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ORIGINAL ARTICLE

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Antimicrobial prophylaxis and the prevention of surgical site infection in cardiac surgery: an analysis of 21 007 patients in Switzerland†

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Key question

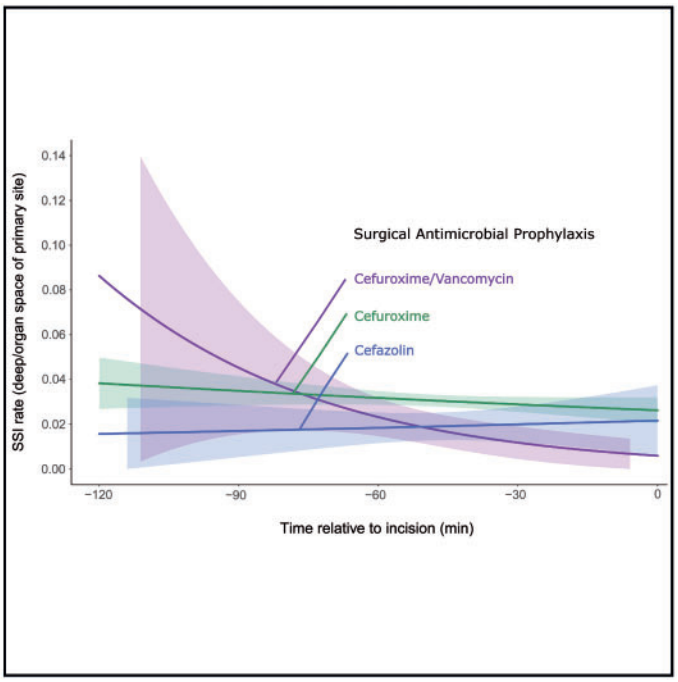
What are the optimal timing and choice of surgical antimicrobial prophylaxis for patients having cardiac surgery?

Key finding(s)

Prophylaxis within 30 min before the incision decreased surgical site infections; cefazolin may be more effective than cefuroxime.

Take-home message

Administration of prophylaxis close to the time of the incision is more effective than early prophylaxis. The choice of surgical prophylaxis also appears to play a significant role.



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Abstract

OBJECTIVES: Our goal was to determine the optimal timing and choice of surgical antimicrobial prophylaxis (SAP) in patients having cardiac surgery.

METHODS: The setting was the Swiss surgical site infection (SSI) national surveillance system with a follow-up rate of >94%. Participants were patients from 14 hospitals who had cardiac surgery from 2009 to 2017 with clean wounds, SAP with cefuroxime, cefazolin or a vancomycin/cefuroxime combination and timing of SAP within 120 min before the incision. Exposures were SAP timing and agents; the main outcome was the incidence of SSI. We fitted generalized additive and mixed-effects generalized linear models to describe effects predicting SSIs.

RESULTS: A total of 21 007 patients were enrolled with an SSI incidence of 5.5%. Administration of SAP within 30 min before the incision was significantly associated with decreased deep/organ space SSI [adjusted odds ratio (OR) 0.73, 95% confidence interval (CI) 0.54–0.98; $P = 0.035$] compared to administration of SAP 60–120 min before the incision. Cefazolin (adjusted OR 0.64, 95% CI 0.49–0.84; $P = 0.001$) but not vancomycin/cefuroxime combination (adjusted OR 1.05, 95% CI 0.82–1.34; $P = 0.689$) was significantly associated with a lower risk of overall SSI compared to cefuroxime alone. Nevertheless, there were no statistically significant differences between the SAP agents and the risk of deep/organ space SSI.

CONCLUSIONS: The results from this large prospective study provide substantial arguments that administration of SAP close to the time of the incision is more effective than earlier administration before cardiac surgery, making compliance with SAP administration easier. The choice of SAP appears to play a significant role in the prevention of all SSIs, even after adjusting for confounding variables.

