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ORIGINAL



# Chlorhexidine-alcohol compared with povidone-iodine-alcohol skin antiseptics protocols in major cardiac surgery: a randomized clinical trial

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## Abstract

**Purpose:** Whether skin disinfection of the surgical site using chlorhexidine-alcohol is superior to povidone-iodine-alcohol in reducing reoperation and surgical site infection rates after major cardiac surgery remains unclear.

**Methods:** CLEAN 2 was a multicenter, open-label, randomized, two-arm, assessor-blind, superiority trial conducted in eight French hospitals. We randomly assigned adult patients undergoing major heart or aortic surgery via sternotomy, with or without saphenous vein or radial artery harvesting, to have all surgical sites disinfected with either 2% chlorhexidine-alcohol or 5% povidone-iodine-alcohol. The primary outcome was any reoperation by day 90 or any reoperation at the peripheral surgical site by day 30.

**Results:** Of 3242 patients (1621 in the chlorhexidine-alcohol group [median age, 69 years; 1276 (78.7%) men] and 1621 in the povidone-iodine-alcohol group [median age, 69 years; 1247 (76.9%) men], the percentage required reoperation within 90 days was similar (7.7% [125/1621] in the chlorhexidine-alcohol group vs 7.5% [121/1621] in the povidone-iodine-alcohol group; risk difference, 0.25 [95% confidence interval (CI), -1.58–2.07],  $P=0.79$ ). The incidence of surgical site infections at the sternum or peripheral sites was similar (4% [65/1621] in the chlorhexidine-alcohol group vs 3.3% [53/1621] in the povidone-iodine-alcohol group; risk difference, 0.74 [95% CI -0.55–2.03],  $P=0.26$ ). Length of hospital stay, intensive care unit or hospital readmission, mortality and surgical site adverse events were similar between the two groups.

**Conclusion:** Among patients requiring sternotomy for major heart or aortic surgery, skin disinfection at the surgical site using chlorhexidine-alcohol was not superior to povidone-iodine-alcohol for reducing reoperation and surgical site infection rates.

**Keywords:** Skin antiseptics, Cardiac surgery, Surgical site infection, Chlorhexidine, Povidone iodine

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The members of the CLEAN 2 Study Group are listed in the Acknowledgement section.

## Introduction

Surgical site infections (SSIs) are the second leading cause of healthcare-related infections. Their incidence varies according to the type of surgery, as does their severity, ranging from simple purulent wound discharge to life-threatening conditions [1]. SSIs are associated with prolonged hospital stays, extended antibiotic use, and occasional reoperation and/or intensive care unit admission. They contribute to increased mortality and healthcare costs, estimated at \$10 billion per year in the United States of America (USA) [2]. Cardiac surgery is major clean surgery performed in patients with frequent comorbidities. SSI incidence ranges from 1 to 7% [3–6], and the consequences, such as mediastinitis or other sternal wound infections, are severe. [5, 7–9] Their occurrence often requires reoperation and readmission to intensive care unit, and lead sometimes to death.

The pathogens involved in SSI after clean surgery mainly originate from the skin. Therefore, perioperative skin disinfection is crucial in preventing SSIs. The two most commonly recommended antiseptic solutions are chlorhexidine-alcohol and povidone-iodine-alcohol. However, a large, randomized trial comparing their effectiveness in cardiac surgery was unavailable. Therefore, the choice was based on the results of studies with limitations, including small sample size, retrospective or prospective but non-randomized design, utilization of surrogates for the primary outcome, and inadequate follow-up periods. These lead to inconsistent international recommendations. The Centers for Disease Control and Prevention (CDC) and the French Society for Hospital Hygiene guidelines recommend skin preparation in patients undergoing surgical procedures using an alcohol-based antiseptic agent, unless contraindicated. They do not state a preference for one antiseptic formulation over another [10, 11]. The World Health Organization (WHO) and the United Kingdom (UK) National Institute for Health and Care Excellence (NICE) guidelines recommend chlorhexidine-alcohol as the first-line antiseptic agent for surgical site preparation. However, these recommendations have stirred controversy [1, 12, 13]. Indeed, WHO's recommendations were deemed premature and based on low-quality evidences. In addition, three trials included in the meta-analysis compared chlorhexidine-alcohol to povidone-iodine in too low or unknown concentration of alcohol [13].

To bridge this gap, we conducted a large, multicenter, open-label, randomized, two-arm, assessor-blinded, superiority trial involving patients undergoing cardiac surgery. The aim was to assess the superiority of chlorhexidine-alcohol over povidone-iodine-alcohol in reducing reoperation and SSI rates.

## Take-home message

In this randomized trial involving patients undergoing major heart or aortic surgery via sternotomy, chlorhexidine-alcohol for skin disinfection prior to surgical incision was not superior to povidone-iodine-alcohol in reducing reoperation and surgical site infection rates.

## Methods

### Ethical statement

The trial protocol was approved by the ethics committee Ile de France VIII. Each participant provided written informed consent before enrolment. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the guidelines for Good Clinical Practice of the International Conference on Harmonization, in accordance with French law [14]. All the authors vouch for the accuracy and completeness of data and fidelity of the trial protocol.

### Trial design and setting

CLEAN 2 was a multicenter, open-label, randomized, two-arm, assessor-blind superiority trial conducted in eight French hospitals. This trial was sponsored by the University Hospital of Poitiers, France. The trial protocol was registered at Clinicaltrials.gov under the number NCT03560193, and has been previously published and is available in the electronic supplementary material (ESM) 1 [15].

