Spironolactone and perioperative atrial fibrillation occurrence in cardiac surgery patients: Rationale and design of the ALDOCURE trial

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Abstract Background After artery bypass grafting (CABG), the presence of perioperative AF (POAF) is associated with greater short- and long-term cardiovascular morbidity. Underlying POAF mechanisms are complex and include the presence of an arrhythmogenic substrate, cardiac fibrosis and electrical remodeling. Aldosterone is a key component in this process. We hypothesize that perioperative mineralocorticoid receptor (MR) blockade may decrease the POAF incidence in patients with a left ventricular ejection fraction (LVEF) ≥50% who are referred for CABG with or without aortic valve replacement (AVR).

Study design The ALDOCURE trial (NCT03551548) will be a multicenter, randomized, double-blind, placebo-controlled trial testing the superiority of a low-cost MR antagonist (MRA, spironolactone) on POAF in 1500 adults referred for on-pump elective CABG surgery with or without AVR, without any history of heart failure or atrial arrhythmia.

The primary efficacy end point is the occurrence of POAF from randomization to within 5 days after surgery, assessed in a standardized manner. The main secondary efficacy end points include the following: postoperative AF occurring within 5 days after cardiac surgery, perioperative myocardial injury, major cardiovascular events and death occurring within 30 days of surgery, hospital and intensive care unit length of stay, need for readmission, LVEF at discharge and significant ventricular arrhythmias within 5 days after surgery. Safety end points, including blood pressure, serum potassium levels and renal function, will be monitored regularly throughout the trial duration.

Conclusion The ALDOCURE trial will assess the effectiveness of spironolactone in addition to standard therapy for reducing POAF in patients undergoing CABG.

Clinical trial registration NCT03551548 (Am Heart J 2019;214:88-96.)

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RCT# NCT03551548

Submitted February 21, 2019; accepted April 26, 2019.

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0002-8703

https://doi.org/10.1016/j.ahj.2019.04.023

Rationale

Impact of POAF on cardiovascular morbimortality

Despite advances in surgical and perioperative care, postoperative complications after cardiac surgery remain frequent, leading to substantial increases in mortality, morbidity, and costs.[1] The incidence of new-onset perioperative atrial fibrillation (POAF) ranges from 20% to 40% after coronary artery bypass graft (CABG) surgery with or without aortic valve replacement (AVR), and the rate is up to 45% in heart failure patients and 64% after a combined CABG and mitral valve surgery.[2-4] POAF incidence increased dramatically when intensive AF detection strategies were used.[5] Historically, postoperative atrial fibrillation (AF) was defined as transient arrhythmia within the first week after cardiac surgery, with a peak incidence between the second and third postoperative days.[2] Although postoperative AF has been

commonly regarded as a benign, transient, and self-limited complication after cardiac surgery, it has been shown to be associated with increased perioperative morbidity, early mortality and greater long-term morbi-mortality.[6-8] The benefits of patients remaining in sinus rhythm include lower hospital readmission rates, reduced length of stay, and fewer postoperative complications (e.g., stroke, myocardial infarction, heart failure, ventricular arrhythmias, and death). Moreover, a recent study tested rate- versus rhythm-control strategies in postoperative AF patients.[9] Both strategies that are used to treat postoperative AF were associated with an equal number of days of hospitalization and similar complication rates, indicating that after postoperative AF has occurred, it is already too late to prevent cardiovascular complications. Finally, the prevalence and risks associated with POAF encourage the development of additional convenient, noninvasive, and cost-effective preventive strategies to avoid its occurrence, especially during the preoperative window, during which the maximum benefit of pharmacologic therapy can still be achieved.[4]

Current knowledge about the mechanism of POAF and pharmacological preventive strategies

While some POAF risk factors have been identified (i.e., advanced age, structural heart disease, metabolic syndrome, and obesity), the pathological mechanisms responsible for the onset and perpetuation of POAF remain unclear.[10] In addition, despite several treatment and preventive strategies, the reported incidence of POAF remains high.[10] To date, β-blockers and amiodarone are recommended as first-line pharmacotherapy to prevent POAF.[10] However, these pharmacological strategies, even when optimized, remain suboptimal since nearly 30% of patients do not receive these therapies.[10,11] The evaluation of new preventive strategies are ongoing, but they have not yielded convincing results to date,[4] leaving opportunities for new approaches.

