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Multicentre, open label, randomised, controlled clinical trial comparing 2% chlorhexidine – 70% isopropanol and 5% povidone iodine – 69% ethanol for skin antisepsis in reducing surgical-site infection after cardiac surgery: the CLEAN 2 study protocol

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ABSTRACT

Introduction: Surgical site infection (SSI) is the second most frequent cause of healthcare-associated infection worldwide and is associated with increased morbidity, mortality and healthcare costs. Cardiac surgery is clean surgery with low incidence of SSI, ranging from 2 to 5%, but with potentially severe consequences.

Perioperative skin antisepsis with an alcohol-based antiseptic solution is recommended to prevent SSI, but the superiority of chlorhexidine (CHG)-alcohol over povidone iodine (PVI)-alcohol, the two most common alcohol-based antiseptic solutions used worldwide, is controversial. We aim to evaluate whether 2% CHG-70% isopropanol is more effective than 5% PVI-69% ethanol in reducing the incidence of reoperation after cardiac surgery.

Methods and analysis: The CLEAN 2 study is a multicentre, open label, randomised, controlled clinical trial of 4100 patients undergoing cardiac surgery. Patients will be randomized in 1:1 ratio to receive either 2% CHG – 70% isopropanol or 5% PVI – 69% ethanol for perioperative skin preparation. The primary endpoint is the proportion of patients undergoing any re-sternotomy between Day 0 and Day 90 after initial surgery and/or any reoperation on saphen venous surgical site between Day 0 and Day 30 after initial surgery. Data will be analysed on the intention-to-treat principle.

Ethics and dissemination: This protocol has been approved by an independent ethics committee and will be carried out according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines. The results of this study will be disseminated through presentation at scientific conferences and publication in peer-reviewed journals.

Trial registration: EudraCT 2017-005169-33 & NCT03560193.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This randomised study is aimed being the largest one performed comparing the efficacy of perioperative skin preparation with either alcohol-based CHG or alcohol-based PVI in reducing severe postoperative complications.
- Cardiac surgery is a clean surgery where most of the pathogens involved in SSI originate from the skin.
- The primary endpoint, the incidence of any reoperation at both surgical sites, is a predefined strong unquestionable criterion, overlooking the need – and the risk of bias - for assessing the reality of SSI.
- In addition, limitations due to the lack of masking related to the nature of the intervention will be reduced by assessment of all SSI by an adjudication committee masked to antiseptic group.

INTRODUCTION

Surgical site infection (SSI) is the second most frequent cause of healthcare-associated infections with an incidence up to 19% depending of the type of surgery, and range from simple wound discharge to life-threatening condition.[1–3] They are associated with increased hospital stay, prolonged antibiotics use and occasional need for reoperation, and are responsible for rising mortality and healthcare costs estimated at € 10 billion per year in the USA.[4]

Cardiac surgery is considered as clean surgery. Incidence of SSI is lower than with other types of surgery, ranging from 2 to 5% depending on the definitions used, but consequences may be greater in terms of both frequency and severity.[5,6] Because pathogens involved in SSI after clean surgery come mostly from skin, perioperative skin antisepsis plays a major role in SSI prevention.

The most common antiseptic agents used for skin disinfection before surgery are aqueous or alcoholic formulations of chlorhexidine (CHG) or povidone iodine (PVI) both of which are available at various concentrations. Several studies have compared their respective efficacy and safety in reducing SSI. Nevertheless, results were contradictory, probably due to different comparators (concentrations, combination with alcohol or water…), different SSI definitions, and different length of follow up.[7–11] In 2010, a meta-analysis of seven randomised-controlled trials (including 3437 patients) compared CHG (at a concentration of 0.5 to 4%) with PVI or other iodophors (at a concentration of 7 to 10%) for preoperative skin antisepsis in clean and clean-contaminated surgery.[12] The use of CHG was associated with fewer SSIs (adjusted RR 0.64; 95%CI 0.51-0.80) compared with iodine. Another meta-analysis of six randomised-controlled trials comparing CHG (at a concentration of 0.5 to 4%) to PVI (at a concentration of 7.5 to 10%) for preoperative skin antisepsis yielded similar findings [OR of 0.68 (0.50-0.94; p=0.019)].[13] However, in most studies CHG was combined with alcohol and PVI was not, which meant that two antiseptics were being compared to only one. A review conducted in 2012 was unable to draw any conclusion about which surgical site antiseptic effectively reduces SSI.[14] Recently, Tuuli and colleagues were the first to conduct a large trial comparing CHG and PVI in alcoholic formulations for skin disinfection before caesarean section.[9] Interestingly, both antiseptic formulations used the same alcohol at the same concentration and both were applied similarly using an applicator. Although this was the first study demonstrating benefit of 2% CHG-70% isopropanol over 8.3% PVI-70% isopropanol, it was monocentre, and did not address all potential methodological limits. Especially, the choice of superficial or deep surgical-site infection as primary endpoint assessed by the surgeon (the diagnosis was made by the treating physician and verified by means of chart review by the principal investigator, who was unaware of the study-group assignments) may generate interpretation biases in an open study. Moreover, the one dual microbial source of pathogens from both skin and vaginal origins in SSI after caesarean delivery and immune modulation in pregnancy raise questions about whether results of trials of preoperative skin antisepsis for caesarean delivery can be extrapolated to others surgical procedures.

Furthermore, the possible superiority of CHG over PVI was not confirmed in a second monocentre trial involving 1404 women requiring caesarean section.[8] Lastly, in a third assessor-blinded, monocentre, randomised trial involving 802 patients scheduled for elective clean-contaminated colorectal surgery, the use of PVI-alcohol failed to meet criterion for non-inferiority for SSI occurrence compared with CHG-alcohol.[11] These contradictory results may explain the lack of universal use of CHG-alcohol for skin antisepsis in surgery despite the recommendations of the World Health Organization (WHO).[15]

The prevalence and potential serious consequences of SSI in cardiac surgery, especially mediastinitis, support a large randomised controlled trial in this setting. We hypothesize that perioperative skin preparation with 2% CHG-70% isopropanol is more effective than 5% PVI-69% ethanol as a means of preventing any reoperation after cardiac surgery.

METHODS AND ANALYSIS

Trial design and setting

The CLEAN 2 trial is an investigator-initiated, publicly-funded multicentre, randomised, controlled, open-label clinical trial with concealed allocation of patients scheduled to undergo cardiac surgery and to receive 1:1 either 2% CHG – 70% isopropanol or 5% PVI– 69% ethanol for perioperative skin preparation. Randomisation will be carried out through a secure web-based randomisation system and stratified by centre (Fig. 1).

The trial will take place at 7 university and non-university hospitals. All participating centres perform more than 500 cardiac surgical procedures per year.

Participant eligibility and consent

During surgery or preoperative anaesthesia consultation, all consecutive patients will be considered candidates for inclusion in the study if they meet all of the inclusion criteria and none of the exclusion criteria. Eligible patients will receive oral and written information and will be enrolled after having given written consent.

Inclusion criteria

- Adult patients (age ≥ 18 years) admitted in one of the participating centres
- Scheduled to undergo surgery of the heart (valve, coronary or combined surgery) or of the aorta via median sternotomy
- Having signed informed consent form

Exclusion criteria

- Patients with known allergies to CHG, PVI, isopropanol or ethanol
- Surgery for heart transplantation
- Any signs of inflammation or sternal instability at the site of sternotomy or operation for infection (sternal wound infection or endocarditis)
- History of cardiac surgery within 3 months preceding enrolment
- Participation in another clinical trial aimed at reducing SSI
- Patients already enrolled in this study
- Pregnant or breastfeeding women and potentially childbearing women without effective contraception
- Patients not benefiting from a Social Security scheme or not benefiting from it through a third party
- Persons benefiting from enhanced protection, namely minors, persons deprived of their liberty by a judicial or administrative decision and adults under legal protection.

Assignment of interventions

A computer-generated block-randomisation sequence will be performed by the statistician not involved in either screening the patients or assessing outcomes. Randomisation will be carried out using a secure web-based randomisation system with stratification by centre. The randomisation will be accessible to investigators through user identification and a personal password and will become effective following confirmation of inclusion and exclusion

criteria. Patients will be randomly assigned (1:1) to one of two study groups according to the antiseptic solution used to disinfect the skin before surgery and during all dressing changes (Fig. 1).

Interventions

1- *CHG group:* The surgical site will be largely disinfected using applicators of 2% CHG-70% isopropanol (ChloraPrep™, CareFusion). According to local practices, antiseptic application will be preceded (two-step procedure) or not (one-step procedure) by skin scrubbing with 4% CHG (Hibiscrub™, Molnlycke Health Care).
2- *PVI group*: The surgical site will be largely disinfected using sterile gauzes soaked with 5% PVI-69% ethanol (Bétadine alcoolique™, MEDA Pharma SAS). According to local practices, antiseptic application will be preceded (two-step procedure) or not (one-step procedure) by skin scrubbing with 4% PVI (Bétadine Scrub™, MEDA Pharma SAS).

In order to ensure respect of treatment group and to achieve traceability, individual boxes containing all disinfecting products required for disinfecting the skin before surgery and during patients' care will be supplied. According to randomisation, each patient will have his own box, which will follow him from the operating room to hospital discharge.

The following care will be applied to all patients and controlled throughout the duration of the study:

- At least one total body shower during the 24 h preceding surgery, using either plain soap or antiseptic soap
- Hair removal if required with clipper (no shaving) before surgery
- Antibiotic prophylaxis according to local protocol applied 30 min prior to incision, and with appropriate reinjection if required for prolonged surgery
- Antiseptic application by moving back and forth for at least 30 s, starting at the incision site and then extending to the entire work area. According to local practices, the antiseptic solution will be applied once or twice, preceded or not by skin scrubbing with an antiseptic soap.
- Application of large sterile drapes once the work area will be dry.

Study outcomes

Primary endpoint

The primary outcome will be the proportion of patients undergoing either any re-sternotomy occurring between Day 0 and Day 90 after surgery or any reoperation on saphen venous site occurring between Day 0 and Day 30 after surgery or both.

Secondary endpoints

- Proportion of patients with mediastinitis according to the Center for Disease Control and Prevention (CDC) criteria [16] occurring by Day 90 after surgery and pathogens involved.
- Proportion of patients with deep incisional SSI at saphen venous site, superficial incisional SSI at sternal or saphen venous sites according to the CDC criteria [16] occurring by Day 30 after surgery and pathogens involved.
- Proportion of patients with sternal wound infection (SWI) requiring reoperation, occurring by Day 90.
- Proportion of patients with SSI at saphen venous site requiring reoperation, occurring by Day 30.

- Proportion of patients with unexpected need for readmission to intensive care unit (ICU) or re-hospitalisation.
- Duration of ICU stay.
- Duration of stay under mechanical ventilation.
- Duration of hospital stay.
- Duration of rehabilitation unit stay.
- All-cause mortality at Day 90 of surgery.
- Proportion of patients with local and systemic side effects possibly linked to antiseptic use.

Two independent assessors masked to the antiseptic group and to the event will review all post-operative reports of patients needing re-sternotomy during the 90 days following surgery and/or reoperation on saphen venous site during the 30 days following surgery. They will classify the case-report as:

- SWI (mediastinitis or superficial sternal SSI)
- And/or deep or superficial saphen venous SSI
- Or no SSI according to CDC criteria

Disagreements between the two assessors will be resolved by consensus conference among all outcome assessors.

Data collection

Independent clinical research assistants will be available at each participating hospital to help with running the study and data collection. Study documents will be de-identified and stored for 15 years, as per the protocol for non-clinical trial notification (CTN) interventional studies. Data will be entered into the web-based eCRF (CSOnline, Clinsight) and electronically stored on double password-protected computers. Hard copies of data (clinical research files) will be stored in a secure locked office. All personnel involved in data analysis will be masked to study groups. Only the principal investigators and the statisticians will have access to the final data set. The following data will be recorded:

Baseline characteristics and preoperative data

Demographic data (age, gender, height, weight and body mass index); American Society of Anaesthesiologists physical status; EuroSCORE II; comorbidities (active smoking; insulin-dependent diabetes; non-insulin-dependent diabetes; hypertension; hypercholesterolaemia; chronic renal failure; COPD; history of cardiac surgery; atrial fibrillation; key laboratory findings; use of preoperative *Staphylococcus aureus* decontamination; hair removal and modality; number and type (soap with or without antiseptic) of preoperative shower.