Keywords: Surgical antimicrobial prophylaxis • Cardiac surgery • Surgical site infection • Infection control • Prevention • Modelling

INTRODUCTION

Surgical site infections (SSIs) contribute significantly to the morbidity and mortality of patients undergoing surgery [1–3]. The optimal timing of surgical antimicrobial prophylaxis (SAP) in cardiac surgery is poorly defined. In their landmark study, Classen *et al.* [4] found that prophylactic administration of antibiotics 2 h before (compared with during or after) any kind of surgery reduces the rate of SSI. However, that study included patients with multiple and different antibiotics, and many started prophylaxis >48 h after the incision. In 2016, the World Health Organization (WHO) extended their previous recommendation on SAP from 60 min to 120 min prior to incision, based on evidence of moderate quality [3]. A recent randomized controlled superiority trial failed to demonstrate the superiority of administrating the SAP 30–60 min prior to the incision (median of 42 min before incision) compared to administrating the SAP 0–30 min (median 16 min) before the incision [5]. These results differed from those of previously published observational studies [6, 7]. One study found a trend towards lower risk of infection when SAP with short infusion times was given within 30 min before the incision [6]; another showed greater effectiveness when cefuroxime was administered 59–30 min before surgery [7]. Of note, the incidence of SSI was low in both studies [6, 7]. In a third, larger study, there was no statistically significant association between the SSI rate and timing within the 120-min period; however, cardiac operations were excluded [8]. Therefore, the optimal timing of SAP in patients having cardiac surgery is an area requiring further investigation.

To date, different cephalosporins are considered to be equally effective in preventing cardiac surgery SSIs [9, 10]. Also, SAP with a glycopeptide was not superior in preventing SSIs compared to beta-lactams in a large meta-analysis [11]. A recent study concluded that the addition of a glycopeptide can reduce the risk of SSI following cardiac surgery, but this result was from a setting notable for a 25% prevalence of methicillin-resistant *Staphylococcus aureus* [12]. Currently, Swiss guidelines suggest the addition of glycopeptide to cephalosporin SAP in patients with known colonization with methicillin-resistant *S. aureus* having cardiac surgery [13]. In addition, individual centres have decided to add a glycopeptide in patients with certain risk factors for SSI by default [14].

The WHO considers SAP a key component in the prevention of SSI, but optimal timing and the most effective SAP agents for patients having cardiac surgery remain to be elucidated [3]. Therefore, we performed a cohort study on prospectively collected, standardized data from hospitals that undergo on-site quality checks and conduct rigorous post-discharge surveillance. Our specific objectives were thus (i) to determine the optimal time to administer SAP within the 120-min window before the incision for patients about to have cardiac surgery and (ii) to identify a potentially superior SAP among the main agents used in Switzerland.

MATERIALS AND METHODS

Study design and setting

This cohort study comprised prospectively collected data from the nationwide Swissnoso SSI surveillance module [15]. We included data from all 14 cardiac surgery centres in Switzerland, including the 5 Swiss university hospitals, from January 2009 through December 2017. The surveillance module included rigorous post-discharge surveillance: all patients were contacted at least 5 times by employees from infection control before being considered 'lost to follow-up': 1 month after the surgical procedure, and again after 1 year if an implant, i.e. sternal plate, wire cerclage or valve replacement, was involved. Follow-up of routine post-discharge surveillance exceeded 94%. *Swissnoso* members periodically performed on-site audits to check data quality, as published elsewhere [15, 16]. Locally collected data were then submitted to *Swissnoso*.

Participants

All patients in the surveillance programme who underwent cardiac surgery procedures, including coronary artery bypass graft, valve repair/replacement and placement of implantable cardiovascular devices (e.g. ventricular assist devices, excluding

