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# Rationale and design of the ARAMIS trial: Anakinra versus placebo, a double blind randomized controlled trial for the treatment of acute myocarditis

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## ABSTRACT

**Background:** Acute myocarditis is an inflammation of the myocardium that can cause life-threatening events. However, anti-inflammatory strategies did not reduce the risk of clinical outcomes in randomized trials. Recently, experimental studies have suggested that specific blockade of the interleukin-1 $\beta$  immune innate pathway could be effective in acute myocarditis.

**Aim:** To test the hypothesis that inhibition of the interleukin-1 $\beta$  immune innate pathway can reduce the risk of clinical events in acute myocarditis.

**Methods:** The "Anakinra versus placebo double blind Randomized controlled trial for the treatment of Acute Myocarditis" (ARAMIS) trial (ClinicalTrials.gov identifier: NCT03018834) is a national multicentre randomized parallel-group double blind study among symptomatic patients with elevated cardiac troponin and cardiac magnetic resonance-proven acute myocarditis. Patients ( $n = 120$ ) are randomized within 72 hours of hospital admission to receive a daily subcutaneous dose of anakinra 100 mg or placebo during the hospitalization, in addition to standard of care, including an angiotensin-converting enzyme inhibitor and a beta-blocker. The primary endpoint is the number of days alive free from any myocarditis complication, including ventricular arrhythmias, heart failure, recurrent chest pain requiring medication and ventricular dysfunction (defined as left ventricular ejection fraction < 50%), from randomization to 28 days after hospital discharge. At 28 days after discharge, patients with normal left ventricular ejection fraction are then randomized to angiotensin-converting enzyme inhibitor continuation or discontinuation and all patients are followed for 1 year, with regular left ventricular function evaluation.

**Conclusions:** ARAMIS is the first trial evaluating inhibition of the interleukin-1 $\beta$  immune innate pathway in the setting of acute myocarditis. Although of small size, it will be the largest randomized trial in acute myocarditis, a serious and poorly studied cardiac condition.

## ABBREVIATIONS:

ACE, Angiotensin-converting enzyme;

ACTION, Allies in Cardiovascular Trials Initiatives and Organized Networks;

ANCOV, Analysis of covariance; AP-HP, Assistance publique-Hôpitaux de Paris;

ARAMIS, Anakinra versus placebo double blind Randomized controlled trial for the treatment of Acute Myocarditis;

CMR, Cardiac magnetic resonance;

COVID-19, Coronavirus disease 2019;

LVEF, Left ventricular ejection fraction; NLRP3, Nucleotide binding domain and leucine-rich repeat pyrin domain containing protein 3;

NT-proBNP, N-terminal prohormone of B-type natriuretic peptide.

## Background

Acute myocarditis is an inflammatory disease of the heart, mostly caused by viruses, ranging from paucisymptomatic to fulminant presentations, with severe arrhythmias and cardiogenic shock [1,2]. Whereas acute myocarditis can resolve spontaneously, an abnormal immune response can lead to impaired left ventricular contractility and clinical progression to chronic heart failure [3]. Beta-blockers and angiotensin-converting enzyme (ACE) inhibitors are commonly used during the first months to prevent these complications [4,5]. The optimal duration of these treatments is unknown and is based on a poor level of evidence [6].

Despite the better understanding of the pathogenetic mechanisms of acute myocarditis, treatments targeting inflammation and the abnormal immune response that occurs during the first days of the disease are still needed [7]. For adults, routine immunosuppressive therapies, including corticotherapy, cyclosporine A, azathioprine and immunoglobulin, are not recommended, and had neutral or minimal effects in intervention trials enrolling patients with acute or chronic myocarditis [6,8]. Recently, blockade of the interleukin-1 $\beta$  immune innate pathway has generated a growing interest, as studies have demonstrated the pivotal role of the central nucleotide binding domain and leucine-rich repeat pyrin domain containing protein 3 (NLRP3) inflammasome in the pathophysiology of acute myocarditis [9–11]. To test the hypothesis that inhibition of the interleukin-1 $\beta$  immune innate pathway can reduce the risk of clinical events in acute myocarditis, we designed the “Anakinra versus placebo double blind Randomized controlled trial for the treatment of Acute Myocarditis” (ARAMIS) trial (ClinicalTrials.gov identifier: NCT03018834).

