Clinical Research Protocol

1. Study Title

Artificial intelligence-enabled management of atrial fibrillation: a randomized clinical trial (ABLE-AF trial)

2. Principal Investigator, Study Site(s), and Study Period

Responsible Research Institution: Korea University Anam Hospital (73 Inchon-ro, Seongbuk-gu, Seoul 02841, Republic of Korea)
Clinical Trial Coordinator: Prof. Jong-Il Choi, Division of Cardiology
Participating Institutions and Site Investigators: See attached list of participating institutions.
Study Period: 5 years from the date of IRB approval (June 2025 – May 2030)

3. Background and Rationale

Atrial fibrillation (AF) is the most common arrhythmia among adults worldwide and imposes a substantial burden not only on patients but also on the healthcare system.[1] In patients with AF, early evaluation of the cardiac substrate—including left ventricular (LV) function—and of any accompanying structural heart disease is required to guide long-term treatment decisions.[2] Transthoracic echocardiography (TTE) is the standard method for assessing LV ejection fraction (LV EF); however, because it must be performed and interpreted by trained personnel, it carries a substantial cost and time burden. In particular, even in situations that require acute management—such as AF with rapid ventricular response—early assessment of cardiac function by TTE is often difficult to obtain in primary care, the emergency department, or the outpatient clinic. Furthermore, the COVID-19 pandemic has created an imbalance between the supply and demand for outpatient TTE, with average waiting times now exceeding six weeks before TTE can be performed.[3]

In recent years, the emergence of artificial intelligence (AI) technology has provided innovative solutions for overcoming the limitations of conventional diagnostic methods, leading to increasing use of AI-based electrocardiography (ECG) analysis. AI prediction models that assess left ventricular systolic dysfunction (LVSD) from the 12-lead ECG have recently emerged; one such model developed and commercialized in Korea is AiTiALVSD, an ECG-based software that estimates LV ejection fraction and degree of heart failure, developed by Medical AI Co., Ltd. and granted manufacturing approval by the Ministry of Food and Drug Safety (MFDS).[4,5] This AI model has demonstrated stable predictive performance across a range of clinical settings in several follow-up and validation studies. In addition, a recent prospective, external cohort study of patients with AF and rapid ventricular response confirmed competitive predictive performance and a high negative predictive value even in patients with concurrent AF and tachycardia.[6] More recently, an AI algorithm has been developed to predict diastolic dysfunction and elevated LV filling pressure from the ECG, and this algorithm (AiTiALVDD) has likewise demonstrated high predictive performance.[7] Elevated left ventricular filling pressure and diastolic dysfunction can present

as a common pathophysiologic finding across a variety of cardiac conditions, including valvular heart disease, hypertrophic cardiomyopathy, infiltrative myocardial disease, hypertensive heart disease, and coronary artery disease. Notably, even among patients with preserved LV EF (i.e., a normal AiTiALVSD result) - in whom systolic dysfunction alone would not identify these conditions - such underlying disease has been reported to co-occur at a substantial rate. When the AiTiALVDD prediction is high, this result will be used as a screening cue to prompt additional detailed evaluation for underlying cardiac disease, including severe valvular disease. This provides a complementary safeguard by enabling early detection of diastolic-dysfunction-related conditions that AiTiALVSD alone would not capture, thereby strengthening subject safety and helping ensure that clinically significant comorbidities are not overlooked. By using both algorithms (AiTiALVSD and AiTiALVDD) together in the present study, we expect to be able to detect, at an early stage, occult LV systolic dysfunction (reduced LV EF) or underlying structural heart disease such as moderate-to-severe valvular disease in the AF population. However, the clinical effectiveness and benefit of such AI-based ECG analysis have not yet been investigated.

4. Study Objective

This is a randomized, non-inferiority trial designed to evaluate the clinical effectiveness and benefit of AI-model-based treatment, compared with conventional treatment (treatment based on TTE findings), in patients with AF and rapid ventricular response.

5. Risk/Benefit Analysis

This study may influence the subsequent treatment direction of patients with AF and rapid ventricular response. However, these patients are relatively stable and able to be managed as outpatients, and the AI model used in the investigational group has shown high predictive performance and a high negative predictive value in prior studies; the additional risk associated with this study is therefore judged to be low.

