Eligibility for early rhythm control in patients with atrial fibrillation in the UK Biobank

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ABSTRACT
Objective The Early Treatment of Atrial Fibrillation for Stroke Prevention (EAST-AFNET4) trial showed a clinical benefit of early rhythm-control therapy in patients with recently diagnosed atrial fibrillation (AF). The generalisability of the results in the general population is not known.

Methods Participants in the population-based UK Biobank were assessed for eligibility based on the EAST-AFNET4 inclusion/exclusion criteria. Treatment of all eligible participants was classified as early rhythm-control (antiarrhythmic drug therapy or AF ablation) or usual care. To assess treatment effects, primary care data and Hospital Episode Statistics were merged with UK Biobank data.

Efficacy and safety outcomes were compared between groups in the entire cohort and in a propensity-matched data set.

Results AF was present in 35,526/502,493 (7.1%) participants, including 8,340 (988 with AF <1 year) with AF at enrolment and 27,186 with incident AF during follow-up. Most participants (22,003/27,186; 80.9%) with incident AF were eligible for early rhythm-control. Eligible participants were older (70 years vs 63 years) and more likely to be female (42% vs 21%) compared with ineligible patients. Of 9,004 participants with full primary care data, 874 (9.02%) received early rhythm-control. Safety outcomes were not different between patients receiving early rhythm-control and controls. The primary outcome of EAST-AFNET 4, a composite of cardiovascular death, stroke/transient ischaemic attack and hospitalisation for heart failure or acute coronary syndrome occurred less often in participants receiving early rhythm-control compared with controls in the entire cohort (HR 0.87, 95% CI 0.72 to 1.04, p=0.124). In the propensity-score matched analysis, early rhythm-control did not significantly decrease of the primary outcome compared with usual care (HR 0.87, 95% CI 0.72 to 1.04, p=0.124).

Conclusion Around 80% of participants diagnosed with AF in the UK population are eligible for early rhythm-control. Early rhythm-control therapy was safe in routine care.

INTRODUCTION
Atrial fibrillation (AF) is the most common arrhythmia, affecting more than 33 million people in 2010.1 Disease prevalence is anticipated to rise in the next decades due to the increased ageing of the population and better screening methods. Oral anticoagulation (OAC) and therapy of concomitant cardiovascular conditions prevent most ischaemic strokes in patients with AF.2 However, even on optimal current therapy, many patients with AF experience cardiovascular death, including sudden death, stroke or worsening of heart failure.3

Due to earlier trials showing no effect of rhythm control therapy compared with rate control on cardiovascular outcomes,4 combined with safety concerns and a higher hospitalisation rate on antiarrhythmic drug therapy (AAD), most patients with newly diagnosed AF are initially managed without rhythm control therapy.5 The ‘Early Treatment of Atrial Fibrillation for Stroke Prevention’ (EAST-AFNET4) trial showed that systematic initiation of rhythm control therapy early after the diagnosis of AF reduces cardiovascular death, stroke or hospitalisation for heart failure or acute coronary syndrome by 21% compared with the current paradigm restricting rhythm control to symptomatic participants.6 The generalisability of those treatment effects is not known. Currently, it is not known how many patients with AF would be eligible for early rhythm control.

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ The randomised controlled Early Treatment of Atrial Fibrillation for Stroke Prevention (EAST-AFNET4) trial showed that early rhythm-control in recently diagnosed atrial fibrillation (AF) leads to a reduced composite outcome of death from cardiovascular causes, stroke or hospitalisation with worsening of heart failure or acute coronary syndrome.

WHAT THIS STUDY ADDS
⇒ The results of the randomised controlled EAST-AFNET4 trial are applicable to 80.9% of patients developing AF in the general population. Early rhythm control as practised in the UK Biobank population appeared safe. Early rhythm control was not associated with fewer outcome events in a propensity-score matched analysis (HR 0.87, 95% CI 0.72 to 1.04, p=0.124) likely due to smaller absolute effect estimator and low power.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ Consideration of early rhythm control should be part of the management in all patients with recently diagnosed AF.
rhythm control and how the safety outside of controlled trial settings would be.