Preliminary results regarding the impact of preoperative aldosterone levels on the occurrence of post-operative AF

Our group previously demonstrated that patients presenting with primary aldosteronism had a significantly higher rate of cardiovascular events than those of matched patients that were affected by essential hypertension.[12] Interestingly, AF was diagnosed in 7.3% of patients with primary aldosteronism and 0.6% of patients with essential hypertension; therefore, primary aldosteronism was associated with a 12-fold higher prevalence of AF compared with that of essential hypertension. Moreover, it is now well established that aldosterone promotes myocardial inflammation and fibrosis,[13] modulates ionic currents[14,15] and induces oxidative stress[16] and therefore could create a substrate for POAF.

We previously published the results of the ALDO-POAF study (ALDOsterone for prediction of Post-Operative Atrial Fibrillation, NCT 02814903) that assessed the impact of preoperative plasma aldosterone levels on postoperative AF incidence in patients with preserved left ventricular ejection fraction (LVEF) who were referred for elective CABG with or without AVR.[17,18] The ALDO-POAF study demonstrated that the preoperative aldosterone level could be a valuable biomarker for identifying patients at high risk of developing postoperative AF and implied that hyperactivation of the mineralocorticoid receptor (MR) in this context may be deleterious. Recently, we validated our results in an independent and external Japanese population from the NU-HIT trial[19] that supported a potential benefit of MR blockade in this context. It has been previously shown that aldosterone levels, which reflects MR activation, could be enhanced after spironolactone introduction ("aldosterone escape") without any effect on MR antagonist benefits.[20-22]

Two meta-analyses[23,24] investigated the impact of MRAs on AF occurrence (of any type and context) and found significant overall reduction of AF risk in MRA treated patients (odds ratio: 0.48, 95% confidence interval:0.38–0.60; relative ratio: 0.69, 95% confidence interval: 0.58–0.83; respectively).

Therefore, we hypothesize that aldosterone receptor blockade with spironolactone starting 14 ± 4 days before cardiac surgery and continuing for 30 days after surgery, in addition to standard therapy, may reduce the incidence of POAF and major cardiovascular events in CABG patients.

Rationale for the use of preoperative oral spironolactone to reduce postoperative atrial fibrillation

There are two candidates for aldosterone inhibition: the more familiar generic drug spironolactone and the most recent drug eplerenone. The important clinical benefits of these two mineralocorticoid receptor blockers are supported by mechanistic animal studies that have demonstrated that these agents reduce interstitial fibrosis, ventricular remodeling, vascular oxidative stress, improved endothelial function and have other favorable actions that could be translate into clinical benefits in patients who are referred for cardiac surgery.[16,25-31] Both drugs have demonstrated improvement in the survival of high-risk cardiovascular patients via mechanisms that likely go well beyond the renal effects of aldosterone inhibition. However, spironolactone, which seems to be the best-known aldosterone antagonist, particularly regarding its anti-arrhythmic and antifibrotic properties that are supposedly independent of the mineralocorticoid receptor.[25,26,28,31] Conversely, spironolactone, in comparison to eplerenone, has been shown to increase HbA1c and cortisol levels in patients with heart failure after a 4 months duration of treatment.[32] As patients will be expose only during a short period to study drugs in the ALDOCURE trial (around 40–45 days), we anticipate no any impact of spironolactone on HbA1c and cortisol. Furthermore, it has been shown that spironolactone

did not improve endothelial dysfunction in patients with diabetes mellitus.[33] However, the expected mechanisms underlying the protection against POAF conferred by spironolactone is not supposed to involve an improve in endothelial function. Spironolactone is associated with a 10% rate of gynecomastia in males, which is not a side effect of eplerenone, that was reported in the Randomized Aldactone Evaluation Study (RALES) trial,[22] and this side effect resulted in negligible discontinuation of the drug (8% after the 24-month follow-up). Finally, spironolactone is less expensive than eplerenone, which allows an intervention at very low cost.

Funding

The study is entirely funded by a grant from the French Ministry of Health (Programme Hospitalier de Recherche Clinique PHRC-17-0608). The authors are solely responsible for the design and conduct of this study including, all study analyses, the drafting and editing of this manuscript, and its final contents. The views expressed are those of the authors and do not necessarily represent the views of the French Ministry of Health.