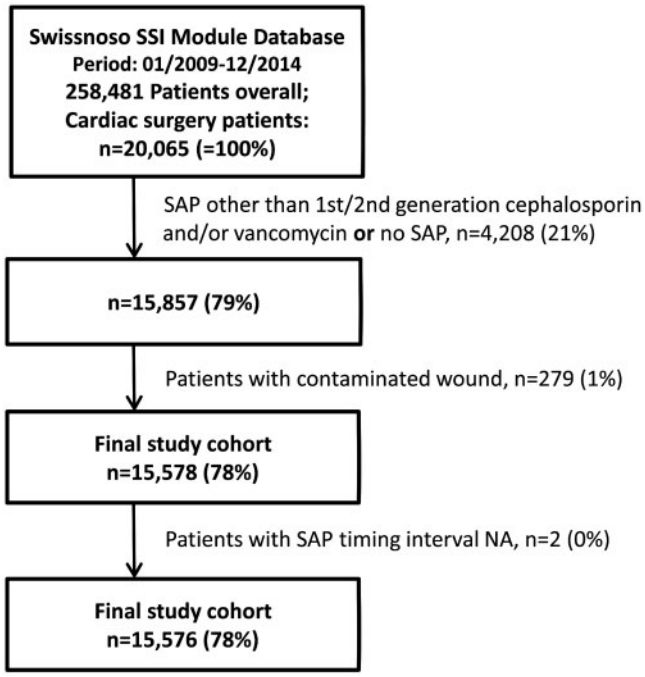

Figure 1: Flow chart of patient inclusion process. NA: not available; SAP: surgical antimicrobial prophylaxis; SSI: surgical site infection.

pacemakers) between 2009 and 2017 (latest follow-up: December 2017) were eligible for the analysis. A complete list of the cardiac surgery codes according to the operation classification system of the Federal Statistical Office [17] is available at the Swissnoso Web site (codes 43, 44, 45: https://www.swissnoso.ch/fileadmin/module/ssi_surveillance/Dokumente_D/2_Formulare/D_3_V_01.10.2018_Liste_der_chirurgischen_Eingriffe.pdf). Patients with contaminated wound procedures were excluded. Patients were also excluded if SAP was not applied within 120 min before the incision or if SAP involved agents other than cefuroxime, cefazolin or the vancomycin/cefuroxime combination (Fig. 1). Overall, SSI cases were defined as patients with SSI according to the definitions of the Centers for Disease Control and Prevention (CDC) [18] and included SSI of secondary incision sites (e.g. vein excision site). The alternative outcome was deep and/or organ space SSIs at the primary incision (e.g. sternitis, mediastinitis and/or endocarditis) [18]. The adapted instructions (which include a second follow-up at 1 year instead of a follow-up at 3 months) are available in 3 official national languages (https://www.swissnoso.ch/module/ssi-surveillance/ueber-ssi-surveillance/das-modul/).

Variables, outcomes, bias and data sources

Variables included were sex, age, SAP agents and timing relative to surgical incision, date of surgery, operation duration, T-time (surgical time exceeding the expected duration), body mass index, American Society of Anesthesiologists (ASA) score, emergent procedure, open versus minimally invasive surgery, cardiac surgery centre, use of bypass grafts (internal mammary artery and/or radial artery or peripheral venous graft) and the occurrence of an SSI as end points. To anonymize participating centres, the centres were grouped for the description of baseline characteristics into 'centre types': private hospitals, public non-university hospitals and university hospitals. For the adjusted analyses, university hospitals were considered single centres. SSIs were defined according to CDC criteria: infection control specialists checked all patient data, and all patients with a suspected SSI were validated by a dedicated physician. The dedicated physicians all had attended a special training course for the SSI surveillance module.

Data were electronically entered into a centralized database. The type of SSI—superficial incisional, deep incisional or organ/space—was recorded, as was the involved incision site (primary versus secondary) and the pathogen: up to 3 different pathogens could be entered for each SSI. We assumed that the first one entered, in the case of multiple organisms, was the main causative pathogen. The primary outcomes were the adjusted risk of overall SSI relative to the antibiotic administration time prior to surgical incision and the SAP agents. The secondary outcome was the deep/organ space SSI risk of the primary incision site.

The data source for the variables was the *Swissnoso* SSI surveillance module. Primary data were obtained from patient charts and telephone interviews with patients.

To analyse the influence of preoperative comorbidity, ASA scores were grouped into scores 1/2, 3 and 4/5. Dates of surgery were grouped into an early (2009–2012) and a late (2013–2017) period.

Data reporting

According to the valid Swissnoso data regulations, the primary data cannot be made available in a public registry [19]. However, data for scientific questions can be requested by means of a scientific proposal, as outlined in the regulations [19].

Statistical analysis

To investigate group differences in terms of baseline characteristics, we used the χ^2 or Wilcoxon test. Unadjusted general additive models (GAMs) were used to estimate the SSI rate relative to the timing of the surgical incision. For SSI prediction, we applied penalized cubic regression spline smoothing to the dependent variable 'timing', using the *mgcv* package/*gam* function in R [20].

