

Impact of Vacuum-Assisted Closure (VAC) Therapy on Clinical Outcomes of Patients with Sternal Wound Infections: A Meta-Analysis of Non-Randomized Studies

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Abstract

Objective: To examine the impact of VAC therapy on mortality of patients with sternal wound infections after cardiothoracic surgery.

Summary Background Data: Controversial results regarding mortality of patients with sternal wound infections were published.

Methods: We performed a systematic search in PubMed and Scopus. Mortality was the primary outcome of the meta-analysis. Recurrences, complications and length of stay were secondary outcomes.

Results: Twenty-two retrospective studies including 2467 patients were eligible for inclusion. Patients treated with VAC had significantly lower mortality compared to those treated without VAC [2233 patients, RR=0.40, (95% CI 0.28, 0.57)]. This finding was consistent regardless of the study design, the exclusion of studies with positive findings, the criteria for establishment of the compared groups, the time of mortality assessment or the type of infections under study, provided that adequate data was available. VAC therapy was associated with fewer recurrences (RR=0.34, 95% CI: 0.19–0.59). The meta-analysis did not show any difference in the length of stay (RR=−2.25, 95% CI: −7.52–3.02).

Conclusions: VAC therapy was associated with lower mortality than other surgical techniques in retrospective cohorts of patients with DSWIs following cardiothoracic surgery.

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Introduction

Deep sternal wound infections (DSWI), namely mediastinitis and osteomyelitis, are a serious complication occurring in 1% to 5% of patients after cardiothoracic operations in individual studies.[1,2] Intravenous antibiotics and several surgical techniques had been used in the past for their treatment; however, they have been associated with increased short- and long-term mortality.[3] A new technique using topical negative pressure by controlled suction has been introduced in the treatment of wounds achieving wound closure through the formation of granulation tissue. This technique, most commonly applied by vacuum-assisted closure (VAC) wound therapy system, has gradually gained ground and replaced most of the conventional types of wound treatment due to the faster wound healing,[4,5,6] lower length of hospital stay[7,8,9] and the subsequent lower in-hospital cost.[6,10].

Moreover, early studies showed that VAC therapy has the potential to reduce both in-hospital and long-term mortality.[11,12] A meta-analysis published in 2011 showed that patients treated with VAC had shorter duration of hospitalization but no

difference in mortality compared to those treated with a non-VAC therapy.[13] Since this publication several new studies became available that expanded our knowledge regarding the effectiveness of VAC application for the treatment of sternal wound infections. We aimed to systematically review and synthesize the available evidence with the methodology of meta-analysis in order to examine the impact of VAC therapy on mortality of patients with sternal wound infections.

Methods

Literature Search

We performed a systematic search in PubMed and Scopus electronic databases in September 2012. The search term that was applied in PubMed was the following: (“negative pressure” OR vac OR “vacuum assisted”) AND (wound) AND (infection). A more conservative search term was applied in Scopus database: (“negative pressure” OR vac OR “vacuum assisted”) AND (sternal wound infection OR dswi OR mediastinitis OR osteomyelitis). In addition, the bibliographies of all relevant articles were searched in

order to identify further potentially eligible studies. Articles written in a language other than English, German, French, Spanish, Italian or Greek were not evaluated. Only published studies were included; abstracts from conferences were excluded.

Study Selection

Articles reporting the comparative outcomes of patients with sternal wound infections treated with VAC versus a non-VAC therapy were considered eligible for the meta-analysis regardless of the study design, patient characteristics, type of surgery and additional used interventions, deep or superficial sternal wound infections. When a patient population was included in more than one published studies, only the study with the bigger total study population was included. Studies focusing primarily in sternal wounds without infections or other types of wounds were excluded.

Data Extraction

Data was extracted regarding the major characteristics of the included studies (first author, country, period of the study, study design), number of patients in each treatment arm, group establishment regarding the type of therapy selected, patient comorbidity regarding the cardiothoracic operations conducted, and time of mortality assessment.

Definitions and Outcomes

Sternal wound infections could comprise both deep and superficial infections developed after a cardiothoracic surgery. The definition of osteomyelitis, mediastinitis and superficial wound infections was based on the definitions provided by the selected individual studies.

The primary outcome of the review was in-hospital mortality. When in-hospital mortality was not provided by the authors of a study, 30-day or 90-day mortality was selected. Secondary outcomes comprised recurrence, as defined by the authors of the included studies, and hospital length of stay (LOS).

Statistical Analysis

The non-randomized studies that were analyzed were considered to be heterogeneous by definition and therefore, the Mantel-Haenszel random effects model (REM) was applied. Pooled risk ratios (RR) and 95% confidence intervals (CI) were calculated regarding all outcomes. Statistical heterogeneity between studies was assessed by using the χ^2 test ($p < 0.10$ was defined to indicate the presence of heterogeneity) and the I^2 (for assessing the degree of heterogeneity). The meta-analysis was performed with Review Manager for Windows, version 5.1.