Intraoperative data

Type of surgery of the heart (valve, coronary, combined surgery, other) or of the aorta; type of scheduling (elective, semi-elective or emergency); skin scrubbing before skin antisepsis; number of antiseptic applications; number of antiseptic products used; antibiotic prophylaxis: molecule, dose, timing and possible redosing; use of iodophor-impregnated incise drapes; number of internal thoracic arteries sampled; sampling of saphen vein and site; length of surgery (incision to closure); duration of cardiopulmonary bypass; minimal and maximal body temperature during surgery; volume infused during surgery and type; number and types of blood transfusion during surgery; type of vasopressor administered during surgery; use of mechanical cardiac support (extra-corporeal life support [ECLS] or intra-aortic balloon pump); adverse events (especially local and systemic side effects possibly linked to antiseptic use).

Postoperative data until hospital discharge

Type and number of blood product given during the 48h following surgery; type and length of vasopressor and/or inotropic drugs administered during the 48h following surgery; use of mechanic cardiac support (ECLS, intra-aortic balloon pump); atrial fibrillation episode; number and results of blood cultures; number, type and results of bacteriological sampling at surgical site; wound status at surgical site (until dressing withdrawal): local signs of infection (local incisional pain/tenderness, localized redness, heat or swelling, purulent drainage from the superficial incision, superficial/deep incision spontaneously or deliberately opened by the surgeon), status of dressing, date of dressing changes; physical examination (temperature, chest pain, sternal instability); antibiotics used (molecule, duration and indication); results of blood samples (standard lab values); duration of mechanical ventilation; length of stay in ICU, surgical ward and high dependency unit; date of hospital discharge; reoperation at sternal site or saphen venous site occurring after surgery (date and reason); SSI occurrence: type (superficial, deep, organ-space), site and date and hour of SSI diagnosis; adverse events (especially local and systemic side effects possibly linked to antiseptic use) and survival status (if the patient is deceased, date of death).

Postoperative data monthly after surgery (until 90 days following surgery)

Phone contact: date; SSI occurence, date of diagnosis, site and type; planned or unplanned surgical consultation; need for hospital readmission: date, total duration of hospital stay; need for reoperation at sternal site (within 90 days following surgery) or at saphen venous site (within 30 days following surgery): date, reason; date of rehabilitation unit discharge and survival status (if the patient is deceased, date of death).

Safety

According to the French Public Health Code, all suspected unexpected serious adverse events will be reported to the Agence Nationale de Sécurité du Médicament (ANSM). Adverse events will be evaluated at each visit during clinical interview and physical examination. In agreement with ANSM, all serious adverse events related to heart disease (except infections) and not related to antiseptic use will not be to declare immediately but will be reported in the eCRF. Each serious adverse event will be described as completely as possible on the report form designed for this purpose. The initial report will be followed by complementary reports of relevant information as soon as possible.

Sample size calculation

Assuming a 6% reoperation rate in the PVI group, 1863 patients in each treatment arm will be required to demonstrate a 33% reduction of reoperation rate with the use of 2% CHG-70% isopropanol, with statistical risks at 5% and 20% for type I and type II errors, respectively. We are planning to enrol 4100 patients to take into account a maximum patient loss of 10%.

Statistical analysis

The data will be analysed blindly on an intention-to-treat basis. No interim analysis is planned. Demographic data will be described as number and percentage or median and IQR and compared with the χ^2 test or Mann-Whitney test, as appropriate. We will assess antiseptic efficacy with a marginal Cox model and adjusted for covariates that will be significantly imbalanced between groups. We will calculate hazard ratios (HR) and 95% CIs, as well as incidence density and Kaplan-Meier estimates. Proportions of each secondary endpoint assessed at day 30 and day 90 will be compared using similar principles. We will use chi-square tests. A multiple logistic regression will be computed in case of covariates imbalance

between groups. All tests will be two-tailed, stratified by centre and unadjusted for multiple comparisons. Analyses will be done with SAS version 9.4 and R softwares.

ETHICS AND DISSEMINATION

Research ethics approval

The clinical trial will be carried out in line with the principles of the Declaration of Helsinki, the guideline for Good Clinical Practice of the International Conference on Harmonization, in accordance with the French law No. 2012-300 of 5 March 2012 on research involving the human person and with the Clinical Trials Directives 2001/20/EC and 2005/28/EC of the European Parliament. Ethical aspects of this research project have been approved by the ethics committee of Ambroise Paré Hospital (CPP Ile de France VIII, Boulogne-Billancourt, France). The CLEAN 2 trial is registered at the European Clinical Trials Database (EudraCT #2017-005169-33) and summarised at ClinicalTrials.gov with the trial identification number NCT03560193.

Consent

Written informed consent will be requested for each patient prior to enrolment. The investigators will provide clear and precise information about the protocol to the patient before requesting him/her for written informed consent.

Confidentiality

People with direct access to the data will take all necessary precautions to maintain confidentiality. All data collected during the study will be rendered anonymous. Only initials and inclusion number will be registered.

Dissemination policy

The results of the study will be released to the participating physicians, referring physicians and medical community no later than one year after completion of the trial through presentation at scientific conferences and publication in peer-reviewed journals.

The main manuscript will mention the name of the sponsor and all trial sites will be acknowledged. All investigators having included or followed participants in the study will appear with their names under “the CLEAN 2 investigators” in an appendix to the final manuscript. Authorship will be done in accordance with the guidelines of the International Committee of Medical Journal.

Funding statement

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DISCUSSION

This study will provide new knowledge in the field of SSI prevention, addressing questions raised by the Cochrane review on preoperative skin antiseptics aimed at preventing surgical wound infections after clean surgery.[17] In clean surgery, the majority of pathogens responsible for infectious complications come from the skin and skin disinfection has the potential to reduce both the frequency and severity of SSI in proportion to the efficacy of disinfection. The choice of cardiac surgery is based on the severity of SSI with this surgery,

especially mediastinitis, which frequently requires reoperation. We selected centres with experience in SSI prevention studies and already applying all the other SSI prevention measures recommended by our national guidelines. Their number is limited so as to ensure high quality of follow-up by independent clinical research assistants. Stratified randomisation will protect against bias linked to potential variability in surgical practices between centres. Individual boxes containing allocated disinfecting products will follow the patient from the operating room to hospital discharge to ensure respect of treatment group and to facilitate product traceability. The choice of reoperation as the main endpoint is not subject to evaluation bias in an open study.

Our study will have several limitations. First, masking will not be feasible, because the two antiseptic solutions differ in both colour and formulation. However, the microbiologists who will perform all microbiological cultures will be unaware of treatment allocation. More importantly, all cases of suspected SSI will be reviewed by masked independent assessors based on internationally accepted definitions.[16] Second, the two antiseptic solutions contain different alcoholic components and use different application methods. However, these products will be used in their commercially available formulations in France and as recommended by our national guidelines. Further studies will be necessary to determine the more efficient type and concentration of alcohol to be combined with CHG or PVI as well as the optimal concentration of CHG and PVI and optimal method for antiseptic application. Third, we choose incidence of reoperation as the primary endpoint. They can be due to non-infectious causes such as postoperative bleeding, valve-dysfunction etc.., for which the impact of skin disinfection is probably low. However, their main advantage is to be a strong unquestionable endpoint not subject to assessment bias in an open trial. Fourth, adhesion to the study protocol will not be regularly checked by formal audits. However, the health-care providers will attend training sessions designed to homogenise skin preparation practices across hospitals before starting the study and independent clinical research assistants will be available at each participating hospital to monitor the conduct of the trial. Moreover, all study centres will be required to follow French recommendations similar to CDC recommendations for prevention of SSI with no modification allowed during the study period.

We will conduct the first large scale randomised trial adequately powered to compare the efficacy and safety of CHX-alcohol over PVI-alcohol in reducing SSI after clean surgery. Reducing SSI after surgery is associated with decreased length of hospital stay, mortality and overall costs and increased patient satisfaction,[4] which should benefit both the patient and the community. The trial is multicentre and almost all eligible patients will be included and will benefit from all the measures recommended by our national guidelines (similar to CDC guidelines) to prevent SSI. As a result, our finding will be reasonably extended to other cardiac surgery centres, to other clean surgeries and, more generally, to all surgical procedures performed worldwide, even if the proportion of skin pathogens involved in SSI is lower than in clean surgery.

Trial status

The current protocol is version 3.0. The trial is currently in the phase of trial tool development and the opening of centres.

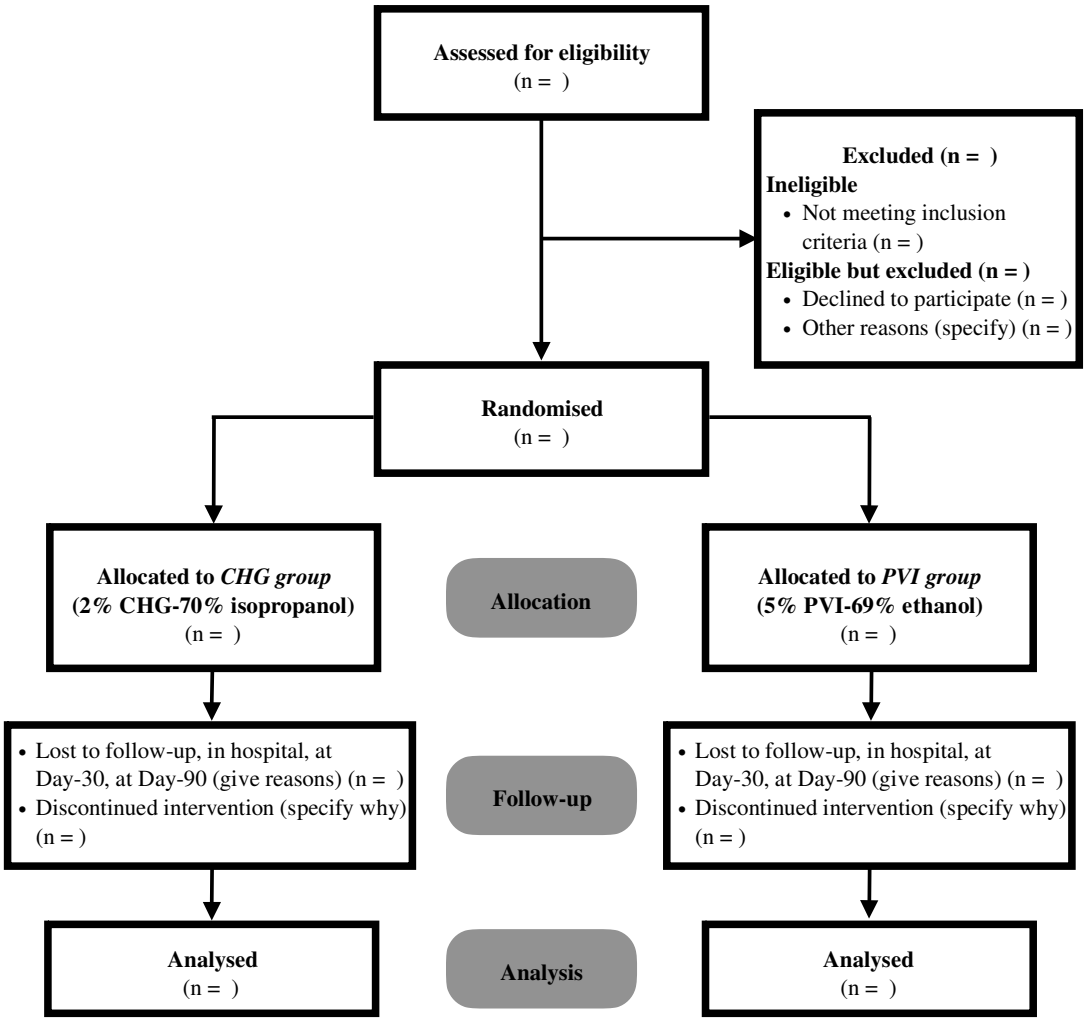


Figure 1. CONSORT diagram (CHG: chlorhexidine, PVI: povidone iodine)

1 World Health Organization. Report on the burden of endemic health care-associated infection worldwide. Geneva: : World Health Organization 2011. http://apps.who.int/iris/bitstream/handle/10665/80135/9789241501507_eng.pdf?sequence=1&isAllowed=y (accessed 30 May 2018).

2 European Centre for Disease Prevention and Control. Annual epidemiological report 2014. Antimicrobial resistance and healthcare-associated infections. 2015.http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-annual-epidemiological-report.pdf (accessed 26 Apr 2016).