## Rationale

### *Targeting the interleukin-1 $\beta$ immune innate pathway in acute myocarditis*

Interleukin-1 $\beta$  is a proinflammatory cytokine of the NLRP3 inflammasome to C-reactive protein signalling pathway of innate immunity that is crucial for host defence [12]. Interleukin-1 $\beta$  production results from activation of the caspase-1 in the NLRP3 inflammasome in response to a wide range of stimuli, including infectious triggers, such as coxsackievirus B3 proteins [13]. Neutralization of interleukin-1 $\beta$  in a mouse model of viral myocarditis was associated with a lower risk of complications, by reducing inflammation, interstitial fibrosis and adverse cardiac remodelling [14]. Therefore, treatments targeting the interleukin-1 $\beta$  pathway, including anakinra, an interleukin-1 receptor antagonist licensed for the treatment of resistant rheumatoid arthritis, are potential candidates to treat myocarditis [7,15]. Of interest, initial studies conducted in rheumatoid arthritis suggested a beneficial effect of interleukin-1 blockade therapy on cardiac function [16]. Since then, anakinra has been tested successfully in a few cases of fulminant acute myocarditis [17,18]. The drug has also been evaluated in two phase II trials of ST-segment elevated myocardial infarction and one phase II trial of heart failure, to improve left ventricular function [19,20]. Finally, The “Anakinra for Treatment of Recurrent Idiopathic Pericarditis” (AIRTRIP) trial has demonstrated the efficacy of anakinra in reducing the risk of recurrence in recurrent pericarditis, a condition that can be associated with myocarditis [21]. We therefore hypothesized that anakinra may provide a substantial benefit in patients presenting with acute myocarditis.

### *ACE inhibitors in acute myocarditis*

As recommended in American and European guidelines, ACE inhibitors are approved in patients with chronic heart failure [22,23]. In practice, this treatment is also administered in the acute setting of myocarditis, to prevent the risk of myocardial fibrosis leading to dilated cardiomyopathy and chronic heart failure [24]. This strategy has never been proven to be effective in patients with acute myocarditis, who can recover normal left ventricular function spontaneously. Whereas the benefit of ACE inhibitors is well demonstrated in patients with heart failure, the efficacy and duration of ACE inhibitors in all comers presenting with acute myocarditis remain unknown, given that side effects, including acute kidney injury, hyperkalaemia and hypotension, can occur [25].

### *Objectives*

The primary objective of the ARAMIS trial is to assess, in a double blind fashion, the efficacy of anakinra in acute myocarditis at 28 days after hospital discharge. The secondary objectives are to determine the effect of anakinra on left ventricular function, and on various clinical and biological outcomes at 1-month follow-up. The safety of anakinra will be analysed separately. The main objective of the second randomization is to evaluate the effect of ACE discontinuation at 1 month in patients with preserved left ventricular ejection fraction (LVEF) at 1-year follow-up.

## Methods

### *Study design*

This study is a multicentre centrally randomized trial with a double randomization. The first part of the study is a phase II randomized double blind placebo-controlled study comparing anakinra with placebo, in addition to standard of care with beta-blockers and ACE inhibitors, in patients with acute myocarditis. Within the first 72 hours of hospital admission, and after confirmation of the diagnosis of myocarditis with cardiac magnetic resonance (CMR), patients are randomly assigned to anakinra or placebo in a 1:1 ratio, after checking all the exclusion and inclusion criteria. Randomization is performed using an electronic case report form, centralized and stratified by centre using four patient block sizes. The treatment is administered once a day during hospitalization, for up to 14 days. The primary endpoint is evaluated at 28 days after hospital discharge. In the second part of the study, for patients with an LVEF  $\geq$  50% at 28 days, a second randomization allocates patients to ACE inhibitor discontinuation or continuation in an open-label evaluation over 1 year of follow-up. Patients with an LVEF  $<$  50% or with an indication for ACE inhibitors are excluded from the second randomization. All patients are followed at 1, 3, 6 and 12 months. LVEF is assessed at 6 months and 1 year with CMR and echocardiography (Central illustration).

### *Study population and inclusion/exclusion criteria*

Adult patients with a diagnosis of acute myocarditis are eligible for inclusion in the study. The diagnosis of acute myocarditis based on the presence of acute symptoms (chest pain, dyspnoea, palpitation, shock or sudden death), elevated cardiac troponin > 1.5 the upper limit of normal and the presence of original Lake Louise criteria on CMR imaging. Participants have to be aged > 18 years and < 65 years and must sign an informed consent form. The diagnosis of myocarditis has to be accompanied by the presence of normal coronary arteries on angiography or on a coronary computed tomography scan in patients aged 40 years or in the presence of risk factors or previous cardiovascular disease (myocardial infarction, stroke or peripheral artery disease).