Results

The systematic search in both databases generated 938 articles (754 PubMed, 172 Scopus, 12 hand-searching). The selection process that was followed for the inclusion of the studies is depicted in Figure 1. Twenty-two studies were finally included in the review.[8,11,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33] The characteristics of the included studies are presented in Table 1. Twenty one studies reported on deep sternal wound infections (16 on mediastinitis,[11,14,15,16,17,18,19,20,21,23,26,27,28,30,32,33] two on osteomyelitis[8,25] and 3 did not specify the type of infections[24,29,31]). One study included both deep (69%) and superficial (31%) sternal wound infections.[22] All included studies were retrospective cohorts. Thirteen of the 22 studies provided data with regard to the VAC system that was applied and in all of them the KCI (Kinetic Concepts, Inc.)

system was used.[8,14,17,18,19,21,22,23,24,28,30,31,32] Data regarding funding was provided by 4 studies;[11,18,22,32] only one was industry funded.[22].

Mortality

Twenty studies (2233 patients) provided data on mortality.[8,11,14,15,16,18,19,20,21,22,23,24,25,26,27,28,30,31,32,33]^{ref8} Nineteen studies reported on deep sternal wound infections (15 on mediastinitis,[11,14,15,16,18,19,20,21,23,25,26,27,28,30,32,33] 2 on osteomyelitis[8,25] and 2 did not specify the type of infections[24,31]). One study included both deep (69%) and superficial (31%) sternal wound infections.[22] In 12 studies, VAC treated patients were compared with a historical control group not receiving VAC therapy,[11,18,19,21,22,23,25,26,27,28,31,32] while in 2 other studies,[8,16] the selection of therapy (VAC or non-VAC) was at the surgeon's discretion, as both types of therapy were simultaneously available. Six studies did not provide the criteria for the selection of therapy in the enrolled patients.[14,15,20,24,30,33] Twelve studies provided data for in-hospital mortality,[8,14,15,16,18,20,21,26,27,31,32,33] 2 on 30-day[28,30] and 2 studies on 90-day mortality,[11,19] while 4 studies did not determine when mortality was assessed.[22,23,24,25].

Pooling of all 20 studies that provided data on mortality showed that patients treated with VAC had significantly lower mortality compared to those treated with a non-VAC therapy, [Figure 2, 2233 patients, RR = 0.40, (95% CI: 0.28, 0.57)]. Heterogeneity was not observed in this analysis ($I^2 = 16\%$). In addition, mortality was lower among patients receiving VAC therapy after the exclusion of studies that showed significantly lower mortality [1058 patients, RR 0.60, (95% CI: 0.41–0.89)]. Lower mortality was found among patients treated with VAC among studies using a historical non-VAC control group [1476 patients, RR = 0.32 (95% CI: 0.20, 0.50)]. Heterogeneity was not observed in this analysis ($I^2 = 5\%$). Similarly, lower mortality was observed for VAC therapy in the studies that did not provide the criteria for the selection of therapy [655 patients, RR = 0.45 (95% CI: 0.23, 0.88)]. No difference was found between the compared groups when the selection of the type of therapy was at the surgeon's discretion [102 patients, RR = 0.99, (95% CI: 0.21, 4.65)].

In-hospital mortality was lower among patients treated with a VAC compared to those treated with a non-VAC therapy, [Figure 3, 1186 patients, RR = 0.40, (95% CI: 0.26, 0.62)]. Heterogeneity was not observed in this analysis ($I^2 = 13\%$). On the other hand, no difference in 30-day [193 patients, RR = 2.28 (95% CI: 0.30, 17.25)] and 90-day mortality [191 patients, RR = 0.21 (95% CI: 0.03, 1.30)]; a small number of patients were included in these 2 analyses. Finally, in the studies that did not provide the time of mortality assessment a trend towards lower mortality was observed [663 patients, RR = 0.39 (95% CI: 0.14, 1.03)].

Patients with mediastinitis and/or undetermined deep sternal wound infections treated with VAC therapy had lower mortality compared to the respective patients treated with a non-VAC therapy, [Figure 4, 1534 patients, RR = 0.38 (95% CI: 0.24, 0.60)] and [117 patients, RR = 0.21 (95% CI: 0.06, 0.73)] respectively. Heterogeneity was not observed in the abovementioned analyses ($I^2 = 23\%$ and $I^2 = 0\%$, respectively). No difference in mortality was found between the compared groups among patients with osteomyelitis [58 patients, RR = 1.78 (95% CI: 0.35, 9.04)]. Last, 1 study including both deep and superficial sternal wound infections showed lower mortality among patients treated with VAC therapy than those treated with a non-VAC therapy [524 patients, RR = 0.36 (95% CI: 0.18, 0.73)].[22].