3 European Centre for Disease Prevention and Control. Surveillance of surgical site infections in Europe 2010–2011. Eur. Cent. Dis. Prev. Control. 2013.http://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/SSI-in-europe-2010-2011.pdf (accessed 24 Oct 2017).

4 World Health Organization. Global guidelines on the prevention of surgical site infection. Geneva: : World Health Organization 2016. http://apps.who.int/iris/bitstream/10665/250680/1/9789241549882-eng.pdf?ua=1 (accessed 30 May 2018).

5 Finkelstein R, Rabino G, Mashiah T, *et al.* Surgical site infection rates following cardiac surgery: the impact of a 6-year infection control program. *Am J Infect Control* 2005;**33**:450–4. doi:10.1016/j.ajic.2005.07.002

6 Lemaignen A, Birgand G, Ghodhbane W, *et al.* Sternal wound infection after cardiac surgery: incidence and risk factors according to clinical presentation. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis* 2015;**21**:674.e11-18. doi:10.1016/j.cmi.2015.03.025

7 Darouiche RO, Wall MJ, Itani KMF, *et al.* Chlorhexidine–Alcohol versus Povidone–Iodine for Surgical-Site Antisepsis. *N Engl J Med* 2010;**362**:18–26. doi:10.1056/NEJMoa0810988

8 Ngai IM, Van Arsdale A, Govindappagari S, *et al.* Skin Preparation for Prevention of Surgical Site Infection After Cesarean Delivery: A Randomized Controlled Trial. *Obstet Gynecol* 2015;**126**:1251–7. doi:10.1097/AOG.0000000000001118

9 Tuuli MG, Liu J, Stout MJ, *et al.* A randomized trial comparing skin antiseptic agents at cesarean delivery. *N Engl J Med* 2016;**374**:647–55. doi:10.1056/NEJMoa1511048

10 Park HM, Han S-S, Lee EC, *et al.* Randomized clinical trial of preoperative skin antisepsis with chlorhexidine gluconate or povidone-iodine. *Br J Surg* Published Online First: 23 November 2016. doi:10.1002/bjs.10395

11 Broach RB, Paulson EC, Scott C, *et al.* Randomized controlled trial of two alcohol-based preparations for surgical site antisepsis in colorectal surgery. *Ann Surg* 2017;**266**:946–51. doi:10.1097/SLA.0000000000002189

12 Lee I, Agarwal RK, Lee BY, *et al.* Systematic review and cost analysis comparing use of chlorhexidine with use of iodine for preoperative skin antisepsis to prevent surgical site infection. *Infect Control Hosp Epidemiol* 2010;**31**:1219–29. doi:10.1086/657134

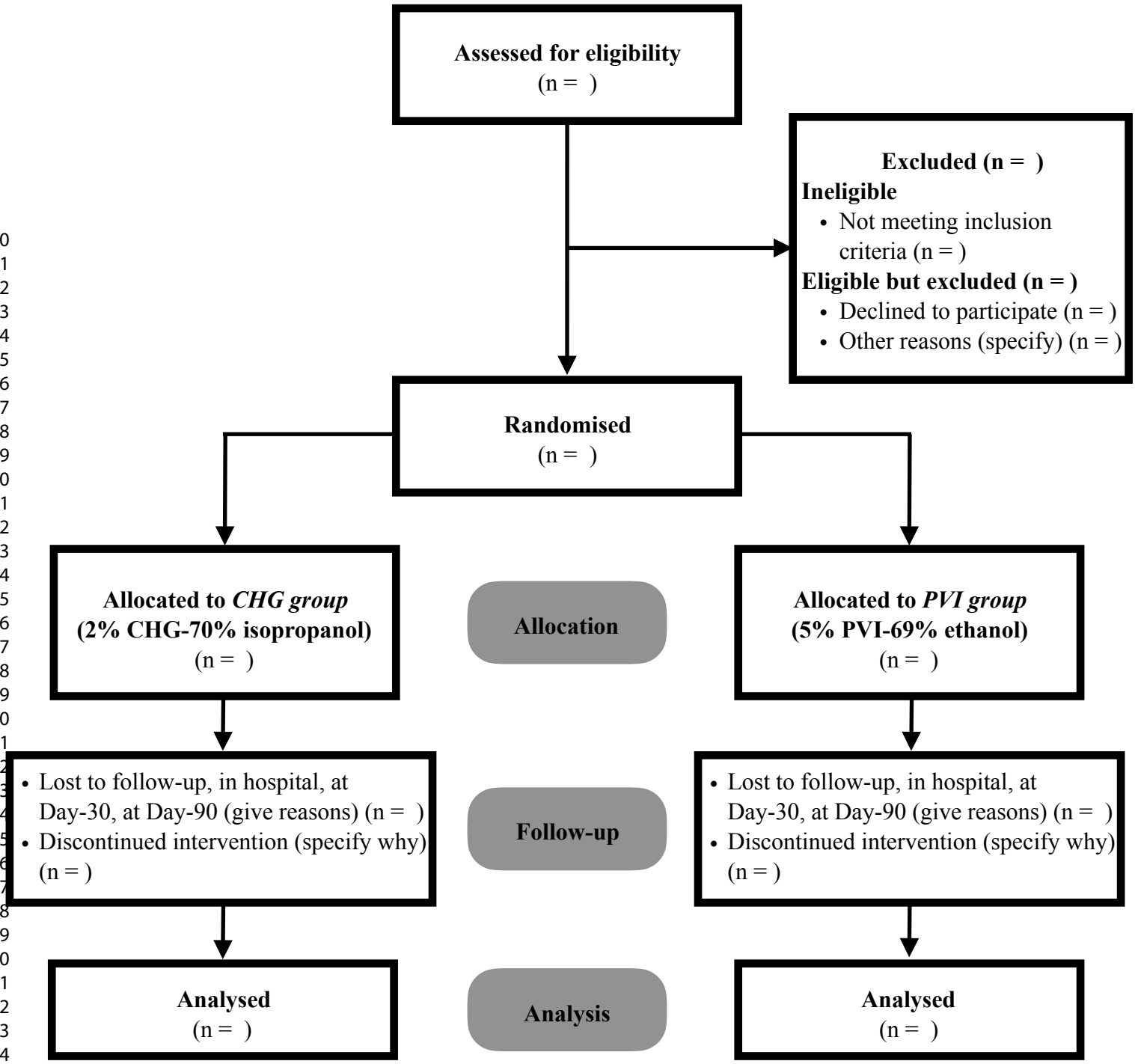
13 Noorani A, Rabey N, Walsh SR, *et al.* Systematic review and meta-analysis of preoperative antisepsis with chlorhexidine versus povidone-iodine in clean-contaminated surgery. *Br J Surg* 2010;**97**:1614–20. doi:10.1002/bjs.7214

14 Kamel C, McGahan L, Polisena J, *et al.* Preoperative skin antiseptic preparations for preventing surgical site infections: a systematic review. *Infect Control Hosp Epidemiol* 2012;**33**:608–17. doi:10.1086/665723

15 Allegranzi B, Bischoff P, de Jonge S, *et al.* New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis* 2016;**16**:e276–87. doi:10.1016/S1473-3099(16)30398-X

16 Center for Disease Control and Prevention, National Healthcare Safety Network. Surveillance definitions for specific types of infections. https://www-cdc-gov.gate2.inist.fr/nhsn/pdfs/pscmanual/17pscnosinfdef_current.pdf (accessed 8 Jul 2018).

17 Edwards PS, Lipp A, Holmes A. Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. *Cochrane Database Syst Rev* 2004;:CD003949. doi:10.1002/14651858.CD003949.pub2


Assessed for eligibility
(n =)
Excluded (n =)
Ineligible
• Not meeting inclusion criteria (n =)
Eligible but excluded (n =)
• Declined to participate (n =)
• Other reasons (specify) (n =)
Randomised
(n =)
Allocated to *CHG group*
(2% CHG-70% isopropanol)
(n =)
Allocated to *PVI group*
(5% PVI-69% ethanol)
(n =)
Allocation
• Lost to follow-up, in hospital, at Day-30, at Day-90 (give reasons) (n =)
• Discontinued intervention (specify why) (n =)
• Lost to follow-up, in hospital, at Day-30, at Day-90 (give reasons) (n =)
• Discontinued intervention (specify why) (n =)
Follow-up
Analysed
(n =)
Analysed
(n =)
Analysis

BMJ Open

Multicentre, open label, randomised, controlled clinical trial comparing 2% chlorhexidine – 70% isopropanol and 5% povidone iodine – 69% ethanol for skin antisepsis in reducing surgical-site infection after cardiac surgery: the CLEAN 2 study protocol

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Multicentre, open label, randomised, controlled clinical trial comparing 2% chlorhexidine – 70% isopropanol and 5% povidone iodine – 69% ethanol for skin antisepsis in reducing surgical-site infection after cardiac surgery: the CLEAN 2 study protocol

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ABSTRACT

Introduction: Surgical site infection (SSI) is the second most frequent cause of healthcare-associated infection worldwide and is associated with increased morbidity, mortality and healthcare costs. Cardiac surgery is clean surgery with low incidence of SSI, ranging from 2 to 5%, but with potentially severe consequences.

Perioperative skin antisepsis with an alcohol-based antiseptic solution is recommended to prevent SSI, but the superiority of chlorhexidine (CHG)-alcohol over povidone iodine (PVI)-alcohol, the two most common alcohol-based antiseptic solutions used worldwide, is controversial. We aim to evaluate whether 2% CHG-70% isopropanol is more effective than 5% PVI-69% ethanol in reducing the incidence of reoperation after cardiac surgery.

Methods and analysis: The CLEAN 2 study is a multicentre, open label, randomised, controlled clinical trial of 4100 patients undergoing cardiac surgery. Patients will be randomized in 1:1 ratio to receive either 2% CHG – 70% isopropanol or 5% PVI – 69% ethanol for perioperative skin preparation. The primary endpoint is the proportion of patients undergoing any re-sternotomy between Day 0 and Day 90 after initial surgery and/or any reoperation on saphen venous/radial artery surgical site between Day 0 and Day 30 after initial surgery. Data will be analysed on the intention-to-treat principle.

Ethics and dissemination: This protocol has been approved by an independent ethics committee and will be carried out according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines. The results of this study will be disseminated through presentation at scientific conferences and publication in peer-reviewed journals.

Trial registration: EudraCT 2017-005169-33 & NCT03560193.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This randomised study is aimed at being the largest one performed comparing the efficacy of perioperative skin preparation with either alcohol-based CHG or alcohol-based PVI in reducing severe postoperative complications.
- The primary endpoint, the incidence of any reoperation at both surgical sites, is a predefined strong and unquestionable criterion, underscoring the need – and the risk of bias – to assess the reality of SSI.

- Limitations due to the lack of masking related to the nature of the intervention will be reduced by assessment of all SSIs by an adjudication committee masked to the antiseptic group.

INTRODUCTION

Surgical site infection (SSI) is the second most frequent cause of healthcare-associated infections with an incidence up to 19% depending of the type of surgery, and ranges from simple wound discharge to life-threatening condition. [1–3] It is associated with increased hospital stay, prolonged antibiotic use and occasional need for reoperation, and is responsible for rising mortality and healthcare costs estimated at € 10 billion per year in the USA. [4]

Cardiac surgery is considered as clean surgery. Incidence of SSI is lower than with other types of surgery, ranging from 2 to 5% depending on the definitions used, but its consequences may be greater in terms of both frequency and severity. [5,6] Because pathogens involved in SSI after clean surgery come mostly from skin, perioperative skin antisepsis plays a major role in SSI prevention.

