Original Investigation

Reappraisal of Routine Oral Care With Chlorhexidine Gluconate for Patients Receiving Mechanical Ventilation
Systematic Review and Meta-analysis

Michael Klompas, MD; Kathleen Speck, MPH; Michael D. Howell, MD; Linda R. Greene, RN; Sean M. Berenholtz, MD

IMPORTANCE Regular oral care with chlorhexidine gluconate is standard of care for patients receiving mechanical ventilation in most hospitals. This policy is predicated on meta-analyses suggesting decreased risk of ventilator-associated pneumonia, but these meta-analyses may be misleading because of lack of distinction between cardiac surgery and non–cardiac surgery studies, conflation of open-label vs double-blind investigations, and insufficient emphasis on patient-centered outcomes such as duration of mechanical ventilation, length of stay, and mortality.

OBJECTIVE To evaluate the impact of routine oral care with chlorhexidine on patient-centered outcomes in patients receiving mechanical ventilation.

DATA SOURCES PubMed, Embase, CINAHL, and Web of Science from inception until July 2013 without limits on date or language.

STUDY SELECTION Randomized clinical trials comparing chlorhexidine vs placebo in adults receiving mechanical ventilation. Of 171 unique citations, 16 studies including 3630 patients met inclusion criteria.

DATA EXTRACTION AND SYNTHESIS Eligible trials were independently identified, evaluated for risk of bias, and extracted by 2 investigators. Differences were resolved by consensus. We stratified studies into cardiac surgery vs non–cardiac surgery and open-label vs double-blind investigations. Eligible studies were pooled using random-effects meta-analysis.

MAIN OUTCOMES AND MEASURES Ventilator-associated pneumonia, mortality, duration of mechanical ventilation, intensive care unit and hospital length of stay, antibiotic prescribing.

RESULTS There were fewer lower respiratory tract infections in cardiac surgery patients randomized to chlorhexidine (relative risk [RR], 0.56 [95% CI, 0.41-0.77]) but no significant difference in ventilator-associated pneumonia risk in double-blind studies of non–cardiac surgery patients (RR, 0.88 [95% CI, 0.66-1.16]). There was no significant mortality difference between chlorhexidine and placebo in cardiac surgery studies (RR, 0.88 [95% CI, 0.25-2.14]) and nonsignificantly increased mortality in non–cardiac surgery studies (RR, 1.13 [95% CI, 0.99-1.29]). There were no significant differences in mean duration of mechanical ventilation or intensive care length of stay. Data on hospital length of stay and antibiotic prescribing were limited.

CONCLUSIONS AND RELEVANCE Routine oral care with chlorhexidine prevents nosocomial pneumonia in cardiac surgery patients but may not decrease ventilator-associated pneumonia risk in non–cardiac surgery patients. Chlorhexidine use does not affect patient-centered outcomes in either population. Policies encouraging routine oral care with chlorhexidine for non–cardiac surgery patients merit reevaluation.

JAMA Intern Med. doi:10.1001/jamainternmed.2014.359
Published online March 24, 2014.

Invited Commentary

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Michael Klompas, MD, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, 133 Brookline Ave, Sixth Floor, Boston, MA 02215 (mklompas@partners.org).

Regular oral care with chlorhexidine gluconate has become standard practice for the prevention of ventilator-associated pneumonia (VAP). Surveys suggest that 60% to 70% of intensive care units in Europe and North America provide oral care with chlorhexidine at least once a day to all patients receiving mechanical ventilation.[1-5] Near-universal penetration of this practice is likely the result of 2 high-profile meta-analyses suggesting that oral care with chlorhexidine can reduce VAP rates by 30% to 40%, guideline publications recommending this practice, and the inclusion of regular oral care with chlorhexidine in the widely adopted ventilator care bundle of the Institute for Healthcare Improvement.[6-9]

Despite near-universal penetration of routine daily oral care with chlorhexidine, there are 3 major limitations to the current evidence base that necessitate a reappraisal. First, existing meta-analyses are heavily influenced by 3 large studies in cardiac surgery patients that accounted for 40% to 60% of patients in prior analyses.[10-12] Including these studies is problematic because the majority of patients who undergo cardiac surgery are extubated within 1 day. The pulmonary outcome in these studies is respiratory tract infections, not VAP. Second, prior meta-analyses have made little distinction between open-label vs double-blind investigations. This is critical because the diagnosis of VAP is notoriously subjective and inaccurate.[13,14] Lack of blinding introduces risk of bias in favor of chlorhexidine use.[15] Third, prior analyses designated VAP as the primary outcome. Rates of VAP are difficult to interpret because of their subjectivity, lack of specificity, and high interobserver variability.[14,16] Duration of mechanical ventilation, length of stay, and mortality are more objective and more patient-centered outcomes.

In light of these limitations, we undertook a reappraisal of the evidence base supporting routine oral care with chlorhexidine for patients receiving mechanical ventilation. We evaluated the impact of oral care with chlorhexidine on nosocomial pneumonia, mortality, duration of mechanical ventilation, intensive care length of stay, hospital length of stay, and antibiotic use. We grouped studies into cardiac surgery vs non-cardiac surgery investigations and then stratified both groups into open-label vs double-blind investigations to assess the potential impact of study design on reported outcomes.

Methods

We sought randomized clinical trials evaluating daily oral care with chlorhexidine (any preparation) vs inert comparators for routine care in adult patients receiving mechanical ventilation. We searched PubMed, Embase, Web of Science, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) for studies on chlorhexidine and oral care in patients receiving mechanical ventilation (full search strategies for each database are available in the eAppendix in the Supplement; search date range, inception to July 2013). There were no date or language restrictions. We also reviewed the inclusion lists of previously published meta-analyses and the reference lists of all suggestive articles retrieved by our searches. We included all trials that provided data on 1 or more of our prespecified outcomes for both the treatment and control groups: pneumonia, mortality, duration of mechanical ventilation, intensive care length of stay, hospital length of stay, and antibiotic dispensing. We excluded trials that provided outcome data on fewer than 80% of randomized patients. Two investigators (M.K., K.S.) independently reviewed potential studies for inclusion. Disagreements were resolved by consensus. The same 2 investigators independently abstracted data from all included studies and rated each trial for quality on the basis of randomization strategy, allocation concealment, blinding, and completeness of follow-up. We attempted to contact the corresponding authors of selected papers to provide clarifications and missing data where needed.