Only 4 of the 20 studies provided data regarding funding; 1 was industry-funded,[22] 2 were funded by universities[11,32] while 1

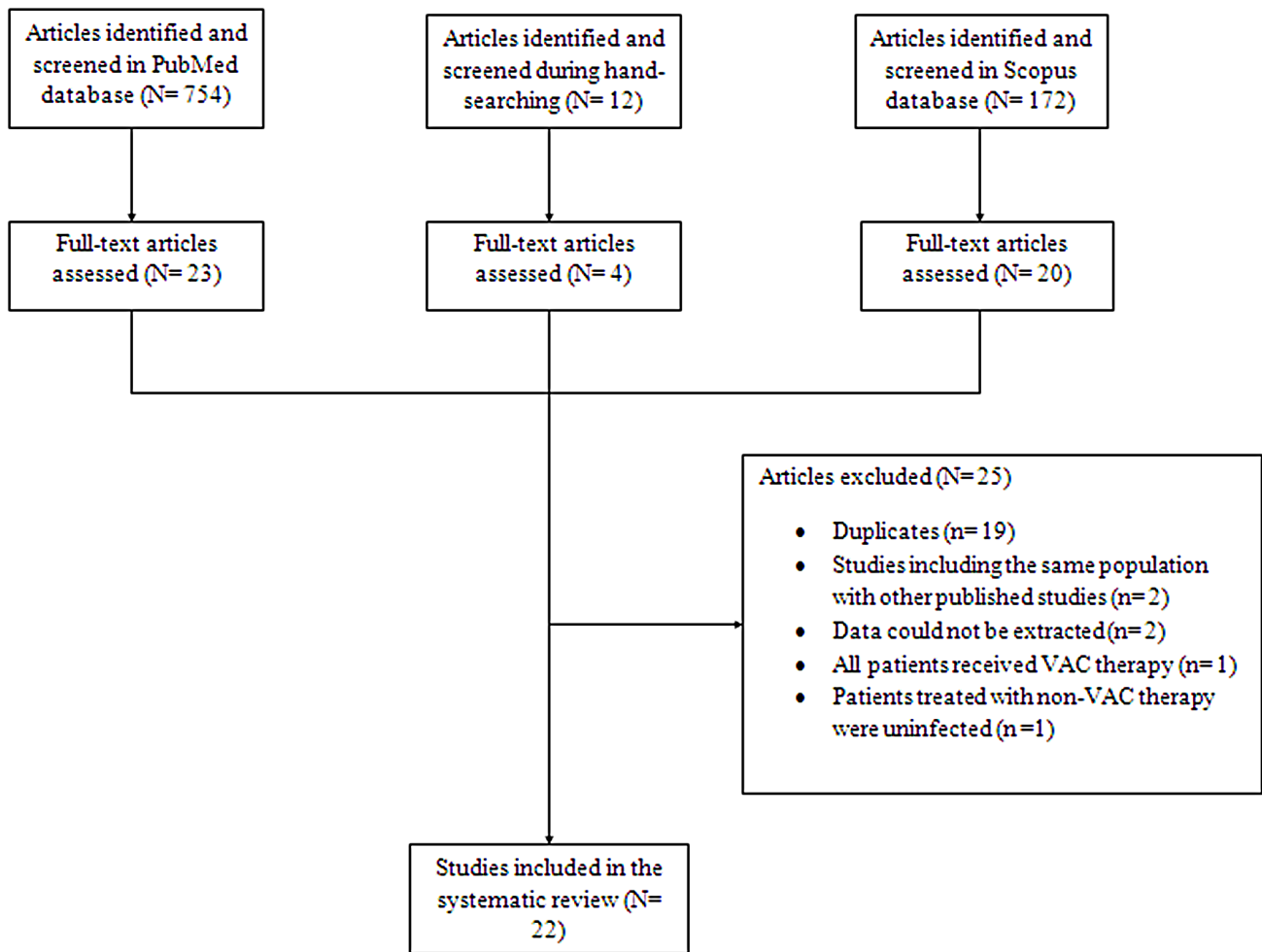


Figure 1. Flow diagram of the systematic search and study selection process.

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study was not funded.[18] Therefore, potential bias arising out of funding could not be adequately investigated.

Recurrences, Complications and Length of Stay

Ten studies provided data on recurrence of DSWIs (1197 patients).[11,17,21,22,25,27,28,30,31,32] Pooling of these studies showed that recurrence was less common among patients treated with VAC compared to those treated with a non-VAC therapy, [RR = 0.34 (95% CI: 0.19, 0.59)]. Moderate heterogeneity was detected in this analysis ($I^2 = 48\%$). Data on complications was available within 4 studies.[11,14,21,31] Different types of complications were reported in the individual studies including remote infections, sepsis, cardiovascular/neurological/gastrointestinal complications, renal failure, bleeding, multiple organ failure, fistula, empyema, dehiscence, skin graft requirement, skin necrosis, seroma, discharging sinus, partial flap loss, new atrial fibrillation. However, only one study presented the total number of complications patients in each treatment arm,[14] while the remaining three studies presented the individual complications in each arm.[11,21,31] Therefore, the data could not be further analyzed.

Finally, ten studies provided data on LOS (983 patients).[8,11,14,16,19,21,27,29,31,33] Pooling of the outcomes of these studies showed that there was no statistically significant

difference in LOS between patients treated with VAC and those treated with a non-VAC therapy, [RR = -2.25 (95% CI: -7.52, 3.02)]. Considerable heterogeneity was detected in this analysis ($I^2 = 82\%$) and individual studies showed that VAC was associated with both significantly lower and higher duration of hospitalization.