### Participants

Adult patients scheduled to undergo major cardiac surgery (valve, coronary artery bypass graft, ascending aorta, or combined surgery) via sternotomy, with or without harvesting of at least one saphenous vein or radial artery, were eligible. The main exclusion criteria included a known allergy to chlorhexidine, povidone-iodine, isopropanol, or ethanol; heart transplant surgery or thoracic infection; any signs of inflammation or sternal instability at the sternotomy site; and a history of cardiac surgery within the preceding three months. The list of exclusion criteria is provided in the ESM.

### Randomization

The patients were randomized 1:1 prior to surgery to receive either 2% chlorhexidine in 70% isopropanol (chlorhexidine-alcohol) or 5% povidone-iodine in 69% ethanol (povidone-iodine-alcohol) for skin disinfection at all surgical sites. Randomization was performed using a secure web-based randomization system. The sequence, computer-generated by a statistician not involved in

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recruitment, used variable block sizes, with stratification by center to account for local characteristics.

### Intervention

Patients randomly assigned to the chlorhexidine-alcohol group had their surgical sites largely disinfected using 26 mL single use applicators (ChlorPrep, Becton Dickinson, Pont-de-Claix, France) before surgery. Patients randomly assigned to the povidone-iodine-alcohol group had their surgical site largely disinfected using sterile disposable sets and 500 mL bottles of povidone-iodine-alcohol (Bétadine Alcoolique, Viatrix Santé, Courbevoie, France). The sets included extra-large sponges, long stick-holder forceps, and one large cup containing the antiseptic solution. According to local practices, the antiseptic solution was applied back and forth once or twice, preceded (two-step procedure) or not (one-step procedure) by skin scrubbing, using 4% aqueous chlorhexidine soap (Hibiscrub, Molnlycke Healthcare) in the chlorhexidine-alcohol group or 4% aqueous povidone-iodine soap (Bétadine Scrub, Viatrix Santé, Courbevoie, France) in the povidone-iodine-alcohol group. In the two-step procedure, the work area was scrubbed with a sterile gauze soaked in antiseptic soap, applied for at least 15 s, rinsed with sterile water, and dried with a sterile gauze before antiseptic application. In both groups, an additional antiseptic was administered at the end of surgery, after skin closure. The surgical staff (surgeons and nurses) at each participating center were trained in antiseptic application modalities before the commencement of the study to standardize practices. Patients were admitted to the intensive care unit for immediate postoperative management and then transferred to the cardiac surgery unit once their clinical condition stabilized. The same antiseptic procedure (with smaller antiseptic volumes) was performed for each dressing change until the first reoperation or discharge from the cardiac surgery unit. All patients received care following the guidelines of the French Society for Hospital Hygiene [11]: at least one total body shower using either plain soap or antiseptic soap before surgery; hair removal with a clipper if necessary (no shaving) before surgery; antibiotic prophylaxis according to the French guidelines [16] applied within 30 min prior to surgical incision, with appropriate reinjection if required for prolonged surgery and no readministration during the postoperative period; and maintenance of normoglycemia during and after surgery. Preoperative screening for nasal carriage of *Staphylococcus aureus* associated with decolonisation if necessary was carried out systematically in four of the eight centers. In one center, decolonisation was carried out for all patients without screening.

All patients were followed-up until day 90 to identify any postoperative complications. Patients discharged before the end of the study were contacted by phone on days 30, 60 and 90 using a standard questionnaire and reviewed in consultation by the surgeon in the event of complications.

### Outcomes

The primary outcome was re-sternotomy within 90 days of surgery, or reoperation at the saphenous vein/radial artery site within 30 days of surgery, regardless of the indication. This criterion was chosen because it is more robust and not open to interpretation in an open study comparing antiseptics that are easily recognized by their different colors. As the need for re-operation is linked to an infectious or non-infectious complication, individual randomization ensured similar numbers of re-operations for non-infectious complications in both arms.

Secondary outcomes included mediastinitis by day 90 after surgery, deep incisional SSI at saphenous vein/radial artery sites by day 30 after surgery and superficial incisional SSI at sternal or saphenous vein/radial artery sites by day 30 according to the CDC criteria (ESM 1) [17, 18], reoperation for SSI for sternal wound infection by day 90 or at saphenous vein/radial artery sites by day 30, unexpected need for readmission to intensive care unit (ICU) or re-hospitalization, length of mechanical ventilation, length of ICU stay, duration of hospital stay, duration of rehabilitation unit stay, death by day 90, and local or adverse effects possibly linked to antiseptic use.

A central adjudication committee, composed of two specialists in SSI, masked to the antiseptic group, reviewed all postoperative records of patients requiring re-sternotomy within 90 days of surgery and/or reoperation at the saphenous vein/radial artery site during the 30 days following surgery. They had access to all anonymized monitored data, surgical report, microbiological documentation, and computed tomography (CT) scan report. They classified the cases as follows: sternal wound infection (mediastinitis or superficial sternal SSI), deep or superficial saphenous vein/radial artery SSI, or no SSI, according to CDC criteria. Disagreements between the two assessors were resolved by a third investigator.

### Statistical analysis

We estimated a 6% reoperation rate with povidone-iodine-alcohol, 1/3 of which being related to infectious complications. Recruitment of 3726 evaluable patients would provide 80% power to detect a 33% relative reduction in the re-intervention rate with chlorhexidine-alcohol. Study recruitment was profoundly impacted by the outbreak of coronavirus disease 2019 in France. Due to

insufficient funding to continue and an overall number of primary outcomes higher than expected ( $n=246$ , 7.6%), the steering committee decided to stop the study after 3269 inclusions.

Analyses were performed on an intention-to-treat basis, using data from all patients who underwent surgery. Continuous variables are presented as medians (interquartile ranges) and categorical variables as absolute frequencies ( $n$ ) and percentages (%). All analyses were two-sided with  $p$  value of less than 0.05 deemed statistically significant. To assess the homogeneity across participating centers in the clinical study, a Cochran's  $Q$  test was performed. A multivariate analysis adjusted on potential disequilibrium between groups was planned.