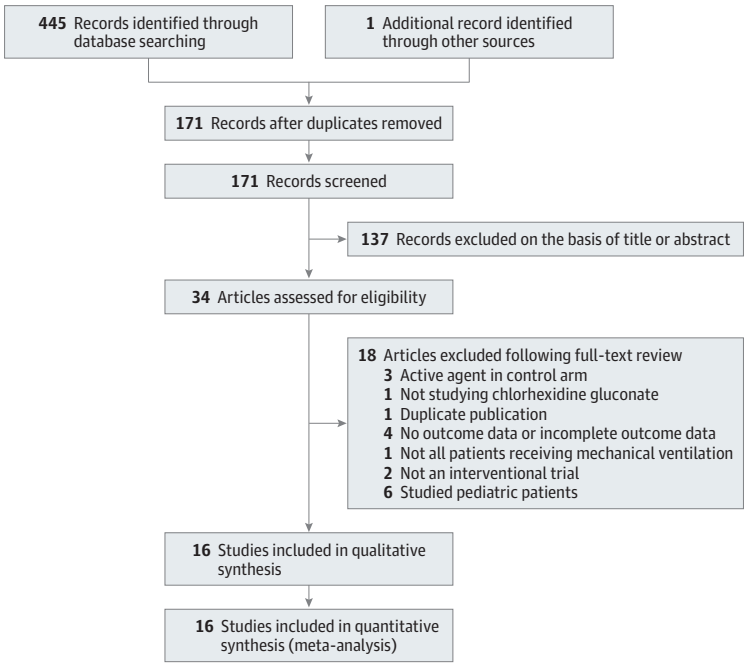
We then conducted meta-analyses for all outcomes using Mantel-Haenszel random-effects models. We constructed forest plots for all outcomes in which 2 or more studies provided analyzable data. We first stratified all studies into cardiac surgery vs non–cardiac surgery studies. Within each group, we then compared open-label vs double-blind investigations. We calculated relative risks (RRs) and weighted mean differences for dichotomous and continuous outcomes, respectively. We summarized results across all studies and within each stratum. We assessed for heterogeneity using the I^2 statistic. We constructed funnel plots to look for evidence of publication bias. All analyses were executed using RevMan, version 5.2 (Cochrane Collaborative). This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[17]

Results

The search strategies yielded 446 citations including 275 duplicates. Of 171 unique citations, 16 met inclusion criteria (**Figure 1**). Two articles were only available in abstract form.[18,19] Included studies are summarized in the **Table**. Of the 16 eligible articles, 3 were set in cardiac surgery units and 13 in non-cardiac surgery units (7 in medical-surgical units, 1 each in surgery, trauma, respiratory, and medical neuroscience units, and 2 in unspecified units). Many studies limited enrollment to patients expected to require at least 48 hours,[18,23,25,30] at least 72 hours,[29] or at least 5 days[20,21] of mechanical ventilation. Studies were conducted around the world: 4 in the United States, 2 in France, 2 in the Netherlands, 2 in Brazil, and 1 each in Australia, India, Iran, Thailand, Turkey, and the United Kingdom. Enrollment varied between 5 and 954 patients. Of the 3 cardiac surgery studies, 2 were double blind and 1 was open label. Of the 13 non-cardiac surgery studies, 7 were double blind and 6 had incomplete or absent blinding.

Study quality was closely aligned with blinding policy (see Table). The 2 double-blind cardiac surgery studies had adequate random sequence generation and adequate allocation concealment and provided outcome data for 96% to 100% of randomized patients, whereas the 1 nonblinded study randomized patients on the basis of medical record numbers and did not conceal allocation assignments. Likewise, 6 of the 7 double-blind non–cardiac surgery studies used adequate random sequence generation and allocation concealment and pro-

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Study Flowchart



vided VAP outcome data for 96% to 100% of patients. One of these 6 studies provided VAP outcome data for all 175 patients but mortality outcome data for only 146 of the 175 patients (83%).[27] The seventh double-blind study was only published in abstract form and did not comment on randomization or allocation concealment strategy.[18] By contrast, 3 of the 6 unblinded studies did not describe their randomization strategy and by definition did not conceal allocations. Of the 12 studies with mortality outcome data, 2 reported intensive care unit mortality,[23,27] 2 reported hospital mortality,[12,26] 1 reported 28-day mortality,[21] and 7 did not specify.

The 16 included studies provided data on 3630 patients. Cardiac surgery studies accounted for 1868 patients (51%), 1307 (70%) in 2 double-blind studies and 561 (30%) in 1 open-label investigation. The non-cardiac surgery investigations included 1762 patients (49%), 1090 (62%) in 7 double-blind studies and 672 (38%) in 6 open-label studies. Only 3 of the 16 studies observed a significant decrease in the incidence of lower respiratory tract infections on intention-to-treat analysis (1 of the 3 cardiac surgery studies, 2 of the 13 non-cardiac surgery studies).[12,20,30] A fourth study found no difference in the RR of VAP but a decreased hazard of VAP using a proportional hazards model.[23] Six additional studies found no differences in overall respiratory tract infection rates but nonetheless suggested that chlorhexidine may still be beneficial by evaluating a composite outcome,[10] focusing on a high-risk subset of patients,[11] noting a longer interval to infection onset,[25] emphasizing decreased rates of oropharyngeal colonization,[21,27] or combining their results with prior investigations.[24]

Studies in Cardiac Surgery vs Other Populations

The studies of cardiac surgery patients differed substantially from the studies of other populations. The pulmonary outcomes in the cardiac surgery studies were specified as "nosocomial pneumonia,"[11] "upper respiratory tract infections,"[10] "lower respiratory tract infections,"[12] or "total respiratory tract infections,"[10] whereas the pulmonary outcome in all non-cardiac surgery studies was specified as "ventilator-associated pneumonia." The time to extubation in the 2 cardiac surgery studies that provided data on this outcome was brief. Segers et al[12] reported mean (SD) durations of 0.5 (0.5) and 0.6 (0.8) days in the chlorhexidine and placebo groups, respectively. Houston et al[11] reported that 87% of patients were extubated within 24 hours. The 7 non-cardiac surgery studies with data on duration of mechanical ventilation, by contrast, reported mean durations of mechanical ventilation ranging from 4 to 18 days.[20-25,27] The overall incidence of nosocomial pneumonia or lower respiratory tract infections in the cardiac surgery studies was 7.7%, whereas the incidence of VAP in the non-cardiac surgery studies was 17%.