Study design and objectives

The ALDOCURE trial will be a multicenter, randomized, double-blind, placebo-controlled trial (NCT03551548) of the mineralocorticoid receptor antagonist (MRA) spironolactone in adults with normal LV function (LVEF ≥50%) who are referred for on-pump elective CABG surgery with or without AVR (Figure 1). The protocol was approved by the Ethics Committee—Comité de Protection des Personnes Nord-Ouest IV—on May 18, 2018.

Study population

To be included in the ALDOCURE trial, patients must be referred for elective CABG surgery with or without AVR and must have a left ventricular ejection fraction (LVEF) of 50% or more, without a previous history of AF. All subjects are to be treated using the most adapted therapy, based on international guidelines. The treatments may be adjusted by the local medical practitioner, if necessary. Investigators and patients will be blinded to the study group allocation. All randomized subjects will be followed, even if the study drug is discontinued ahead of schedule, unless consent is withdrawn.

The eligibility criteria are detailed in Table 1.

Randomization and treatment protocol

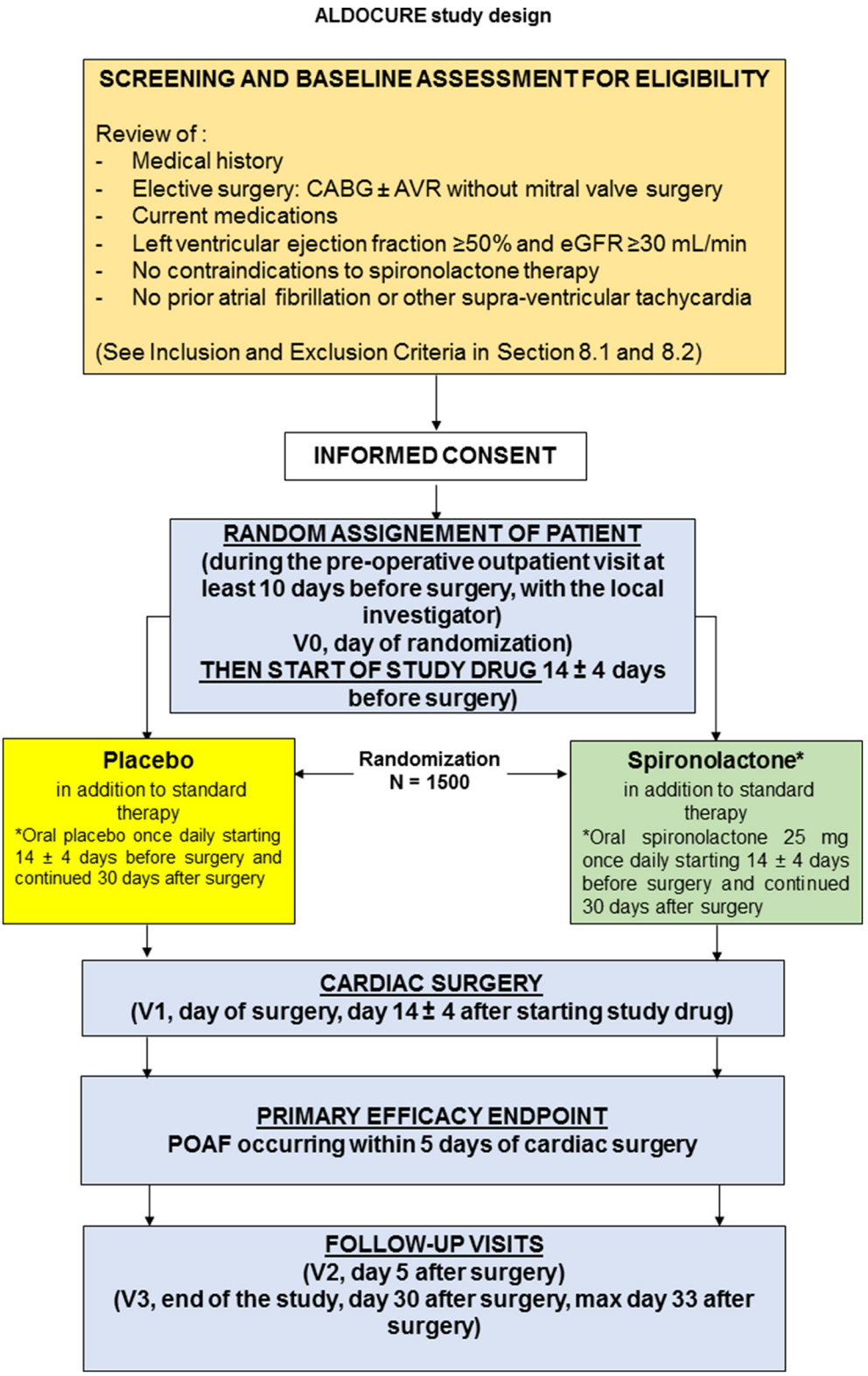
After the assessment of inclusion and exclusion criteria and obtaining written informed consent, the patients will be randomized in a 1:1 ratio to receive standard therapy with either oral spironolactone (25 mg) or placebo once daily, starting 14 ± 4 days before cardiac surgery and continuing for 30 days after surgery. Subjects will be randomly assigned in a 1:1 ratio using permuted blocks to receive either spironolactone or a matching placebo after obtaining written informed consent. Randomization will be stratified on centers and on age (<70 years old and ≥ 70 years old) and will be accomplished using the online Ennov Clinical system accessed via a secure website. After verifying key eligibility criteria, the randomization software will return a treatment allocation code that corresponds to either spironolactone or placebo. Patients are intended to be included for a total period of 3 years, with 1 month of follow-up and a total duration of participation for the patient of 44 ± 4 days.