The exclusion criteria are the presence of coronary disease and clinical suspicion or evidence of the following diseases: any chronic inflammatory or autoimmune disease; systemic lupus; antiphospholipid antibodies; Lyme disease, trypanosomiasis diseases, myositis, sarcoidosis, giant-cell myocarditis, tuberculosis, infection with human immunodeficiency virus, hepatitis B virus or hepatitis C virus. Patients with drug-induced myocarditis are also excluded, as are those with a latex allergy, malignancy or any comorbidity limiting survival, conditions predicting inability to complete the study, renal failure (defined as creatinine clearance < 30 mL/min [modification of diet in renal disease equation]) or hepatic impairment (Child-Pugh Class C) or who have used a non-steroidal anti-inflammatory drug or corticosteroids within the past 14 days. The other exclusion criteria are pregnancy, breastfeeding and absence of affiliation to the French Health Care System.

Finally, during the last year of the study (2020–2021), patients presenting with myocarditis associated with coronavirus disease 2019 (COVID-19) were not included. As the presentation and optimal treatment of COVID-19-associated myocarditis were clearly unknown at the beginning of the pandemic, and despite it not being a prespecified exclusion criterion, all the investigators decided to systematically test and exclude these patients from the ARAMIS trial.

For the second randomization, evaluating ACE inhibitor continuation versus discontinuation, only patients with LVEF 50% are included. Patients with an unquestionable indication for ACE inhibition<sub>≥</sub> such as severe hypertension with at least three anti-hypertensive drugs or proteinuria, are excluded from the second randomization.

### *Tested drug and placebo*

Anakinra is a recombinant non-glycosylated form of the human interleukin-1 receptor antagonist, produced by recombinant deoxyribonucleic acid (DNA) technology, and differs from native human interleukin-1 receptor antagonist by the addition of a single methionine residue at its amino terminus. Anakinra is supplied in single-use prefilled glass syringes for daily subcutaneous administration [26]. There are no data on the optimal dosage of anakinra in acute myocarditis, as this drug has not been properly tested in this setting. However, an anakinra dose of 100 mg/0.67 mL has been evaluated in several studies enrolling patients with coronary artery disease or autoimmune disease [27]. We decided to use the currently approved dose of 100 mg daily, with subcutaneous injection, during the hospitalization period. No dose adjustment was planned for patients with mild renal impairment or low weight. As a result of the complete academic funding of this study, the placebo was not provided by the pharmaceutical laboratory producing anakinra; the drug (anakinra) was purchased from Sobi Company. The Assistance publique–Hôpitaux de Paris (AP–HP) pharmaceutical central agency (AGEPS) conceived a placebo graduated syringe, similar to the syringe provided with anakinra. Unblinded research personnel, not participating in the study recruitment and follow-up, were designated to fill the syringe with physiological serum. The tested drug (anakinra) and placebo are both stored in similar white boxes.

The second part of the study is open label. The choice and dosage of the ACE inhibitor are left to the treating physician's discretion. When continued, the ACE inhibitors are given for at least 6 months.

### *Study endpoints*

To assess the efficacy of anakinra, the primary endpoint is the number of days alive free of any myocarditis complications, defined as the presence of ventricular arrhythmia, hospitalization for heart failure, chest pain requiring medication or occurrence of ventricular dysfunction (defined as LVEF < 50%), from randomization to 28 days after hospital discharge. Thus, the duration of follow-up may vary according to the duration of hospitalization. The secondary efficacy endpoints will be exploratory: LVEF at 1 month (assessed by transthoracic echocardiography), and at 6 months and 1 year (assessed by transthoracic echocardiography and CMR); all-cause death, cardiovascular death and non-cardiovascular death; the occurrence of acute heart failure (worsening or hospitalization); the rate of ventricular tachycardia (clinically reported or based on electrocardiogram/Holter, sustained or not); and concentrations of N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) and troponin at discharge from the index hospitalization. To assess the effect of ACE inhibitor continuation, the efficacy endpoint is the difference in LVEF between baseline and 6 months, measured with CMR.