Nosocomial Pneumonia

Forest plots for RRs of nosocomial pneumonia are shown in **Figure 2**. All 16 studies in this meta-analysis provided data on pneumonia, but only the 13 non-cardiac surgery studies specifically focused on VAP. There were significantly fewer lower respiratory tract infections among cardiac surgery patients randomized to chlorhexidine (RR, 0.56 [95% CI, 0.41-0.77]). There was a nonsignificant finding of fewer VAP cases in non-cardiac surgery studies (RR, 0.78 [95% CI, 0.60-1.02]; I^2 = 44%). The point estimate for the RR of VAP was lower in open-label studies (RR, 0.61 [95% CI, 0.35-1.04]; I^2 = 40%) than in double-blind studies (RR, 0.88 [95% CI, 0.66-1.16]; I^2 = 42%). Results were similar when the 1 double-blind study published in abstract form alone[18] was excluded: RR, 0.83 (95% CI, 0.59-1.15; I^2 = 44%). On sensitivity analysis among the non-cardiac surgery studies, RR

Table. Randomized Clinical Trials of Chlorhexidine Gluconate vs Placebo for Oral Care of Patients Receiving Mechanical Ventilation

Source	N	ICU Type (Country)	Chlorhexidine Preparation and Frequency	Comparator	Random Sequence Generation	Allocation Concealment	Blinding	Completeness of Outcome Data, Proportion[a]
Cardiac surgery								
DeRiso et al,[10] 1996	353	Cardiac surgery (US)	0.12% solution BID	Identical placebo	Yes	Yes	Double	353/353
Houston et al,[11] 2002	561	Cardiac surgery (US)	0.12% solution BID	Listerine	Based on MRN	No	None	561/561
Segers et al,[12] 2006	954	Cardiac surgery (Netherlands)	0.12% oral rinse QID + 0.12% nasal gel	Identical placebo	Yes	Yes	Double	954/991
Non-cardiac surgery								
Fourrier et al,[20] 2000	60	Medical-surgical (France)	0.2% gel TID	Placebo gel	Yes	Yes	Single	60/60
Macnaughton et al,[18] 2004[b]	179	Medical-surgical (UK)	0.2% solution BID	Identical placebo	Not described	Not described	Double	179/179
Fourrier et al,[21] 2005	228	Medical-surgical (France)	0.2% gel TID	Placebo gel	Yes	Yes	Double	228/228
Bopp et al,[22] 2006	5	Critical care (US)	0.12% solution BID	Half-strength hydrogen peroxide	Yes	Yes	None	5/5
Koeman et al,[23] 2006	257	Medical-surgical (Netherlands)	2% in petroleum jelly QID	Vaseline	Yes	Yes	Double	257/257
Jafari et al,[19] 2007[b]	80	Not specified (Iran)	0.2% solution BID	Normal saline	Not described	Not described	None	80/80
Tantipong et al,[24] 2008	207	Medical-surgical (Thailand)	2% solution QID	Normal saline	Not described	Not described	None	207/207
Bellissimo-Rodrigues et al,[25] 2009	133	Medical-surgical (Brazil)	0.12% solution TID	Identical placebo	Yes	Yes	Double	133/133
Panchabhai et al,[26] 2009	171	Medical-neurological (India)	0.2% solution BID	0.01% potassium permanganate	Not described	Not described	None	171/171
Scannapieco et al,[27] 2009	175	Trauma (US)	0.12% solution group 1: QID group 2: BID	Identical placebo	Yes	Yes	Double	175/175 for VAP, 146/175 for mortality
Berry et al,[28] 2011	149	Medical-surgical (Australia)	0.2% solution BID	Sterile water	Yes	Yes	Single	149/149
Meinberg et al,[29] 2012	52	Surgical (Brazil)	2% gel QID	Placebo gel	Yes	Yes	Double	52/52
Ozcaka et al,[30] 2012	66	Respiratory (Turkey)	0.2% solution QID	Normal saline	Yes	Yes	Double	66/66

Abbreviations: BID, twice daily; MRN, medical record number; QID, 4 times daily; TID, 3 times daily; UK, United Kingdom; US, United States; VAP, ventilator-associated pneumonia.

[a] Completeness of outcome data reported as number of patients with outcomes reported divided by number of patients randomized. Unless otherwise stated, outcomes data were available for the same number of patients for each outcome included in the article.

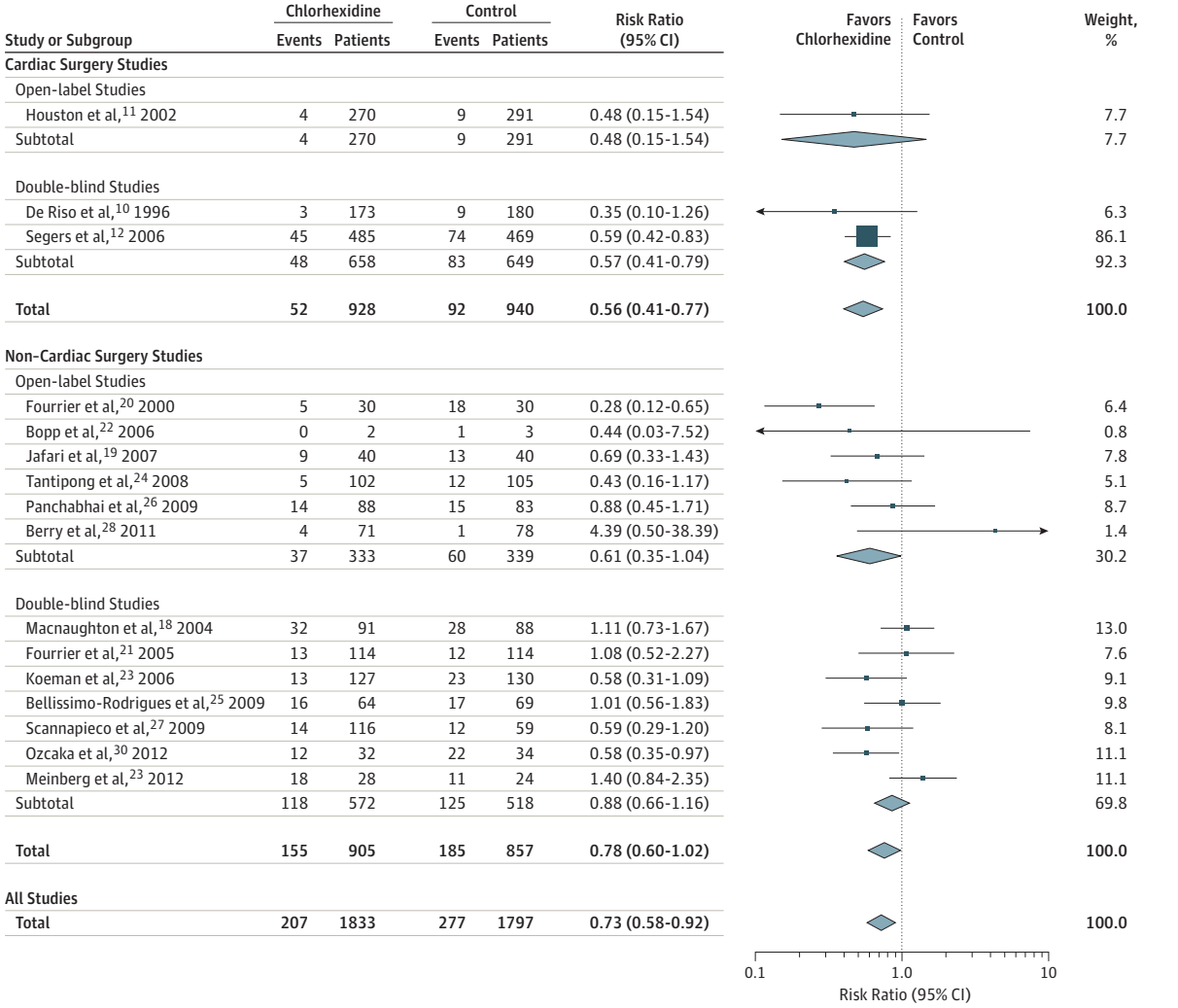
[b] Only abstracts were available for review.