The most common antiseptic agents used for skin disinfection before surgery are aqueous or alcoholic formulations of chlorhexidine (CHG) or povidone iodine (PVI), both of which are available at various concentrations. Several studies have compared their respective efficacy and safety in reducing SSI. Nevertheless, results have been contradictory, probably due to different comparators (concentrations, combination with alcohol or water…), different SSI definitions, and different lengths of follow-up.[7–11] In 2010, a meta-analysis of seven randomised-controlled trials (including 3437 patients) compared CHG (at a concentration of 0.5 to 4%) with PVI or other iodophors (at a concentration of 7 to 10%) for preoperative skin antisepsis in clean and clean-contaminated surgery.[12] The use of CHG was associated with fewer SSIs (adjusted RR 0.64; 95%CI 0.51-0.80) compared with iodine. Another meta-analysis of six randomised-controlled trials comparing CHG (at a concentration of 0.5 to 4%) to PVI (at a concentration of 7.5 to 10%) for preoperative skin antisepsis yielded similar findings [OR of 0.68 (0.50-0.94; p=0.019)].[13] However, in most studies CHG was combined with alcohol and PVI was not, which meant that two antiseptics were being compared to only one. A review conducted in 2012 was unable to draw any conclusion about which surgical site antiseptic more effectively reduces SSI.[14] Recently, Tuuli and colleagues were the first to conduct a large trial comparing CHG and PVI in alcoholic formulations for skin disinfection before caesarean section.[9] Interestingly, both antiseptic formulations used the same alcohol at the same concentration and both were applied similarly, using an applicator. Although this was the first study demonstrating a benefit of 2% CHG-70% isopropanol over 8.3% PVI-70% isopropanol, it was monocentre, and did not address all potential methodological limits. Especially, the choice of superficial or deep surgical-site

infection as primary endpoint assessed by the surgeon (the diagnosis was made by the treating physician and verified through chart review by the principal investigator, who was unaware of the study-group assignments) may generate interpretation biases in an open study. Moreover, the one dual microbial source of pathogens of both skin and vaginal origins in SSI after caesarean delivery and immune modulation in pregnancy raises questions about whether the results of trials of preoperative skin antisepsis for caesarean delivery can be extrapolated to other surgical procedures.

Furthermore, the possible superiority of CHG over PVI was not confirmed in a second monocentre trial involving 1404 women requiring caesarean section.[8] Lastly, in a third assessor-blinded, monocentre, randomised trial involving 802 patients scheduled for elective clean-contaminated colorectal surgery, the use of PVI-alcohol failed to meet the criterion for non-inferiority in SSI occurrence compared with CHG-alcohol.[11] These contradictory results may explain the lack of universal use of CHG-alcohol for skin antisepsis in surgery despite the recommendations of the World Health Organization (WHO).[15]

The prevalence and potential serious consequences of SSI in cardiac surgery, especially mediastinitis, support a large randomised controlled trial in this setting. We hypothesize that perioperative skin preparation with 2% CHG-70% isopropanol is more effective than 5% PVI-69% ethanol as a means of preventing any reoperation after cardiac surgery.

METHODS AND ANALYSIS

Trial design and setting

The CLEAN 2 trial is an investigator-initiated, publicly-funded multicentre, randomised, controlled, open-label clinical trial with concealed allocation of patients scheduled to undergo cardiac surgery and to receive 1:1 either 2% CHG – 70% isopropanol or 5% PVI– 69% ethanol for perioperative skin preparation. Randomisation will be carried out through a secure web-based randomisation system and stratified by centre (Fig. 1).

The trial will take place at seven university and non-university French hospitals. All participating centres perform more than 500 cardiac surgical procedures per year.

Participant eligibility and consent

During surgery or preoperative anaesthesia consultation, all consecutive patients will be considered candidates for inclusion in the study if they meet all of the inclusion criteria and

none of the exclusion criteria. Eligible patients will receive oral and written information and will be enrolled after having given written consent.

Inclusion criteria

- Adult patients (age ≥ 18 years) admitted in one of the participating centres
- Scheduled to undergo surgery of the heart (valve, coronary or combined surgery) or of the aorta via median sternotomy
- Having signed informed consent form

Exclusion criteria

- Patients with known allergies to CHG, PVI, isopropanol or ethanol
- Surgery for heart transplantation
- Any signs of inflammation or sternal instability at the site of sternotomy or operation for infection (sternal wound infection or endocarditis)
- History of cardiac surgery within 3 months preceding enrolment
- Participation in another clinical trial aimed at reducing SSI
- Patients already enrolled in this study
- Pregnant or breastfeeding women and potentially childbearing women without effective contraception
- Patients not benefiting from a Social Security scheme or not benefiting from it through a third party
- Persons benefiting from enhanced protection, namely minors, persons deprived of their liberty by a judicial or administrative decision and adults under legal protection.

Assignment of interventions

A computer-generated block-randomisation sequence will be performed by a statistician not involved in either screening the patients or assessing outcomes. Randomisation will be carried out using a secure web-based randomisation system with stratification by centre. The randomisation will be accessible to investigators through user identification and a personal password and will become effective following confirmation of inclusion and exclusion criteria. Patients will be randomly assigned (1:1) to one of two study groups according to the antiseptic solution used to disinfect the skin before surgery and during all dressing changes (Fig. 1). To avoid randomisation of a patient with cancelled surgery, this will be done a few days before or on the day of surgery.

Interventions

1- *CHG group:* The surgical site will be largely disinfected using applicators of 2% CHG-70% isopropanol (ChloraPrep™, CareFusion). According to local practices, antiseptic application will be preceded (two-step procedure) or not (one-step procedure) by skin scrubbing with 4% CHG (Hibiscrub™, Molnlycke Health Care).

2- *PVI group*: The surgical site will be largely disinfected using sterile gauzes soaked with 5% PVI-69% ethanol (Bétadine alcoolique™, MEDA Pharma SAS). According to local practices, antiseptic application will be preceded (two-step procedure) or not (one-step procedure) by skin scrubbing with 4% PVI (Bétadine Scrub™, MEDA Pharma SAS).

In order to ensure respect of treatment group and to achieve traceability, individual boxes containing all disinfecting products required for disinfecting the skin before surgery and during patient care will be supplied. According to randomisation, each patient will have his own box, which will follow him from the operating room to hospital discharge.

The following care procedures will be applied to all patients and controlled throughout the duration of the study:

- At least one total body shower during the 24 h preceding surgery, using either plain soap or antiseptic soap
- Hair removal if required with clipper (no shaving) before surgery
- Antibiotic prophylaxis according to the French recommendations [16] applied 30 min prior to incision, and with appropriate reinjection if required for prolonged surgery. No re-administration during the postoperative period.
- Antiseptic application by moving back and forth for at least 30 s, starting at the incision site and then extending to the entire work area. The surgical field extends from the jaw to the shoulders and down to the tip of both feet in case of surgery with harvesting of the saphenous vein. In the event of surgery without saphenous vein harvesting, the field stops at the knees. According to local practices, the antiseptic solution will be applied once or twice, preceded or not by skin scrubbing with an antiseptic soap.
- Application of large sterile drapes once the work area is dry.

In each centre, before the beginning of the inclusion, a list of care policy for prevention of SSI (*Staphylococcus aureus* decontamination, antimicrobial-coated sutures, adhesive incises

drapes with antiseptics, antimicrobial dressings…) will be established and will not be modified throughout the duration of the study.

Study outcomes

Primary endpoint

The primary outcome will be the proportion of patients undergoing either any re-sternotomy occurring between Day 0 and Day 90 after surgery or any reoperation on saphen venous/radial artery site occurring between Day 0 and Day 30 after surgery or both.

Secondary endpoints

- Proportion of patients with mediastinitis according to the Center for Disease Control and Prevention (CDC) criteria [17] occurring by Day 90 after surgery and pathogens involved.
- Proportion of patients with deep incisional SSI at saphen venous/radial artery site, superficial incisional SSI at sternal or saphen venous/radial artery sites according to the CDC criteria [17] occurring by Day 30 after surgery and the pathogens involved.
- Proportion of patients with sternal wound infection (SWI) requiring reoperation, occurring by Day 90.
- Proportion of patients with SSI at saphen venous/radial artery site requiring reoperation, occurring by Day 30.
- Proportion of patients with unexpected need for readmission to intensive care unit (ICU) or re-hospitalisation.
- Duration of ICU stay.
- Duration of stay under mechanical ventilation.
- Duration of hospital stay.
- Duration of rehabilitation unit stay.
- All-cause mortality at Day 90 of surgery.
- Proportion of patients with local and systemic side effects possibly linked to antiseptic use.

Two independent assessors masked to the antiseptic group and to the event will review all post-operative reports of patients needing re-sternotomy during the 90 days following surgery and/or reoperation on saphen venous/radial artery site during the 30 days following surgery. They will classify the case-report as:

- SWI (mediastinitis or superficial sternal SSI)
- And/or deep or superficial saphen venous/radial artery SSI
- Or no SSI according to CDC criteria

Disagreements between the two assessors will be resolved by consensus conference among all outcome assessors.

Data collection

Independent clinical research assistants will be available at each participating hospital to help in running the study and with data collection. Study documents will be de-identified and stored for 15 years, as per the protocol for non-clinical trial notification (CTN) interventional studies. Data will be entered into the web-based eCRF (CSOnline, Clinsight) and electronically stored on double password-protected computers. Hard copies of data (clinical research files) will be stored in a secure locked office. All personnel involved in data analysis will be masked to study groups. Only the principal investigators and the statisticians will have access to the final data set. The following data will be recorded:

Baseline characteristics and preoperative data

Demographic data (age, gender, height, weight and body mass index); American Society of Anaesthesiologists physical status; EuroSCORE II; comorbidities (active smoking; insulin-dependent diabetes; non-insulin-dependent diabetes; hypertension; hypercholesterolaemia; chronic renal failure; COPD; history of cardiac surgery; atrial fibrillation; key laboratory findings; use of preoperative *Staphylococcus aureus* decontamination; hair removal and modality; number and type (soap with or without antiseptic) of preoperative showers.

Intraoperative data

Type of surgery of the heart (valve, coronary, combined surgery, other) or of the aorta; type of scheduling (elective, semi-elective or emergency); skin scrubbing before skin antisepsis; number of antiseptic applications; number of antiseptic products used; antibiotic prophylaxis: molecule, dose, timing and possible redosing; use of iodophor-impregnated incise drapes; number of internal thoracic arteries sampled; sampling of saphen vein or radial artery, site open or endoscopic; length of surgery (incision to closure); duration of cardiopulmonary bypass; minimal and maximal body temperature during surgery; volume infused during surgery and type; number and types of blood transfusion during surgery; type of vasopressor administered during surgery; use of mechanical cardiac support (extra-corporeal life support

[ECLS] or intra-aortic balloon pump); adverse events (especially local and systemic side effects possibly linked to antiseptic use).

Postoperative data until hospital discharge

Type and number of blood products given during the 48h following surgery; type and length of vasopressor and/or inotropic drugs administered during the 48h following surgery; use of mechanical cardiac support (ECLS, intra-aortic balloon pump); atrial fibrillation episode; number and results of blood cultures; number, type and results of bacteriological sampling at surgical site; wound status at surgical site (until dressing withdrawal): local signs of infection (local incisional pain/tenderness, localized redness, heat or swelling, purulent drainage from the superficial incision, superficial/deep incision spontaneously or deliberately opened by the surgeon), status of dressing, date of dressing changes; physical examination (temperature, chest pain, sternal instability); antibiotics used (molecule, duration and indication); results of blood samples (standard lab values); duration of mechanical ventilation; length of stay in ICU, surgical ward and high dependency unit; date of hospital discharge; reoperation at sternal site or saphen venous/radial artery site occurring after surgery (date and reason); SSI occurrence: type (superficial, deep, organ-space), site and date and hour of SSI diagnosis; adverse events (especially local and systemic side effects possibly linked to antiseptic use) and survival status (if the patient is deceased, date of death).

Postoperative data monthly after surgery (until 90 days following surgery)

Phone contact: date; SSI occurrence, date of diagnosis, site and type; planned or unplanned surgical consultation; need for hospital readmission: date, total duration of hospital stay; need for reoperation at sternal site (within 90 days following surgery) or at saphen venous/radial artery site (within 30 days following surgery): date, reason; date of rehabilitation unit discharge and survival status (if the patient is deceased, date of death).

Safety

According to the French Public Health Code, all suspected unexpected serious adverse events will be reported to the Agence Nationale de Sécurité du Médicament (ANSM). Adverse events will be evaluated at each visit during clinical interview and physical examination. In agreement with ANSM, all serious adverse events related to heart disease (except infections) and not related to antiseptic use will not be declared immediately but will be reported in the eCRF. Each serious adverse event will be described as completely as possible on the report

form designed for this purpose. The initial report will be followed by complementary reports of relevant information as soon as possible.

Sample size calculation

Assuming a 6% reoperation rate in the PVI group,[6] 1863 patients in each treatment arm will be required to demonstrate a 33% reduction of reoperation rate with the use of 2% CHG-70% isopropanol, with statistical risks at 5% and 20% for type I and type II errors, respectively. The sample size calculation is based on the two-sided test. We are planning to enrol 4100 patients to take into account a maximum patient loss of 10%.