To answer these questions, we interrogated the UK Biobank (UKB), a prospective cohort study enrolling a population-based sample of middle-aged individuals in the UK.

**METHODS**

**UK Biobank**

The UKB is a prospective, population-based cohort study of 502,493 participants enrolled between 2006 and 2010 in the UK. Randomly selected persons aged 40–69 years were invited to participate. Comprehensive medical information was collected at baseline. Informed consent was obtained before enrolment. Data on incidence of disease and mortality were obtained via UK death registers and inpatient records from the Hospital Episode Statistics (HES) for England, Scottish Morbidity Records and Patient Episode Database for Wales. Primary care (general practitioner (GP)) data providing information on treatment is available for around 45% of the participants using the TPP, Vision and EMIS databases. Self-reported outcomes were collected at baseline. Follow-up was obtained until March 2021.

**Patient involvement**

The patient involvement in the UKB is widely known. This analysis was conducted anonymised data from the UKB. There was no specific patient involvement in this data science project. There is no plan to share study results with patients.

**Definition of eligibility for early rhythm control**

To determine eligibility for early rhythm control, the inclusion and exclusion criteria of the EAST-AFNET4 trial were applied as far as possible in the UKB (see online supplemental definitions file). International Classification of Diseases-10 (ICD-10) coding was used to define the presence of a diagnosis. Eligibility was defined as a diagnosis of AF within 1 year and presence of cardiovascular conditions and risk factors, namely age >75 years, a previous stroke or transient ischaemic attack (TIA), or two of the following: age >65 years, female sex, hypertension, diabetes mellitus, severe coronary artery disease, heart failure, chronic kidney disease or peripheral artery disease. Exclusion criteria were the combination of female sex and age <45 years, drug abuse, previous AF ablation, severe mitral stenosis, prosthetic mitral valve, hepatic dysfunction, thyroid dysfunction without treatment and severe renal dysfunction (stage V or dialysis). Eligibility for early rhythm control was determined in the entire UKB dataset. To compare outcomes in participants receiving early rhythm control to others, all participants with sufficient information on therapy, that is, those with GP data, were considered. Participants were assigned to early rhythm control if they received either AAD therapy (amiodarone, dronedarone, flecainide, propafenone or sotalol) or AF ablation within 1 year of diagnosing AF. Those not receiving rhythm control within 1 year of AF diagnosis were assigned to usual care. Efficacy and safety outcomes were compared between groups.

**Outcomes**

Outcomes in this analysis were aligned with the primary outcome of the EAST-AFNET4 trial. The primary efficacy outcome was a composite of cardiovascular death, stroke or TIA, or hospitalisation due to worsening of heart failure or acute coronary syndrome. The main safety outcome was defined as a composite of stroke, death or a serious adverse event related to early rhythm control (non-fatal cardiac arrest, drug-induced bradycardia, atrioventricular block, torsade de pointes tachycardia, pericardial tamponade, and preprocedural bleeding, or blood pressure event).

**Statistical analysis**

**Data sources and versions**

This project was approved as UKB project 31224. The UKB data used were sourced from the main field data, bulk hospital inpatient data (see previous, called HES for simplicity) and primary care records (GP) with prescription data. Participants that died within 6 months after the date of AF were excluded from the main efficacy analysis to ensure adequate time for treatment effects to affect mortality, similar to previous analyses. Additionally, the 6-month threshold was used to exclude patients who were diagnosed shortly before their death and therefore only received usual care.

A sensitivity analysis limiting follow-up to March 2020 was conducted to evaluate the influence of the COVID-19 pandemic. Another sensitivity analysis for safety and efficacy included every patient and all events to provide comprehensive safety information on early rhythm control.

**Propensity-score matching and falsification analysis**

To reduce the effect of confounders of the outcomes of interest, participants were propensity-score matched based on a number of parameters, namely sex, hypertension, heart failure, coronary artery disease, history of myocardial infarction, chronic kidney disease, stroke/TIA, peripheral artery disease, diabetes, obstructive sleep apnoea, dyslipidaemia, chronic obstructive pulmonary disease, malignancy, history of alcohol abuse, valvular heart disease, age, body mass index, CHA2DS2-VASc score, chronic kidney disease, dilated cardiomyopathy, gastrointestinal bleeding, gastrointestinal ulcer, history of endocarditis, hypertrophic cardiomyopathy, hypothyroidism, myocardial infarction, osteoporosis, pulmonary embolism, smoking and OAC. The distance applied is Mahalanobis distance, and the nearest sample matching method was used. All resulting matches were assessed to ensure a standardised difference under 20% for each variable. To detect potential bias between groups, a falsification analysis of 23 random outcomes in the unmatched and the propensity-score matched group was performed.