Discussion

The currently available data from retrospective cohort studies suggest that the use of VAC therapy was associated with lower mortality than non-VAC therapy for the treatment of patients with DSWIs after cardiovascular surgery. This finding was consistently present regardless the study design, the inclusion of studies with positive findings, the criteria for establishment of the compared groups, the time of mortality assessment or the type of infections under study, provided that adequate data was available. In addition, VAC therapy was associated with fewer recurrences of infections. On the contrary, this meta-analysis did not show any difference in the duration of hospitalization.

The main limitation of the current meta-analysis is the retrospective nature of the available data. No randomized controlled trial has been published yet and one protocol had been registered –to our knowledge? regarding the effectiveness and safety of VAC therapy for the treatment of patients with DSWIs in

Table 1. Characteristics of the studies included in the meta-analysis.

First author Year	Study design; period, country	Number of analyzed patients (VAC vs non-VAC)	Patient co-morbidity	Group establishment	System of VAC used	Mortality assessed at	Funded or non-funded study
Deniz 2012 ¹⁹	Retrospective cohort; 2000–2011, Turkey	90 (47 vs 43)	60% coronary artery bypass revascularization, isolated 32% valvular procedure, 8% valvular in combination with coronary bypass procedures	2000–2003: non-VAC 2003–2011: VAC	KCI system	90-day	NR
Fleck 2012 ²²	Retrospective cohort; 1995–2011, Austria	524 (326 vs 198)	Cardiac operations (VAC group: 62% aorto-coronary artery bypass, 39% VR, 17% congenital surgery or aortic surgery or heart transplantation)	1995–2001: non-VAC 2002–2011: VAC	KCI system	Undetermined	KCI, USA
Risnes 2012 ²⁸	Retrospective cohort; 1997–2010, Norway	104 (64 vs 66)	CABG	1997–2002: non-VAC 2002–2006: both non-VAC and VAC 2006–2010: VAC	KCI system	30-day	NR
Rodriguez Cetina Biefler 2012 ²⁹	Retrospective cohort; 1999–2008, Portugal	159 (105 vs 54)	51% CABG, 18% isolated valve, 18% CABG/valve, 14% other procedures (thoracic aneurysms, aortic dissections, congenital repair procedures)	According to the surgeon's discretion; VAC available for use at the clinic after 2002	NR	NA	NR
Simek 2012 ³¹	Retrospective cohort; 2002–2007, Czech Republic	62 (34 vs 28)	76% CABG, 6% valve, 18% CABG+valve	2002–2004: non-VAC 2004–2007: VAC	KCI system	In-hospital	NR
Steingrimsón 2012 ³²	Retrospective cohort; 2000–2010, Iceland	43 (20 vs 23)	63% CABG, 16% AVR+CABG, 7% aortic valve replacement alone	2000–2005: non-VAC 2005–2010: VAC	KCI system	In-hospital	Landsþítali University Research Foundation
Vos 2012 ³³	Retrospective cohort; 2000–2011, Netherlands	132 (89 vs 43)	81% CABG, 75% LIMA, 21% RIMA, 22% AVR, 8% MVR	VAC or non-VAC; no reasons are reported	NR	In-hospital	NR
Assmann 2011 ¹⁴	Retrospective cohort; 2004–2008, Germany	154 (82 vs 72)	68% CABG	VAC or non-VAC; no reasons are reported	KCI system	In-hospital	NR
De Feo 2011 ¹⁸	Retrospective cohort; 1979–2009, Italy	200 (55 vs 145)	57% coronary artery bypass, 26% valve surgery, 18% other procedures	1979–2002: non-VAC 2002–2009: VAC	KCI system	In-hospital	Non-funded
Kobayashi 2011 ²⁵	Retrospective cohort; 2001–2007, Japan	16 (9 vs 7)	44% CABG, 19% AVR, 31% thoracic aortic surgery, 6% cardiac trauma	2001–2003: non-VAC 2003–2007: VAC	NR	Undetermined	NR
Morisaki 2011 ²⁶	Retrospective cohort; 1991–2010, Japan	59 (8 vs 51)	58% CABG, 20% single-valve surgery, 8% OPCAB, 5% modified Bentall procedure, 5% thoracic aneurysm operation, 5% combined operations, 5% other, 2% CABG+infarct exclusion	1991–2006: non-VAC 2006–2010: VAC	NR	In-hospital	NR
Ballot 2010 ¹⁵	Retrospective cohort; 2002–2007, Canada	149 (125 vs 24)	(B) IMA	VAC or non-VAC; no reasons are reported	NR	In-hospital	NR
De Feo 2010 ¹⁷	Retrospective cohort; 2000–2009, Italy	75 (45 vs 30)	Cardiac surgery	VAC or non-VAC; no reasons are reported	KCI system	NA	NR
Petzina 2010 ²⁷	Retrospective cohort; 2004–2009, Germany	118 (69 vs 49)	84% CABG ± valve procedure	2004–2006: non-VAC 2006–2009: VAC	NR	In-hospital	NR

Table 1. Cont.