### Primary outcome

Primary statistical analysis compared the incidence of re-sternotomy on day 90 or reoperation at the saphenous venous/radial artery site on day 30, using a two-tailed Cochran–Mantel–Hanzel test, stratified by center with relative risks and risk differences.

Antiseptic efficacy was assessed using a Cox model adjusted for unbalanced variables, stratified by center. Cumulative incidence curves were calculated using the Kaplan–Meier method and compared using the log-rank test. No risk of local infection between days 30 and 90 was considered in the event of reoperation on the saphenous vein/radial artery. A subgroup analysis by center was also performed.

### Secondary outcomes

Secondary outcomes were analyzed using a two-tailed Cochran–Mantel–Haenszel test, stratified by center, for binary outcomes, with relative risks and risk differences. For continuous outcomes, the  $p$ -values were obtained using the Van Elteren test (stratified Wilcoxon by center), while the effect estimates and 95% confidence intervals (CIs) were derived from stratified linear regressions by center.

No corrections were made for multiple comparisons. Statistical analyses of secondary outcomes should be interpreted as exploratory.

All data were analyzed using SAS, version 9.4 (SAS Institute, Cary, North Carolina, USA), and R, version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

Between September 2018 and December 2021, 3269 eligible patients provided informed consent and were randomized. Of these, 21 did not undergo surgery and 6 withdrew consent before surgery. Consequently, 3242 patients (99%) were included in the analysis: 1 621 each

in the chlorhexidine-alcohol and povidone-iodine-alcohol groups (Fig. 1).

Demographic and intraoperative characteristics were largely similar between the groups, except for the increased use of iodophor-impregnated incise drapes in the povidone-iodine-alcohol group (Table 1, supplementary eTable1 and eTable2 in ESM 1).

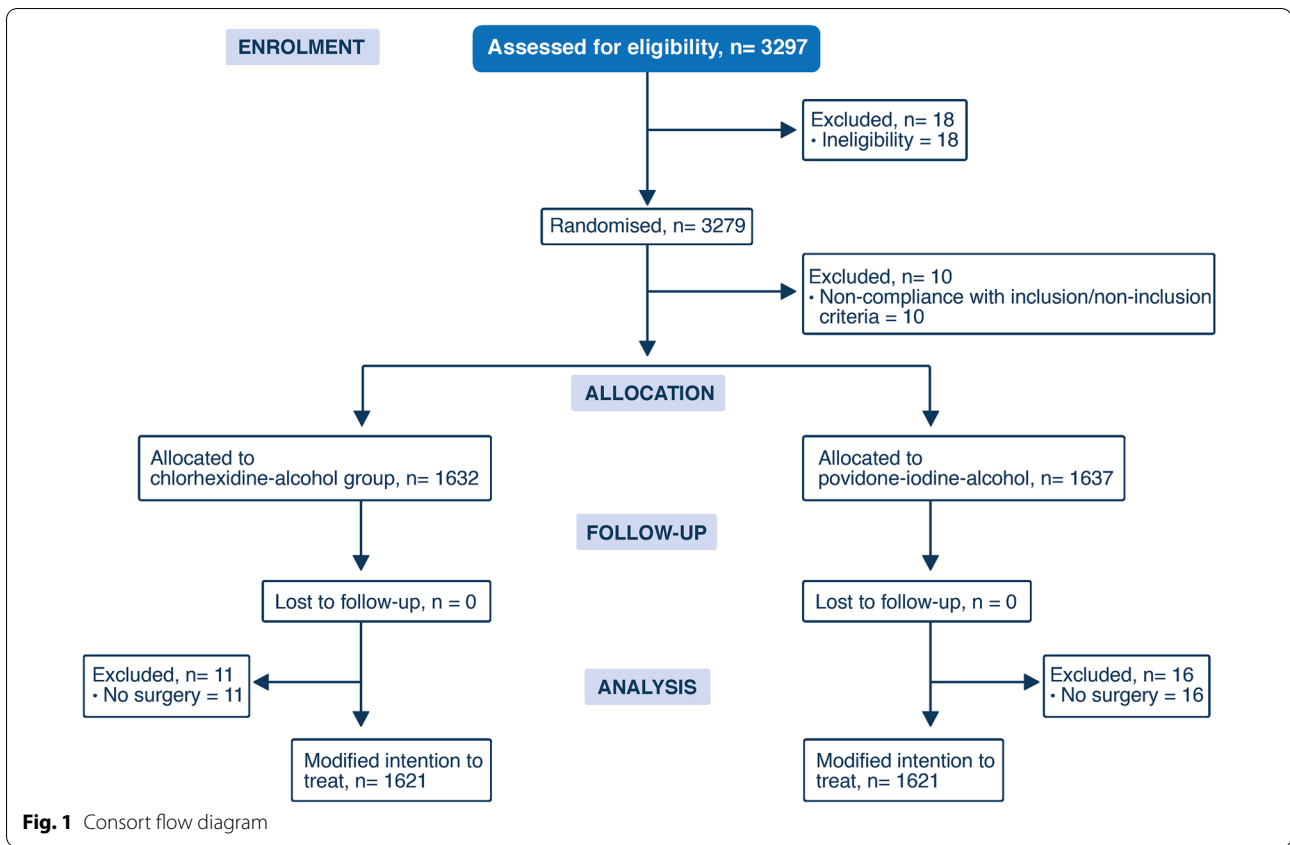
A total of 125 (7.7%) and 121 (7.5%) patients in the chlorhexidine-alcohol and povidone-iodine-alcohol groups, respectively (risk difference 0.25 [95% CI,  $-1.58$ – $2.07$ ],  $P=0.74$ ; Fig. 2, ESM, supplementary Tables 2, 3), required reoperation, with no difference between centers (ESM, supplementary eFigure 1).