Statistical analysis

The data will be analysed blindly on an intention-to-treat basis. No interim analysis is planned. Demographic data will be described as number and percentage or median and IQR and compared with the χ^2 test or Mann-Whitney test, as appropriate. For primary analysis, incidence of reoperation between groups will be compared with χ^2 test. We will assess antiseptic efficacy with a marginal Cox model and adjusted for covariates that will be significantly imbalanced between groups. We will calculate hazard ratios (HR) and 95% CIs, as well as incidence density and Kaplan-Meier estimates. Proportions of each secondary endpoint assessed at day 30 and day 90 will be compared using similar principles. We will use chi-square tests. A multiple logistic regression will be computed with covariates clinically relevant as regard as our outcomes (*Centre*; *Patients' characteristics:* age, gender, body mass index, EuroSCORE II, active smoking, insulin-dependent diabetes, use of preoperative *Staphylococcus aureus* decontamination; *Intraoperative data:* type of surgery of the heart [valve, coronary, combined surgery, other] or of the aorta, type of scheduling [elective, semi-elective or emergency], skin scrubbing before skin antisepsis; number of antiseptic application, use of iodophor-impregnated incise drapes, number of internal thoracic arteries sampled, length of surgery, duration of cardiopulmonary bypass, minimal body temperature during surgery, volume infused during surgery, use of mechanic cardiac support) and with covariates statistically relevant (covariates with difference between groups < 0.20 in the

univariate analysis). All tests will be two-tailed, stratified by centre and unadjusted for multiple comparisons. Analyses will be done with SAS version 9.4 and R software.

Patient and Public Involvement

The ethical committee, composed of patients' representatives, considered if the research is conformed to patients' priorities, experience and preferences. Each patient, admitted in a participating centre, is screened and enrolled by the attending physicians according to the protocol. The burden of the intervention is assessed by patients themselves. Each patient, after the end of the study, will have the opportunity to obtain the results if they are interested, all information is provided at inclusion in consent and information forms. No patient was involved in the recruitment to and the conduct of the study.

ETHICS AND DISSEMINATION

Research ethics approval

The clinical trial will be carried out in line with the principles of the Declaration of Helsinki, the guideline for Good Clinical Practice of the International Conference on Harmonization, in accordance with the French law No. 2012-300 of 5 March 2012 on research involving the human person and with the Clinical Trials Directives 2001/20/EC and 2005/28/EC of the European Parliament. Ethical aspects of this research project have been approved by the ethics committee of Ambroise Paré Hospital (CPP Ile de France VIII, Boulogne-Billancourt, France). The CLEAN 2 trial is registered at the European Clinical Trial Database on 27 December 2017 (EudraCT #2017-005169-33) and summarised at ClinicalTrials.gov with the trial identification number NCT03560193.

Consent

Written informed consent will be requested for each patient prior to enrolment. The investigators will provide clear and precise information to the patient about the protocol before asking him/her for written informed consent.

Confidentiality

People with direct access to the data will take all necessary precautions to maintain confidentiality. All data collected during the study will be rendered anonymous. Only initials and inclusion number will be registered.

Dissemination policy

The results of the study will be released to the participating physicians, referring physicians and medical community no later than one year after completion of the trial through presentation at scientific conferences and publication in peer-reviewed journals.

The main manuscript will mention the name of the sponsor and all trial sites will be acknowledged. All investigators having included or followed participants in the study will appear with their names under "the CLEAN 2 investigators" in an appendix to the final manuscript. Authorship will be done in accordance with the guidelines of the International Committee of Medical Journal. No professional writer will be used.

DISCUSSION

This study will provide new knowledge in the field of SSI prevention, addressing questions raised by the Cochrane review on preoperative skin antiseptics aimed at preventing surgical wound infections after clean surgery.[18] In clean surgery, the majority of pathogens responsible for infectious complications come from the skin and skin disinfection has the potential to reduce both the frequency and severity of SSI in proportion to the efficacy of disinfection. The choice of cardiac surgery is based on the severity of SSI with this surgery, especially mediastinitis, which frequently requires reoperation. We selected centres with experience in SSI prevention studies and already applying all the other SSI prevention measures recommended by our national guidelines. Their number is limited so as to ensure high quality of follow-up by independent clinical research assistants. Stratified randomisation will protect against bias linked to potential variability in surgical practices between centres. Individual boxes containing allocated disinfecting products will follow the patient from the operating room to hospital discharge to ensure respect of treatment group and to facilitate product traceability. The choice of reoperation as the main endpoint is not subject to evaluation bias in an open study.

Our study will have several limitations. First, masking will not be feasible, because the two antiseptic solutions differ in both colour and formulation. However, the microbiologists who will perform all microbiological cultures will be unaware of treatment allocation. More importantly, all cases of suspected SSI will be reviewed by masked independent assessors based on internationally accepted definitions.[17] Second, the two antiseptic solutions contain different alcoholic components and use different application methods. However, these products will be used in their commercially available formulations in France and as recommended by our national guidelines. Further studies will be necessary to determine the

more efficient type and concentration of alcohol to be combined with CHG or PVI as well as the optimal concentration of CHG and PVI and optimal method for antiseptic application. Third, we have chosen incidence of reoperation as the primary endpoint. They can be due to non-infectious causes such as postoperative bleeding, valve-dysfunction etc.., for which the impact of skin disinfection is probably low. However, their main advantage is to be a strong unquestionable endpoint not subject to assessment bias in an open trial. Fourth, adhesion to the study protocol will not be regularly checked by formal audits. However, the health-care providers will attend training sessions designed to homogenise skin preparation practices across hospitals before starting the study and independent clinical research assistants will be available at each participating hospital to monitor the conduct of the trial. Moreover, all study centres will be required to follow French recommendations similar to CDC recommendations for prevention of SSI with no modification allowed during the study period.

We will conduct the first large scale randomised trial adequately powered to compare the efficacy and safety of CHX-alcohol over PVI-alcohol in reducing SSI after clean surgery. Reducing SSI after surgery is associated with decreased length of hospital stay, mortality and overall costs and increased patient satisfaction,[4] which should benefit both the patient and the community. The trial is multicentre and almost all eligible patients will be included and will benefit from all the measures recommended by our national guidelines (similar to CDC guidelines) to prevent SSI. As a result, our findings will be reasonably extended to other cardiac surgery centres, to other clean surgeries and, more generally, to all surgical procedures performed worldwide, even if the proportion of skin pathogens involved in SSI is lower than in clean surgery.

Trial status

The current protocol is version 3.0 dated 12 September 2018. The trial is currently recruiting patients. The inclusion process started on 17 September 2018 and the number of patients included to date (22 January 2019) is 218. The estimated length of inclusion time is 18 months.

CONTRIBUTOR SHIP STATEMENT

MB and OM conceived the study, coordinated its design, wrote the manuscript and drafted the manuscript. PC, TK, LC, MD, PD, VE, EF, LL, DL, PL, NN, JYN, AO, JCR, BR, SR, JCL and JFT read and were involved in critical appraisal and revision of the manuscript. SR and JFT provided statistical expertise. All authors approved the final manuscript prior to submission.

COMPETITING INTERESTS

OM has received grant support from 3M and Carefusion-BD and honoraria for giving lectures from 3M and Carefusion-BD.

FUNDING

This work is being funded by unrestricted research grants from the French Ministry of Social Affairs and Health (#16-0619) and CareFusion/ Becton Dickinson. Funders will have no role in the trial initiation, study design, choice of antiseptic products, data collection, data analysis, data interpretation or writing of the report.

DATA SHARING STATEMENT

University Hospital of Poitiers is responsible for obtaining the agreement of all parties involved in the study so as to guarantee direct access to all study sites, source data, source documents, and reports.

REFERENCES

1 World Health Organization. Report on the burden of endemic health care-associated infection worldwide. Geneva: World Health Organization 2011. http://apps.who.int/iris/bitstream/handle/10665/80135/9789241501507_eng.pdf?sequence=1&isAllowed=y (accessed 30 May 2018).

2 European Centre for Disease Prevention and Control. Annual epidemiological report 2014. Antimicrobial resistance and healthcare-associated infections. 2015.http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-annual-epidemiological-report.pdf (accessed 26 Apr 2016).

3 European Centre for Disease Prevention and Control. Surveillance of surgical site infections in Europe 2010–2011. Eur. Cent. Dis. Prev. Control. 2013.http://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/SSI-in-europe-2010-2011.pdf (accessed 24 Oct 2017).

4 World Health Organization. Global guidelines on the prevention of surgical site infection. Geneva: World Health Organization 2016. http://apps.who.int/iris/bitstream/10665/250680/1/9789241549882-eng.pdf?ua=1 (accessed 30 May 2018).

5 Finkelstein R, Rabino G, Mashiah T, *et al.* Surgical site infection rates following cardiac surgery: the impact of a 6-year infection control program. *Am J Infect Control* 2005;**33**:450–4. doi:10.1016/j.ajic.2005.07.002

6 Lemaignen A, Birgand G, Ghodhbane W, *et al.* Sternal wound infection after cardiac surgery: incidence and risk factors according to clinical presentation. *Clin Microbiol Infect* 2015;**21**:674.e11-18. doi:10.1016/j.cmi.2015.03.025

7 Darouiche RO, Wall MJ, Itani KMF, *et al.* Chlorhexidine–Alcohol versus Povidone–Iodine for Surgical-Site Antisepsis. *N Engl J Med* 2010;**362**:18–26. doi:10.1056/NEJMoa0810988

8 Ngai IM, Van Arsdale A, Govindappagari S, *et al.* Skin Preparation for Prevention of Surgical Site Infection After Cesarean Delivery: A Randomized Controlled Trial. *Obstet Gynecol* 2015;**126**:1251–7. doi:10.1097/AOG.0000000000001118

9 Tuuli MG, Liu J, Stout MJ, *et al.* A randomized trial comparing skin antiseptic agents at cesarean delivery. *N Engl J Med* 2016;**374**:647–55. doi:10.1056/NEJMoa1511048

10 Park HM, Han S-S, Lee EC, *et al.* Randomized clinical trial of preoperative skin antisepsis with chlorhexidine gluconate or povidone-iodine. *Br J Surg* 2017;104:e145–50. doi:10.1002/bjs.10395

11 Broach RB, Paulson EC, Scott C, *et al.* Randomized controlled trial of two alcohol-based preparations for surgical site antisepsis in colorectal surgery. *Ann Surg* 2017;**266**:946–51. doi:10.1097/SLA.0000000000002189

12 Lee I, Agarwal RK, Lee BY, *et al.* Systematic review and cost analysis comparing use of chlorhexidine with use of iodine for preoperative skin antisepsis to prevent surgical site infection. *Infect Control Hosp Epidemiol* 2010;**31**:1219–29. doi:10.1086/657134

13 Noorani A, Rabey N, Walsh SR, *et al.* Systematic review and meta-analysis of preoperative antisepsis with chlorhexidine versus povidone-iodine in clean-contaminated surgery. *Br J Surg* 2010;**97**:1614–20. doi:10.1002/bjs.7214

14 Kamel C, McGahan L, Polisena J, *et al.* Preoperative skin antiseptic preparations for preventing surgical site infections: a systematic review. *Infect Control Hosp Epidemiol* 2012;**33**:608–17. doi:10.1086/665723

15 Allegranzi B, Bischoff P, de Jonge S, *et al.* New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis* 2016;**16**:e276–87. doi:10.1016/S1473-3099(16)30398-X

16 SFAR. Antibioprophylaxie en chirurgie et médecine interventionnelle (patients adultes). 2018. https://sfar.org/antibioprophylaxie-en-chirurgie-et-medecine-interventionnelle-patients-adultes-maj2018/ (accessed 7 Jan 2019).

17 Center for Disease Control and Prevention, National Healthcare Safety Network. Surveillance definitions for specific types of infections. https://www-cdc-gov.gate2.inist.fr/nhsn/pdfs/pscmanual/17pscnosinfdef_current.pdf (accessed 8 Jul 2018).