To determine risk factors for SSI, covariate adjusted mixed-effects generalized linear models were fitted. To account for the hierarchical structure of the data, the individual healthcare institutions were considered as a random effect, whereas all other variables were treated as fixed effects. The private hospitals and public non-university hospitals were grouped together into 1 'centre type' due to the relatively low number of cardiac procedures performed at an individual institution and due to the presumed similar baseline characteristics of their patients. The mixed-effects approach enabled us to adjust for inherent differences between the institutions/centre types regarding baseline levels of SSI but also regarding potential differences in reporting SSI. Further, we investigated interactions between timing and the SAP regimens.

Timing periods relative to the incision were grouped into different SAP timing windows (120–60, 59–45, 44–30, 29–0 min). A subgroup analysis was performed for all patients excluding minimally invasive procedures.

Missing data (including loss to follow-up) were investigated using multiple imputation, assuming missingness was random [21].

Table 1: SSI rates, stratified according to the timing of administration of surgical antimicrobial prophylaxis

Minutes before incision	-120 to -60	-59 to -45	-44 to -30	-29 to 0	*P*-value
Number	5536	5724	6780	2967	
All SSI, *n* (%)	327 (5.9)	318 (5.6)	371 (5.5)	149 (5.0)	0.048
SSI, deep and/or organ space of primary incision site, *n* (%)	166 (3.0)	152 (2.7)	185 (2.7)	69 (2.3)	0.047

SSI: surgical site infection.

Table 2: SAP timing and SSI rates, stratified by surgical antimicrobial prophylaxis regimen

	Cefuroxime	Cefazolin	Vancomycin/cefuroxime	*P*-value
Number	17 598	1957	1452	
Timing of SAP, median (IQR) (minutes)	-45 (-60 to -35)	-45 (-62 to -32)	-50 (-60 to -39)	<0.001
All SSI, *n* (%)	989 (5.6)	88 (4.5)	88 (6.1)	<0.001
SSI, deep and/or organ space of primary incision site, *n* (%)	508 (2.9)	36 (1.8)	28 (1.9)	<0.001

IQR: interquartile range; SAP: surgical antimicrobial prophylaxis; SSI: surgical site infection.

A *P*-value <0.05 was considered statistically significant throughout. All statistics and plots were created in R [20].

Ethics approval

SSI surveillance by Swissnoso is mandated by Swiss health care policies and is considered a quality improvement project. All patients were informed about their automatic inclusion in SSI surveillance on admission and given the opportunity to opt out. Summary results of the SSI incidences are published yearly (www.anq.ch).

RESULTS

Of a total of 27 563 patients, 21 007 (76%) fulfilled the inclusion criteria and were analysed (Fig. 1). The median age of the participants was 68.3 years [interquartile range (IQR) 60–75]; 26% were women. The detailed baseline patient and procedural characteristics stratified by 4 time windows (120–60, 59–45, 44–30, 29–0 min) before surgical incision are shown in Supplementary Material, Table S1. To illustrate potential differences between baseline characteristics, these were further stratified by centre type and the date of the cardiac surgery (early versus late period; Supplementary Material, Table S2) as well as the SAP agents (Supplementary Material, Table S3).

The overall SSI incidence was 5.5%, and the incidence of deep/organ space primary site SSI was 2.7%. The unadjusted incidences of SSI were marginally lower for timing windows closer to the incision for overall SSI ($P = 0.048$) and deep SSI ($P = 0.047$, Table 1). The most frequently used SAP agent was cefuroxime (17 598; 83%) followed by cefazolin (1957; 9%) and the vancomycin/cefuroxime combination (1452; 8%, Table 2). In the unadjusted analysis, the SSI rate was lower for cefazolin (4.5%) than for cefuroxime (5.6%) and for the vancomycin/cefuroxime combination (6.1%, $P < 0.001$). For deep SSI, the rate was lower for cefazolin (1.8%) and the vancomycin/cefuroxime combination (1.9%) than for cefuroxime (2.9%, $P < 0.001$). The median time of administration of the first SAP was 45 min (IQR 35–60) prior to incision. The vancomycin/cefuroxime combination was given earlier [median 50 min (IQR 39–60)] than cefazolin [45 min (IQR 32–62)] and cefuroxime [45 min (IQR 35–60); $P < 0.001$, Table 2].