An electrocardiogram (ECG) will be performed at baseline and at each follow-up visit, and continuous ECG monitoring (in the intensive care unit [ICU] or by Holter-ECG/ECG telemetry in the stepdown unit stay) will be performed during the first 5 postoperative days to detect AF (no continuous ECG monitoring between randomization and cardiac surgery). AF will be defined according to 2014 American Association for Thoracic Surgery (AATS) guidelines as AF requiring treatment or anticoagulation, with ECG features of AF.[10] In addition to routine blood tests, 5 ml of blood will be collected at the time of patient enrolment to measure the aldosterone plasma level while the patients rest quietly in a semi recumbent position for at least 10 min. Aldosterone levels will be centrally measured by the biochemistry department of the Caen University Hospital. With patient consent, blood samples (30 ml) will be collected during the same biological sample collection and will be rapidly centrifuged and stored at −80 °C to generate a biobank for future ancillary studies. The biobank will be managed by and stored at the "Centre de Ressources Biologiques (CRB)" of the Caen University Hospital. All clinical endpoints will be adjudicated by a clinical events committee in a blinded fashion. The daily dose of spironolactone (25 mg) was chosen to reduce the risks and side effects associated with this drug (side effects are dose-dependent and more frequent at 75 mg/day), according to a previous clinical trial that used this drug in a cardiovascular context.[34] A data safety monitoring board (DSMB) has been designated and will meet at least twice (for the intermediate analyses after the first 460 and 918 inclusions) to ensure the continued scientific validity and merit of the study, but it will also be able to be convened at any time in case of any safety event occurrence. The DSMB chair will be notified of any event considered potentially or definitely related to the study drug that occurs from randomization until the end of the study. At the time of a notification, he/she will determine if an additional DSMB meeting is required.

End points

The end points are detailed in Table 2. The primary efficacy end point of the study is the occurrence of POAF that occurs from randomization to within 5 days after surgery, assessed in a standardized manner by continuous

Figure 1



ALDOCURE study design.

Table 1. Eligibility criteria of the ALDOCURE trial.

Inclusion criteria
Male or female; Age ≥ 18 years
On-pump elective CABG surgery ± AVR
In sinus rhythm
Patient signed consent and willing to comply with scheduled visits, as outlined in the protocol
Speaks French
Recipient of the social security program
Exclusion criteria
Contraindications to spironolactone therapy: intolerance, hyperkalemia (>5.0 mmol/L), severe renal dysfunction (defined as an estimated glomerular filtration rate (eGFR, MDRD-EPI formula) <30 ml/min/1.73m^2. Subjects with serum creatinine ≥2.5 mg/dl are also excluded, even if their eGFR is ≥30 ml/min/1.73m^2), severe liver dysfunction (Child-Pugh Class 3), and patients treated by other potassium sparing medication (except in the case of hypokalemia).
Patients treated with MRAs (spironolactone or eplerenone)
LVEF <50% obtained within 6 months prior to V0
Mitral valve surgery associated with the CABG
Off-pump beating or emergent/urgent CABG
History of AF or another atrial arrhythmia
Use of antiarrhythmic medication (other than β-blockers)
Previous heart surgery and heart transplant recipients
Unstable conditions: angina or acute coronary syndrome or heart failure during the last 3 months and cardiogenic shock
Patients included or planning to be included in another medical research protocol
Patients unable to complete the protocol follow-up
Pregnant or nursing women or adults with protective measures (curatorship or tutorship or safeguarding justice or juridical protection)

ECG monitoring (during the ICU stay) or Holter-ECG/ECG telemetry monitoring (during the stepdown unit stay) started from cardiac surgery to 5 days after surgery.