18 Edwards PS, Lipp A, Holmes A. Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. *Cochrane Database Syst Rev* 2004;CD003949. doi:10.1002/14651858.CD003949.pub2

546 Figure 1. CONSORT diagram (CHG: chlorhexidine, PVI: povidone iodine)

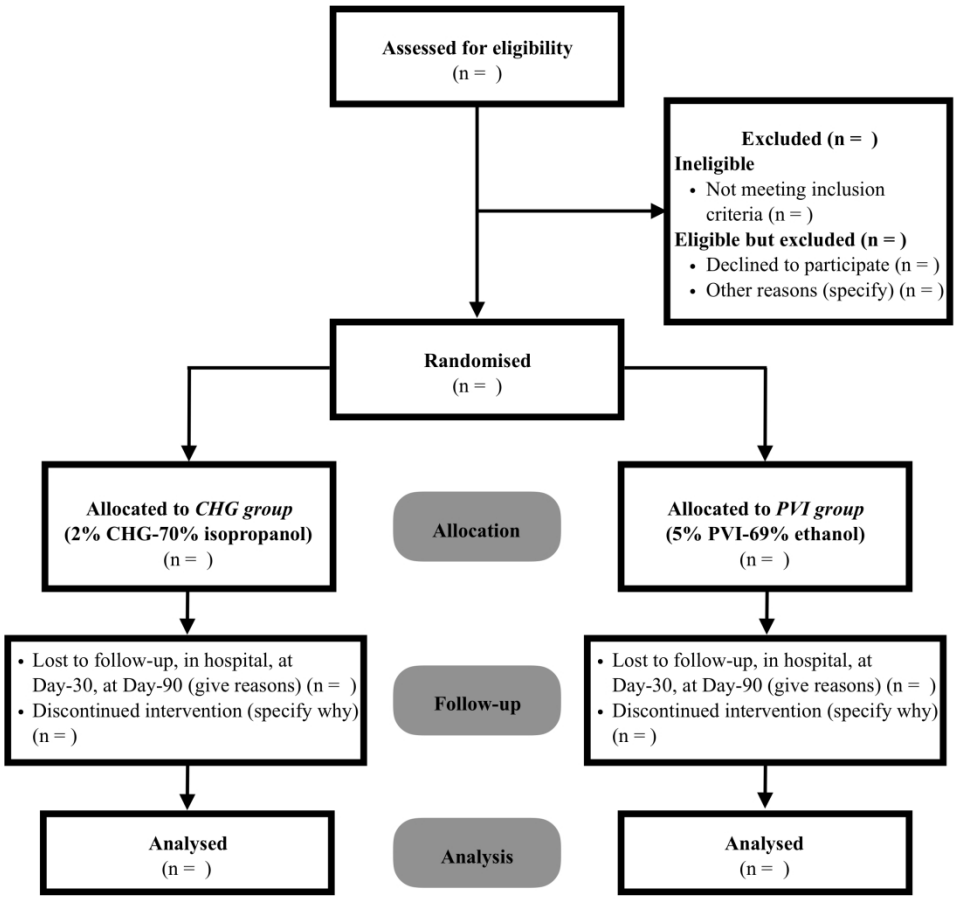

Figure 1. CONSORT diagram (CHG: chlorhexidine, PVI: povidone iodine)

209x209mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4 & 13
	2b	All items from the World Health Organization Trial Registration Data Set	1, 3, 4, 7, 8, 9, 10, 12, 13, 14, 16
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 2, 3, 17
	5b	Name and contact information for the trial sponsor	3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6
	6b	Explanation for choice of comparators	6, 7
Objectives	7	Specific objectives or hypotheses	7

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9, 11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9, 16
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7, 11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10, 11, 13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11, 12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9, 10, 11, 12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11, 12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, 8, 14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11, 12, 13, 17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11, 13, 17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	15
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Multicentre, open label, randomised, controlled clinical trial comparing 2% chlorhexidine – 70% isopropanol and 5% povidone iodine – 69% ethanol for skin antisepsis in reducing surgical-site infection after cardiac surgery: the CLEAN 2 study protocol

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Infectious diseases, Anaesthesia
Keywords:	Surgical site infection, skin antisepsis, Cardiac surgery < SURGERY, chlorhexidine, povidone iodine

Multicentre, open label, randomised, controlled clinical trial comparing 2% chlorhexidine – 70% isopropanol and 5% povidone iodine – 69% ethanol for skin antisepsis in reducing surgical-site infection after cardiac surgery: the CLEAN 2 study protocol

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Surgical site infection, skin antisepsis, cardiac surgery, chlorhexidine, povidone iodine

ABSTRACT

Introduction: Surgical site infection (SSI) is the second most frequent cause of healthcare-associated infection worldwide and is associated with increased morbidity, mortality and healthcare costs. Cardiac surgery is clean surgery with low incidence of SSI, ranging from 2 to 5%, but with potentially severe consequences.

Perioperative skin antisepsis with an alcohol-based antiseptic solution is recommended to prevent SSI, but the superiority of chlorhexidine (CHG)-alcohol over povidone iodine (PVI)-alcohol, the two most common alcohol-based antiseptic solutions used worldwide, is controversial. We aim to evaluate whether 2% CHG-70% isopropanol is more effective than 5% PVI-69% ethanol in reducing the incidence of reoperation after cardiac surgery.

Methods and analysis: The CLEAN 2 study is a multicentre, open label, randomised, controlled clinical trial of 4100 patients undergoing cardiac surgery. Patients will be randomized in 1:1 ratio to receive either 2% CHG – 70% isopropanol or 5% PVI – 69% ethanol for perioperative skin preparation. The primary endpoint is the proportion of patients undergoing any re-sternotomy between Day 0 and Day 90 after initial surgery and/or any reoperation on saphenous vein/radial artery surgical site between Day 0 and Day 30 after initial surgery. Data will be analysed on the intention-to-treat principle.

Ethics and dissemination: This protocol has been approved by an independent ethics committee and will be carried out according to the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines. The results of this study will be disseminated through presentation at scientific conferences and publication in peer-reviewed journals.

Trial registration: EudraCT 2017-005169-33 & NCT03560193.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This randomised study is aimed at being the largest one performed comparing the efficacy of perioperative skin preparation with either alcohol-based CHG or alcohol-based PVI in reducing severe postoperative complications.
- The primary endpoint, the incidence of any reoperation at both surgical sites, is a predefined strong and unquestionable criterion, underscoring the need – and the risk of bias – to assess the reality of SSI.

- Limitations due to the lack of masking related to the nature of the intervention will be reduced by assessment of all SSIs by an adjudication committee masked to the antiseptic group.

INTRODUCTION

Surgical site infection (SSI) is the second most frequent cause of healthcare-associated infections with an incidence up to 19% depending of the type of surgery, and ranges from simple wound discharge to life-threatening condition.[1–3] It is associated with increased hospital stay, prolonged antibiotic use and occasional need for reoperation, and is responsible for rising mortality and healthcare costs estimated at € 10 billion per year in the USA. [4]

Cardiac surgery is considered as clean surgery. Incidence of SSI is lower than with other types of surgery, ranging from 2 to 5% depending on the definitions used, but its consequences may be greater in terms of both frequency and severity.[5,6] Because pathogens involved in SSI after clean surgery come mostly from skin, perioperative skin antisepsis plays a major role in SSI prevention.

The most common antiseptic agents used for skin disinfection before surgery are aqueous or alcoholic formulations of chlorhexidine (CHG) or povidone iodine (PVI), both of which are available at various concentrations. Several studies have compared their respective efficacy and safety in reducing SSI. Nevertheless, results have been contradictory, probably due to different comparators (concentrations, combination with alcohol or water…), different SSI definitions, and different lengths of follow-up.[7–11] In 2010, a meta-analysis of seven randomised-controlled trials (including 3437 patients) compared CHG (at a concentration of 0.5 to 4%) with PVI or other iodophors (at a concentration of 7 to 10%) for preoperative skin antisepsis in clean and clean-contaminated surgery.[12] The use of CHG was associated with fewer SSIs (adjusted RR 0.64; 95%CI 0.51-0.80) compared with iodine. Another meta-analysis of six randomised-controlled trials comparing CHG (at a concentration of 0.5 to 4%) to PVI (at a concentration of 7.5 to 10%) for preoperative skin antisepsis yielded similar findings [OR of 0.68 (0.50-0.94; p=0.019)].[13] However, in most studies CHG was combined with alcohol and PVI was not, which meant that two antiseptics were being compared to only one. A review conducted in 2012 was unable to draw any conclusion about which surgical site antiseptic more effectively reduces SSI.[14] Recently, Tuuli and colleagues were the first to conduct a large trial comparing CHG and PVI in alcoholic formulations for skin disinfection before caesarean section.[9] Interestingly, both antiseptic formulations used the same alcohol at the same concentration and both were applied similarly, using an applicator. Although this was the first study demonstrating a benefit of 2% CHG-70% isopropanol over 8.3% PVI-70% isopropanol, it was monocentre, and did not address all potential methodological limits. Especially, the choice of superficial or deep surgical-site

infection as primary endpoint assessed by the surgeon (the diagnosis was made by the treating physician and verified through chart review by the principal investigator, who was unaware of the study-group assignments) may generate interpretation biases in an open study. Moreover, the one dual microbial source of pathogens of both skin and vaginal origins in SSI after caesarean delivery and immune modulation in pregnancy raises questions about whether the results of trials of preoperative skin antisepsis for caesarean delivery can be extrapolated to other surgical procedures.

Furthermore, the possible superiority of CHG over PVI was not confirmed in a second monocentre trial involving 1404 women requiring caesarean section.[8] Lastly, in a third assessor-blinded, monocentre, randomised trial involving 802 patients scheduled for elective clean-contaminated colorectal surgery, the use of PVI-alcohol failed to meet the criterion for non-inferiority in SSI occurrence compared with CHG-alcohol.[11] These contradictory results may explain the lack of universal use of CHG-alcohol for skin antisepsis in surgery despite the recommendations of the World Health Organization (WHO).[15]

The prevalence and potential serious consequences of SSI in cardiac surgery, especially mediastinitis, support a large randomised controlled trial in this setting. We hypothesize that perioperative skin preparation with 2% CHG-70% isopropanol is more effective than 5% PVI-69% ethanol as a means of preventing any reoperation after cardiac surgery.

METHODS AND ANALYSIS

Trial design and setting

The CLEAN 2 trial is an investigator-initiated, publicly-funded multicentre, randomised, controlled, open-label clinical trial with concealed allocation of patients scheduled to undergo cardiac surgery and to receive 1:1 either 2% CHG – 70% isopropanol or 5% PVI– 69% ethanol for perioperative skin preparation. Randomisation will be carried out through a secure web-based randomisation system and stratified by centre (Fig. 1).

The trial will take place at seven university and non-university French hospitals. All participating centres perform more than 500 cardiac surgical procedures per year.

Participant eligibility and consent

During surgery or preoperative anaesthesia consultation, all consecutive patients will be considered candidates for inclusion in the study if they meet all of the inclusion criteria and

none of the exclusion criteria. Eligible patients will receive oral and written information and will be enrolled after having given written consent.

Inclusion criteria

- Adult patients (age ≥ 18 years) admitted in one of the participating centres
- Scheduled to undergo surgery of the heart (valve, coronary or combined surgery) or of the aorta via median sternotomy
- Having signed informed consent form

Exclusion criteria

- Patients with known allergies to CHG, PVI, isopropanol or ethanol
- Surgery for heart transplantation
- Any signs of inflammation or sternal instability at the site of sternotomy or operation for infection (sternal wound infection or endocarditis)
- History of cardiac surgery within 3 months preceding enrolment
- Participation in another clinical trial aimed at reducing SSI
- Patients already enrolled in this study
- Pregnant or breastfeeding women and potentially childbearing women without effective contraception
- Patients not benefiting from a Social Security scheme or not benefiting from it through a third party
- Persons benefiting from enhanced protection, namely minors, persons deprived of their liberty by a judicial or administrative decision and adults under legal protection.

Assignment of interventions

A computer-generated block-randomisation sequence will be performed by a statistician not involved in either screening the patients or assessing outcomes. Randomisation will be carried out using a secure web-based randomisation system with stratification by centre. The randomisation will be accessible to investigators through user identification and a personal password and will become effective following confirmation of inclusion and exclusion criteria. Patients will be randomly assigned (1:1) to one of two study groups according to the antiseptic solution used to disinfect the skin before surgery and during all dressing changes (Fig. 1). To avoid randomisation of a patient with cancelled surgery, this will be done a few days before or on the day of surgery.

Interventions

1- *CHG group:* The surgical site will be largely disinfected using applicators of 2% CHG-70% isopropanol (ChloraPrep™, CareFusion). According to local practices, antiseptic application will be preceded (two-step procedure) or not (one-step procedure) by skin scrubbing with 4% CHG (Hibiscrub™, Molnlycke Health Care).