The results from fitting an unadjusted GAM suggested that the timing of SAP administration closer to incision within the 120 min was associated with a significantly lower overall SSI rate ($P = 0.027$) but not with the deep/organ space SSI rate ($P = 0.10$). The incidence rates seem to favour timing closer to incision (Fig. 2A, B).

In the unadjusted GAM analyses subgrouped per SAP regimen (marginal models), overall SSI risks were not associated with SAP timing (vancomycin/cefuroxime combination, $P = 0.28$; cefuroxime, $P = 0.07$; cefazolin, $P = 0.44$; Fig. 2C). On the contrary, deep/organ space SSI risks were decreased when the cefuroxime/vancomycin combination SAP was administered closer to incision ($P = 0.012$), but not for cefuroxime ($P = 0.13$) or cefazolin ($P = 0.71$; Fig. 2D). The adjusted marginal models for deep/organ space SSI are shown in Supplementary Material, Fig. S1.

In the adjusted mixed-effect generalized linear models, decreasing the timing of the SAP to within 0–29 min before the incision was significantly associated with decreased deep/organ space SSI [adjusted odds ratio (OR) 0.73, 95% confidence interval (CI) 0.54–0.98; $P = 0.035$] compared to SAP administration between 60 min and 120 min before incision, Supplementary Material, Table S4). Results of sensitivity analyses with adjusted GAMs were consistent with those of the main analysis (data not shown). No statistically significant interactions between timing and SAP agents were identified (data not shown).

The significant association between the SAP regimen and SSI reduction was confirmed in the covariate adjusted analysis: cefazolin (adjusted OR 0.64, 95% CI 0.49–0.84; $P = 0.001$) but not the vancomycin/cefuroxime combination (adjusted OR 1.05, 95% CI 0.82–1.34; $P = 0.689$) was associated with a lower risk of overall SSI compared to cefuroxime alone. For the alternative outcome,