**Statistical reporting**

Numerical parameters were reported as median (1st–3rd quartile) for non-normal variables and mean (SD) for normal variables. An Anderson-Darling test was performed when the number of elements was equal or above 5000. For all other analyses, the Shapiro-Wilk test was used. The Kruskal-Wallis Rank test was used to compare non-normal variables, and one-way analysis of variance was employed for normal variables. For categorical variables, Fisher’s exact test was performed to check for independence. If there were more than 2×2 options, a p value Monte Carlo simulation was performed. Data processing was performed using Python V 3.7.4, and all analysis was conducted in R V4.0.3. The propensity-score matching was performed using the MatchIt R package. The set of packages used can be found in the supplementary data.

**RESULTS**

**Eligibility for early rhythm control**

AF was diagnosed in 35,526/502,493 participants of the UKB (7.1%, figure 1). At the time of enrollment, AF was prevalent in 8340 participants, and 27,186 participants developed AF.
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Of the 9004 participants with therapy data, 874 participants (9.02%) were treated with early rhythm control, while 8817 participants were managed without early rhythm control (table 1). A propensity-score matching identified 868 pairs of participants receiving early rhythm control and usual care. Participants in the early rhythm control group were slightly younger (68 years vs 70 years, p<0.001) compared with those with usual care. OAC was initiated in 69% of participants receiving early rhythm control compared with 29% in usual care despite a median CHA$_2$DS$_2$-VASc score of 3 in both groups. In the matched analysis, the rate of OAC was comparable in both groups (69% vs 60%, p=0.554).

Participants treated with early rhythm control were more likely to receive treatment with beta blockers, digoxin or AAD, with sotalol (28.8%) and amiodarone (43%) being the most common drugs followed by flecainide (15.6%). After propensity-score matching, no differences in baseline characteristics were observed (online supplemental table 2). The follow-up duration was 4.94 (2.99–6.92) years in participants treated with early rhythm control and 2.54 (0.58–5.50) years in participants treated usual care (p<0.001). After matching, follow-up was comparable with 4.92 (2.98–6.91) years and 4.13 (1.65–6.69) years, respectively.

**Safety of early rhythm control**

The composite safety outcome (stroke, death or serious adverse event related to rhythm control therapy) occurred in 5.20 events/100 patient-years (table 2) in early rhythm control and 6.00 events/100 patient-years in participants treated with usual care (HR 0.85 (95% CI 0.74 to 0.98), p=0.024). After matching, no statistically significant differences in the composite safety outcome were observed (figure 2). The total mortality was lower in patients receiving early rhythm control in the unmatched (3.13 events/100 patient-years vs 4.05 events/100 patient-years; HR 0.76 (95% CI 0.64 to 0.90), p=0.002) but not in the matched comparison (3.14 events/100 patient-years vs 3.05 events/100 patient-years; HR 1.02 (95% CI 0.80 to 1.31), p=0.866).

**Efficacy of early rhythm control**

The composite outcome of cardiovascular death, stroke/TIA or hospitalisation for worsening heart failure or acute coronary syndrome occurred in 5.72 events/100 person-years (table 3) in early rhythm control and 6.92 events/100 person-years in controls (HR 0.82 (95% CI 0.71 to 0.94), p=0.005) in the unmatched cohort (figure 3). Significantly reduced components

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**Figure 1** A flow chart of patient selection and proband selection. AF, atrial fibrillation; EAST-AFNET4, Early Treatment of Atrial Fibrillation for Stroke Prevention Trial; FU, follow-up.
Sensitivity analyses

In the propensity-score matching analysis identified 5,73 events/100 person-years in participants treated with early rhythm control and 6,60 events/100 person-years in participants treated with usual care (HR 0.87; 95% CI 0.72 to 1.04, p=0.124). After matching, nights spent in hospital were higher in those who received early rhythm control with 3.14±6.70/year compared with 3.76±11.89 nights/year in controls (<0.001). The efficacy outcomes in the overall cohort, as well as in the matched cohort, were significantly reduced in early rhythm control (online supplemental figure 4).

