Topical rifampicin for prevention of deep sternal wound infections in patients undergoing coronary artery bypass grafting

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Deep sternal wound infections (DSWI), although an infrequent complication, significantly impair postoperative outcomes after coronary artery bypass grafting (CABG) surgery. Among several preventive strategies, topical antibiotic therapy immediately before sternal closure has been strongly advocated. In this retrospective analysis, the incidence of DSWI in 517 patients undergoing isolated CABG and receiving rifampicin irrigation of mediastinum, sternum and suprasternal tissues was compared to an historical consecutive cohort of 448 patients. To account for the inherent selection bias, a 1:1 propensity matched analysis was performed. Patients receiving topical rifampicin experienced significantly less occurrence of postoperative DSWI (0.2% vs 2.5%, p = 0.0016 in the unmatched analysis; 0.3% vs 2.1%, p = 0.0391 in the matched analysis). Intensive care unit stay, hospital stay, and operative mortality were similar between groups. This study shows that topical rifampicin in combination with commonly prescribed preventative strategies significantly reduces the incidence of DSWI to less than 0.3% in unselected patients undergoing a full median sternotomy for CABG. Further studies, including a larger number of patients and with a randomization design, would establish the potential preventative role of topical rifampicin in reducing the occurrence of DSWI.

Materials and methods
Setting, patient sample and principles of surgical and clinical care. Study setting was the Division of Cardiac Surgery of the “Casa di Cura Montevergine”. This is a private facility in Mercogliano, Avellino, Italy, where nearly 700 patients undergo cardiac surgery annually. Standardized case report forms allow daily collection of clinical parameters from these patients. All of these peri-operative data are entered into an electronic

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introduced as a standard of care, the need for informed consent was waived. Montevergine Ethics and Research Committee (protocol number 29/2017). Since the novel closure protocol was the logit of the propensity score. To evaluate the balance between the matched groups, paired sample t-test for continuity score matching was performed using the greedy algorithm and a caliper of 0.2 of the standard deviation of internal mammary artery usage, perioperative transfusion, any postoperative reoperation. One-to-one propensity score was calculated to select two groups of patients with similar baseline characteristics, with patients treated with the new protocol as the fixed group. Those variables known to be associated non-parsimonious propensity score was calculated to select two groups of patients with similar baseline characteristics, with patients treated with the new protocol as the fixed group. Those variables known to be associated were: age, gender, diabetes, COPD, obesity, extracardiac vascular disease, LVEF, chronic kidney disease, previous cardiac surgery, surgical priority, operative technique, bilateral internal mammary artery usage, perioperative transfusion, any postoperative reoperation. One-to-one propensity score matching was performed using the greedy algorithm and a caliper of 0.2 of the standard deviation of the logit of the propensity score. To evaluate the balance between the matched groups, paired sample t-test for continuous variables, the McNemar test for dichotomous variables, and analysis of the standardized differences after matching have been used. Standardized differences lower than 0.10 were considered an acceptable imbalance between the treatment groups. These tests were used to evaluate any difference in the adverse events of propensity score matched pairs.

Study aims and clinical outcomes. All definitions were established as part of the original study design. Primary outcome of this study was the incidence of DWSI. The Centers for Disease Control and Prevention classification of surgical site infections was adopted. Combined results of bacterial cultures, clinical parameters and surgical findings allowed the diagnosis of DWSI. Baseline characteristics and operative risk were defined according to the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II definition criteria. Secondary outcomes were hospital and Intensive Care Unit (ICU) length of stay and all-cause mortality. Study protocol complies with the Helsinki Declaration (as revised in 2013) and was approved by the Clinica Montevergine Ethics and Research Committee (protocol number 29/2017). Since the novel closure protocol was introduced as a standard of care, the need for informed consent was waived.

Statistical analysis. SAS version 9.4 (SAS Institute, Cary, NC) was employed for all statistical analyses. Continuous variables are reported as mean and standard deviation, whereas categorical variables as absolute number and percentage. Preoperative and postoperative data were compared with unpaired T-test, chi-square and Kruskall-Wallis test. Statistical significance was set at an alpha level of 0.05. To reduce selection bias, a non-parsimonious propensity score was calculated to select two groups of patients with similar baseline characteristics, with patients treated with the new protocol as the fixed group. Those variables known to be associated with a high risk for DWSI were included in the model: age, gender, diabetes, COPD, obesity, extracardiac vascular disease, LVEF, chronic kidney disease, previous cardiac surgery, surgical priority, operative technique, bilateral internal mammary artery usage, perioperative transfusion, any postoperative reoperation. One-to-one propensity score matching was performed using the greedy algorithm and a caliper of 0.2 of the standard deviation of the logit of the propensity score. To evaluate the balance between the matched groups, paired sample t-test for continuous variables, the McNemar test for dichotomous variables, and analysis of the standardized differences after matching have been used. Standardized differences lower than 0.10 were considered an acceptable imbalance between the treatment groups. These tests were used to evaluate any difference in the adverse events of propensity score matched pairs.