In the investigational group, pharmacologic treatment can be initiated relatively earlier than with conventional treatment, which is expected to provide benefit through improvement of AF-related symptoms and morbidity. Earlier initiation of pharmacologic treatment may, in turn, allow earlier procedural treatment (catheter ablation) if drug therapy is refractory, which is expected to be of benefit to the investigational group. However, in the subset of patients for whom the AI model's prediction of LV function is inaccurate (false positive or false negative), pharmacotherapy that does not match the patient's true LV EF could be administered, with a resulting risk of adverse effects. Nonetheless, in the false-positive group (LV EF predicted to be low when it is not actually low), pharmacotherapy does not increase harm, because the true LV EF is in fact higher. In addition, potential harm may arise in the false-negative group (patients in whom LV EF is predicted to be high when it is not actually high). In this scenario, investigators would select antiarrhythmic drug therapy on the premise that the patient's LV function is normal, which creates the possibility that (1) an agent that is relatively contraindicated or requires caution in patients with structural heart disease or reduced LV systolic function could be selected, and (2) initiation of guideline-directed heart failure therapy that is in fact needed could be delayed. However, the negative predictive value

(NPV) confirmed in a prior study (an AI model validation study) was 0.88, so the probability of a false-negative result is limited[6]. In addition, the study population is restricted to relatively stable patients who are able to be managed as outpatients, and high-risk patients with acute decompensated heart failure or significant coronary artery disease are excluded from the study. Furthermore, the same clinical monitoring that is part of standard care will be conducted in parallel in the investigational group as well. In other words, provided the patient does not have decompensated heart failure status or significant coronary artery disease, the risk associated with short-term antiarrhythmic drug therapy is not expected to be high.

In summary, this study is justified from a risk/benefit standpoint. All clinical information collected for research purposes (medical records, laboratory results, etc.) will remain confidential, will be used only for research purposes, and will be stored securely.

6. Target Sample Size and Justification

According to the Korean Atrial Fibrillation Fact Sheet, over the most recent 10-year period (2013–2022), the annual incidence of all-cause death among Korean patients with AF was approximately 4.9–5.9%, ischemic stroke 1.2–1.6%, myocardial infarction 0.6–0.9%, and hospitalization for heart failure approximately 4%.[8] While the incidence of ischemic stroke has been decreasing, all-cause death, myocardial infarction, and heart-failure hospitalization have been increasing.

In the EAST-AFNET4 trial, which evaluated early rhythm control in patients with AF, the composite of cardiovascular death, stroke, hospitalization for heart failure, or hospitalization for acute coronary syndrome occurred at a rate of 3.9 per 100 person-years in the early-rhythm-control group versus 5.0 per 100 person-years in the usual-care group.[9] A retrospective analysis based on Korean national health insurance data in a similar population reported that cardiovascular death, ischemic stroke, heart-failure hospitalization, and acute myocardial infarction occurred at a rate of 7.4 per 100 person-years in the early-rhythm-control group.[10] In the CABANA trial, another randomized study of early rhythm control, all-cause death, disabling stroke, serious bleeding, or cardiac arrest occurred in 8.0–9.2% of patients with ≥1 cardiovascular risk factor and recurrent AF over a mean follow-up of 4 years.[11]

Patients with AF are known to have an increased rate of hospitalization for AF and other cardiovascular causes. Large AF cohorts (Danish registry, ORBIT-AF, ROCKET-AF) have reported a 1-year cardiovascular hospitalization rate of 15%.[12] In the CABANA trial, cardiovascular hospitalization occurred in 50–55% of patients over a mean follow-up of 4.1 years, and in the EARLY-AF trial (a randomized study comparing cryoballoon ablation with antiarrhythmic drug therapy as initial treatment for AF), AF/tachycardia-related hospitalization during 1 year of follow-up was reported in 3.2–8.7% of patients.[11,13]
The population to be enrolled in this study comprises patients recently diagnosed with AF who have rapid ventricular response with a heart rate ≥110 bpm. This is a population similar to those in the studies cited above, restricted to the subset with rapid ventricular response. A retrospective analysis of the Korean multicenter AF observational registry (CODE-AF) found no difference in the occurrence of major adverse cardiovascular events (all-cause death, ischemic stroke, systemic embolism, transient ischemic attack, major bleeding, myocardial

infarction) between patients with and without rapid ventricular response.[14] Accordingly, the incidence of the primary efficacy endpoint in this study (all-cause death, stroke, acute myocardial infarction, hospitalization for heart failure, or cardiovascular hospitalization occurring during 1 year of follow-up) is expected to be similar to the rates reported in the studies above.

The target sample size was calculated using PASS 2024, based on non-inferiority tests for two survival curves using Cox's proportional hazards model. Based on the existing literature, assuming a 20% incidence of the primary efficacy endpoint in the control group during follow-up, and allocating the investigational and control groups in a 1:1 ratio, 478 subjects per group are required to demonstrate, at 80% power and a one-sided α of 0.025 (97.5% one-sided confidence level), a non-inferiority margin of 50% for the investigational group relative to the control group (upper boundary of the hazard ratio = 1.5). An event rate of 20% was assumed for both groups during the study period. A non-inferiority margin of 50% was selected because, in trials for which no prior data exist on the expected difference between the investigational and control groups, 50% is considered an appropriate default, and randomized trials employing non-inferiority testing in AF populations have commonly used a margin of approximately 50%.[15-18] Accounting for a 5% dropout rate over the 36-month study period (24 months of enrollment plus 12 months of follow-up), 503 subjects per group (1,006 subjects in total) will be required.