Sixty-five (4%) and 53 (3.3%) patients in the chlorhexidine-alcohol and povidone-iodine-alcohol groups, respectively, had a diagnosis of SSI (risk difference 0.74 [95% CI  $-0.55$ – $2.03$ ],  $P=0.26$ ). Thirty-seven (2.3%) and 39 (2.4%) patients in the chlorhexidine-alcohol and povidone-iodine-alcohol groups, respectively (risk difference  $-0.12$  [95% CI  $-1.17$ – $0.92$ ],  $P=0.81$ ; Table 2), experienced mediastinitis. Thirty-nine of 125 (31.2%) and 41 of 121 (33.9%) patients in the chlorhexidine-alcohol and povidone-iodine-alcohol groups, respectively, required reoperation at the sternotomy site due to sternal wound infection ( $P=0.81$ ) (Table 3). Only one patient in the povidone-iodine-alcohol group required reoperation for superficial incisional SSI at the saphenous vein site by day 30 ( $P=0.32$ ) (Table 2). The proportions of patients with deep incisional SSIs at saphenous vein/radial artery sites by day 30 after surgery and superficial incisional SSIs at sternal or saphenous vein/radial artery sites by day 30 were comparable between the groups, one (0.1%) in each group ( $P=0.99$ ) (Table 2).

A multivariate model including the use of iodophor-impregnated incise drapes and the type of shower followed gave similar results (supplementary eTable 6 in ESM).

Fifty and 63 pathogens were isolated from patients with mediastinitis in the chlorhexidine-alcohol and povidone-iodine-alcohol groups, respectively ( $P=0.15$ ). *S. aureus* was the most common isolate (10% in the chlorhexidine-alcohol group and 15.9% in the povidone-iodine-alcohol group). Coagulase-negative Staphylococcus represented 18% and 12.7% of the isolates in the chlorhexidine-alcohol and povidone-iodine-alcohol groups, respectively. Enterobacterales represented 24% and 33.3% of the isolates, respectively (Table 4). Pathogens isolated from sternal wound infections and superficial SSIs are listed in the appendix (supplementary eTable 3, eTable 4 in ESM).

No significant differences in the length of hospital stay ( $P=0.59$ ), need for hospital readmission ( $P=0.42$ ), or mortality ( $P=0.20$ ) were observed between the two groups (Table 2).



Local reactions at surgical sites were reported in 5 (0.3%) and 12 (0.7%) patients in the chlorhexidine-alcohol and povidone-iodine-alcohol groups, respectively (risk difference - 0.43 [95% CI - 0.93-0.07],  $P=0.09$ ). No systemic reactions attributable to any of the antiseptic solutions or alcohol ignition fires were observed (supplementary eTable 5 in ESM).

## Discussion

The proportion of participants requiring reoperation at sternotomy (by day 90) or saphenous vein/radial artery sites (by day 30) after skin disinfection with 2% chlorhexidine-alcohol or 5% povidone-iodine-alcohol was similar. Approximately one-third of reoperations at the sternal site were due to sternal wound infection, and the proportion of SSIs, including mediastinitis, was similar between the two groups. Local reactions were rare, with no significant differences between the two groups.

This is one of the largest randomized clinical trials to compare the efficacy of two commonly used alcohol-based antiseptic solutions in preventing surgical site complications and the second in cardiac surgery. The

decision to include patients who underwent clean surgery was based on the source of the pathogens involved in SSIs, primarily originating from the skin and, therefore, accessible to skin disinfection. Surgical reoperation was chosen as the primary outcome because (1) it is a robust and uncontroversial criterion, minimizing the risk of bias in an open-label study and (2) its consequences in patients with multiple comorbidities often leads to readmission to intensive care, and sometimes death. Finally, assessors blinded to the study arm reviewed all cases of reoperation to grade the SSIs according to well-established criteria.

The results of the present trial showed no differences between the two antiseptic strategies in terms of reoperation rate, proportion of SSIs, length of hospital stay, hospital readmission, and mortality. Our results are in line with those recently published by Widmer and colleagues [19]. In a large study in patients with cardiac or abdominal surgery, they demonstrated a non-inferiority of povidone-iodine-alcohol compared to chlorhexidine alcohol group. This well-conducted study nevertheless has differences with the present study. Firstly, patients were