Results

Table 1 summarizes patient population features, surgical priority and preoperative risk scoring. In the unmatched cohort, patients operated during 2015–2016 were more hypertensive and had a greater estimated surgical risk, according to EuroSCORE II. However, propensity matched cohorts proved to be homogeneous.

Operative details are reported in Table 2. Briefly, no differences were observed between groups in terms of number of target vessels, number of grafts, type of graft selected, as well as length of cardiopulmonary bypass, aortic cross-clamping time and operation time.

Table 3 reports major outcomes in the overall populations as well as in matched cohorts. Deep sternal wound infections were present in 12 patients (1.24%). DWSI were diagnosed early (<30 days) after surgery in most of the cases (11 pts). No relation was found between incidence of DSWI and surgical technique (OPCABG OR 0.342, 95% CI 0.192–1.71, p = 0.07). Similarly, number of grafts (OR 1.213, 95% CI 0.397–2.341, p = 0.12) and surgical time (OR 2.851, 95% CI 0.875–4.382, p = 0.23) did not emerged as univariate predictors of DSWI.

Patients in the rifampicin group performed significantly better (1 vs 11 DSWI, 2.5% vs 0.2%). The percentage of Gram-positive infections was 100%. Positive swabs for Coagulase Negative Staphylococcus species accounted for 75% of the cases. There were 2 cases of staphylococcus aureus infections (one in each study period, with no methicillin resistant strain) and 1 case of enterococcus faecalis isolation. Negative pressure wound therapy was applied in all cases. Final closure technique was sternal re-wiring in 4, pectoral muscle flap in 6 and subcutaneous closure in 2 patients. No adverse reaction has been observed in the group of patients receiving topical rifampicin.

Incidence of SVG wound infections was similar in both groups, but topical antibiotic application was limited to 75% of the cases. There were 2 cases of staphylococcus aureus infections (one in each study period, with no methicillin resistant strain) and 1 case of enterococcus faecalis isolation. Negative pressure wound therapy was applied in all cases. Final closure technique was sternal re-wiring in 4, pectoral muscle flap in 6 and subcutaneous closure in 2 patients. No adverse reaction has been observed in the group of patients receiving topical rifampicin. Incidence of SVG wound infections was similar in both groups, but topical antibiotic application was limited to the chest incision.

As to secondary outcomes, no significant difference emerged for hospital and ICU length of stay. Similarly, no difference emerged as to hospital mortality. Noteworthy, all patients experiencing DSWI were discharged home or to a rehabilitation program, according their clinical conditions.
DSWI significantly jeopardise hard outcomes and impact on the overall periprocedural economic burden\textsuperscript{17,18}. This study shows that topical rifampicin in combination with commonly prescribed preventive strategies significantly reduces the incidence of DSWI in an unselected cohort of CABG patients operated on through a full median sternotomy. The overall incidence of DSWI was 1.24%, a rate that closely matches what has been previously reported\textsuperscript{11,19}. This rate was reduced to a promising 0.2% by the new closing protocol. As reported in a recent authoritative literature review, given several biases, the variation in the incidence of DSWI is so high to preclude any systematic analysis. In other words it is still impossible to define a benchmark standard for outcome comparison\textsuperscript{20}. A recent Japanese nationwide survey on cardiac surgical procedures, demonstrated that CABG surgery, despite implying the lowest odds ratio for operative mortality, actually entails the highest potential for DSWI development (1.36 [95% CI: 1.24–1.49]) and 1.52 [95% CI: 1.32–1.76] respectively\textsuperscript{21}. In the same analysis it is also shown that DSWI should be considered independently of the surgical mortality. Indeed those hospital reaching the lowest risk-adjusted mortality rate do not always have the same performance as to the incidence of DSWI\textsuperscript{17}. This tertiary care center displays an high case load (>220 cases per year) with a satisfactory mortality