To achieve the target sample size, subjects with AF will be enrolled over approximately 2 years at participating sites capable of providing the study treatment.

7. Inclusion/Exclusion Criteria

1) Inclusion Criteria

All of the following criteria must be met for a subject to be eligible for enrollment.

1. AF with rapid ventricular response confirmed on the day of screening or within 90 days before screening.
   * *Rapid ventricular response is defined as (i) a ventricular rate ≥110 bpm, or (ii) a ventricular rate ≥100 bpm with related symptoms.*
   ** *AF can be confirmed by any one of the ECG methods accepted as guideline-based evidence for AF diagnosis (12-lead ECG, Holter ECG, or single-lead ECG [patch ECG, smartwatch, etc.]). AF must be present for at least 10 seconds on a 12-lead ECG, or for at least 30 seconds on Holter or single-lead ECG.*

2) Exclusion Criteria

1. LV EF assessed by TTE within the past 6 months*
2. Hemodynamically unstable patients requiring immediate direct current cardioversion
3. Acute decompensated heart failure requiring immediate hospitalization
4. Contraindication to AF pharmacotherapy (e.g., pregnancy)
5. Hospitalization for acute myocardial infarction (STEMI or NSTEMI) within the past 3 months
6. 12-lead ECG not in a format analyzable by the AI model
7. Minors aged 18 years or younger
8. Diagnosis of severe valvular disease (e.g., severe aortic stenosis)
   * *If TTE was performed at another institution within the past 6 months, this exclusion criterion*

applies only when objective imaging data confirming LV EF are available.

8. Medical Device Information

- Device name: ECG Analysis Software AiTiALVSD
- Classification code (grade): E01020.01(2)
- Mechanism of action: When biosignal data (12-lead ECG) from an ECG device are automatically transmitted, or uploaded by the user, this software applies an artificial intelligence algorithm to the ECG data to predict the likelihood of left ventricular systolic dysfunction and displays the analysis results on a web-based screen.

- Device name: ECG Analysis Software AiTiALVDD
- Classification code (grade): B2ABXA1(3)
- Mechanism of action: When biosignal data (raw 12-lead ECG data) measured by an ECG device are automatically transmitted or uploaded, an artificial intelligence algorithm displays a score and risk level for the likelihood of left ventricular diastolic dysfunction, for use as a diagnostic aid. Analyzed ECGs can be stored in HL7 aECG XML, JPG, or DICOM format.
- Manufacturer: Medical AI Co., Ltd.

9. Study Design (Investigational/Control Groups, Allocation, Blinding, Flow Diagram)

This is a randomized, non-inferiority trial. If the non-inferiority hypothesis for the primary efficacy endpoint is met, a subsequent test for superiority will be performed.

Subjects who provide written consent to participate will be assigned a screening number in the order in which consent is obtained and will undergo screening-visit assessments to confirm study eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will then be assigned a randomization number through the Interactive Web-based Response System (IWRS). Randomization will be performed by an independent biostatistician, who will generate the randomization list using SAS® version 9.4 (or later). The generated randomization list will be provided to the IWRS developer.

Eligible subjects—meeting the inclusion criteria and none of the exclusion criteria—will be randomly assigned in a 1:1 ratio to one of two groups (investigational or control). Randomization will use a stratified block randomization method, stratified by study site, CHA2DS2-VASc score (<3 vs. ≥3), and age (<75 vs. ≥75 years).

Investigators will obtain a randomization number through the IWRS, in the order in which eligible subjects enter the study, and will initiate AF treatment according to the assignment provided by the IWRS.

The control group will receive conventional treatment (treatment based on LV function measured by TTE), while the investigational group will be treated based on LV systolic and diastolic function as predicted by the AI model. Investigators will not be blinded to treatment assignment; however, assigned subjects will be blinded, making this a single-blind study. The study flow diagram is shown below.