First author Year	Study design; period, country	Number of analyzed patients (VAC vs non-VAC)	Patient co-morbidity	Group establishment	System of VAC used	Mortality assessed at	Funded or non-funded study
Eyiletlen 2009 ²¹	Retrospective cohort; 2000–2007, Turkey	65 (33 vs 32)	75% CABG, 9% MVR, 5% MVR+CABG, 5% AVR, 2% AVR+CABG, 2% Bentall procedure	2000–2004: non-VAC 2005–2007: VAC	KCI system	In-hospital	NR
Fuchs 2005 ²³	Retrospective cohort; 1998–2003, Germany	68 (35 vs 33)	Bypass operations, heart valve replacements	1998–2000: non-VAC 2000–2003: VAC	KCI system	Undetermined	NR
Immer 2005 ²⁴	Retrospective cohort; 1998–2003, Switzerland	55 (38 vs 17)	76% CABG, 58% unilateral mammarian artery, 15% bilateral mammarian artery, 1% reoperation	VAC or non-VAC; [§] no reasons are reported	KCI system	Undetermined	NR
Segers 2005 ³⁰	Retrospective cohort; 1992–2003, Netherlands	63 (29 vs 34)	64% CABG, 14% valve surgery, 21% CABG+valve surgery, 2% other	VAC or non-VAC; no reasons are reported	KCI system	30-day	NR
Sjögren 2005 ¹¹	Retrospective cohort; 1994–2003, Sweden	101 (61 vs 40)	72% CABG, 28% other procedures	1994–1998: non-VAC 1999–2003: VAC	NR	90-day	County of Skåne Medical Science Fund, University Hospital of Lund Donation Funds
Domkowski 2003 ²⁰	Retrospective cohort; 1997–2002, United Kingdom	102 (96 vs 6)	Cardiac surgery	VAC or non-VAC; no reasons are reported	NR	In-hospital	NR
Doss 2002 ⁸	Retrospective cohort; 1998–2000, Germany	42 (20 vs 22)	69% CABG, 14% CABG+AVR, 5% CABG+carotid endarterectomy, 5% CABG + concomitant left ventricular aneurysm resection, 5% isolated AVR, 2% CABG + concomitant AVR+mitral valve repair	1998–1999: non-VAC 1999–2000: both non-VAC and VAC, according to the surgeon's discretion	KCI system	In-hospital	NR
Berg 2000 ¹⁶	Retrospective cohort; 1989–1997, Netherlands	60 (31 vs 29)	35% CABG with venous graft, 58% CABG with IMA, 5% valve replacement, 2% CABG+valve replacement	VAC or non-VAC; according to the surgeon's discretion	NR	In-hospital	NR

[§]For patients treated for sternal wound infections between 1997 and 2001, no mortality data was available and therefore, they were not included in the analysis.

[§]In this study, in a few patients, despite the availability of the VAC, a non-VAC therapy has been chosen due to the poor quality of the sternum (fractured, white aspect, fragile) or on the clinical situation with uncontrollable infection and hemodynamic instability.

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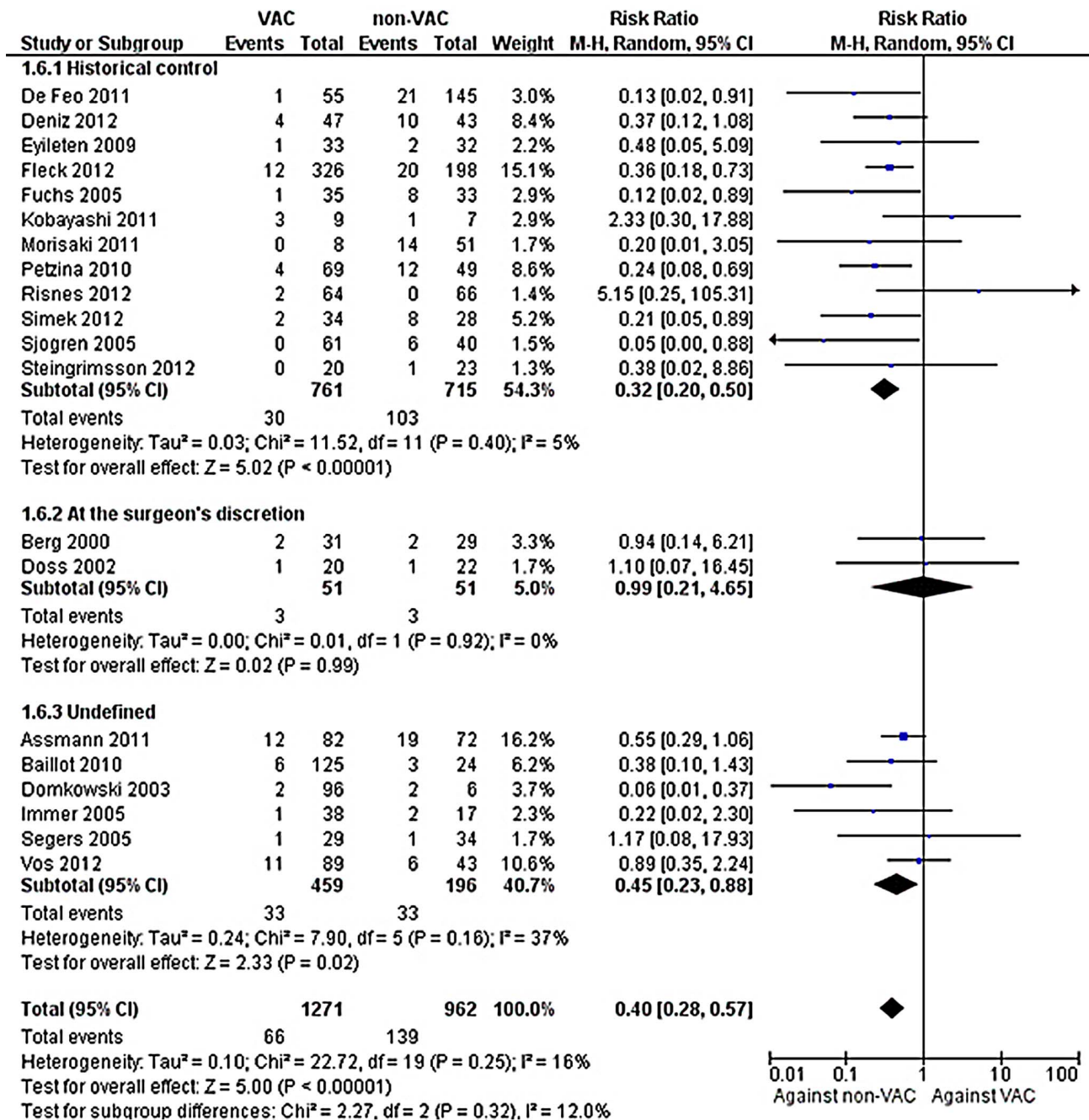