estimates were not significant, highly heterogeneous, and similar for all concentrations of chlorhexidine: a 0.12% solution was associated with an RR of 0.80 (95% CI, 0.51-1.25; I^2 = 0%), a 0.2% solution was associated with an RR of 0.76 (95% CI, 0.47-1.20; I^2 = 61%), and a 2% solution was associated with an RR of 0.75 (95% CI, 0.35-1.63; I^2 = 73%). There was no significant difference in VAP RR for gel vs solution preparations. On funnel plot inspection, there was no obvious evidence of publication bias (see eFigure in Supplement).

Mortality

Forest plots for the RR of mortality in patients randomized to chlorhexidine vs control preparations are presented in **Figure 3**. There were sufficient data on this outcome for meta-analysis of 12 studies, 3 in cardiac surgery patients and 9 in non-cardiac surgery patients. Among cardiac surgery patients, there was substantial heterogeneity and broad confidence intervals but no apparent association between chlorhexidine use and mortality (RR, 0.88 [95% CI, 0.25-3.14]; I^2 = 65%). Among non-cardiac surgery patients, there was a nonsignificant finding of increased mortality in patients randomized to chlorhexidine use (RR, 1.13 [95% CI, 0.99-1.29]; I^2 = 0%). The point estimate for mortality was higher in double-blind studies (RR, 1.15 [95% CI, 0.96-1.38]; I^2 = 0%) than in open-label studies (RR, 1.06 [95% CI, 0.80-1.41]; I^2 = 36%). When all studies were combined, the mortality point estimate remained elevated in patients randomized to chlorhexidine, with a lower 95% confidence interval very close to 1 (RR, 1.13 [95% CI, 0.99-1.28]; I^2 = 0%). We reanalyzed the non-cardiac surgery studies usinga Mantel-Haenszel random-effects model with odds ratios rather than RRs because RR methods can assign disproportionate weights to small studies with high event rates. The point estimate for mortality remained elevated (OR, 1.20 [95% CI, 0.95-1.50]; I^2 = 0%). This finding was still evident when all studies with possible methodological concerns were excluded (all the open-label studies, Macnaughton et al[18] be-

Figure 2. Impact of Chlorhexidine Gluconate Use vs Comparators on Nosocomial Pneumonia in Cardiac Surgery Patients and Ventilator-Associated Pneumonia in Non–Cardiac Surgery Patients



Size of the data marker corresponds to the relative weight assigned in the pooled analysis using the Mantel-Haenszel random-effects model. For open-label cardiac surgery studies, heterogeneity was not applicable; test for overall effect, $z = 1.24$ ($P = .22$). For double-blind cardiac surgery studies, heterogeneity, $\tau^2 = 0.00$; $\chi^2 = 0.60$, $df = 1$ ($P = .44$); $I^2 = 0\%$; test for overall effect, $z = 3.31$ ($P < .001$). For all cardiac surgery studies, heterogeneity, $\tau^2 = 0.00$; $\chi^2 = 0.68$, $df = 2$ ($P = .71$); $I^2 = 0\%$; test for overall effect, $z = 3.52$ ($P < .001$); test for subgroup differences, $\chi^2 = 0.07$, $df = 1$ ($P = .78$); $I^2 = 0\%$. For open-label non–cardiac surgery studies, heterogeneity, $\tau^2 = 0.17$; $\chi^2 = 8.27$, $df = 5$ ($P = .14$); $I^2 = 40\%$; test for overall effect, $z = 1.80$ ($P = .07$). For double-blind non–cardiac surgery studies, heterogeneity, $\tau^2 = 0.06$; $\chi^2 = 10.29$, $df = 6$ ($P = .11$); $I^2 = 42\%$; test for overall effect, $z = 0.91$ ($P = .36$). For all non–cardiac surgery studies, heterogeneity, $\tau^2 = 0.10$; $\chi^2 = 21.61$, $df = 12$ ($P = .04$); $I^2 = 44\%$; test for overall effect, $z = 1.82$ ($P = .07$); test for subgroup differences, $\chi^2 = 1.39$, $df = 1$ ($P = .24$); $I^2 = 28\%$. For all studies, heterogeneity, $\tau^2 = 0.09$; $\chi^2 = 26.51$, $df = 15$ ($P = .03$); $I^2 = 43\%$; test for overall effect, $z = 2.66$ ($P = .008$); test for subgroup differences, $\chi^2 = 4.56$, $df = 2$ ($P = .10$); $I^2 = 56\%$.