**Table 1 Characteristics of patients in the modified intention to-treat population**

| Demographic characteristics                              | Patient with surgery<br>(N = 3242) | Chlorhexidine-alcohol<br>(N = 1621) | Povidone-iodine-alcohol<br>(N = 1621) |
|--|------------------------------------|-------------------------------------|---------------------------------------|
| Age—year   | 69 (62–74)                         | 69 (61–74)                          | 69 (62–74)                            |
| Male Sex   | 2523 (77.8)                        | 1276 (78.7)                         | 1247 (76.9)                           |
| Body mass index  | 27 (24–30)                         | 27 (24–30)                          | 27 (24–30)                            |
| Euroscore II   | 1.2 (0.8–2.2)                      | 1.2 (0.8–2.1)                       | 1.2 (0.8–2.2)                         |
| Smoker status  | 596 (18.4)                         | 302 (18.6)                          | 294 (18.1)                            |
| Diabetes mellitus  | 804 (24.8)                         | 402 (24.8)                          | 402 (24.8)                            |
| Preoperative nasal decontamination                       | 1219 (37.6)                        | 610 (37.7)                          | 609 (37.6)                            |
| <b>Skin preparation</b>                                  |                                    |                                     |                                       |
| Number of preoperative shower(s)                         |                                    |                                     |                                       |
| Day before surgery                                       | 3122 (96.4)                        | 1576 (97.2)                         | 1546 (95.5)                           |
| Day of surgery   | 3074 (94.9)                        | 1538 (94.9)                         | 1536 (94.9)                           |
| At least one   | 3238 (99.9)                        | 1621 (100)                          | 1617 (99.9)                           |
| Type of preoperative shower—day of surgery<br>(N = 3074) |                                    |                                     |                                       |
| Plain soap   | 483 (15.7)                         | 247 (16.1)                          | 236 (15.4)                            |
| Antiseptic soap  | 2591 (84.3)                        | 1291 (83.9)                         | 1300 (84.6)                           |
| Skin antiseptics (N = 3235)                              |                                    |                                     |                                       |
| Two-step procedure                                       | 3225 (99.8)                        | 1610 (99.7)                         | 1615 (99.8)                           |
| Number of antiseptic applications                        |                                    |                                     |                                       |
| 1  | 67 (2.1)                           | 32 (2)                              | 35 (2.2)                              |
| 2  | 3166 (97.9)                        | 1583 (98)                           | 1583 (97.8)                           |
| Iodophor-impregnated incise drapes                       | 784 (24.2)                         | 190 (11.7)                          | 594 (36.7)                            |
| <b>Surgery characteristics</b>                           |                                    |                                     |                                       |
| Type of surgery  |                                    |                                     |                                       |
| Only aortic  | 114 (3.5)                          | 62 (3.8)                            | 52 (3.2)                              |
| Only cardiac   | 2711 (83.6)                        | 1335 (82.4)                         | 1376 (84.9)                           |
| Both   | 414 (12.8)                         | 221 (13.6)                          | 193 (11.9)                            |
| Unknown  | 3 (0.1)                            | 3 (0.2)                             | 0 (0)                                 |
| Cardiac Surgery (N = 3125)**                             |                                    |                                     |                                       |
| Coronary   | 1132 (36.2)                        | 576 (37)                            | 556 (35.4)                            |
| Valve  | 1378 (44.1)                        | 688 (44.2)                          | 690 (44)                              |
| Combined   | 453 (14.5)                         | 212 (13.6)                          | 241 (15.4)                            |
| Others   | 162 (5.2)                          | 80 (5.1)                            | 82 (5.2)                              |
| Elective surgery   | 3028 (93.4)                        | 1516 (93.6)                         | 1512 (93.3)                           |
| Duration of surgery                                      | 203 (158–252)                      | 202 (157–252)                       | 204 (159–252)                         |
| Cardiopulmonary bypass                                   |                                    |                                     |                                       |
| Yes  | 3229 (99.6)                        | 1615 (99.7)                         | 1614 (99.6)                           |
| Duration   | 87 (65–116)                        | 86 (65–115)                         | 88 (66–117)                           |
| Postoperative mechanical cardiac support                 |                                    |                                     |                                       |
| Extra-corporeal life support                             | 158 (4.9)                          | 82 (5.1)                            | 76 (4.7)                              |
| Intra-aortic balloon pump                                | 17 (0.5)                           | 10 (0.6)                            | 7 (0.4)                               |
| Number of mammary arteries used                          |                                    |                                     |                                       |
| 0  | 1707 (52.7)                        | 857 (52.9)                          | 850 (52.4)                            |
| 1  | 553 (17.1)                         | 257 (15.9)                          | 296 (18.3)                            |
| 2  | 981 (30.3)                         | 506 (31.2)                          | 475 (29.3)                            |
| Saphenous vein sampling                                  | 591 (18.2)                         | 293 (18.1)                          | 298 (18.4)                            |
| Radial artery sampling                                   | 187 (5.8)                          | 85 (5.2)                            | 102 (6.3)                             |

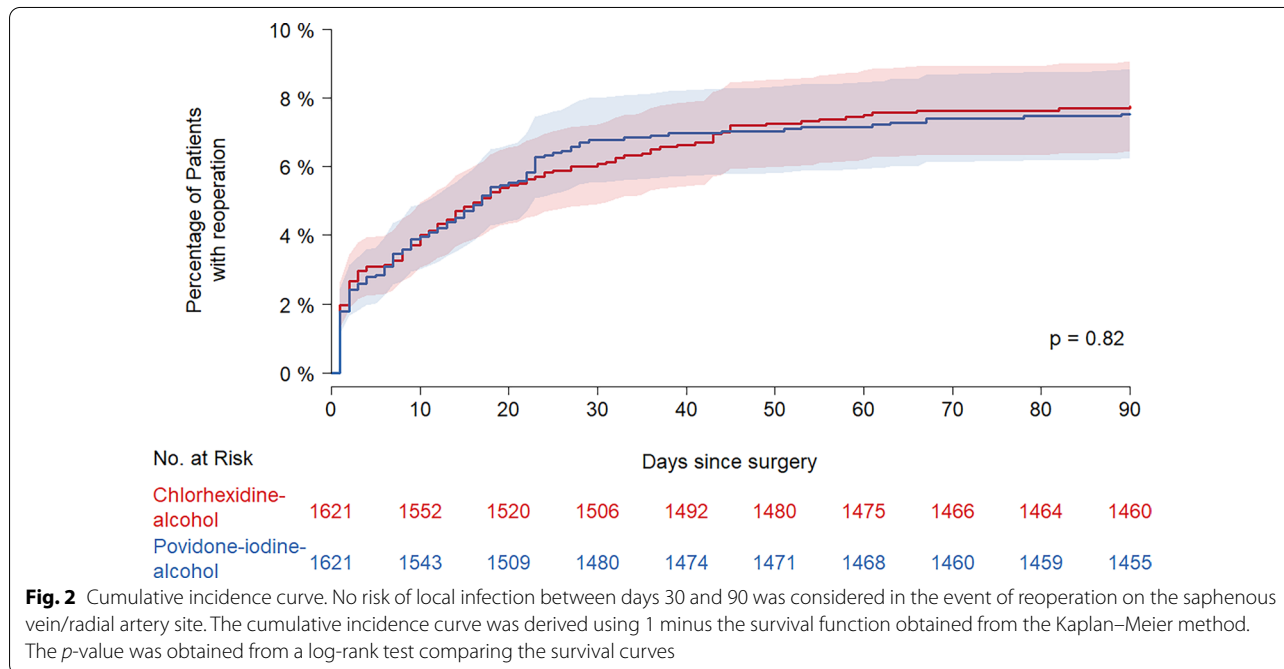
Data are median (interquartile range, IQR), n (%)