The safety endpoints are the number of serious adverse events in both arms at 28 days, 6 months and 1 year after hospital discharge, with detailed information on serious infections, elevation of aminotransferases > 10 times normal upper limit, neutropenia < 1 g/L, thrombopenia < 50 g/L, serious haemorrhage (Bleeding Academic Research Consortium) 3, anaphylactic reactions, increase in low-density lipoprotein > 100% compared with baseline and renal failure (defined as a 50% increase in baseline serum creatinine and hyperkalaemia).

### *Statistical analysis*

The primary analysis will be based on the intention-to-treat population, defined as all randomized patients who have signed an informed consent form. All secondary criteria corresponding to the incidence of events will be carried out using multivariable (exact or asymptotic)

regression analysis. All estimates of treatment effects for secondary endpoints will be presented with 95% confidence intervals, no inferential tests will be performed and no *P* value will be calculated for these endpoints. Disposition of patients, patient status and patients excluded from intention-to-treat, per protocol and safety populations will be summarized by treatment group. The per protocol population is defined as all patients randomized and treated without major protocol violations/deviations. The per protocol analysis will be considered as secondary. Continuous baseline variables will be summarized using descriptive statistics, normally distributed data by the mean and standard deviation and non-normally distributed data by the median and interquartile range. Minimum and maximum values will also be presented. All summarized descriptive statistics will be presented to one further decimal place unless otherwise specified. Categorical baseline variables will be summarized by frequency counts and percentages. The standardized differences in baseline characteristics between two groups will be calculated. The primary analysis will be compared between the two groups using analysis of covariance (ANCOVA) or ANCOVA on ranks, as judged appropriate by normality and homogeneity of variance tests, and will include age and baseline LVEF as covariates, with site as the random effect. If the statistical model stratified by site does not converge as a result of the small number of subjects or small number of events in one or more sites, site will be included as fixed effect. In addition, least squares means and mean difference between two treatments will be presented, together with two-sided 95% confidence intervals. A landmark analysis of the primary endpoint from hospital discharge to 28 days after hospital discharge, and a comparison of number of days with an event during the hospitalization will be performed as complementary analyses. All statistical analyses will be performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

#### *Sample size calculation*

To our knowledge, no data have been published on the primary endpoint of our study. We have, a priori, considered that an augmentation of the number of days free from myocarditis complication by > 1.5 days would be clinically meaningful. The standard deviation of the primary endpoint was estimated to be 2.3, and we therefore estimated that the inclusion of 60 patients in each group would allow an 80% power to demonstrate a 1.5-day difference in myocarditis evolution between the two groups, with a Mann-Whitney test at a 5% two-sided significance level. The power calculation was based on a simple Mann-Whitney test.

#### **Substudies**

##### *Predefined subgroups of patients*

Patients aged > 40 years, women, patients with fulminant presentation, patients with low LVEF (< 50%) at baseline, patients with ST-segment elevation or not on the baseline electrocardiogram, patients with a history of myocarditis, patients with associated pericarditis, patients with elevated C-reactive protein > 2 mg/L and patients with elevated B-type natriuretic peptide or NT-proBNP are predefined subgroups of interest.

##### *CMR substudies*

In total, 360 CMR scans should be performed during the study period. A centralized analysis of all CMR scans will be performed at the Institute of Cardiometabolism and Nutrition (ICAN) Core Lab. The modification effect of CMR characteristics on the primary endpoint and secondary endpoints will be assessed between the different arms of the study.

##### *Economic substudy*

An economic evaluation will assess the cost effectiveness and cost utility of anakinra compared with placebo for patients hospitalized with acute myocarditis. Our methodology will follow the French and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines. The hypothesis is that the extra drug costs will be offset by a reduction in hospital length of stay. We will undertake both a cost-effectiveness analysis and a cost-utility analysis because of the impact of myocarditis and heart failure on patients' quality of life, estimated by the EQ-5D-3L (European Quality of Life, 5-Dimensions, 3-Level version) questionnaire at baseline, 6 months and 12 months. These analyses will be presented separately from the main analysis.