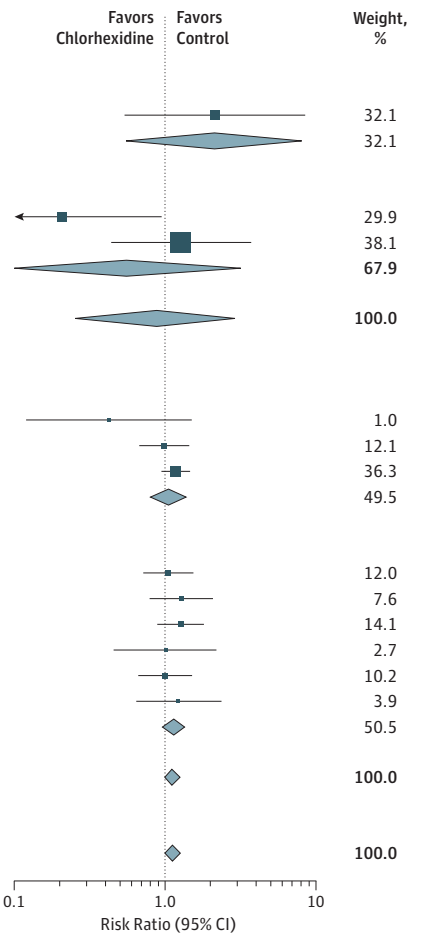
cause it was only published in abstract form, Scannapieco et al[27] because it provided incomplete outcome data for mortality): RR, 1.20 (95% CI, 0.97-1.48; $I^2 = 0\%$). We conducted several sensitivity analyses among the non–cardiac surgery studies. We found a stepwise increase in mortality RR point estimates with increasing concentrations of chlorhexidine (although all associations were statistically insignificant and had broad confidence intervals): 0.12% preparations were associated with an RR of 1.01 (95% CI, 0.46-2.20; $I^2 = 0\%$), 0.2% preparations were associated with an RR of 1.13 (95% CI, 0.96-1.32; $I^2 = 0\%$), and 2% preparations were associated with a RR of 1.16 (95% CI, 0.92-1.46; $I^2 = 0\%$). Effect estimates were slightly higher for gel preparations (RR, 1.23 [95% CI, 0.96-1.57]; $I^2 = 0\%$) vs liquid preparations (RR, 1.10 [95% CI, 0.95-1.28]; $I^2 = 0\%$). On funnel plot inspection, there was no obvious evidence of publication bias (see eFigure in Supplement).

Duration of Mechanical Ventilation

Forest plots for weighted mean differences in ventilator days between patients randomized to chlorhexidine vs control preparations are presented in **Figure 4**. Data were available for meta-analysis from 1 cardiac surgery and 5 non-cardiac sur-

Figure 3. Impact of Chlorhexidine Gluconate Use vs Comparators on Mortality

Study or Subgroup	Chlorhexidine Events	Chlorhexidine Patients	Control Events	Control Patients	Risk Ratio (95% CI)	Weight, %
Cardiac Surgery Studies						
Open-label Studies						
Houston et al,[11] 2002	6	270	3	291	2.16 (0.54-8.53)	32.1
Subtotal	6	270	3	291	2.16 (0.54-8.53)	32.1
Double-blind Studies						
De Riso et al,[10] 1996	2	173	10	180	0.21 (0.05-0.94)	29.9
Segers et al,[12] 2006	8	485	6	469	1.29 (0.45-3.69)	38.1
Subtotal	10	658	16	649	0.56 (0.09-3.40)	**67.9**
Total	**16**	**928**	**19**	**940**	**0.88 (0.25-3.14)**	**100.0**
Non-Cardiac Surgery Studies						
Open-label Studies						
Fourrier et al,[20] 2000	3	30	7	30	0.43 (0.12-1.50)	1.0
Tantipong et al,[24] 2008	36	102	37	105	1.00 (0.69-1.45)	12.1
Panchabhai et al,[26] 2009	64	88	51	83	1.18 (0.96-1.46)	36.3
Subtotal	103	220	95	218	1.06 (0.80-1.41)	49.5
Double-blind Studies						
Macnaughton et al,[18] 2004	36	91	33	88	1.05 (0.73-1.53)	12.0
Fourrier et al,[21] 2005	31	114	24	114	1.29 (0.81-2.06)	7.6
Koeman et al,[23] 2006	49	127	39	130	1.29 (0.91-1.81)	14.1
Scannapieco et al,[27] 2009	16	97	8	49	1.01 (0.46-2.20)	2.7
Ozcaka et al,[30] 2012	19	32	20	34	1.01 (0.68-1.51)	10.2
Meinberg et al,[29] 2012	13	28	9	24	1.24 (0.65-2.38)	3.9
Subtotal	164	489	133	439	1.15 (0.96-1.38)	50.5
Total	**267**	**709**	**228**	**657**	**1.13 (0.99-1.29)**	**100.0**
All Studies						
Total	**283**	**1637**	**247**	**1597**	**1.13 (0.99-1.28)**	**100.0**



Size of the data marker corresponds to the relative weight assigned in the pooled analysis using the Mantel-Haenszel random-effects model. For open-label cardiac surgery studies, heterogeneity was not applicable; test for overall effect, $z = 1.09$ ($P = .27$). For double-blind cardiac surgery studies, heterogeneity, $\tau^2 = 1.26$; $\chi^2 = 3.88$, $df = 1$ ($P = .05$); $I^2 = 74\%$; test for overall effect, $z = 0.63$ ($P = .53$). For all cardiac surgery studies, heterogeneity, $\tau^2 = 0.81$; $\chi^2 = 5.71$, $df = 2$ ($P = .06$); $I^2 = 65\%$; test for overall effect, $z = 0.19$ ($P = .85$); test for subgroup differences, $\chi^2 = 1.35$, $df = 1$ ($P = .24$); $I^2 = 26\%$. For open-label non-cardiac surgery studies, heterogeneity, $\tau^2 = 0.02$; $\chi^2 = 3.13$, $df = 2$ ($P = .21$); $I^2 = 36\%$; test for overall effect, $z = .40$ ($P = .69$). For double-blind non-cardiac surgery studies, heterogeneity, $\tau^2 = 0.00$; $\chi^2 = 1.44$, $df = 5$ ($P = .92$); $I^2 = 0\%$; test for overall effect, $z = 1.52$ ($P = .13$). For all non-cardiac surgery studies, heterogeneity, $\tau^2 = 0.00$; $\chi^2 = 4.36$, $df = 8$ ($P = .82$); $I^2 = 0\%$; test for overall effect, $z = 1.88$ ($P = .06$); test for subgroup differences, $\chi^2 = 0.22$, $df = 1$ ($P = .64$); $I^2 = 0\%$. For all studies, heterogeneity, $\tau^2 = 0.00$; $\chi^2 = 10.23$, $df = 11$ ($P = .51$); $I^2 = 0\%$; test for overall effect, $z = 1.84$ ($P = .07$); test for subgroup differences, $\chi^2 = 1.65$, $df = 3$ ($P = .65$); $I^2 = 0\%$.

gery studies. There were significant differences in mean duration of mechanical ventilation neither within the single cardiac surgery study (mean difference, −0.05 days [95% CI, −0.14 to 0.04 days]), the 5 non-cardiac surgery studies (mean difference, −0.15 days [95% CI, −2.18 to 1.89 days]; $I^2 = 51\%$), nor among all studies combined (mean difference, 0.01 days [95% CI, −1.12 to 1.14 days]; $I^2 = 40\%$).