| Characteristics | Overall Series | Propensity Score Matched Pairs |
|-----------------|--------------|-------------------------------|
|                 | 2015–2016 (n = 448) | 2017–2018 (n = 517) | p | Standardized differences | 2015–2016 (n = 362) | 2017–2018 (n = 362) | p | Standardized differences |
| Age             | 66.8±8.9 | 66.1±8.7 | 0.16 | 0.09 | 66.7±8.7 | 66.1±8.7 | 0.34 | 0.10 |
| Female          | 89 (19.9) | 90 (17.4) | 0.33 | 0.06 | 63 (17.4) | 59 (16.3) | 0.76 | 0.03 |
| Obesity         | 44 (9.8) | 57 (11.0) | 0.54 | 0.04 | 39 (10.8) | 43 (11.9) | 0.72 | 0.04 |
| Systemic Hypertension | 367 (81.9) | 381 (73.7) | 0.0023 | 0.20 | 287 (79.3) | 277 (76.5) | 0.30 | 0.03 |
| Diabetes Mellitus | 189 (42.2) | 216 (41.8) | 0.90 | 0.008 | 149 (41.2) | 153 (42.3) | 0.81 | 0.02 |
| NIDDM           | 154 (34.4) | 182 (35.2) | 0.79 | 0.02 | 124 (34.3) | 121 (33.4) | 0.87 | 0.02 |
| IDDM            | 35 (7.8) | 34 (6.6) | 0.46 | 0.05 | 25 (6.9) | 32 (8.4) | 0.38 | 0.07 |
| Chronic Kidney Disease | 28 (6.3) | 39 (7.5) | 0.43 | 0.05 | 24 (6.6) | 30 (8.3) | 0.46 | 0.07 |
| COPD            | 75 (16.7) | 74 (14.3) | 0.30 | 0.07 | 59 (16.3) | 73 (20.2) | 0.22 | 0.10 |
| Extracardiac Arteriopathy | 49 (10.9) | 38 (7.4) | 0.05 | 0.12 | 32 (8.8) | 25 (6.9) | 0.37 | 0.07 |
| LVEF            | 0.60 | 0.04 | 0.0093 | 0.17 | 2.91±0.95 | 2.53±0.62 | 0.28 | 0.09 |

Table 1. Baseline characteristics of the study cohort. (N)IDDM: (non) insulin-dependent diabetes mellitus; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction.

| Details                  | Overall Series | Propensity Score Matched Pairs |
|--------------------------|--------------|-------------------------------|
|                          | 2015–2016 (n = 448) | 2017–2018 (n = 517) | p | Standardized differences | 2015–2016 (n = 362) | 2017–2018 (n = 362) | p | Standardized differences |
| Operative technique      | <0.0001 | 0.59 |
| On pump                  | 281 (62.7) | 435 (84.1) | 0.16 | 0.09 | 276 (76.2) | 280 (77.4) | 0.28 | 0.08 |
| OPCABG                   | 167 (37.3) | 82 (15.9) | 0.52 | 0.05 | 86 (23.8) | 82 (22.7) | 0.33 | 0.08 |
| LIMA                     | 446 (99.6) | 513 (99.2) | 0.52 | 0.05 | 359 (99.2) | 357 (98.6) | 0.48 | 0.08 |
| BIMA                     | 38 (8.5) | 31 (6.0) | 0.14 | 0.07 | 28 (7.7) | 30 (8.3) | 0.89 | 0.08 |
| SVG                      | 382 (85.3) | 446 (86.3) | 0.67 | 0.07 | 320 (88.4) | 324 (89.5) | 0.64 | 0.07 |
| Number of grafts         | 2.73±0.92 | 2.84±0.94 | 0.07 | 0.008 | 2.68±0.86 | 2.75±0.87 | 0.28 | 0.08 |
| CPB (minutes)            | 86±32 | 88±37 | 0.37 | 0.07 | 86±24 | 87±35 | 0.65 | 0.07 |
| Operation time (minutes) | 232±57 | 237±65 | 0.21 | 0.07 | 234±58 | 239±62 | 0.27 | 0.07 |

Table 2. Operative details. OPCABG: off-pump coronary artery bypass graft; LIMA: left internal mammary artery; BIMA: bilateral internal mammary arteries; SVG: saphenous vein graft; CPB: cardiopulmonary bypass; XCT: aortic cross-clamping time.