The modified intention-to-treat population included all patients who underwent randomization or the assigned surgery. The percentage may not total 100 because of rounding or missing values. The following data were missing: European System for Cardiac Operative Risk Evaluation (EuroSCORE) for 15 patients in the chlorhexidine-

**Table 1 (continued)**

alcohol group (CHX-A) and 17 patients in the povidone-iodine-alcohol group (PVI-A); preoperative nasal decontamination for 1 patient in CHX-A; number of preoperative showers for 2 patients in PVI-A; skin antiseptics for 6 patients in CHX-A and 3 patients in PVI-A; iodophor-impregnated incise drapes for 1 patient in CHX-A and 1 patient in PVI-A; type of surgery is unknown for 3 patients in CHX-A; elective surgery for 1 patient in CHX-A; duration of surgery for 17 patients in CHX-A and 9 patients in PVI-A; cardiopulmonary bypass for 1 patient in CHX-A; cardiopulmonary bypass duration for 17 patients CHX-A and 5 patients in PVI-A; postoperative mechanical cardiac support for 1 patient in CHX-A; number of mammary arteries used for 1 patient CHX-A

\*\*For patients that underwent at least one cardiac surgery. Two patients underwent cardiac surgery based on their results; however, the aortic surgery was unknown



not randomized individually, but a cluster-randomized crossover design was used, which may have reduced the power of the study. Secondly, the concentration of free iodine (1%) used in the povidone-iodine group corresponds to a higher value than in the solutions usually used in previous studies (0.5–0.8%). Thirdly, only 2/3 of the patients included had undergone cardiac surgery, and 10% had no clean surgery, the incidence and pathophysiology of which may be different from those of clean surgery. Fourthly, the assigned antiseptic solution appears to have been used only in the operating room and not for post-operative care, diminishing a potential difference in efficacy between the 2 antiseptic solutions. Moreover, another large multicentre, randomized controlled trial setting in low-resource countries failed to demonstrate superiority of 2% chlorhexidine-alcohol compare to 10% aqueous povidone-iodine for reducing SSIs in clean-contaminated, contaminated or dirty abdominal surgeries [20]. In view of the higher cost in many countries, the preferential choice of 2% chlorhexidine-alcohol suggested by the WHO is questionable [21].

The overall incidence of mediastinitis was 2.4% and did not differ between the antiseptics. This finding is

consistent with those of previous studies reporting mediastinitis rates ranging from 0.6% to 2% according to the definition used [3, 5, 22–24]. With no difference in the rate of sternal wound infection, our results challenge the previous literature suggesting that chlorhexidine solutions are more effective than povidone-iodine solutions in preventing SSIs, although the literature on clean surgery is scarce [25–32]. The risk factors for SSI could not explain this result, as the populations in the two groups had comparable characteristics in terms of body mass index, smoking status, insulin-requiring diabetes, number of mammary arteries used, European System for Cardiac Operative Risk Evaluation (Euroscore) II, or urgent surgery.

In our study, less than 15% of mediastinitis cases were associated with *S. aureus*. Only 18.5% of isolated bacteria were commensal skin microorganisms (including coagulase-negative staphylococci), and one-third of isolated bacteria were Enterobacterales, which is consistent with findings from previous studies [3, 33]. The diminished presence of *S. aureus* might be attributed to the fact that nearly two-thirds of the patients included were screened for nasal carriage of *S. aureus* and that a relatively large