Intensive Care Unit Length of Stay

Forest plots for the weighted mean difference in intensive care unit length of stay are presented in **Figure 5**. Data were available for meta-analysis from 1 cardiac surgery and 5 non-cardiac surgery studies. There were significant differences in intensive care unit length of stay within neither the single cardiac surgery study (mean difference, −0.10 days [95% CI, −0.25 to 0.05 days]), the 5 non-cardiac surgery studies (mean difference, 0.08 days [95% CI, −1.41 to 1.57 days]; $I^2 = 0\%$), nor among all studies combined (mean difference, −0.10 days [95% CI, −0.25 to 0.05 days]; $I^2 = 0\%$).

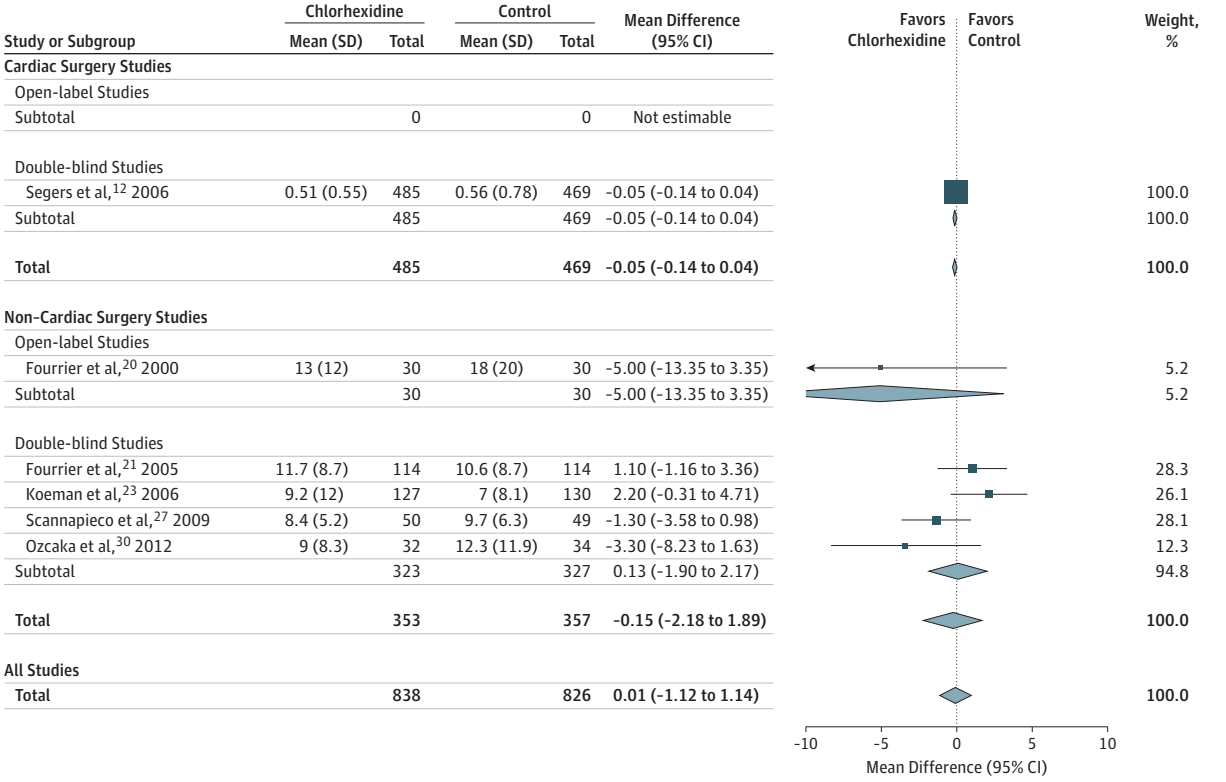
Hospital Length of Stay

One cardiac surgery and 2 double-blind non-cardiac surgery studies reported on hospital length of stay.[12,25,29] None of the 3 investigations found a significant difference between patients who received chlorhexidine oral care and controls.

Antibiotic Exposures

Four studies reported on antibiotic exposures. Each used different metrics, however, therefore precluding meta-analysis. DeRiso et al,[10] reporting on a cardiac surgery population, noted

Figure 4. Impact of Chlorhexidine Gluconate Use vs Comparators on Mean Duration of Mechanical Ventilation



Size of the data marker corresponds to the relative weight assigned in the pooled analysis using inverse variance random-effects model. Because no open-label cardiac surgery studies measured this outcome, heterogeneity and test for overall effect were not applicable to this subgroup. For double-blind cardiac surgery studies, heterogeneity was not applicable; test for overall effect, $z = 1.14$ ($P = .25$). For all cardiac surgery studies, heterogeneity was not applicable; test for overall effect, $z = 1.14$ ($P = .25$); test for subgroup differences, heterogeneity was not applicable. For open-label non-cardiac surgery studies, heterogeneity was not applicable; test for overall effect, $z = 1.17$ ($P = .24$). For double-blind non-cardiac surgery studies, heterogeneity, $\tau^2 = 2.28$; $\chi^2 = 6.63$, $df = 3$ ($P = .08$); $I^2 = 55\%$; test for overall effect, $z = 0.13$ ($P = .90$). For all non-cardiac surgery studies, heterogeneity, $\tau^2 = 2.49$; $\chi^2 = 8.15$, $df = 4$ ($P = .09$); $I^2 = 51\%$; test for overall effect, $z = 0.14$ ($P = .89$); test for subgroup differences, $\chi^2 = 1.37$, $df = 1$ ($P = .24$); $I^2 = 27\%$. For all studies, heterogeneity, $\tau^2 = 0.71$; $\chi^2 = 8.26$, $df = 5$ ($P = .14$); $I^2 = 40\%$; test for overall effect, $z = 0.02$ ($P = .98$); test for subgroup differences, $\chi^2 = 1.38$, $df = 2$ ($P = .50$); $I^2 = 0\%$.

a 43% decrease in nonprophylactic intravenous antibiotics dispensed to patients randomized to chlorhexidine oral care but did not report on total antibiotic exposures. Among the 3 studies that provided data for non-cardiac surgery patients, there were no significant differences in antibiotic exposures between patients randomized to chlorhexidine use vs placebo.[18,23,27]