Discussion
DSWI significantly jeopardise hard outcomes and impact on the overall periprocedural economic burden\textsuperscript{17,18}. This study shows that topical rifampicin in combination with commonly prescribed preventive strategies significantly reduces the incidence of DSWI in an unselected cohort of CABG patients operated on through a full median sternotomy. The overall incidence of DSWI was 1.24%, a rate that closely matches what has been previously reported\textsuperscript{11,19}. This rate was reduced to a promising 0.2% by the new closing protocol. As reported in a recent authoritative literature review, given several biases, the variation in the incidence of DSWI is so high to preclude any systematic analysis. In other words it is still impossible to define a benchmark standard for outcome comparison\textsuperscript{20}. A recent Japanese nationwide survey on cardiac surgical procedures, demonstrated that CABG surgery, despite implying the lowest odds ratio for operative mortality, actually entails the highest potential for DSWI development (1.36 [95% CI: 1.24–1.49]) and 1.52 [95% CI: 1.32–1.76] respectively\textsuperscript{21}. In the same analysis it is also shown that DSWI should be considered independently of the surgical mortality. Indeed those hospital reaching the lowest risk-adjusted mortality rate do not always have the same performance as to the incidence of DSWI\textsuperscript{17}. This tertiary care center displays an high case load (>220 cases per year) with a satisfactory mortality
rate (overall 1.4%). Topical application of antibiotics has been recently recommended by expert consensus statements⁵⁻⁷ despite an unpredictable potential for the development of antibiotic resistance. Topical vancomycin and gentamicin have been recommended as a standard of care even though the level of evidence is low and published data are somewhat conflicting⁵⁻⁷⁻⁸. The burden of bacterial biofilms is highest in musculoskeletal infections as DSWI. Vancomycin has minimal eradication effect on this respect. In vitro and in vivo studies have shown that Rifampicin is an effective Staphylococcal biofilm eradicator with no adverse effects on bone healing. Rifampicin’s mechanism of action is independent of cellular replication since its target is bacterial protein synthesis. This antibiotic displays strong bactericidal effect on both gram positive and negative species. Other relevant features include: unexpensiveness and easiness of preparation and handling. It has also been consistently shown to decrease wound infection in other surgical settings⁵⁻⁷⁻⁸. The present study is the first large scale trial to evaluate its preventive potential. It expands the findings of the pivotal study by Aygün and colleagues with the inherent merit of an all comer design which is more close to a real world setting. More, it enclosed procedure performed both on pump and off-pump as well as a fair number of procedures with bilateral mammary artery harvesting which are representative of current surgical practice pattern. Several methodological features of the present analysis should be underscored for a thorough data evaluation. Major strengths of this study are: the adherence to standardised definition of both patients features and outcomes events, and the single centre setting along with its inherent standardised perioperative care pathway. Such a combination significantly limited the variability due to the influence of individual and institutional practice on hospital and ICU length of stay and pattern of resource utilisation. A benchmark for outcomes measures in morbidity studies. Speculatively, the single center setting might imply one-sided results not readily transferable to other patient populations due to the influence of specific standards of clinical practice and a unique patient population features. More, it is a retrospective analysis of prospectively collected data. Though all known risk factors have been accounted for, there might be still a potential for unknown predictors. Moreover, the study involves separate time periods. Nevertheless, the large sample size, no change in perioperative management algorithms, and accurate propensity matching for predictors of DSWI should have prevented major biases. Finally, despite the large study sample, the study analysis may still be statistically underpowered. Indeed, the relatively small number of index cases, which prevented any meaningful regression analysis for DSWI development, might theroretically imply a definite probability of type II error.

Conclusions

Topical rifampicin in combination with known preventive perioperative strategies significantly reduces the incidence of DSWI after CABG. Clearly, our study is hypothesis-generating given its proper nature, and to finally clarify the issue at stake, further trials are mandatory.

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Table 3. Postoperative outcomes. ICU: intensive care unit; DSWI: deep sternal wound infection; SVG: saphenous vein graft.

| Details                        | Overall Series | Propensity Score Matched Pairs |
|-------------------------------|----------------|-------------------------------|
|                               | 2015–2016 (n = 448) | 2017–2018 (n = 517) | p       | 2015–2016 (n = 362) | 2017–2018 (n = 362) | p       |
| In-hospital stay (days)       | 13.8 ± 8.6     | 12.8 ± 6.0                  | 0.054   | 13.3 ± 8.3     | 13.3 ± 8.7     | >0.99   |
| ICU stay (days)               | 2.4 ± 3.0      | 2.1 ± 2.2                   | 0.07    | 2.3 ± 2.3      | 2.3 ± 2.5      | 0.98    |
| Reoperation                   | 18 (4.0)       | 6 (1.2)                     | 0.0045  | 5 (1.4)        | 6 (1.7)        | >0.99   |
| Bleeding                      | 15 (3.3)       | 6 (1.2)                     | 4 (1.1) | 6 (1.7)        | >0.99   |
| Graft failure                 | 3 (0.7)        | 0                            | 1 (0.3) | 0                |
| RBC transfusion               | 194 (43.3)     | 202 (39.1)                  | 0.18    | 145 (40.1)     | 152 (42.0)     | 0.65    |
| DSWI                          | 11 (2.5)       | 1 (0.2)                     | 0.0016  | 8 (2.1)        | 1 (0.3)        | 0.0391  |
| SVG wound infection           | 3 (0.67)       | 3 (0.58)                    | 0.86    | 2 (0.55)       | 1 (0.28)       | 0.56    |
| Death                         | 8 (1.8)        | 6 (1.2)                     | 0.42    | 5 (1.4)        | 6 (1.7)        | >0.99   |
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