**Table 2 Primary and secondary efficacy outcomes in the modified intention-to-treat population**

|  | Chlorhexidine-alcohol<br>(N = 1621) | Povidone-iodine-alcohol<br>(N = 1621) | Effect estimate <sup>†</sup> | Effect estimate (95% CI) | P value |
|--|-------------------------------------|---------------------------------------|------------------------------|--------------------------|---------|
| <b>Primary outcome</b>   |                                     |                                       |                              |                          |         |
| Any re-sternotomy on d90 or reoperation on saphenous vein/radial artery site on d30 <sup>‡</sup> | 125 (7.7)                           | 121 (7.5)                             | RD                           | 0.25 (– 1.58; 2.07)      | 0.79    |
|  |                                     |                                       | RR                           | 1.03 (0.81; 1.31)        |         |
| <b>Secondary outcome</b>   |                                     |                                       |                              |                          |         |
| Mediastinitis at d90 <sup>‡</sup>  | 37 (2.3)                            | 39 (2.4)                              | RD                           | – 0.12 (– 1.17; 0.92)    | 0.81    |
|  |                                     |                                       | RR                           | 0.95 (0.61; 1.45)        |         |
| Sternal wound infection requiring surgery at d90 <sup>‡§</sup>                                   | 39 (2.4)                            | 41 (2.5)                              | RD                           | – 0.12 (– 1.19; 0.94)    | 0.81    |
|  |                                     |                                       | RR                           | 0.95 (0.62; 1.47)        |         |
| Superficial saphenous vein/radial artery infection requiring surgery on d30 <sup>‡</sup>         | 0 (0)                               | 1 (0.1)                               | RD                           | – 0.06 (– 0.18; 0.06)    | 0.32    |
|  |                                     |                                       | RR                           | NC                       |         |
| Deep saphenous vein/radial artery infection on d30 <sup>‡</sup>                                  | 1 (0.1)                             | 1 (0.1)                               | RD                           | 0 (– 0.17; 0.17)         | 0.99    |
|  |                                     |                                       | RR                           | 1.00 (0.06; 15.97)       |         |
| Superficial sternum infection/saphenous vein/radial on d30 <sup>‡</sup>                          | 38 (2.3)                            | 31 (1.9)                              | RD                           | 0.43 (– 0.56; 1.43)      | 0.40    |
|  |                                     |                                       | RR                           | 1.23 (0.77; 1.96)        |         |
| Unexpected need for re-admission to the ICU at d90 <sup>‡</sup>                                  | 78 (4.8)                            | 99 (6.1)                              | RD                           | – 1.30 (– 2.86; 0.27)    | 0.11    |
|  |                                     |                                       | RR                           | 0.78 (0.59; 1.05)        |         |
| Unexpected need for re-hospitalization at d90 <sup>‡</sup>                                       | 227 (14)                            | 211 (13)                              | RD                           | 0.99 (– 1.37; 3.34)      | 0.42    |
|  |                                     |                                       | RR                           | 1.08 (0.90; 1.28)        |         |
| D90 death <sup>‡</sup>   | 39 (2.4)                            | 51 (3.1)                              | RD                           | – 0.74 (– 1.87; 0.39)    | 0.20    |
|  |                                     |                                       | RR                           | 0.76 (0.51; 1.15)        |         |
| Adverse events related to antiseptics <sup>‡</sup>   | 5 (0.3)                             | 12 (0.7)                              | RD                           | – 0.43 (– 0.93; 0.07)    | 0.09    |
|  |                                     |                                       | RR                           | 0.42 (0.15; 1.18)        |         |
| Surgical site infection <sup>‡</sup>   | 65 (4)                              | 53 (3.3)                              | RD                           | 0.74 (– 0.55; 2.03)      | 0.26    |
|  |                                     |                                       | RR                           | 1.23 (0.86; 1.75)        |         |
| Length of mechanical ventilation on d90 <sup>¶</sup>   | 1 (1–3)                             | 1 (1–3)                               | sLR                          | 0.02 (– 0.31; 0.35)      | 0.77    |
|  |                                     |                                       | MD                           | 0.00 (0.00; 0.00)        |         |
| Length of the ICU stay <sup>¶</sup>  | 3 (2–5)                             | 3 (3–5)                               | sLR                          | – 0.04 (– 0.51; 0.44)    | 0.20    |
|  |                                     |                                       | MD                           | 0.00 (0.00; 0.00)        |         |
| Length of the hospital stay <sup>¶</sup>   | 10 (8–14)                           | 10 (8–14)                             | sLR                          | – 0.32 (– 1.18; 0.54)    | 0.59    |
|  |                                     |                                       | MD                           | 0.00 (0.00; 0.00)        |         |
| Length of the rehabilitation unit stay <sup>¶</sup>  | 19 (0–24)                           | 19 (0–24)                             | sLR                          | – 0.16 (– 1.03; 0.70)    | 0.66    |
|  |                                     |                                       | MD                           | 0.00 (0.00; 0.00)        |         |

RD risk difference, RR relative risk, MD median difference, LR stratified linear regression by centers

The modified intention-to-treat population included all patients who underwent randomization or the assigned surgery

<sup>‡</sup> Cochran–Mantel–Hanzel test stratified by center

<sup>¶</sup> Van Elteren test

<sup>§</sup> Wound infection was defined as mediastinitis (day 90 [d90]) or superficial sternal infection (day 30 [d30])

<sup>†</sup> For the qualitative variables difference between the proportion of the chlorhexidine-alcohol and povidone-iodine-alcohol group. For quantitative variables, the differences between the means of the chlorhexidine-alcohol and povidone-iodine-alcohol groups

percentage of patients (38%) received preoperative nasal decontamination [34].

Antiseptics are generally well-tolerated. Systemic reactions are extremely rare and local reactions uncommon [35]. Our study confirms these data, with no systemic reactions observed and local reactions occurring in less than 1% of the patients included, with no statistically significant difference between the two groups. Traditionally,

the incidence of local reactions following surgical site disinfection using chlorhexidine or povidone-iodine has been similar. However, a recent systematic review and network meta-analysis comparing the efficacy of chlorhexidine gluconate and povidone-iodine antiseptics in preventing infection during clean surgery reported that adverse events related to antiseptic application were

**Table 3 Reasons for re-sternotomy in the modified intention-to-treat population\***

|  | Chlorhexidine-alcohol<br>(N = 139) | Povidone-iodine-alcohol<br>(N = 137) |
|--|------------------------------------|--------------------------------------|
| Mediastinitis                          | 39 (28.1)                          | 41 (29.9)                            |
| Tamponade                              | 34 (24.5)                          | 41 (29.9)                            |
| Excessive post-operative bleeding      | 36 (25.9)                          | 32 (23.4)                            |
| Superficial infection                  | 7 (5)                              | 6 (4.4)                              |
| Detachment or dysfunction of the valve | 4 (2.9)                            | 5 (3.6)                              |
| Mechanical sternal disunion            | 4 (2.9)                            | 0 (0)                                |
| Bypass resumption                      | 1 (0.7)                            | 2 (1.5)                              |
| Other                                  | 14 (10.1)                          | 10 (7.3)                             |

Data are n (%). In the chlorhexidine-alcohol group, 8 patients had 2 re-sternotomy, 1 patient had 3 re-sternotomy and 1 patient had 5 re-sternotomy. In the povidone-iodine-alcohol group, 11 patients had 2 re-sternotomy, 1 patient had 3 re-sternotomy and 1 patient had 4 re-sternotomy