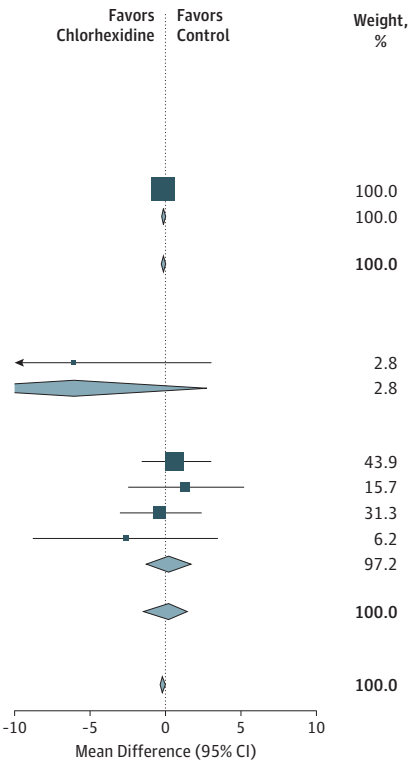
Discussion

Regular oral care with chlorhexidine is standard of practice for patients receiving mechanical ventilation in many hospitals. Our updated review of the evidence, however, suggests that caution is warranted. Although chlorhexidine does seem to protect against postoperative lower respiratory tract infections in cardiac surgery patients, it may not prevent VAP according to double-blind investigations of non-cardiac surgery patients. We found no significant difference between chlorhexidine and placebo with regard to mean duration of mechanical ventilation or intensive care length of stay in either cardiac surgery or non-cardiac surgery studies. We found a nonsignificant result of increased mortality with chlorhexidine among non-cardiac surgery studies.

Possible explanations for the discrepant findings between cardiac surgery vs non-cardiac surgery studies include differences in patient populations and differences in the outcomes tracked by these different studies. Most cardiac surgery patients are extubated in less than 1 day, whereas the mean duration of mechanical ventilation was 1 to 2 weeks among non-cardiac surgery patients. Moreover, the pneumonia outcome in cardiac surgery studies is lower respiratory tract infection, not VAP. Preventing VAP in persistently intubated patients may be more difficult than preventing postoperative infections in extubated patients. The endotracheal tube acts as an ongoing reservoir and conduit for microorganisms into the lungs and disrupts patients' normal mechanisms for clearing secretions. It is possible that chlorhexidine oral care may provide sufficient oral decontamination in extubated patients but is inadequate to overcome the infectious hazard of an endotracheal tube.

Figure 5. Impact of Chlorhexidine Gluconate Use vs Comparators on Intensive Care Length of Stay

Study or Subgroup	Chlorhexidine Mean (SD)	Chlorhexidine Total	Control Mean (SD)	Control Total	Mean Difference (95% CI)	Weight, %
Cardiac Surgery Studies						
Open-label Studies						
Subtotal		0		0	Not estimable	
Double-blind Studies						
Segers et al,[12] 2006	1.2 (1.1)	485	1.3 (1.3)	469	-0.10 (-0.25 to 0.05)	100.0
Subtotal		485		469	-0.10 (-0.25 to 0.05)	100.0
Total		**485**		**469**	**-0.10 (-0.25 to 0.05)**	**100.0**
Non-Cardiac Surgery Studies						
Open-label Studies						
Fourrier et al,[20] 2000	18 (16)	30	24 (19)	30	-6.00 (-14.89 to 2.89)	2.8
Subtotal		30		30	-6.00 (-14.89 to 2.89)	2.8
Double-blind Studies						
Fourrier et al,[21] 2005	14 (8.5)	114	13.3 (8.8)	114	0.70 (-1.55 to 2.95)	43.9
Koeman et al,[23] 2006	13.8 (17.4)	127	12.5 (12.9)	130	1.30 (-2.45 to 5.05)	15.7
Scannapieco et al,[27] 2009	11 (6.8)	50	11.3 (6.7)	49	-0.30 (-2.96 to 2.36)	31.3
Ozcaka et al,[30] 2012	12.7 (11.3)	32	15.4 (13.5)	34	-2.70 (-8.69 to 3.29)	6.2
Subtotal		323		327	0.26 (-1.25 to 1.77)	97.2
Total		**353**		**357**	**0.08 (-1.41 to 1.57)**	**100.0**
All Studies						
Total		**838**		**826**	**-0.10 (-0.25 to 0.05)**	**100.0**



Size of the data marker corresponds to the relative weight assigned in the pooled analysis using inverse variance random-effects model. Because no open-label cardiac surgery studies measured this outcome, heterogeneity and test for overall effect were not applicable to this subgroup. For double-blind cardiac surgery studies, heterogeneity was not applicable; test for overall effect, $z = 1.28$ ($P = .20$). For all cardiac surgery studies, heterogeneity was not applicable; test for overall effect, $z = 1.28$ ($P = .20$); test for subgroup differences, heterogeneity was not applicable. For open-label non-cardiac surgery studies, heterogeneity was not applicable; test for overall effect, $z = 1.32$ ($P = .19$). For double-blind non-cardiac surgery studies, heterogeneity, $\tau^2 = 0.00$; $\chi^2 = 1.55$, $df = 3$ ($P = .67$); $I^2 = 0\%$; test for overall effect, $z = 0.34$ ($P = .74$). For all non-cardiac surgery studies, heterogeneity, $\tau^2 = 0.00$; $\chi^2 = 3.40$, $df = 4$ ($P = .49$); $I^2 = 0\%$; test for overall effect, $z = 0.11$ ($P = .91$); test for subgroup differences, $\chi^2 = 1.85$, $df = 1$ ($P = .17$); $I^2 = 46\%$. For all studies, heterogeneity, $\tau^2 = 0.00$; $\chi^2 = 3.46$, $df = 5$ ($P = .63$); $I^2 = 0\%$; test for overall effect, $z = 1.26$ ($P = .21$); test for subgroup differences, $\chi^2 = 1.91$, $df = 2$ ($P = .39$); $I^2 = 0\%$.