**DISCUSSION**

**Main findings**

This analysis of a population-based cohort yielded important findings (figure 4):

1. The majority of participants with newly diagnosed AF (approximately 80% in the UKB population) are eligible for early rhythm control therapy.

2. Early rhythm control appeared safe in this population-based sample receiving routine care.

Following the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and RACE (Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation) trials, utilisation of rhythm control in AF therapy (electrical cardioversions and AAD) declined in the USA. Similar observations are made in Europe where 75%–90% of participants with AF are managed without rhythm control therapy. Recently, several relatively small, randomised trials identified a positive effect of rhythm control therapy using AF ablation in participants with AF and heart failure with reduced ejection fraction. The EAST-AFNET4 trial reported a 21% reduction in a composite outcome of death from cardiovascular causes, stroke or hospitalisation with worsening of heart failure or acute coronary syndrome in participants receiving rhythm control within 1 year of diagnosis compared with those who received usual care (HR 0.79; 96% CI 0.66 to 0.94; p=0.005). The clinical effectiveness of early rhythm control therapy was consistent in asymptomatic and symptomatic participants. These findings support a paradigm shift towards offering rhythm control therapy to all participants with recently diagnosed AF.

The present analysis demonstrates that most participants (approximately 80%), with newly detected AF, are eligible for early rhythm control in a large, population-based sample. Furthermore, our analyses confirm the safety of modern rhythm control therapy in routine care replicating the clinical effectiveness of early rhythm control reported in the EAST-AFNET4 trial. Our findings, based on a European population dataset, mirror those of a study related to the analysis of a nationwide South Korean health insurance dataset. This study included over 22,000 participants and demonstrated that rhythm control therapy was consistent in asymptomatic and symptomatic participants. The present analysis demonstrates that most participants (approximately 80%), with newly detected AF, are eligible for early rhythm control in a large, population-based sample. Furthermore, our analyses confirm the safety of modern rhythm control therapy in routine care replicating the clinical effectiveness of early rhythm control reported in the EAST-AFNET4 trial.

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**Sensitivity analyses**

To exclude the influence of reduced patient to healthcare provider contact during the COVID-19 pandemic, a sensitivity analysis limiting follow-up to March 2020 was carried out. Findings (online supplemental figures 1; 2) were consistent with the main analysis. The second sensitivity analysis was conducted without excluding participants due to death within 6 months of treatment as well as counting all events (online supplemental figures 3; 4). A reduction in the safety outcome was observed in early rhythm control. The efficacy outcomes in the overall cohort, as well as in the matched cohort, were significantly reduced in early rhythm control (online supplemental figure 4).
population cohort, including participants who were never treated in hospital, the overall disease burden will be different compared with inpatient cohorts. Moreover, the early rhythm control therapies differed between the studies: in EAST-AFNET4 trial, the main antiarrhythmic drugs were flecainide and propafenone. In our analysis, sotalol and amiodarone were the main agents, while in the Korean dataset, amiodarone was the most common drug, closely followed by flecainide and propafenone. AF ablation was
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Table 3  Efficacy outcomes in participants receiving early rhythm control or usual care

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Early rhythm control (n=874)</th>
<th>Usual care (n=8817)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite efficacy outcome</td>
<td>5.72</td>
<td>6.92</td>
<td>0.82 (0.71 to 0.94)</td>
<td>0.005</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>1.03</td>
<td>1.07</td>
<td>0.93 (0.88 to 1.27)</td>
<td>0.657</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>1.17</td>
<td>1.23</td>
<td>0.93 (0.70 to 1.25)</td>
<td>0.642</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>0.68</td>
<td>0.98</td>
<td>0.68 (0.47 to 0.99)</td>
<td>0.046</td>
</tr>
<tr>
<td>Worsening of heart failure</td>
<td>3.89</td>
<td>4.74</td>
<td>0.82 (0.70 to 0.97)</td>
<td>0.018</td>
</tr>
<tr>
<td>Nights spent in hospital per year</td>
<td>3.14±6.71</td>
<td>3.76±11.89</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Propensity-score matching