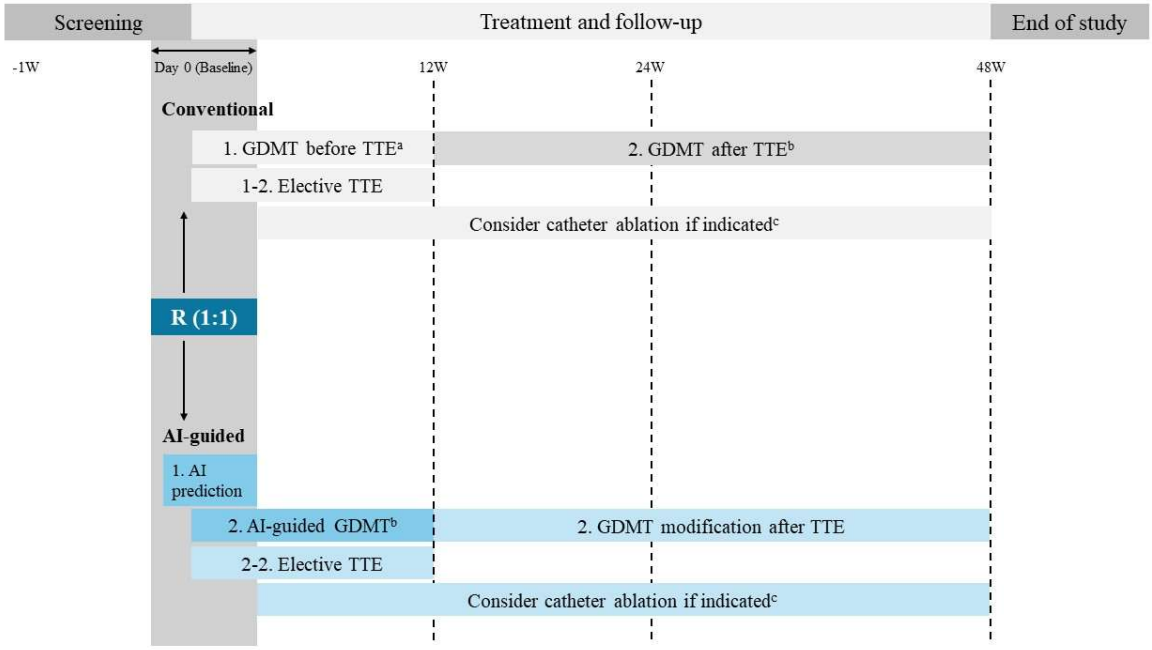


Figure 1. Study Design (Study Flow)

a. *Medications that may be used regardless of LV EF (NOAC, beta-blocker, digoxin, diuretics)*
b. *NOAC, beta-blocker, diltiazem, verapamil, digoxin, antiarrhythmic drugs, diuretics, ARNI, SGLT2i*

   For antiarrhythmic drugs/rate-control medications, the recommended first-line agent may be initiated according to LV EF:
   - LV EF ≥50%: beta-blocker, digoxin, diltiazem, verapamil, flecainide, propafenone, pilsicainide, dronedarone
   - LV EF 41–49%: beta-blocker, digoxin, diltiazem, verapamil, amiodarone, dronedarone, sotalol
   - LV EF ≤40%: beta-blocker, digoxin, amiodarone

c. *Catheter ablation may be considered in accordance with existing domestic insurance criteria for AF catheter ablation.*

Abbreviations: AI, artificial intelligence; GDMT, guideline-directed medical therapy; LVEF, left ventricular ejection fraction; R, randomization; TTE, transthoracic echocardiography.

- Overall management of AF will follow current ESC and ACC/AHA/ACCP/HRS AF guideline recommendations.[1,2,13]

1) Control Group (Conventional Treatment)

- Pharmacologic treatment will be initiated after TTE is performed, in accordance with guideline recommendations.
- Rate control: In accordance with guideline recommendations, the choice of rate-control agent may be based on LV EF (≤40% or not). However, in patients requiring acute rate control, agents that can be used regardless of LV EF (beta-blocker, digoxin) may be used without prior TTE.[1]
- Rhythm control: In accordance with guideline recommendations, antiarrhythmic drug

therapy may be initiated after assessment of LV EF and structural heart disease. Because oral amiodarone is not recommended as first-line therapy when LV EF >40%, it may not be used preferentially without information on LV EF. [1,2]

- When underlying heart failure is suspected, guideline-recommended pharmacotherapy will also be administered; however, when acute or congestive heart failure is suspected, agents that can be used without LV EF information (e.g., diuretics) may be initiated.

2) Investigational Group (AI-Guided Treatment)

- Guideline-directed AF pharmacotherapy may be initiated based on the AI-predicted LV EF obtained on the day of enrollment. Because patients with AF undergo a 12-lead ECG for clinical purposes, in the investigational group the AI-predicted LV EF becomes available immediately once the AI-enabled 12-lead ECG is performed.
- TTE may also be performed in the investigational group, in accordance with guideline recommendations, to assess structural heart disease and left atrial substrate, and treatment may be modified based on the TTE results.
- Rate control: The choice of agent may be based on the AI-predicted LV EF.[1]
- Rhythm control: If the AI-predicted LV EF is >40%, there is no history of coronary artery disease, and there is no suspicion of moderate-to-severe valvular disease (e.g., no murmur), a Class IC antiarrhythmic drug (propafenone, flecainide, etc.) may be used in accordance with guideline recommendations. If the AI-predicted LV EF is ≤40%, oral amiodarone may be administered.[1,2] However, even when the predicted LV EF is >40%, if there is a contraindication to Class IC agents (e.g., prior MI/PCI) or severe heart failure (e.g., NYHA class ≥III dyspnea) cannot be excluded, a Class III antiarrhythmic drug (amiodarone, dronedarone, etc.) may be used instead of a Class IC agent, based on clinical judgment.
- If AF persists despite ≥6 weeks of antiarrhythmic drug therapy, catheter ablation may be performed in accordance with domestic insurance criteria. However, proceeding directly to procedural treatment based solely on the AI-predicted LV EF—without a TTE result and without a trial of antiarrhythmic drug therapy—is not permitted.
- When underlying heart failure is suspected, guideline-recommended pharmacotherapy will also be administered; when acute or congestive heart failure is suspected, therapy may be initiated based on the AI-predicted LV EF.