The possible association between chlorhexidine use and increased mortality in non-cardiac surgery studies is surprising. This observation is guarded given that the result is statistically nonsignificant. Nonetheless, given the magnitude of the signal (RR, 1.13), the proximity of the lower limit of the confidence interval to 1 (95% CI, 0.99-1.29), the stepwise increase in RR estimates with increasing chlorhexidine concentrations, and the potential public health importance of this observation, we believe that this finding merits careful consideration and further evaluation. One potential explanation is the possibility that some patients may aspirate small amounts of chlorhexidine, leading to acute lung injury.[31-33] The studies in our review did not include acute respiratory distress syndrome as an outcome, so we have no specific data to confirm or refute this hypothesis. Of note, however, other investigators have raised the possibility that microaspiration of oral antiseptics can cause acute respiratory distress syndrome. Seguin and colleagues,[34] for example, observed a 6% rate of acute respiratory distress syndrome among patients randomized to oral care with povidone-iodine solution vs 0% in patients randomized to placebo. Another possible explanation is that chlorhexidine use may interfere with VAP diagnosis by contaminating respiratory tract specimens and inhibiting pathogen recovery in the laboratory. False-negative VAP diagnoses may lead to withholding antibiotics. Notably, some investigators have found that culture-negative VAP is associated with higher mortality rates than culture-positive VAP.[35]

The lack of clear evidence that adding chlorhexidine to routine oral care benefits non-cardiac surgery patients should prompt reexamination of hospital policies mandating its use. Nursing time for critically ill patients is scarce and precious. One hospital estimated that nurses spend up to 2 hours per day per patient providing oral care, including a median (interquartile range) of 20 (10-30) minutes per patient for chlorhexidine rinses.[36] If oral care with chlorhexidine has less impact than imagined, it might paradoxically be hurting patients by decreasing the time, resources, and organizational focus available for more robust interventions that are more likely to speed extubation, decrease length of stay, and decrease mortality. In the case of patients receiving mechanical ventilation, these include strategies such as minimizing the use of sedatives, coordinating spontaneous breathing trials with spontaneous

awakening trials, early mobilization, conservative fluid management, conservative red blood cell transfusion strategies, and low tidal volume ventilation.[37-42] Settling agitated patients using nonpharmacologic means and early mobilization in particular can require substantial nursing time and effort. Chlorhexidine also incurs costs, can stain patients' teeth, and requires formal procedures for storage and administration because the US Food and Drug Administration classifies it as a drug.

It is to be noted that our analysis only pertains to the specific question of whether adding chlorhexidine to routine oral care confers additional benefits beyond routine oral care alone. The studies included in our analysis did not compare oral care with no oral care. A small number of observational studies suggest that routine oral care may decrease VAP rates compared with no oral care, but there are few data on its impact on more objective outcomes.[26,43] Nonetheless, there are independent compelling reasons to provide routine oral care to patients receiving mechanical ventilation, such as maintaining periodontal health and enhancing patient comfort. Our analysis only suggests that adding chlorhexidine to routine oral care confers little or no additional benefit in non-cardiac surgery patients.

The discrepancy between chlorhexidine's possible impact on VAP in open-label studies and lack of impact on VAP in double-blind trials (and lack of impact on patient-centered outcomes in either set of trials) serves as a reminder that VAP is an unreliable outcome for assessing quality of care for patients receiving mechanical ventilation.[44-46] The diagnosis of VAP is subjective and prone to both false-positive and false-negative assignments.[47] Open-label studies of interventions to prevent VAP are vulnerable to bias given the broad range of subjective signs included in VAP definitions and the substantial room permitted by VAP definitions for observer discretion. Alternative metrics such as the US Centers for Disease Control and Prevention's new ventilator-associated events definitions, mean duration of mechanical ventilation, length of stay, and mortality rates may be more useful outcomes to follow because they are less prone to bias and help broaden the focus of prevention activities beyond pneumonia alone.

The findings of this investigation need to be tempered by limitations of the source data and our analysis. The possible association between chlorhexidine use and increased mortality is not statistically significant. Many of the studies included in this analysis provided data on only a subset of our target outcomes. The analyses of chlorhexidine use and duration of mechanical ventilation, intensive care length of stay, and antibiotic dispensing in particular included data from only a small fraction of investigations and had wide confidence intervals. There were also broad differences between studies in country of evaluation, inclusion criteria for enrolling patients, nursing care protocols for applying chlorhexidine, chlorhexidine preparation and strength, the use of corollary measures such as toothbrushing, the time point at which mortality was measured, and methods of seeking and defining pneumonia that may have increased the heterogeneity of results and dampened some signals favoring chlorhexidine using selected strategies in selected patients. Nonetheless, we found that the raw signals from each study were broadly consistent with each other, particularly with regard to mortality.

Our findings differ from those of prior meta-analyses.[6,7,48] Reasons for discrepancies include the distinctions that we made between cardiac surgery vs non-cardiac surgery studies and between open-label vs double-blind investigations, the restriction of our analysis to studies in adult populations, the exclusion of studies with outcome data on fewer than 80% of enrolled patients, and the addition of studies published after prior meta-analyses were closed. We believe that these distinctions and additions create a more nuanced picture of the potential benefits, risks, and limitations of chlorhexidine oral care.

Conclusions

Routine oral care with chlorhexidine may prevent lower respiratory tract infections in cardiac surgery patients but seems to be of limited benefit for non-cardiac surgery patients. Meta-analysis of double-blind investigations suggests that chlorhexidine's capacity to prevent VAP and improve outcomes is questionable. Large randomized clinical trials powered to detect a 10% or greater difference in mortality rates are needed to definitively evaluate the safety and benefits of routine oral care with chlorhexidine. In addition, we suggest that future trials include acute respiratory distress syndrome as an outcome. While our findings are not conclusive, they are sufficiently concerning to prompt a reevaluation of policies and initiatives that encourage or compel hospitals to include chlorhexidine in routine oral care for non-cardiac surgery patients.

ARTICLE INFORMATION

Accepted for Publication: December 17, 2013.

Published Online: March 24, 2014. doi:10.1001/jamainternmed.2014.359.

Author Affiliations: Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts (Klompas); Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts (Klompas); Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland (Speck, Berenholtz); Department of Medicine, University of Chicago, Chicago, Illinois (Howell); Highland Hospital, University of Rochester Medical Center Affiliate, Rochester, New York (Greene); Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland (Berenholtz); Department of Health Policy and Management, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland (Berenholtz).

Author Contributions: Dr Klompas had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Klompas, Howell, Greene.
Acquisition of data: Klompas, Speck.
Analysis and interpretation of data: Klompas, Howell, Greene, Berenholtz.
Drafting of the manuscript: Klompas, Speck, Greene.
Critical revision of the manuscript for important intellectual content: Klompas, Howell, Berenholtz.
Statistical analysis: Klompas.

Conflict of Interest Disclosures: Dr Klompas has received grant support from the Centers for Disease Control and Prevention and the Agency for Healthcare Research and Quality for research on

VAP surveillance and prevention. Dr Klompas has also received honoraria for lectures on VAP surveillance from Premier Healthcare Alliance, the Association of Professionals in Infection Control, Duke Infection Control Outreach Network, the Infectious Disease Association of California, and the Texas Hospital Association. No other disclosures are reported.

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