\*The modified intention-to-treat population included all the patients who had undergone randomization and the assigned surgery

**Table 4 Microorganisms associated with mediastinitis in the modified intention-to-treat population\***

|                                  | Chlorhexidine-alcohol<br>(N = 50) | Povidone-iodine-alcohol<br>(N = 63) |
|----------------------------------|-----------------------------------|-------------------------------------|
| Gram positive cocci              |                                   |                                     |
| <i>Staphylococcus aureus</i>     | 5 (10)                            | 10 (15.9)                           |
| Coagulase negative Staphylococci | 9 (18)                            | 8 (12.7)                            |
| <i>Streptococcus spp.</i>        | 3 (6)                             | 1 (1.6)                             |
| <i>Enterococcus spp.</i>         | 2 (4)                             | 4 (6.3)                             |
| Gram negative bacillus           |                                   |                                     |
| Enterobacterales                 | 12 (24)                           | 21 (33.3)                           |
| <i>Pseudomonas aeruginosa</i>    | 3 (6)                             | 3 (4.8)                             |
| Other                            | 0 (0)                             | 2 (3.2)                             |
| Gram positive bacillus aerobes   | 8 (16)                            | 3 (4.8)                             |
| Anaerobes                        | 5 (10)                            | 10 (15.9)                           |
| Others                           | 3 (6)                             | 1 (1.6)                             |

Data are n (%). Percentages may not total 100 because of rounding or missing values and polymicrobial infections. 9 patients among the 76 with mediastinitis had no germs found

\*The modified intention-to-treat population included all the patients who had undergone randomization and the assigned surgery

observed only in patients exposed to povidone-iodine [36].

## Limits

Our trial has some limitations. First, there is a lack of standardization of antiseptic strategies (number of body showers and type of soap, scrubbing prior to skin antiseptics, number of antiseptic applications, and use of iodophor-impregnated incise drapes). However, the strategy was broadly similar in each center, regardless of the antiseptic used. Due to the lack of availability in France of povidone-iodine with applicator, the antiseptic application methods differed between the two groups according to manufacturers' recommendations. A higher proportion of patients in the povidone-iodine-alcohol group received impregnated incise drapes. However, the efficacy of impregnated incise drapes for preventing SSI is not established [37]. In addition, the use of iodophor-impregnated incise drapes was not a protective factor against reoperation or mediastinitis in multivariate analysis, which is consistent with current guidelines [12, 29]. Second, study recruitment was profoundly impacted by the outbreak of coronavirus disease 2019 in France and was stopped prematurely after 3 269 inclusions due to insufficient funding to continue. But the overall number of primary outcomes was higher than expected ( $n=246$ , 7.6%) ensuring sufficient power. Third, the choice of primary endpoint could appear as a study limitation, given the high proportion of reoperation for non-infectious causes. This choice was based on the wish to have a robust and objective criterion. In addition, the number of subjects required was calculated for this primary endpoint but considered that only 1/3 of reoperations would be related to an SSI. Finally, due to a long period of follow-up, patients discharged from the hospital prior to milestones were contacted by phone using a standardised questionnaire. Even if telephone assessment is frequent and quite accurate for SSI surveys [38], it may have missed some patients with superficial SSI not requiring reoperation.

## Conclusions

While chlorhexidine-alcohol has undeniable superiority over povidone-iodine-alcohol in preventing intravascular catheter-related infections [35, 39], no difference was observed among patients undergoing cardiac surgery. The prolonged antimicrobial suppressive activity of chlorhexidine may be more advantageous for catheters, given the longer skin opening, than after surgical incision [40]. Our results do not support claims of superiority of chlorhexidine-alcohol over povidone-iodine-alcohol for reducing reoperation and SSI rates after major cardiac surgery. We suggest that WHO and NICE recommendations should be modified accordingly [2, 12].

## Supplementary Information

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## Author contributions

MB, JCL, JFT, and OM designed the trial. MB and OM coordinated the study and wrote the first draft of the manuscript. AL, SR, and JFT performed the data analyses. GA, JCR, NO, SB, PD, PMM, FL, TK, BR, VE, KZ, PL, WO, VM, and SS participated in data collection and data interpretation, and were involved in critical appraisal and revision of the manuscript. MB, GA, TK, JCL, and OM participated in the masked central adjudication committee.

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## Declarations

## Conflicts of interest

MB reports grants from Becton Dickinson; consulting fees from Becton Dickinson and Edwards Lifesciences; honoraria for lectures from Becton Dickinson;

and payment for participation on an advisory board for Becton Dickinson and Edwards Lifesciences. BR reports grants from Aguetant and i-SEP; consulting fees from LFB, Aguetant and Nordic Pharma; and attending meetings or travel from i-SEP. JFT reports grants from MSD and Pfizer; honoraria for lectures from Becton Dickinson and Shionogi; and payment for participation on an advisory board for MSD, Pfizer, Gilead, Advanz, Roche and Becton Dickinson. OM reports grants from 3 M and Becton Dickinson; consulting fees from 3 M and Becton Dickinson; honoraria for lectures from 3 M and Becton Dickinson; support for attending meetings or travel from 3 M and Becton Dickinson; and payment for participation on an advisory board for 3 M and Becton Dickinson. All other authors declare no competing interests.

## Role of the funder

The funders had no role in the design or execution of the trial, data analysis, or writing or reviewing of the manuscript.

## Data sharing

Data collected for the study, including participant data, the data dictionary defining each field in the set, and the study protocol, will be made available to others. Data will be communicated as de-identified participant data according to French law, and will be available after publication of the manuscript. Data will be made available at the Direction de la Recherche, Poitiers University Hospital, Poitiers, France ([drci@chu-poitiers.fr](mailto:drci@chu-poitiers.fr)), with investigator support, after approval of a proposal with a signed data access agreement.

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