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Early rhythm control (n=868)</th>
<th>Usual care (n=868)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite efficacy outcome</td>
<td>5.73</td>
<td>6.60</td>
<td>0.87 (0.72 to 1.04)</td>
<td>0.124</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>1.04</td>
<td>1.33</td>
<td>0.78 (0.52 to 1.16)</td>
<td>0.224</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>1.16</td>
<td>1.37</td>
<td>0.85 (0.57 to 1.25)</td>
<td>0.403</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>0.66</td>
<td>1.01</td>
<td>0.66 (0.41 to 1.08)</td>
<td>0.096</td>
</tr>
<tr>
<td>Worsening of heart failure</td>
<td>3.93</td>
<td>4.09</td>
<td>0.96 (0.77 to 1.21)</td>
<td>0.743</td>
</tr>
<tr>
<td>Nights spent in hospital per year</td>
<td>3.14±6.70</td>
<td>2.88±7.41</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Event rates are reported as events per 100 patient years. Composite efficacy outcome defined as cardiovascular death, stroke/TIA, hospitalisation for worsening heart failure or acute coronary syndrome. P-values<0.05 were considered significant.

TIA, transient ischaemic attack.

In all three analyses, limited by the non-randomised treatment allocation in our analysis and in the Korean data set, early rhythm control was associated with fewer cardiovascular events during follow-up. AF ablation is more effective than AAD in preventing recurrent AF and may have positive effect on cardiovascular outcomes in patients with heart failure. It remains to be tested whether a broader use of AF ablation influences cardiovascular outcomes beyond the clinical effectiveness shown in EAST-AFNET4 trial. Another difference to the trial is that we use coding data for event analysis, which is dependent on data entry and does not reflect adjudication by clinicians. However, ICD-10 codes have been shown to be valid indicators for safety events in a hospital setting.

Larger prospective studies would be helpful in assessing large-scale changes in treatment patterns to thoroughly investigate the safety of therapies. Recently, an analysis of a US administrative database found approximately 3/4 of all patients with newly diagnosed AF would be eligible for early rhythm control, which is comparable with our findings.

Several factors could explain the low use of OAC in the UKB. For one, we capture a part of the whole population since we focused on optimal data quality and excluded those without
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Figure 4  Summary figure showing the study design and the efficacy and safety outcomes in events/100 patient-years of EAST-AFNET4 eligible participants in the UK Biobank receiving either early rhythm control or usual care in the overall cohort and a propensity-score matched analysis. The HRs and the 95% CIs are presented in brackets. HR <1 favours early rhythm control. AF, atrial fibrillation; EAST-AFNET4, Early Treatment of Atrial Fibrillation for Stroke Prevention Trial.

CONCLUSION
Approximately 80% of participants with recently diagnosed AF are eligible for early rhythm control in this population-based cohort. There was no safety signal attached to early rhythm control therapy, confirming the safety of early rhythm control found in the EAST-AFNET4 trial in a routine care setting. The rate of OAC in the EAST-AFNET4 trial eligible patients was low and highlights the need for anticoagulation of AF patients at risk for stroke.

Early rhythm control should become a routine part of the clinical management of most patients with recently diagnosed AF.

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Disclaimer The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research, the Medical Research Council or the Department of Health.

Competing interests RS has received lecture fees and advisory board fees from BMS/Pfizer outside this work. LF and PK are listed as inventor on two patents held by University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783). LF has received institutional research grants and non-financial support from European Union, DFG, British Heart Foundation, Medical Research Council (UK), National Institute of Health Research NIHR and several biomedical companies. PK receives research support for basic, translational and clinical research projects from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK) and German Centre for Cardiovascular Research, from several drug and device companies active in atrial fibrillation and has received honoraria from several such companies in the past but not in the last 3 years. All other authors declared no conflict of interest.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This project was approved as UKB project 31 224. Part of the UK Biobank data exempted this study. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. All data are available via the UK Biobank.

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