10. Study Methods

1) Primary Efficacy Endpoint (Primary Outcome)

Major adverse cardiovascular events (MACE), a composite outcome consisting of:

1. All-cause death or cardiovascular death
2. Stroke (ischemic or hemorrhagic)
3. Acute coronary syndrome
4. Cardiovascular hospitalization

* *For cardiovascular hospitalization, planned (elective) admissions for scheduled procedures and admissions of less than 24 hours are excluded; unexpected emergency department visits or admissions of 24 hours or longer are included.*

* *Admissions for elective procedures (catheter ablation, DCCV, etc.) are excluded. Treatment*

received at other hospitals will also be recorded via questionnaire at follow-up visits.

2) Secondary Outcomes

Secondary efficacy outcomes

1. All-cause death
2. Stroke (ischemic or hemorrhagic)
3. Acute myocardial infarction
4. Hospitalization for heart failure
5. Emergency department visit or hospitalization for cardiovascular causes
6. Additional outpatient visits for cardiovascular causes

Secondary exploratory outcomes

1. AF rate control: achievement of rate control (<110 bpm) and time to AF rate control (days)
2. Time to initiation of oral antiarrhythmic drug therapy for AF (days)
3. Time to AF catheter ablation (days)
4. Time to restoration of sinus rhythm from AF (days)
5. Predictive performance of the AI-predicted LV function (systolic and diastolic) in the investigational group: assessed by area under the curve, sensitivity, specificity, positive predictive value, and negative predictive value, and compared with the predictive performance of NT-proBNP
6. AF burden at 1 year: AF burden (%) assessed by 3-day Holter ECG monitoring
7. AF-related quality-of-life questionnaire (Atrial Fibrillation Effect on QualiTy-of-life [AFEQT] questionnaire)[19]: AFEQT scores at baseline and at the 1-year follow-up visit

3) Data Collection

Clinical information

1. Medical history and clinical information (type of symptoms, age at symptom onset, age at disease onset, etc.)
2. Physical examination findings
3. 12-lead ECG (obtained at the time of AF with rapid ventricular response)
4. NT-proBNP (result at the time of AF with rapid ventricular response)

Imaging information

1. Transthoracic echocardiography
2. Coronary angiography or coronary CT angiography results

AF-related medications and procedural treatment

1. Pharmacologic treatment administered after AF diagnosis (anticoagulation, rate-control agents, antiarrhythmic drugs) and non-pharmacologic treatment (cardioversion, catheter ablation)

11. Study Procedures and Assessments

The subject enrollment period is set at 2 years from the start of the study, with a minimum follow-up period of 12 months after enrollment targeted (assessments at 3, 6, and 12 months).

[Study Visit Schedule]

Study Visit	V1 Screening & Baseline	V2	V3	V4	Early Withdrawal	Unscheduled Visit
Month	0	3	6	12	–	–
Week	0	12 (±4 wks)	24 (±4 wks)	48 (±4 wks)	–	–
Written informed consent[a]	X					
Assignment of screening number	X					
Confirmation of inclusion/exclusion criteria	X					
Demographic survey[b]	X					
Prior medication history & medical history/procedures[c]	X					
Randomization	X					
Laboratory tests[d]	X	(X)	(X)	X	X	X
Vital signs	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X
ECG[e]	X	X	X	X	X	X
CHA2DS2-VASc score	X					
Transthoracic echocardiography[f]	X					
Other AF-related medical evaluation[g]	X	X				
Outcome event ascertainment		X	X	X	X	X
Healthcare utilization[h]		X	X	X	X	X
Concomitant medications & procedures[i]		X	X	X	X	X
Holter ECG (3 days)[j]				(X)	(X)	(X)
AF-related quality-of-life questionnaire (AFEQT)[k]	X			(X)	(X)	(X)
Adverse reaction [m]		X	X	X	X	X

a. *Written informed consent: No study procedures may begin before the subject's informed consent form has been obtained.*
b. *Demographic survey: After written consent is obtained, demographic information (sex, date of birth, height, weight, smoking and alcohol use, etc.) will be collected.*
c. *Prior medication history & medical history/procedures: Medication history includes cardiovascular medications administered within 1 month before the screening visit. Medical history is defined as clinically significant medical conditions or abnormal findings observed before enrollment. History other than AF is collected by distinguishing conditions ongoing at V1 from historical conditions. Information on non-valvular AF is collected regardless of duration,*

including date of diagnosis, diagnostic information, and treatment method.