#### **Organization**

##### *Leadership and funding*

The ARAMIS study is an academic study led by the Academic Research Organization ACTION (Allies in Cardiovascular Trials, Initiatives and Organized Networks; Institut de cardiologie, Pitié-Salpêtrière University Hospital, Paris, France), the coordinating centre being the Institut de cardiologie, Pitié-Salpêtrière Hospital; it is sponsored by AP-HP and, by delegation, the Clinical Research and Development Department carries out the research missions in accordance with Article L.1121-1 of the French Public Health Code. The authors are responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

This study is funded by a research grant from the French Ministry of Health, Programme Hospitalier de Recherche Clinique (PHRC) 2015 and ACTION Coeur ([www.action-coeur.org](http://www.action-coeur.org)). The pharmaceutical company did not provide any financial or non-financial support to the study organization, to the ACTION group or to any investigator involved in the trial.

##### *Study organization and quality control*

The steering committee is composed of clinical investigators in cardiology, internal medicine and intensive care medicine, and a statistician (M.K., F.C., G.M., A.C., E.V.). A clinical events committee, blinded to the strategy assignment and independent of the funder, adjudicate all clinical events (G.H., J.E.-S., E.G.); it is composed of physicians not participating in patient recruitment and follow-up, who will be provided with all necessary data from medical records to perform optimal adjudication. An independent data safety and monitoring board is appointed to monitor the progress of the study, and to ensure that the safety of patients enrolled in the study is not compromised. The data safety and monitoring board

consists of a clinical chairperson, an experienced physician in clinical trials and a statistician (see Acknowledgments section); these members are independent of the study and of the sponsors.

The study is performed according to the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization/Good Clinical Practice and applicable regulatory requirements. All patients are informed and provided written informed consent.

### Timelines

The first patient was randomized in May 2017. Enrolment ended in March 2021 (Fig. 1).

### Comments

ARAMIS is the first study evaluating an interleukin inhibitor in the setting of acute myocarditis; it also evaluates the optimal duration of ACE inhibitor treatment. This study is also one of the very few randomized intervention studies in myocarditis. With 120 patients, ARAMIS should be the largest randomized therapeutic study conducted in myocarditis, reflecting the limited evidence available in this area of cardiovascular medicine.

Of importance, ARAMIS differs from previous studies in acute myocarditis for several reasons. First, because endomyocardial biopsy is optional, left to the discretion of the investigator, acute myocarditis being defined with CMR. This is in line with current practice in many countries, biopsy being performed in approximately 4% of all comers with acute myocarditis in the USA [28], reflecting the increased use of CMR as the preferred diagnosis strategy for myocarditis [29]. Large datasets evaluating the sensibility and specificity of CMR for the diagnosis of acute viral myocarditis provide robust evidence to safely enrol patients with definite myocarditis on the basis of CMR, when associated with symptoms, elevated cardiac troponin and absence of coronary artery disease [30]. In the recent proposal of a definition for immune checkpoint related myocarditis, the association of these three variables (imaging, symptoms and biomarkers) were sufficient for the diagnosis of “definite acute myocarditis” [31]. Finally, the latest American Heart Association statement on the diagnosis and management of fulminant myocarditis reports that biopsy is not required for patients presenting with non-fulminant acute myocarditis, and thus should not be performed routinely [32]. We believe that ARAMIS represents contemporary practice, and will likely enrol viral myocarditis, all clinical suspicion of autoimmune disease-related, drug-induced and giant-cell myocarditis being excluded from the trial.

Of interest, the rapid inclusion in the trial, within 72 hours of hospital admission, requires the diagnosis to be obtained in a timely fashion. The goal of this strategy is to treat the patients early during the acute phase, and not later, when the immune response is already established or when the disease has evolved to a chronic stage [1]. Despite the limited duration of treatment, which may vary according to the duration of hospitalization, the hypothesis of the ARAMIS study is that targeting of interleukin-1 early can block the inflammation cascade until recovery. Recently, the efficacy of interleukin-1 immune innate pathway blockade with 12 weeks of anakinra has been demonstrated on surrogate endpoints in patients with acute heart failure [20].

The risk profile of participants enrolled in ARAMIS differs from previous studies evaluating anti-inflammatory drugs among patients with myocarditis, who were at an advanced stage of the disease, including dilated cardiomyopathy. The risk of adverse events with acute myocarditis is particularly high, especially during the first month, in patients with acutely impaired left ventricular function, who have a death or heart transplantation rate of up to 10% [33]. In contrast, a recently published large cohort of patients with acute myocarditis demonstrated that those with normal LVEF or non-fulminant forms have a very low rate of cardiac death or heart transplantation [4,33]. The patients enrolled in ARAMIS will have mostly non-fulminant myocarditis, and should be at low risk of death compared with the previous studies enrolling patients with giant-cell myocarditis or severely impaired cardiac function [34,35]. For these lower-risk patients, there are limited data on the recurrence of chest pain, the risk of ventricular tachycardia and rehospitalization for heart failure. A Finnish cohort study of unselected patients with acute myocarditis reported a recurrence rate of 7.0% at 1 month. The overall readmission/recurrence rate during a 4.5-year follow-up was 10.3% [36].