Secondary efficacy end points include the following:

- Postoperative AF that occurs from cardiac surgery to within 5 days after surgery;
- Perioperative myocardial injury within 2 days after surgery (assessed by serial troponin measurements at day 0 (immediately after surgery) and at days 1 and 2 after surgery);
- Major cardiovascular events and death (all-cause mortality, stroke, myocardial infarction, and heart failure) occurring within 30 days of surgery;
- Hospital and ICU stay;
- Need for readmission;
- Left ventricular ejection fraction (LVEF) at discharge from both the ICU and the hospital;
- Significant ventricular arrhythmias that occur from cardiac surgery to within 5 days after surgery;
- Blood pressure, serum potassium levels and renal function 3 days after enrollment, on the day of surgery, and then at days 1, 2, 3, 4 and 5 after surgery, and then each week until day 30 after surgery;
- To evaluate whether the Aldoscore[17] could predict POAF occurrence, cardiovascular complications and mortality that occurs within 30 days of surgery. The Aldoscore was calculated as previously described (−8.3217+ 0.0842 x Age+ 0.00729 x Aldosterone level).[17]

Safety evaluation

The safety evaluation parameters were determined in consideration of the potential risks associated with the protocol and the drug (spironolactone). The main safety evaluation parameters are blood pressure, kalemia and renal function. These evaluations are performed routinely in all patients after cardiac surgery, and we have strengthened this monitoring for ALDOCURE as follows: blood pressure measurement at each study visit (the study drug will be stopped in cases of blood pressure< 100/60 mmHg) and a monitoring of biochemical variables (creatinine and electrolytes) at each study visit, daily during the first 5 postoperative days and then once a week until the end of the study. At any time during the follow-up, any hypotension considered significant by the local investigator and/or need to use vasoactive drugs will be captured to ensure an optimal safety.

Regarding changes in potassium levels, discontinuation or maintenance rules of the study drug after randomization are presented in Table 3 and were adapted from previous MRA trials (EPHESUS[35] and RALES[22] trials). Regarding renal function, any increase in plasma creatinine levels of ≥25% compared to baseline levels or any need for dialysis or ultrafiltration will result in drug discontinuation.

Statistical design and analysis

Based on data from recent trials that examined the postoperative AF rate in a population similar to ours,[4,36] we estimated that the incidence of POAF would be approximately 25% (range from 20.5 to 32.7% in control groups).[4,36] Based on the assumption that spironolactone would reduce this figure to 18.75% (corresponding to a relative reduction of 25%), the inclusion of 1376 patients guarantees a power of 80% with a one-sided alpha = 0.025. To take into account a potential 5% loss, we plan to include a total of 1500 patients.