d. *Laboratory tests: Results obtained within 3 months before the screening visit may be used for the Visit 1 assessment. A single repeat test is allowed at screening if needed, and the repeat result will then be used. Tests performed at Visits 2–3 are determined at the investigator's discretion; an NT-proBNP test is recommended at Visit 4. Detailed test item – blood chemistry: NT-proBNP.*
e. *ECG: At Visit 1, the ECG obtained at the time AF with rapid ventricular response was confirmed will be collected. In the investigational group, the AI-predicted LV EF based on that ECG will also be collected.*
f. *Transthoracic echocardiography: TTE will be ordered at Visit 1, and results will be collected according to the scheduled examination date.*
g. *Other AF-related medical evaluation: If deemed necessary by the investigator's clinical judgment, results of AF-related evaluations other than ECG, laboratory tests, or TTE (e.g., coronary angiography) will be collected.*
h. *Healthcare utilization: Information on hospitalization (total length of stay, ICU/CCU days), emergency department visits, unscheduled outpatient visits, bleeding, surgery, and other scheduled procedures (inpatient and outpatient) will be collected.*
i. *Concomitant medications and procedures: Information on AF-related oral medication history and type, and AF-related procedures (e.g., cardioversion), will be collected.*
j. *Holter ECG (3 days): A 3-day Holter ECG will be performed at the end of follow-up (Visit 4 or early withdrawal) to assess AF burden.*
k. *AF-related quality of life: The AFEQT questionnaire will be completed in writing at Visit 1 and Visit 4 (or early withdrawal) to assess and compare AF-related quality of life.*[19]
l. *Procedures marked with parentheses "( )" are collected as needed, based on the investigator's clinical judgment.*
m. *Adverse reactions occurring in association with pharmacologic treatment administered after randomization will be monitored, collected, assessed, and reported in accordance with standard adverse event assessment criteria and procedures.*

12. Withdrawal Criteria

A subject who has been enrolled in the study will be discontinued from participation under any of the following circumstances:

1) Withdrawal of consent by the subject or the subject's legal representative
2) Any other circumstance in which the investigator judges that continuation of the study is not feasible

13. Adverse Event Assessment Criteria, Methods, and Reporting

The medical device used in this study, the ECG analysis software AiTiALVSD, is software that applies a non-invasive, ECG-data-based artificial intelligence algorithm to predict the likelihood of left ventricular systolic dysfunction, displaying the analysis results on a web-based screen. This software does not involve any direct electrical stimulation, energy delivery, or implantation into the subject's body, and there is no physical hazard directly associated with its use. Accordingly, in this study, any symptoms, signs, or diagnoses that occur during the course of the study will be considered attributable to standard clinical care and will not be collected as adverse events.

However, because in this study the AiTiALVSD prediction may influence the subsequent

direction of pharmacologic treatment, including the choice of antiarrhythmic drug, adverse reactions occurring in association with pharmacotherapy administered based on the prediction result (e.g., adverse drug reactions) will be monitored, and will be collected, assessed, and reported in accordance with standard adverse event assessment criteria and procedures.
- Assessment criteria: The severity of an adverse event and its causal relationship to the study treatment (pharmacotherapy) will be assessed according to the NCI-CTCAE or institutional standard criteria.
- Assessment method: The treating physician will identify and collect adverse events occurring during the subject's follow-up period.
- Reporting: Serious adverse events (SAEs) and any events requiring reporting will be reported in accordance with this protocol and the IRB reporting criteria and procedures of each participating institution.

1) Adverse Event Assessment

For adverse events collected during the study period, the investigator will assess severity, seriousness, causal relationship to pharmacologic treatment, and outcome.

1. Severity

The severity of an adverse event will be assessed according to the following criteria:
- Mild: Does not significantly affect daily activities and does not require separate treatment or intervention.
- Moderate: Affects daily activities to some degree and requires treatment or intervention.
- Severe: Significantly limits the ability to perform daily activities or requires active treatment or intervention.

2. Seriousness

An adverse event will be assessed as a serious adverse event (SAE) if it meets any of the following criteria:
- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- Is otherwise judged to be a medically important event

3. Causality

The causal relationship between the pharmacologic treatment and the adverse event will be assessed by comprehensively considering the temporal relationship, underlying conditions, concomitant medications, concomitant treatments, and other possible causes.
- Related
- Not Related
- Unknown

4. Outcome

The outcome of an adverse event will be assessed according to the following criteria:
- Recovered: The signs and symptoms of the adverse event have completely resolved.
- Recovering: The adverse event is improving but has not yet fully resolved.

- Not Recovered: The adverse event is ongoing, with no confirmed recovery or improvement.
- Recovered with Sequelae: The adverse event itself has resolved, but related sequelae or functional impairment remain.
- Fatal: The subject died as a result of the adverse event.
Unknown: The final outcome of the adverse event could not be confirmed because follow-up was not possible.