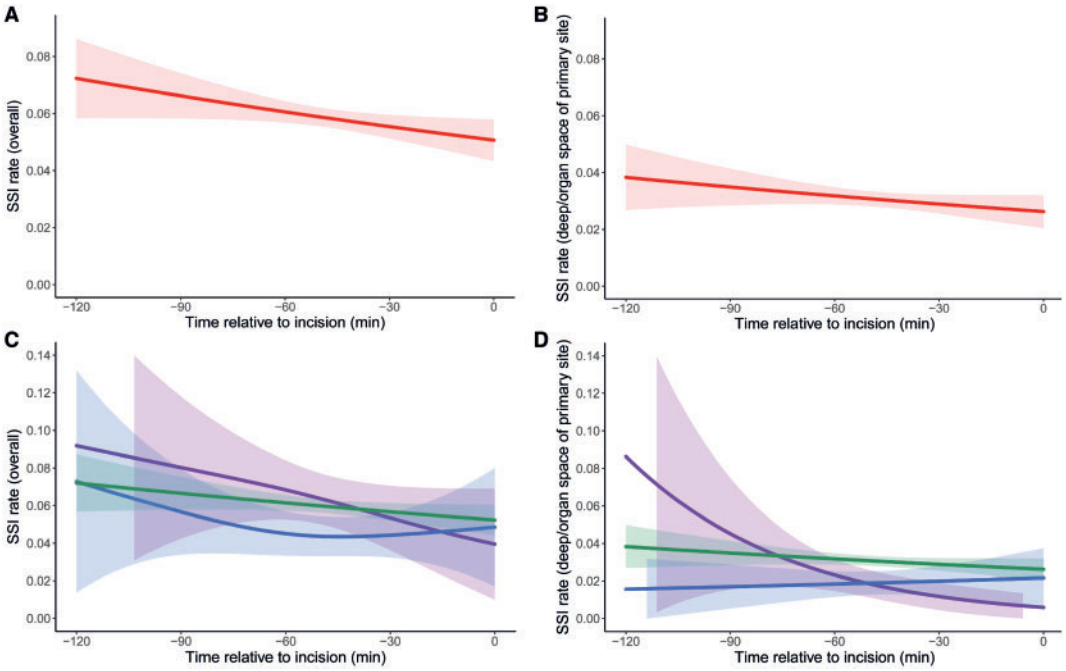

Figure 2: Unadjusted generalized additive models with surgical site infection as the dependent variable and time prior to incision as the independent variable (for the 120 min prior to the incision). The SSI rates include the 95% confidence intervals for the risk of surgical site infection relative to the timing of the administration of surgical antimicrobial agents before the incision. On the left: all SSI, right: deep/organ space SSI; (**A**, **B**): model for all antibiotics, including all SAP regimen (red); (**C**, **D**): fitted results of the unadjusted marginal (subgroup) models were plotted for the individual SAP regimens; blue: cefazolin, green: cefuroxime and violet: vancomycin/cefuroxime combination. SAP: surgical antimicrobial prophylaxis; SSI: surgical site infection.

deep/organ space SSI, neither cefazolin (adjusted OR 0.75, 95% CI 0.49–1.15; $P = 0.191$) nor the vancomycin/cefuroxime combination (adjusted OR 0.75, 95% CI 0.49–1.15; $P = 0.150$) was significantly associated with decreased SSI compared with cefuroxime SAP alone.

Furthermore, we found increases in body mass index of 1 kg/m^2, higher ASA score, increasing operative duration (per 30 min) and date of surgery in the early period (2009–2012) as independent predictors of overall and deep SSIs. Cardiac operations with an internal mammary artery bypass graft, cardiac surgery with a radial artery and/or peripheral vein graft bypass graft, and female gender were additionally associated with an increased overall SSI rate. Increasing age was additionally associated with deep SSI (Supplementary Material, Table S4).

These findings were confirmed in a subgroup analysis excluding the 2123 patients (10%) who had minimally invasive cardiac surgery (Supplementary Material, Table S5).

Coagulase-negative staphylococci (CoNS) SSIs ($n = 262/950$; 27.6%) and methicillin-susceptible *S. aureus* ($n = 99/950$; 10.4%) were the most common pathogens causing SSIs. Missing data on pathogens (no cultures performed or no growth) were frequent for the overall SSI, because superficial infections were included in this group. The overall methicillin-resistant *S. aureus* SSI rate was low, accounting for <2% of all SSI cases (Supplementary Material, Tables S6 and S7). Of note, deep SSI with CoNS occurred in 0.34% of patients who had vancomycin/cefuroxime SAP, and in 0.97% and 1.39% of patients who had cefazolin and cefuroxime SAP, respectively.

In missing data analyses, there was no evidence to suggest that missing data were not at random. Apart from the SSI variable itself (5.3%), there were relatively low numbers of missing baseline covariates (<1.3%; Supplementary Material, Table S8). The point estimates after fitting the primary analysis model (the generalized linear model) to multiply imputed data sets assuming missing at random were within the 95% CIs from the complete case analysis (Supplementary Material, Tables S9 and S10).

DISCUSSION

This large prospective observational study with excellent follow-up was designed to evaluate the relationship between timing of SAP and the choice of antibiotic in cardiac surgery and the occurrence of SSI. The quality of our study appears to improve on the quality of earlier studies based on SSIs that occurred during primary hospitalization [22]: it incorporated standardized evaluation of SSI cases by dedicated physicians, 2 post-discharge surveillances at 30 days and at 1 year with <6% lost to follow-up, and routine on-site monitoring of the quality of data collection. In addition, it is the second SSI study to assess SAP timing as a continuous variable [8]. Our study results suggest a lower SSI risk when SAP is administered within 30 min prior to incision. These results therefore challenge the latest WHO recommendation, which extends the window to administer SAP from 60 min to 120 min prior to the incision [3]. The WHO recommendations were supported by a recent SAP timing meta-analysis of 54 552 patients, but patients who had cardiac surgery were excluded [23]. Our results remained unchanged when the model was corrected for variations across institutions.

Our study did not identify a precise period within the -30 to 0-min window for optimal administration of SAP. It is currently unclear if administration of SAP a few min before the incision is associated with fewer SSI than its administration earlier in this window, as our fitted model might suggest.