Finally, all of our patients have a longitudinal imaging follow-up with CMR (at inclusion, 6 and 12 months) and echocardiography (at 1, 6 and 12 months). This is particularly important, as prospective data on the evolution and prognosis value of CMR and echocardiography characteristics are lacking in acute myocarditis. With a total of 360 CMR scans and 480 echocardiograms, the ARAMIS study should provide new insights into the natural history of the disease and the prognostic value of early and late imaging characteristics.

### Conclusions

ARAMIS is a national multicentre prospective randomized double blind study with parallel arms to test the hypothesis that administration of an antagonist of the interleukin-1 receptor, anakinra, in acute myocarditis is both effective and safe. The role of ACE inhibitors is also explored in this study (Central Illustration).



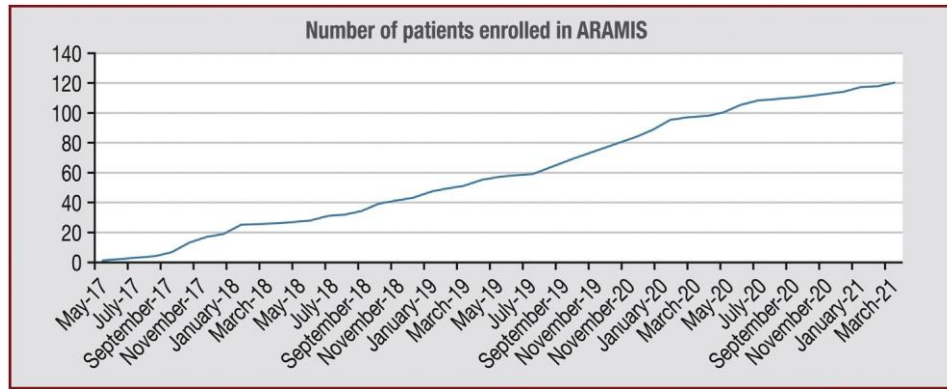
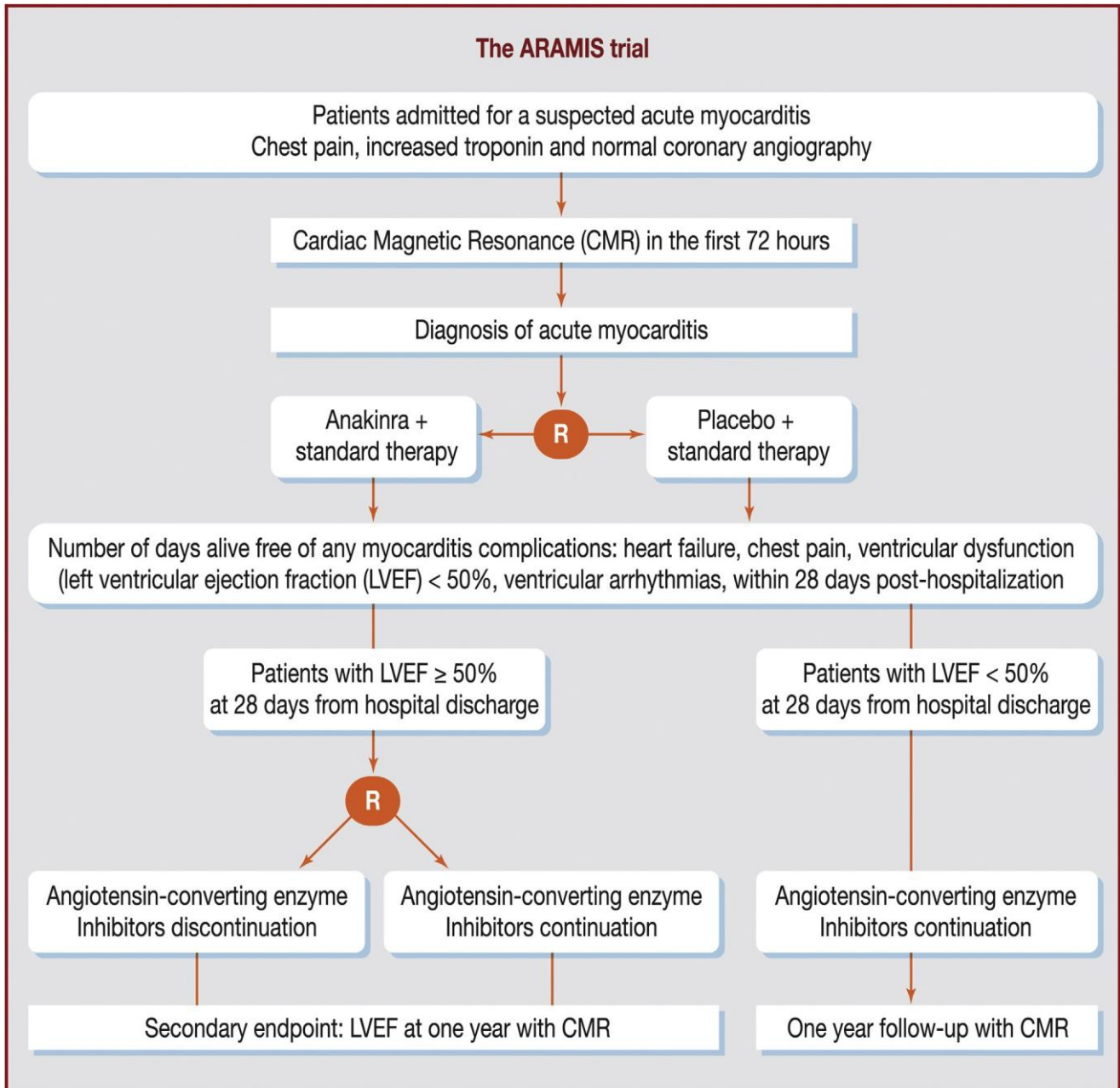