14. Data Analysis and Statistical Considerations

Statistical analyses will be performed at a two-sided significance level of 5%, using SPSS (version 26.0 or later), SAS, or R. For demographic and clinical history data, continuous variables will be presented as mean, standard deviation, and range. For markedly skewed data, geometric mean and geometric standard deviation, or median and range, will be presented. When the sample size is small or the data do not meet the assumptions required for parametric testing, an appropriate nonparametric method will be used instead. The primary statistical analysis will be performed using Cox proportional-hazards regression.

For the non-inferiority test, the null hypothesis is defined as 'the investigational group is inferior to the control group (HR ≥1.5)' and the alternative hypothesis as 'the investigational group is non-inferior to the control group (HR <1.5).' Non-inferiority will be considered demonstrated when the upper bound of the 95% confidence interval is less than 1.5. Non-inferiority will be considered established only if it is shown in both the intention-to-treat (ITT) and per-protocol (PP) analysis sets. If non-inferiority is demonstrated, a superiority test will subsequently be performed. For the superiority test, the null hypothesis is 'there is no difference between the investigational and control groups (HR ≥1.0)' and the alternative hypothesis is 'the investigational group is superior to the control group (HR <1.0).' Superiority will be considered demonstrated when the upper bound of the 95% confidence interval is less than 1.0. This sequential testing approach, based on the closed testing principle, can be performed without adjustment for multiplicity, as specified in official EMA and FDA guidance for the sequential transition from a non-inferiority test to a superiority test on the primary endpoint. The analysis set for the superiority test is defined as the ITT analysis set. Any additional analyses of secondary endpoints or subgroup analyses will be interpreted as exploratory in nature. The proportional-hazards assumption of the Cox model will be examined using the Schoenfeld residuals test.

15. Measures for Protection of Personal Information and Confidentiality of Research Data

Efforts will be made to protect the personal information and confidentiality of research subjects.

1. Personal information: age, sex, date of birth
2. Sensitive information: health-related information including past medical records and disease history, height, and weight
3. Health-related information such as medical records and data generated during the routine clinical care provided by the investigating physician during the course of the study

Subjects' sensitive information will be retained and used only until the purpose of its

collection has been achieved. Such information will be collected only with the subject's consent, and subjects may freely decide whether to accept or decline the collection and use of their sensitive information.

If a subject discontinues participation, is withdrawn, or withdraws consent, research data lawfully collected up to the point of withdrawal may be included in the study analysis in order to ensure the reliability of the study and the integrity of its results.
After withdrawal of consent, no additional research-related information or data will be collected unless separately consented to by the subject, except that safety information such as adverse events may continue to be collected to the extent necessary to ensure subject safety or as required by applicable laws and regulations.

All individuals involved in the study will protect subjects' personal information in accordance with applicable regulations, and collected data will be stored in a secure location. Except in response to inspection requests from relevant authorities as required by law, subject personal identifying information will not be included in any sponsor forms, reports, publications, or other public disclosures, and subjects' personal information will be kept confidential. Subject data will be shared and used only within the scope specified above and will be strictly protected as personal information in accordance with applicable laws. Data related to this study will be retained at the hospital for 10 years from the date of study completion.

16. Management, Storage, and Disposal of Human-Derived Materials and Genetic Information

This study does not involve the collection of human-derived materials or genetic information.

17. Subject Recruitment Method and Consent Procedure

Subjects will be recruited from among patients diagnosed with AF who are receiving care at university hospitals. The principal investigator (or a physician designated by the principal investigator) will provide a full explanation of the study to the subject in a private setting, in a manner that allows the subject to understand the study, and will obtain voluntary written informed consent.

18. Protection Measures for Recruitment of Vulnerable Subjects

This study does not plan to recruit vulnerable subjects such as minors or students. However, subjects who lack decision-making capacity may be included if written consent is obtained from their legal representative.

19. Quality Control and Reliability Assurance Plan (Data Safety Monitoring Plan)

The additional risk resulting from participation in this study is expected to be minimal. Subjects participating in this study will receive continuous monitoring by the medical staff until the end of the study and will receive appropriate treatment. After subject recruitment begins, the safety monitor (the principal investigator) will continuously monitor the study data. During the course of the study, careful attention will be paid to any symptoms, signs, or diagnoses that occur; if an adverse event occurs, the responsible medical staff will be notified

and the best available treatment will be provided.