2- *PVI group*: The surgical site will be largely disinfected using sterile gauzes soaked with 5% PVI-69% ethanol (Bétadine alcoolique™, MEDA Pharma SAS). According to local practices, antiseptic application will be preceded (two-step procedure) or not (one-step procedure) by skin scrubbing with 4% PVI (Bétadine Scrub™, MEDA Pharma SAS).

In order to ensure respect of treatment group and to achieve traceability, individual boxes containing all disinfecting products required for disinfecting the skin before surgery and during patient care will be supplied. According to randomisation, each patient will have his own box, which will follow him from the operating room to hospital discharge.

The following care procedures will be applied to all patients and controlled throughout the duration of the study:

- At least one total body shower during the 24 h preceding surgery, using either plain soap or antiseptic soap
- Hair removal if required with clipper (no shaving) before surgery
- Antibiotic prophylaxis according to the French recommendations [16] applied 30 min prior to incision, and with appropriate reinjection if required for prolonged surgery. No re-administration during the postoperative period.
- Antiseptic application by moving back and forth for at least 30 s, starting at the incision site and then extending to the entire work area. The surgical field extends from the jaw to the shoulders and down to the tip of both feet in case of surgery with harvesting of the saphenous vein. In the event of surgery without saphenous vein harvesting, the field stops at the knees. According to local practices, the antiseptic solution will be applied once or twice, preceded or not by skin scrubbing with an antiseptic soap.
- Application of large sterile drapes once the work area is dry.

In each centre, before the beginning of the inclusion, a list of care policy for prevention of SSI (*Staphylococcus aureus* decontamination, antimicrobial-coated sutures, adhesive incises

drapes with antiseptics, antimicrobial dressings…) will be established and will not be modified throughout the duration of the study.

Study outcomes

Primary endpoint

The primary outcome will be the proportion of patients undergoing either any re-sternotomy occurring between Day 0 and Day 90 after surgery or any reoperation on saphenous vein/radial artery site occurring between Day 0 and Day 30 after surgery or both.

Secondary endpoints

- Proportion of patients with mediastinitis according to the Center for Disease Control and Prevention (CDC) criteria [17] occurring by Day 90 after surgery and pathogens involved.
- Proportion of patients with deep incisional SSI at saphenous vein/radial artery site, superficial incisional SSI at sternal or saphenous vein/radial artery sites according to the CDC criteria [17] occurring by Day 30 after surgery and the pathogens involved.
- Proportion of patients with sternal wound infection (SWI) requiring reoperation, occurring by Day 90.
- Proportion of patients with SSI at saphenous vein/radial artery site requiring reoperation, occurring by Day 30.
- Proportion of patients with unexpected need for readmission to intensive care unit (ICU) or re-hospitalisation.
- Duration of ICU stay.
- Duration of stay under mechanical ventilation.
- Duration of hospital stay.
- Duration of rehabilitation unit stay.
- All-cause mortality at Day 90 of surgery.
- Proportion of patients with local and systemic side effects possibly linked to antiseptic use.

Two independent assessors masked to the antiseptic group and to the event will review all post-operative reports of patients needing re-sternotomy during the 90 days following surgery and/or reoperation on saphenous vein/radial artery site during the 30 days following surgery. They will classify the case-report as:

- SWI (mediastinitis or superficial sternal SSI)
- And/or deep or superficial saphenous vein/radial artery SSI
- Or no SSI according to CDC criteria

Disagreements between the two assessors will be resolved by consensus conference among all outcome assessors.

Data collection

Independent clinical research assistants will be available at each participating hospital to help in running the study and with data collection. Study documents will be de-identified and stored for 15 years, as per the protocol for non-clinical trial notification (CTN) interventional studies. Data will be entered into the web-based eCRF (CSOnline, Clinsight) and electronically stored on double password-protected computers. Hard copies of data (clinical research files) will be stored in a secure locked office. All personnel involved in data analysis will be masked to study groups. Only the principal investigators and the statisticians will have access to the final data set. The following data will be recorded:

Baseline characteristics and preoperative data

Demographic data (age, gender, height, weight and body mass index); American Society of Anaesthesiologists physical status; EuroSCORE II; comorbidities (active smoking; insulin-dependent diabetes; non-insulin-dependent diabetes; hypertension; hypercholesterolaemia; chronic renal failure; COPD; history of cardiac surgery; atrial fibrillation; key laboratory findings; use of preoperative *Staphylococcus aureus* decontamination; hair removal and modality; number and type (soap with or without antiseptic) of preoperative showers.

Intraoperative data

Type of surgery of the heart (valve, coronary, combined surgery, other) or of the aorta; type of scheduling (elective, semi-elective or emergency); skin scrubbing before skin antisepsis; number of antiseptic applications; number of antiseptic products used; antibiotic prophylaxis: molecule, dose, timing and possible redosing; use of iodophor-impregnated incise drapes; number of internal thoracic arteries sampled; sampling of saphen vein or radial artery, site open or endoscopic; length of surgery (incision to closure); duration of cardiopulmonary bypass; minimal and maximal body temperature during surgery; volume infused during surgery and type; number and types of blood transfusion during surgery; type of vasopressor administered during surgery; use of mechanical cardiac support (extra-corporeal life support

[ECLS] or intra-aortic balloon pump); adverse events (especially local and systemic side effects possibly linked to antiseptic use).

Postoperative data until hospital discharge

Type and number of blood products given during the 48h following surgery; type and length of vasopressor and/or inotropic drugs administered during the 48h following surgery; use of mechanical cardiac support (ECLS, intra-aortic balloon pump); atrial fibrillation episode; number and results of blood cultures; number, type and results of bacteriological sampling at surgical site; wound status at surgical site (until dressing withdrawal): local signs of infection (local incisional pain/tenderness, localized redness, heat or swelling, purulent drainage from the superficial incision, superficial/deep incision spontaneously or deliberately opened by the surgeon), status of dressing, date of dressing changes; physical examination (temperature, chest pain, sternal instability); antibiotics used (molecule, duration and indication); results of blood samples (standard lab values); duration of mechanical ventilation; length of stay in ICU, surgical ward and high dependency unit; date of hospital discharge; reoperation at sternal site or saphenous vein/radial artery site occurring after surgery (date and reason); SSI occurrence: type (superficial, deep, organ-space), site and date and hour of SSI diagnosis; adverse events (especially local and systemic side effects possibly linked to antiseptic use) and survival status (if the patient is deceased, date of death).

Postoperative data monthly after surgery (until 90 days following surgery)

Phone contact: date; SSI occurrence, date of diagnosis, site and type; planned or unplanned surgical consultation; need for hospital readmission: date, total duration of hospital stay; need for reoperation at sternal site (within 90 days following surgery) or at saphenous vein/radial artery site (within 30 days following surgery): date, reason; date of rehabilitation unit discharge and survival status (if the patient is deceased, date of death).

Safety

According to the French Public Health Code, all suspected unexpected serious adverse events will be reported to the Agence Nationale de Sécurité du Médicament (ANSM). Adverse events will be evaluated at each visit during clinical interview and physical examination. In agreement with ANSM, all serious adverse events related to heart disease (except infections) and not related to antiseptic use will not be declared immediately but will be reported in the eCRF. Each serious adverse event will be described as completely as possible on the report

form designed for this purpose. The initial report will be followed by complementary reports of relevant information as soon as possible.

Sample size calculation

Assuming a 6% reoperation rate in the PVI group,[6] 1863 patients in each treatment arm will be required to demonstrate a 33% reduction of reoperation rate with the use of 2% CHG-70% isopropanol, with statistical risks at 5% and 20% for type I and type II errors, respectively. The sample size calculation is based on the two-sided test. We are planning to enrol 4100 patients to take into account a maximum patient loss of 10%.

Statistical analysis

The data will be analysed blindly on an intention-to-treat basis. No interim analysis is planned. Demographic data will be described as number and percentage or median and IQR and compared with the χ^2 test or Mann-Whitney test, as appropriate. For primary analysis, incidence of reoperation between groups will be compared with χ^2 test. We will assess antiseptic efficacy with a marginal Cox model and adjusted for covariates that will be significantly imbalanced between groups. We will calculate hazard ratios (HR) and 95% CIs, as well as incidence density and Kaplan-Meier estimates. Proportions of each secondary endpoint assessed at day 30 and day 90 will be compared using similar principles. We will use chi-square tests. A multiple logistic regression will be computed with covariates clinically relevant as regard as our outcomes (*Centre*; *Patients' characteristics:* age, gender, body mass index, EuroSCORE II, active smoking, insulin-dependent diabetes, use of preoperative *Staphylococcus aureus* decontamination; *Intraoperative data:* type of surgery of the heart [valve, coronary, combined surgery, other] or of the aorta, type of scheduling [elective, semi-elective or emergency], skin scrubbing before skin antisepsis; number of antiseptic application, use of iodophor-impregnated incise drapes, number of internal thoracic arteries sampled, length of surgery, duration of cardiopulmonary bypass, minimal body temperature during surgery, volume infused during surgery, use of mechanic cardiac support) and with covariates statistically relevant (covariates with difference between groups < 0.20 in the univariate analysis). All tests will be two-tailed, stratified by centre and unadjusted for multiple comparisons. Analyses will be done with SAS version 9.4 and R software.

Patient and Public Involvement

The ethical committee, composed of patients' representatives, considered if the research is conformed to patients' priorities, experience and preferences. Each patient, admitted in a

participating centre, is screened and enrolled by the attending physicians according to the protocol. The burden of the intervention is assessed by patients themselves. Each patient, after the end of the study, will have the opportunity to obtain the results if they are interested, all information is provided at inclusion in consent and information forms. No patient was involved in the recruitment to and the conduct of the study.

ETHICS AND DISSEMINATION

Research ethics approval

The clinical trial will be carried out in line with the principles of the Declaration of Helsinki, the guideline for Good Clinical Practice of the International Conference on Harmonization, in accordance with the French law No. 2012-300 of 5 March 2012 on research involving the human person and with the Clinical Trials Directives 2001/20/EC and 2005/28/EC of the European Parliament. Ethical aspects of this research project have been approved by the ethics committee of Ambroise Paré Hospital (CPP Ile de France VIII, Boulogne-Billancourt, France). The CLEAN 2 trial is registered at the European Clinical Trial Database on 27 December 2017 (EudraCT #2017-005169-33) and summarised at ClinicalTrials.gov with the trial identification number NCT03560193.

Consent

Written informed consent will be requested for each patient prior to enrolment. The investigators will provide clear and precise information to the patient about the protocol before asking him/her for written informed consent.

Confidentiality

People with direct access to the data will take all necessary precautions to maintain confidentiality. All data collected during the study will be rendered anonymous. Only initials and inclusion number will be registered.

Dissemination policy

The results of the study will be released to the participating physicians, referring physicians and medical community no later than one year after completion of the trial through presentation at scientific conferences and publication in peer-reviewed journals.

The main manuscript will mention the name of the sponsor and all trial sites will be acknowledged. All investigators having included or followed participants in the study will appear with their names under "the CLEAN 2 investigators" in an appendix to the final manuscript. Authorship will be done in accordance with the guidelines of the International Committee of Medical Journal. No professional writer will be used.

Funding statement

This work is being funded by unrestricted research grants from the French Ministry of Social Affairs and Health (#16-0619) and CareFusion/ Becton Dickinson. Funders will have no role in the trial initiation, study design, choice of antiseptic products, data collection, data analysis, data interpretation or writing of the report.

Conflict of interest

OM has received grant support from 3M and Carefusion-BD and honoraria for giving lectures from 3M and Carefusion-BD.

DISCUSSION

This study will provide new knowledge in the field of SSI prevention, addressing questions raised by the Cochrane review on preoperative skin antiseptics aimed at preventing surgical wound infections after clean surgery.[18] In clean surgery, the majority of pathogens responsible for infectious complications come from the skin and skin disinfection has the potential to reduce both the frequency and severity of SSI in proportion to the efficacy of disinfection. The choice of cardiac surgery is based on the severity of SSI with this surgery, especially mediastinitis, which frequently requires reoperation. We selected centres with experience in SSI prevention studies and already applying all the other SSI prevention measures recommended by our national guidelines. Their number is limited so as to ensure high quality of follow-up by independent clinical research assistants. Stratified randomisation will protect against bias linked to potential variability in surgical practices between centres. Individual boxes containing allocated disinfecting products will follow the patient from the operating room to hospital discharge to ensure respect of treatment group and to facilitate product traceability. The choice of reoperation as the main endpoint is not subject to evaluation bias in an open study.