Fig. 1. Randomization curve of the “Anakinra versus placebo double blind Randomized controlled trial for the treatment of Acute Myocarditis” (ARAMIS) trial.



**Central Illustration.** Study design of the “Anakinra versus placebo double blind Randomized controlled trial for the treatment of Acute Myocarditis” (ARAMIS) trial. CMR: cardiac magnetic resonance; LVEF: left ventricular ejection fraction.

## Disclosure of interest

M.K. has received fees for lectures and/or consulting from Kiniksa, Bayer, Sanofi and Servier. E.P. has received fees for lectures and/or consulting from Amgen, AstraZeneca, Bristol Myers Squibb, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Lilly, MSD, Novartis, Pfizer, The Medicine Company, Sanofi, Saint Jude Medical, Servier and Siemens. J.A. has received advisory board fees and lecture fees from AstraZeneca, and lecture fees from Bayer and Bristol Myers Squibb. J.S. has received consulting and lecture or travel support from AstraZeneca, Bayer HealthCare SAS, Biotronik, BPI France, Boehringer Ingelheim France, CSL Behring SA, Gilead Science, Sanofi-Aventis France, Terumo France SAS, Abbott Medical France SAS and Zoll, and is a stockholder of 4D Pharma. B.L. has received research grants from Biotronik, Boston Scientific, Daiichi Sankyo, the Fédération française de cardiologie and the Institute of CardioMetabolism and Nutrition, consultant fees from Daiichi Sankyo and Eli Lilly, and lecture fees from AstraZeneca, Medtronic and Novartis. A.C. has received personal fees from Getinge and Baxter. E.V. has received consulting or speaker fees from Abbott, Bristol Myers Squibb, Celgene, Edwards, Pfizer, Sanofi and Novartis. G.M. has received research grants and consulting or speaker fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cell Prothera, CSL Behring, Europa, Idorsia, IRIS-Servier, Medtronic, MSD, Novartis, Pfizer, Quantum Genomics and Sanofi-Aventis. J.-E.S. has received research grants and consulting or speaker fees from AstraZeneca, Bristol Myers Squibb, MSD and Novartis. E.G. has received fees for lectures and/or consulting from Boston, Abbott, Bayer, Medtronic and Microport. J.-G.D. has received consulting and lecture fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb/Pfizer, Sanofi and Daiichi Sankyo, and grants from Bayer, Bristol Myers Squibb/Pfizer and Biosensors. M.H.-M. has received lecture fees from Biotronik. The other authors declare that they have no competing interest.



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