20. Study Implementation Timeline

Activity	Timeline (48 months)												
	1	…	4	5	6	…	…	28	…	40	41	…	48
Study planning & IRB approval	■	■	■										
Patient enrollment (2 years)				■	■	■	■	■					
Follow-up (1 year)				■	■	■	■	■	■	■			
Analysis & results reporting											■	■	■

21. References

1. Van Gelder IC, Rienstra M, Bunting KV, Casado-Arroyo R, Caso V, Crijns H, De Potter TJR, Dwight J, Guasti L, Hanke T, et al. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2024;45:3314–3414. doi: 10.1093/eurheartj/ehae176
2. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, Deswal A, Eckhardt LL, Goldberger ZD, Gopinathannair R, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2024;149:e1–e156. doi: 10.1161/CIR.0000000000001193
3. Rahimi AR, York M, Gheewala N, Markson L, Hauser TH, Manning WJ. Trends in outpatient transthoracic echocardiography: impact of appropriateness criteria publication. *Am J Med*. 2011;124:740–746. doi: 10.1016/j.amjmed.2011.03.030
4. Kwon JM, Kim KH, Jeon KH, Kim HM, Kim MJ, Lim SM, Song PS, Park J, Choi RK, Oh BH. Development and Validation of Deep-Learning Algorithm for Electrocardiography-Based Heart Failure Identification. *Korean Circ J*. 2019;49:629–639. doi: 10.4070/kcj.2018.0446
5. Kwon JM, Jo YY, Lee SY, Kang S, Lim SY, Lee MS, Kim KH. Artificial Intelligence-Enhanced Smartwatch ECG for Heart Failure-Reduced Ejection Fraction Detection by Generating 12-Lead ECG. *Diagnostics (Basel)*. 2022;12. doi: 10.3390/diagnostics12030654
6. Jeong JH, Kang S, Lee HS, Lee MS, Son JM, Kwon JM, Lee HS, Choi YY, Kim SR, Cho DH, et al. Deep learning algorithm for predicting left ventricular systolic dysfunction in atrial fibrillation with rapid ventricular response. *Eur Heart J Digit Health*. 2024;5:683–691. doi: 10.1093/ehjdh/ztae062
7. Lim J, Lee MS, Suh JH, Kang S, Lee HS, Jang JH, Son JM, Kwon JM, Kim YJ, Kim KH, et al. Artificial Intelligence-Enabled ECG for Elevated E/e' on Echocardiography: Hemodynamic Relevance and Prognostic Value. *J Am Heart Assoc*. 2026;15:e046989. doi: 10.1161/JAHA.125.046989
8. So-Ryoung Lee DK, Sung Ho Lee, Woo-Hyun Lim, Kwang Jin Chun, Won-Seok Choe, Hyo-Jeong Ahn, Kyung-Yeon Lee, JungMin Choi, Bong-Seong Kim, Kyung-Do Han, Eue-Keun Choi. Atrial fibrillation fact sheet in Korea 2024 (part 1): epidemiology of atrial fibrillation in Korea. *International Journal of Arrhythmia*. 2024. doi: 10.1186/s42444-024-00119-4
9. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, Fetsch T, van Gelder IC, Haase D, Haegeli LM, et al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. *N Engl J Med*. 2020;383:1305–1316. doi: 10.1056/NEJMoa2019422
10. Kim D, Yang PS, You SC, Sung JH, Jang E, Yu HT, Kim TH, Pak HN, Lee MH, Lip GYH, et al. Treatment timing and the effects of rhythm control strategy in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2021;373:n991. doi: 10.1136/bmj.n991
11. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, Noseworthy PA, Rosenberg YD, Jeffries N, Mitchell LB, et al. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA*. 2019;321:1261–1274. doi: 10.1001/jama.2019.0693
12. Bhat A, Khanna S, Chen HHL, Gan GCH, MacIntyre CR, Tan TC. Drivers of hospitalization in atrial fibrillation: A contemporary review. *Heart Rhythm*. 2020;17:1991–1999. doi: 10.1016/j.hrthm.2020.06.015
13. Andrade JG, Wells GA, Deyell MW, Bennett M, Essebag V, Champagne J, Roux JF, Yung D, Skanes

A, Khaykin Y, et al. Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation. *N Engl J Med*. 2021;384:305–315. doi: 10.1056/NEJMoa2029980
14. Jeong JH, Baek YS, Park J, Park HW, Choi EK, Park JK, Kang KW, Kim J, Lee YS, Kim JB, et al. Impact of Atrial Fibrillation with Rapid Ventricular Response on Atrial Fibrillation Recurrence: From the CODE-AF Registry. *J Clin Med*. 2024;13. doi: 10.3390/jcm13185469
15. Lange S, Freitag G. Choice of delta: requirements and reality--results of a systematic review. *Biom J*. 2005;47:12–27; discussion 99–107. doi: 10.1002/bimj.200410085
16. Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, Hillege HL, Bergsma-Kadijk JA, Cornel JH, Kamp O, et al. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med*. 2010;362:1363–1373. doi: 10.1056/NEJMoa1001337
17. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891. doi: 10.1056/NEJMoa1009638
18. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–2104. doi: 10.1056/NEJMoa1310907
19. Spertus J, Dorian P, Bubien R, Lewis S, Godejohn D, Reynolds MR, Lakkireddy DR, Wimmer AP, Bhandari A, Burk C. Development and validation of the Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) Questionnaire in patients with atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2011;4:15–25. doi: 10.1161/CIRCEP.110.958033

Appendix

Attachment 1. ABLE-AF List of Participating Institutions