Figure 2. Forest plot depicting the risk ratios (RR) of mortality of patients according to the selection of the type of therapy. (Vertical line = "no difference" point between the two regimens. Squares = risk ratios; Diamonds = pooled risk ratios for all studies. Horizontal lines = 95% CI). doi:10.1371/journal.pone.0064741.g002

which mortality is the primary end-point.[34] In addition, only one of the included studies performed a multivariate analysis to identify independent predictors for survival; VAC therapy was not introduced into this model and methicillin-resistant *Staphylococcus aureus* was the sole independent predictor for mortality.[26] Therefore, only unadjusted data were available for comparisons. A variety of techniques were used for the management of DSWIs in the control groups of both the individual studies and between studies; in addition, VAC was not the sole intervention applied in the VAC group of patients in all studies. As this clinical heterogeneity was expected, a random effect model was selected

for all comparisons prior to the implementation of the meta-analysis. On the other hand, statistical heterogeneity was not observed in any of the performed analyses and all subgroup analyses consistently confirmed the results of the primary analysis, thus strengthening the validity of the results of the meta-analysis. Data regarding the offending bacteria and corresponding antibiotic treatment was not available. Finally, outcomes regarding the way of using VAC (i.e. pressure or duration) were not available within the included studies.

A recent international consensus conference suggested certain non-surgical interventions that are documented as decreasing

