hours to 14 days) at 12 months, the absence of continuous monitoring with implantable loop recorders throughout the study period remains a limitation. Routine implantable loop recorder use was unfeasible owing to nationwide regulatory constraints in South Korea, where its implantation is reimbursed only for patients with embolic stroke of undetermined source. Fourth, although "time to first recurrence" has inherent limitations compared with continuous burden monitoring, it remains a clinically actionable metric in the South Korean health care system, where treatment escalation is tied to documented recurrence after a minimum 6-week AAD trial. Fifth, it should be noted that although this study evaluates MACEs as a secondary endpoint, the sample size was determined based on the primary efficacy outcome (AF recurrence). Therefore, the study may have limited statistical power to detect significant differences in hard clinical outcomes such as MACE or cardiovascular mortality. These results should be interpreted as exploratory and as a basis for generating hypotheses for future larger-scale investigations. Finally, although we allow the use of W-ECG monitoring for arrhythmia detection to reflect current trends, the variability in monitoring intensity between patients could affect the documented recurrence rate, although randomization is expected to balance this factor between groups.

Conclusion

The DRIVE-AF trial will provide pivotal evidence regarding the optimal pharmacologic strategy for early rhythm control in patients with AF. By comparing the widely used class Ic agents with dronedarone in a randomized setting, this study aims to establish whether prioritizing safety and tolerability with dronedarone offers a viable and potentially superior alternative to the traditional class Ic–based approach. The results of this trial are expected to inform future clinical practice

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guidelines and aid clinicians in making personalized treatment decisions for the growing population of patients with early AF.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Gemini (Google) to translate the original protocol from Korean to English and to improve the clarity and readability of the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: A written informed consent will be obtained from all participants by the investigators before enrollment.

Ethics Statement: The study protocol and informed consent forms have been reviewed and approved by the IRB of Inha University Hospital (Coordinating IRB; approval no. 2025-06-013) and by the local IRBs of all participating centers. The study will be conducted in full accordance with the Declaration of Helsinki and Korean Good Clinical Practice guidelines.

Data Availability: Data sharing is not applicable to this article given that no datasets were generated or analyzed during the current study.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2026.05.019.

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