Our study will have several limitations. First, masking will not be feasible, because the two antiseptic solutions differ in both colour and formulation. However, the microbiologists who

will perform all microbiological cultures will be unaware of treatment allocation. More importantly, all cases of suspected SSI will be reviewed by masked independent assessors based on internationally accepted definitions.[17] Second, the two antiseptic solutions contain different alcoholic components and use different application methods. However, these products will be used in their commercially available formulations in France and as recommended by our national guidelines. Further studies will be necessary to determine the more efficient type and concentration of alcohol to be combined with CHG or PVI as well as the optimal concentration of CHG and PVI and optimal method for antiseptic application. Third, we have chosen incidence of reoperation as the primary endpoint. They can be due to non-infectious causes such as postoperative bleeding, valve-dysfunction etc.., for which the impact of skin disinfection is probably low. However, their main advantage is to be a strong unquestionable endpoint not subject to assessment bias in an open trial. Fourth, adhesion to the study protocol will not be regularly checked by formal audits. However, the health-care providers will attend training sessions designed to homogenise skin preparation practices across hospitals before starting the study and independent clinical research assistants will be available at each participating hospital to monitor the conduct of the trial. Moreover, all study centres will be required to follow French recommendations similar to CDC recommendations for prevention of SSI with no modification allowed during the study period.

We assumed a 33% reduction in reoperation with the use of alcoholic chlorhexidine in our study. This choice may appear too ambitious. However, it is based on the existence of several surgical sites in the majority of patients, the major role of SSI in reoperation and the expected effect of antiseptic choice on SSI prevention. In clean contaminated surgery, a 50% reduction in SSI with alcoholic chlorhexidine use has been reported in digestive[7] or obstetrical[9] surgery. In these types of surgery, a significant fraction of pathogens involved comes from the digestive or gynaecological flora not accessible to the action of antiseptics. In intensive care, an 85% reduction in infections related to short-term central venous and arterial catheters has been reported with alcoholic chlorhexidine use.[19] As in clean surgery, the skin flora is the main reservoir of pathogens involved in these infections, and the effectiveness of skin disinfection is essential to prevent them. In total, if we consider that among the 6% of reoperation in the povidone iodine group, half are related to an SSI (which is probably underestimated), we can expect an incidence of reoperation in the chlorhexidine group between 3.5% (hypothesis very favourable to alcoholic chlorhexidine use) and 4.5% (hypothesis not very favourable to alcoholic chlorhexidine use). In the event of negative

results, the choice of the antiseptic strategy could be based on the incidence of secondary endpoints in both arms of our study, and finally, on the cost of antiseptic strategies, even if it is insignificant compared to that of SSI.

We will conduct the first large scale randomised trial adequately powered to compare the efficacy and safety of CHX-alcohol over PVI-alcohol in reducing SSI after clean surgery. Reducing SSI after surgery is associated with decreased length of hospital stay, mortality and overall costs and increased patient satisfaction,[4] which should benefit both the patient and the community. The trial is multicentre and almost all eligible patients will be included and will benefit from all the measures recommended by our national guidelines (similar to CDC guidelines) to prevent SSI. As a result, our findings will be reasonably extended to other cardiac surgery centres, to other clean surgeries and, more generally, to all surgical procedures performed worldwide, even if the proportion of skin pathogens involved in SSI is lower than in clean surgery.

Trial status

The current protocol is version 3.0 dated 12 September 2018. The trial is currently recruiting patients. The inclusion process started on 17 September 2018 and the number of patients included to date (12 February 2019) is 311. The estimated length of inclusion time is 18 months.

AUTHORS' CONTRIBUTIONS

MB and OM conceived the study, coordinated its design, wrote the manuscript and drafted the manuscript. PC, TK, LC, MD, PD, VE, EF, LL, DL, PL, NN, JYN, AO, JCR, BR, SR, JCL and JFT read and were involved in critical appraisal and revision of the manuscript. SR and JFT provided statistical expertise. All authors approved the final manuscript prior to submission.

REFERENCES

1 World Health Organization. Report on the burden of endemic health care-associated infection worldwide. Geneva: World Health Organization 2011. http://apps.who.int/iris/bitstream/handle/10665/80135/9789241501507_eng.pdf?sequence=1&isAllowed=y (accessed 30 May 2018).

2 European Centre for Disease Prevention and Control. Annual epidemiological report 2014. Antimicrobial resistance and healthcare-associated infections. 2015.http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-annual-epidemiological-report.pdf (accessed 26 Apr 2016).

3 European Centre for Disease Prevention and Control. Surveillance of surgical site infections in Europe 2010–2011. Eur. Cent. Dis. Prev. Control. 2013.http://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/SSI-in-europe-2010-2011.pdf (accessed 24 Oct 2017).

4 World Health Organization. Global guidelines on the prevention of surgical site infection. Geneva: World Health Organization 2016. http://apps.who.int/iris/bitstream/10665/250680/1/9789241549882-eng.pdf?ua=1 (accessed 30 May 2018).

5 Finkelstein R, Rabino G, Mashiah T, *et al.* Surgical site infection rates following cardiac surgery: the impact of a 6-year infection control program. *Am J Infect Control* 2005;**33**:450–4. doi:10.1016/j.ajic.2005.07.002

6 Lemaignen A, Birgand G, Ghodhbane W, *et al.* Sternal wound infection after cardiac surgery: incidence and risk factors according to clinical presentation. *Clin Microbiol Infect* 2015;**21**:674.e11-18. doi:10.1016/j.cmi.2015.03.025

7 Darouiche RO, Wall MJ, Itani KMF, *et al.* Chlorhexidine–Alcohol versus Povidone–Iodine for Surgical-Site Antisepsis. *N Engl J Med* 2010;**362**:18–26. doi:10.1056/NEJMoa0810988

8 Ngai IM, Van Arsdale A, Govindappagari S, *et al.* Skin Preparation for Prevention of Surgical Site Infection After Cesarean Delivery: A Randomized Controlled Trial. *Obstet Gynecol* 2015;**126**:1251–7. doi:10.1097/AOG.0000000000001118

9 Tuuli MG, Liu J, Stout MJ, *et al.* A randomized trial comparing skin antiseptic agents at cesarean delivery. *N Engl J Med* 2016;**374**:647–55. doi:10.1056/NEJMoa1511048

10 Park HM, Han S-S, Lee EC, *et al.* Randomized clinical trial of preoperative skin antisepsis with chlorhexidine gluconate or povidone-iodine. *Br J Surg* 2017;104:e145–50. doi:10.1002/bjs.10395

11 Broach RB, Paulson EC, Scott C, *et al.* Randomized controlled trial of two alcohol-based preparations for surgical site antisepsis in colorectal surgery. *Ann Surg* 2017;**266**:946–51. doi:10.1097/SLA.0000000000002189

12 Lee I, Agarwal RK, Lee BY, *et al.* Systematic review and cost analysis comparing use of chlorhexidine with use of iodine for preoperative skin antisepsis to prevent surgical site infection. *Infect Control Hosp Epidemiol* 2010;**31**:1219–29. doi:10.1086/657134

13 Noorani A, Rabey N, Walsh SR, *et al.* Systematic review and meta-analysis of preoperative antisepsis with chlorhexidine versus povidone-iodine in clean-contaminated surgery. *Br J Surg* 2010;**97**:1614–20. doi:10.1002/bjs.7214

14 Kamel C, McGahan L, Polisena J, *et al.* Preoperative skin antiseptic preparations for preventing surgical site infections: a systematic review. *Infect Control Hosp Epidemiol* 2012;**33**:608–17. doi:10.1086/665723

15 Allegranzi B, Bischoff P, de Jonge S, *et al.* New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis* 2016;**16**:e276–87. doi:10.1016/S1473-3099(16)30398-X

16 SFAR. Antibioprophylaxie en chirurgie et médecine interventionnelle (patients adultes). 2018. https://sfar.org/antibioprophylaxie-en-chirurgie-et-medecine-interventionnelle-patients-adultes-maj2018/ (accessed 7 Jan 2019).

17 Center for Disease Control and Prevention, National Healthcare Safety Network. Surveillance definitions for specific types of infections. https://www-cdc-gov.gate2.inist.fr/nhsn/pdfs/pscmanual/17pscnosinfdef_current.pdf (accessed 8 Jul 2018).

18 Edwards PS, Lipp A, Holmes A. Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. *Cochrane Database Syst Rev* 2004;CD003949. doi:10.1002/14651858.CD003949.pub2

19 Mimoz O, Lucet J-C, Kerforne T, *et al.* Skin antisepsis with chlorhexidine-alcohol versus povidone iodine-alcohol, with and without skin scrubbing, for prevention of intravascular-catheter-related infection (CLEAN): an open-label, multicentre, randomised, controlled, two-by-two factorial trial. *Lancet* 2015;**386**:2069–77. doi:10.1016/S0140-6736(15)00244-5

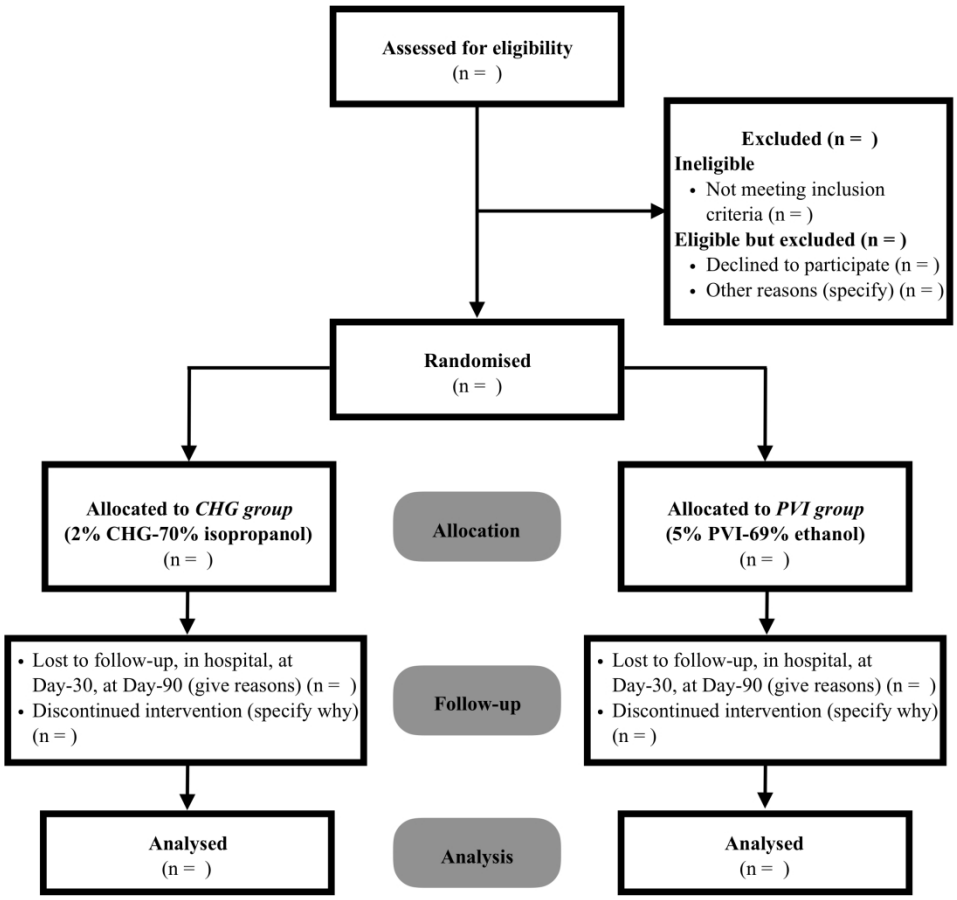

Figure 1. CONSORT diagram (CHG: chlorhexidine, PVI: povidone iodine)

209x209mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4 & 13
	2b	All items from the World Health Organization Trial Registration Data Set	1, 3, 4, 7, 8, 9, 10, 12, 13, 14, 16
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 2, 3, 17
	5b	Name and contact information for the trial sponsor	3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6
	6b	Explanation for choice of comparators	6, 7
Objectives	7	Specific objectives or hypotheses	7

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9, 11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9, 16
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7, 11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10, 11, 13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11, 12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9, 10, 11, 12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11, 12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, 8, 14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11, 12, 13, 17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11, 13, 17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	15
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.