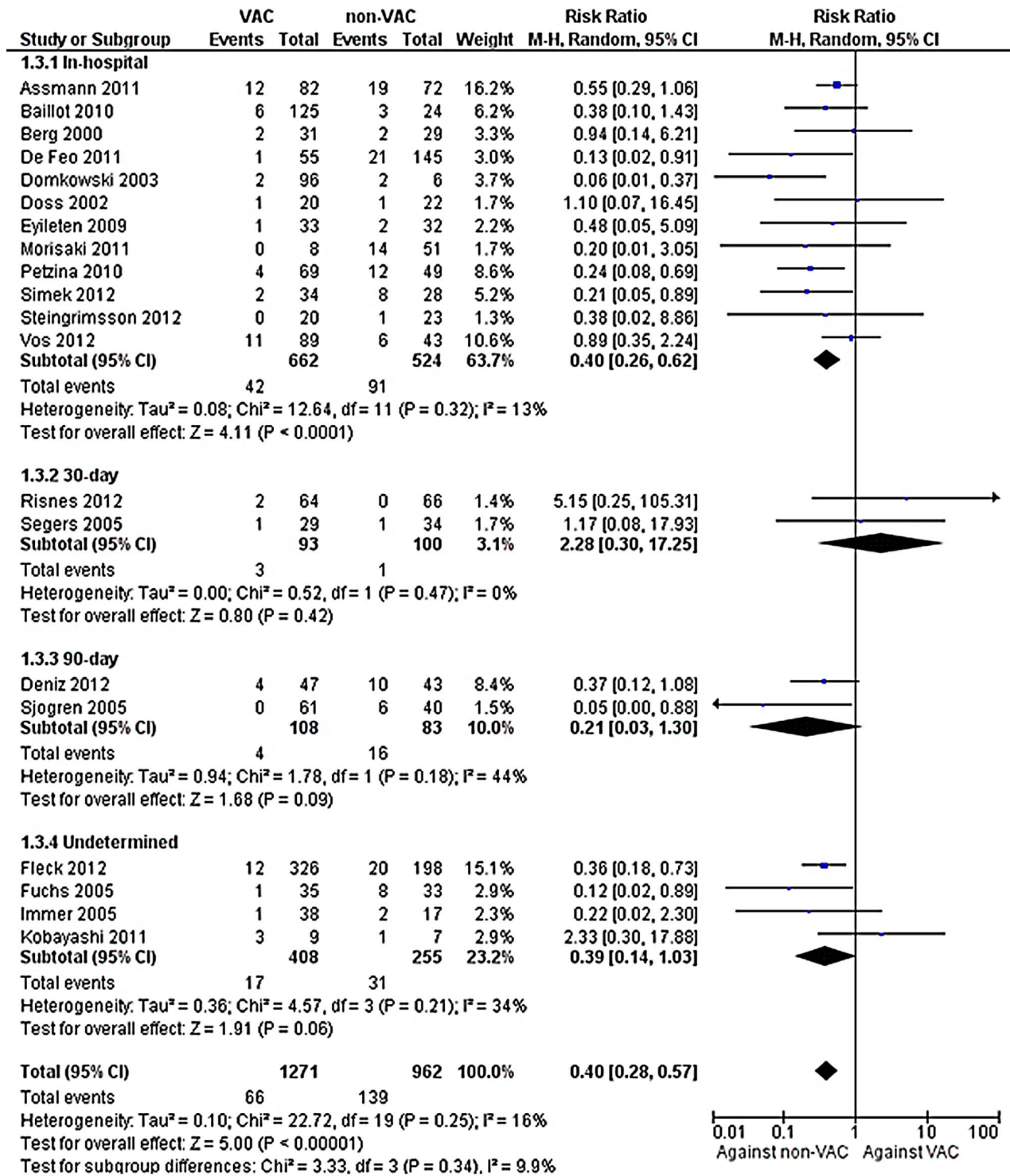


Figure 3. Forest plot depicting the risk ratios (RR) of mortality of patients according to the time of mortality assessment. (Vertical line = "no difference" point between the two regimens. Squares = risk ratios; Diamonds = pooled risk ratios for all studies. Horizontal lines = 95% CI). doi:10.1371/journal.pone.0064741.g003

mortality after a cardiac surgery and need further study;[35] administration of insulin, levosimendan, volatile anesthetics, statins, chronic beta-blockade, early aspirin therapy, the use of preoperative intra-aortic balloon counterpulsation are encountered among them. VAC therapy could be also included in this list if the lower mortality finding is confirmed in randomized studies.

VAC therapy is not approved officially for the treatment of DSWIs. However, the positive findings of early studies showing lower mortality (although not uniformly) or decreased duration of hospitalization,[8,11,12,16] in addition to better outcomes in favor of VAC therapy from RCTs in other patient populations, prompted the experts in the field to recommend the wider use