Table 2. End point definitions

Primary endpoint	Definition
Perioperative AF (POAF)	POAF occurrence (AF defined as atrial arrhythmia requiring treatment or anticoagulation with ECG features of AF[10]) from randomization to within 5 days after surgery, assessed in a standardized manner by continuous ECG monitoring (during the ICU stay) or Holter-ECG/ECG telemetry monitoring (during the stepdown unit stay) started from cardiac surgery to 5 days after surgery
Secondary endpoints	Definitions
Postoperative AF	AF occurrence (AF defined as atrial arrhythmia requiring treatment or anticoagulation with ECG features of AF[10]) from cardiac surgery to within 5 days after CABG surgery (+/− AVR), assessed in a standardized manner by continuous ECG monitoring (during the ICU stay) or Holter-ECG monitoring (during the stepdown unit stay)
Perioperative myocardial injury	Serial measurements of the cardiac troponin I concentration at day 0 (immediately after surgery) and days 1 and 2 after surgery
Death	Death of any cause occurring after randomization
Cardiovascular death	Documented death due to any cardiac, vascular or cerebrovascular conditions
Noncardiovascular death	Documented death due to any noncardiac, nonvascular and noncerebrovascular conditions
Heart failure	Newly occurring or worsening of previously existing symptoms such as: dyspnea upon exertion in the absence of new pulmonary disease, paroxysmal nocturnal dyspnea or orthopnea, sign(s) of venous congestion; additionally, the need for new or increased specific treatment, including diuretics, angiotensin converting enzyme inhibitors, other vasodilators, and positive inotropes used either de novo or with an increased dosage if previously authorized and administered.
Myocardial infarction	Two of the 3 criteria: - Typical chest pain symptoms. - Documented STEMI. ST-segment elevation (measured at the J-point) is considered suggestive of ongoing coronary artery acute occlusion in the following cases: at least two contiguous leads with ST-segment elevation ≥2.5 mm in men <40 years, ≥2 mm in men ≥40 years, or ≥1.5 mm in women in leads V2–V3 and/or ≥1 mm in the other leads [in the absence of left ventricular hypertrophy or left bundle branch block].[31] - Documented NSTEMI and elevation of troponin greater than the upper limit of the laboratory reference range.[32]
Stroke	Cerebrovascular event causing a focal neurological deficit lasting more than 24 hours.
Hospital and ICU stay	Number of days from cardiac surgery to ICU and hospital discharge, respectively, differentiating day of "medical" discharge (day for which the patient is medically available for discharge) and day of "effective" discharge (day for which the patient is truly discharge).
Need for readmission	Need for hospital readmission for cardiovascular reasons between discharge and the end of the study (day 30 after surgery). Cardiovascular reasons include myocardial infarction, heart failure, stroke, pericardial effusion, need for surgical revision, need for coronary angiography or coronary revascularization, ventricular or supraventricular arrhythmias and bradycardia.
LVEF at discharge from both the ICU and hospital stay	Evaluation of the LVEF by echocardiography at discharge from both the ICU and hospital stay
Significant ventricular arrhythmias	Any lethal ventricular arrhythmia, any sustained (at least 30 sec) ventricular arrhythmia requiring any medical therapy (antiarrhythmic drugs, electric shock or any medical intervention), and the need for an implantable cardioverter device.
Acute renal failure	Any increase in plasma creatinine levels or eGFR of ≥25% compared to baseline levels or any need for dialysis or ultrafiltration.
Hyperkalemia	Serum potassium (K+) level ≥5.0 mmol/L
Low blood pressure	Blood pressure <100/60 mmHg

AF, Atrial fibrillation; *AVR*, aortic valve replacement; *CABG*, coronary artery bypass graft; *ICU*, intensive care unit; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infraction; *MRAs*, mineralocorticoid receptor antagonists; *NSTEMI*, non-ST elevation MI, *POAF*, perioperative atrial fibrillation; *STEMI*, ST elevation MI.

Table 3. Changes in potassium levels and the discontinuation or maintenance rules of the study drug after randomization

Serum potassium (K^+) level (mmol/L)	Attitude to adopt
<5.0	Continue study drug (spironolactone 25 mg/day or placebo)
≥5.0	Withhold dose – recheck K^+ within 72 hours If K^+ <5.0, restart study drug If K^+ ≥5.0, continue to monitor K^+, restart study drug only when K^+ is <5.0

Because the effect size is largely unknown, we considered a sequential plan with 2 interim and one final analysis, with the possibility of stopping the trial for futility or efficacy at each step (PROC SEQDESIGN in SAS 9.4). Following a Haybittle-Peto model with one interim analysis after 33% of data is collected (460 patients) and a second interim analysis after 67% of data is collected (918 patients), the total sample size for the final analysis will be 1500 patients. Accordingly, the study will stop for efficacy if the nominal z-values (corresponding P-values) are above (below) 3.0 ($P < .0027$) and 3.0 ($P < .0027$) at stage 1 (460 patients) and stage 2 (918 patients), respectively. The study will stop for futility if the nominal z-values (corresponding p-values) are below (above) -1.3765 ($P > .91567$) and– 0.70402 ($P > .75929$) at stages 1 and 2, respectively. If the study continues to the final analysis (i.e., stage 3, 1376 patients), the P-value for statistical significance will be 0.0483, corresponding to a nominal z-value of 1.97487. These analyses will be conducted independently from investigators and will be presented to the DSMB.

A flow chart will describe the patients who are screened, randomized and analyzed according to the CONSORT Figure. Baseline characteristics will be described with numbers (percentages), mean (standard deviation) and median (interquartile range), as appropriate, according to the randomized group.