Limitations

Limitations of the study are the lack of detailed information concerning the type of surgical procedure, the individual surgeons, the type of operating room and ventilation and patient comorbidities/characteristics (such as diabetes, glycaemic control, smoking, nutritional status, intraoperative temperature and oxygenation). None of these variables are routinely recorded in the Swissnoso database. However, the type of air conditioning in the operating room has not been shown to have a significant effect on SSIs [24]. In addition, data on detection and decolonization of *S. aureus* carriers were not routinely recorded, nor was compliance with redosing during and after surgery and the time the patient was on the heart–lung machine. These limitations notwithstanding, the Swiss national guidelines recommend a second dose of SAP after the patient is removed from the heart–lung machine [13]. According to a previous study, underdosing, for example, of vancomycin, could play a role in influencing SSI rates [25]. The antimicrobial susceptibility of some of the causative pathogens (such as CoNS) was not available; however, data from a single Swiss centre revealed that CoNS (of which 70% were resistant to methicillin) caused 40% of their sternal SSI [26]. Another limitation was that for SAP with a combination of antibiotics, we only considered the timing of the first agent applied earliest before the incision, a potential confounder we were unable to control for. However, the WHO, when making recommendations on the timing of SAP, refers to the start point of administration of the antibiotics, not the time when the infusion of SAP ended [3].

Surprisingly, for the vancomycin/cefuroxime combination, the first agent was only given 5 min ahead of the single cephalosporin SAP agents in relation to the time of incision. This result indicates that the earlier administration of vancomycin relative to other agents, as recommended by the Swiss guidelines, is not fully observed in clinical practice [13].

Our primary exposure variable was timing of SAP: however, our data show that factors other than the specific time of SAP administration within the 120-min window prior to incision are more significantly associated with the risk of SSI. Many institutions focused their SSI prevention efforts in cardiac surgery on administering SAP within 60 min prior to the incision. This process notwithstanding, in 2014/2015, compliance with these guidelines was achieved in only 73% of Swiss patients having cardiac surgery [27]. Our data indicate that an implication for day-to-day practice is the administration of SAP closer to the time of the incision, which makes handling from a practical perspective easier. The results therefore slightly differ from a recent randomized controlled trial that showed that SSI rates did not differ between early and late administration of SAP in general surgery [5]. Our study results allow administration of SAP when the surgeon is putting on his/her sterile gown and will likely increase compliance with proper timing. Earlier administration may result in inappropriate administration because there may be an unexpected delay in making the incision.

Optimal SAP agents for prevention of SSI in cardiac surgery are still being debated. The authors of a meta-analysis came to the conclusion that first or second generation cephalosporins are similarly effective in preventing SSIs [9], which is reflected in the current guidelines [28]. Our large sample gave more insights into the association between the choice of SAP and SSI. Overall SSIs were reduced by >35% when cefazolin was compared to cefuroxime. This effect, however, was no longer valid for the alternate outcome deep/organ space SSI.

Cefazolin has a longer half-life than cefuroxime [13]. This pharmacodynamic property may be the reason for the lower SSI rates. However, we cannot prove this hypothesis with our data, because a time-dependent effect was absent from our analysis after stratification for the individual SAP regimens. Unadjusted analysis provided flatter SSI rates over time for cefazolin than for the other antibiotics tested (Fig. 2C, D).

Cefazolin instead of cefuroxime might be the preferable cephalosporin as the SAP in cardiac surgery. However, we cannot exclude confounding in a prospective observational study. A large randomized clinical study should confirm these findings before a strong recommendation can be made.

Further discussion of SAP agents can be found in the Supplementary Material.

The main strengths of our study included assessing timing as a continuous variable and the availability of a variety of clinical and epidemiological data. Patients with a suspected SSI were given a rigorous follow-up by a dedicated physician, and data monitors did on-site checks of the quality of data electronically entered into a centralized database. The analysis of such large prospective cohorts may indeed be the ideal source for high-quality scientific data. It is possible that the external validity of our study is higher than that of a randomized controlled trial [29].

CONCLUSION

In conclusion, this large prospective study provides substantial arguments that administration of SAP close to the time of the incision is more effective than the earlier provision of prophylaxis in cardiac surgery, making compliance with SAP administration easier. The choice of SAP appears to play a significant role in the prevention of all SSIs, even after adjusting for confounding variables.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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