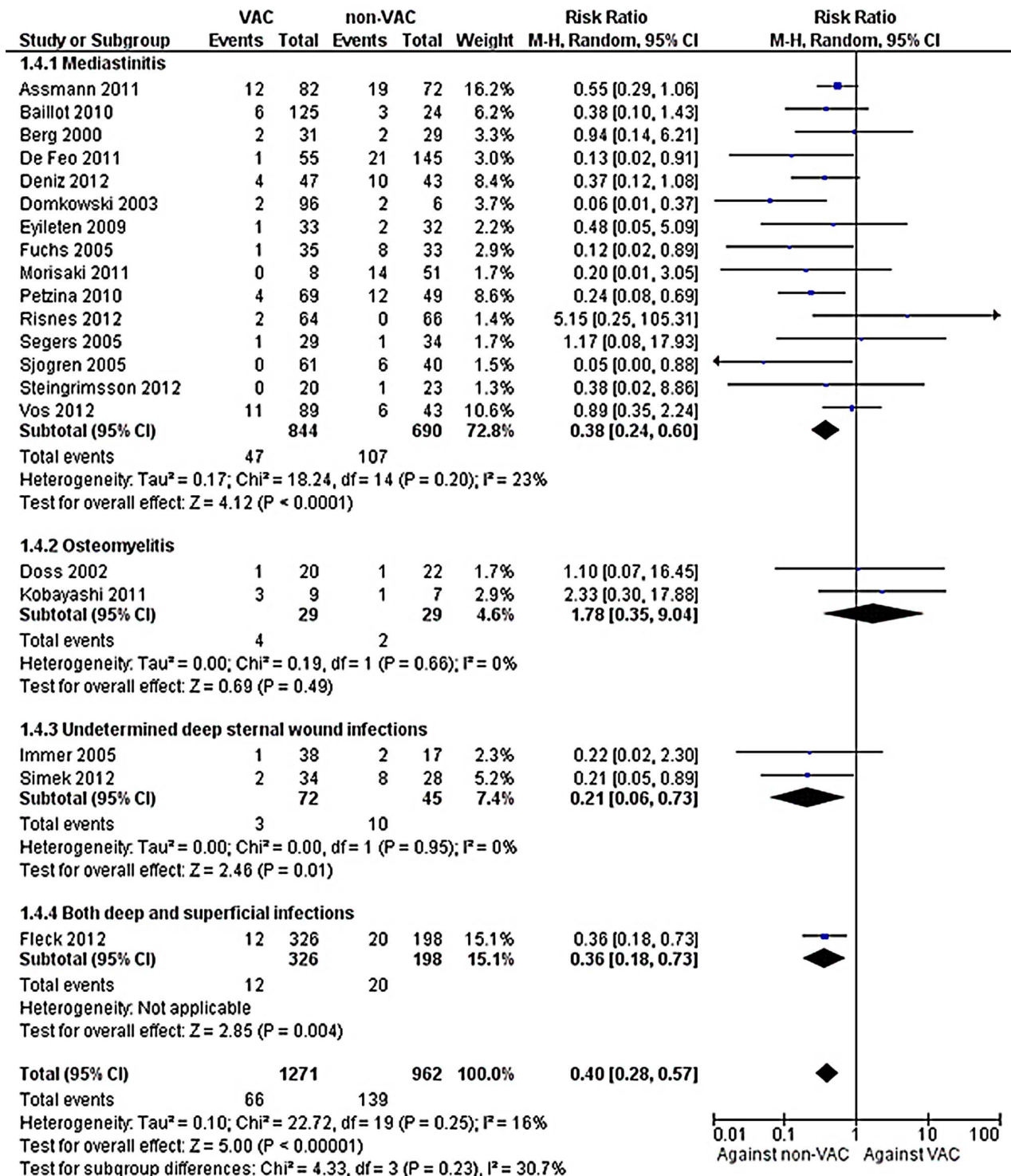


Figure 4. Forest plot depicting the risk ratios (RR) of mortality of patients according to the type of infection studied. (Vertical line = "no difference" point between the two regimens. Squares = risk ratios; Diamonds = pooled risk ratios for all studies. Horizontal lines = 95% CI). doi:10.1371/journal.pone.0064741.g004

of VAC for the treatment of patients with DSWIs.[1,2] It should be noted that VAC is recommended "before primary closure, as preparation for secondary closure with vascularised tissue and as an adjunct to flap healing".[1,2].

Few studies provided data regarding recurrent DSWIs and even fewer for systemic or related to the surgical interventions

complications. VAC therapy was associated with fewer recurrences than conventional treatment in the meta-analysis. Data regarding complications could not be further analyzed and adverse events following VAC and non-VAC therapy were not studied in this meta-analysis. In face of potentially lower mortality, the development of complications and adverse events seems

negligible. However, surgeons should be aware of them in order to improve the quality of life of their patients. Complications of VAC treatment include bleeding (although sometimes its presence can be attributed to factors other than the VAC itself),[36] decrease of cardiac output when it is applied directly on the heart,[37] and adhesion formation and organ injury after the application of vacuum.[2] Advisory panels also warn against the use of VAC therapy when the patient has excessive or uncontrolled bleeding or uses anticoagulants that results in international normalized ratio over 2, untreated or unbridged osteomyelitis, and chest or pulmonary malignancy.[2].

Infections are among the major complications that prolong hospitalization. Controversial results were reported regarding this outcome in the studies included in the meta-analysis; six studies reported that LOS was significantly lower in patients receiving VAC therapy, while two reported that LOS was significantly prolonged. The meta-analysis including 10 studies showed no difference in the LOS when VAC was used, but considerable statistical heterogeneity was found. Therefore, it is difficult to draw conclusions regarding LOS. A recently published meta-analysis concluded that LOS was shortened with the use of VAC.[13] This meta-analysis included data from 6 studies; 3 of them were also included in the present meta-analysis. One did not provide the mean and standard deviation,[7] one provided the mean but not the standard deviation,[30] and one provided separate data for

two groups of patients receiving VAC;[24] since we did not contact with the corresponding authors to request additional data, these data could not be included in the meta-analysis. Since hospital cost is associated mainly with LOS, these findings question the cost-effectiveness of VAC therapy in this patient population. Different findings in favor or against VAC regarding cost-effectiveness have been published.[38,39,40,41].

In conclusion, the currently available data suggest a lower mortality and support the use of VAC therapy for the treatment of patients with DSWIs following cardiothoracic surgery. The retrospective design of the studies included in the meta-analysis and the lack of adjusted data highlighting VAC as an independent predictor of survival suggest that a well designed RCT is warranted to study the effects of VAC therapy, alone or in combination with other techniques, on mortality of patients with DSWIs. The effect of VAC on LOS and the related cost should be further investigated in this patient population.

Author Contributions

Conceived and designed the experiments: MEF. Analyzed the data: MEF GST AK KZV. Wrote the paper: MEF GST AK KZV. Drafting the article or revising it critically for important intellectual content: MEF GST AK KZV. Final approval of the version to be published: MEF GST AK KZV.

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