Regarding the analysis of the primary endpoint, the percentages of POAF occurrence between randomized groups will be compared with the use of Fisher's exact test. The effect size of the experimental group will be quantified by the Cochran–Mantel–Haenszel Estimate for a Risk Ratio and its 95% confidence interval stratified on age group (< versus ≥70 years old), as appropriate.

Regarding the analysis of secondary endpoints, the following fixed sequence will be conducted to preserve the overall type I alpha risk; each test will use $P < .05$ to denote statistical significance and the procedure will stop when a test is nonsignificant:

1) Postoperative AF;

2) Perioperative myocardial injury assessed by troponin measurements;

3) Major cardiovascular events and death (all-cause mortality, stroke, myocardial infarction, heart failure).

The other secondary endpoints will be tested in an exploratory manner: hospital and ICU stay, need for readmission, LVEF at discharge (from both ICU and hospital), the occurrence of ventricular arrhythmias, blood pressure, serum potassium levels and renal function.

The comparison between groups for qualitative secondary endpoints will follow the same statistical plan as the primary endpoint, and the comparison between groups for quantitative secondary endpoints will be computed by Student's t-test or Mann–Whitney U test, as appropriate.

Subgroup analysis based on the primary judgment criteria will be performed. The Aldoscore, age (<70 years old and ≥70 years old), presence or absence of β-blockers, troponin I, history of heart failure at baseline, creatinine and eGFR (MDRD formula) at baseline, duration of assigned regimen before surgery, procedure (CABG alone or CABG + AVR), EuroSCORE and other medications that could interact with spironolactone (angiotensin converting enzyme inhibitors, angiotensin receptor antagonist, calcium blockers, and glucocorticoids) will be considered for these analyses.

The full-set analysis will include all randomized subjects. The analyses will be carried out in an intention-to-treat manner to minimize potential bias. In the case of missing data regarding the primary outcome, multiple imputations will be performed to comply with the intent-to-treat approach, and the complete case analysis will be performed as a sensitivity analysis.

A *P*-value below the Haybittle-Peto bounds will be considered statistically significant (see above).

The statistical analysis will be performed using SAS software version 9.4 (NC, Cary) by Prof. Jean-Jacques Parienti at the Unit of Biostatistics and Clinical Research of the Caen University Hospital in France.

Study organization

The coordinating center of the ALDOCURE trial is the Caen University Hospital in Normandy, France. Twenty French cardiac surgery centers will participate. The data management and statistical analyses will be managed by the Unit of Biostatistics and Clinical Research of the Caen University Hospital in France. The trial is sponsored by the Caen University Hospital and is funded by a public grant from the Programme Hospitalier de Recherche Clinique of the French Ministry of Health (PHRC-17-0608). The study was designed by the principal investigators with insights from the Steering Committee. The Steering Committee will be in charge of the scientific decisions concerning the ALDOCURE. The Steering Committee is composed of the study designers, data coordinating center representatives, and experts in the field. A Data Safety Monitoring Board will be responsible for the independent assessment of the safety data and will meet at least twice (for the intermediate analyses after the first 460 and 918 inclusions) to ensure the continued scientific validity and merit of the study, but it will also be able to be convened at any time in case of any safety event occurrence. A Clinical Events Committee will be responsible for adjudicating protocol-specific events.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Summary and significance

To our knowledge, the ALDOCURE study represents the first large trial to specifically assess the effectiveness

of spironolactone in addition to standard therapy for reducing POAF in 1500 patients undergoing elective CABG surgery with or without AVR, without any history of heart failure or atrial arrhythmia.

Current status

Currently, 7 of the 20 planed investigative centers are open and 3 are actively recruiting patients. The other 13 investigative centers will gradually open over the next few months with deadlines constrained by administrative procedures. The first patient was recruited on October 10, 2018. Fifty-one patients have already been enrolled at the date of manuscript submission. The study was registered under the reference NCT03551548 on ClinicalTrials.gov on June 11, 2018.

Participation of a research network

The protocol of the study was approved by the scientific council of the REMOD-VHF FHU (University Hospital Federation "Remodeling in Valvulopathy and Heart Failure"), involving the academic centers of Caen, Rouen, Amiens and Lille in France.

Author contributions

All authors have read and approved this manuscript.

Table 1 legend: AF, atrial fibrillation; AVR, aortic valve replacement; CABG, coronary artery bypass graft; MRAs, mineralocorticoid receptor antagonists.

Acknowledgements

None.

Conflict of interest: none declared.

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