**MAJOR ARTICLE**

# Association Between Statin Use and Daptomycin-related Musculoskeletal Adverse Events: A Mixed Approach Combining a Meta-analysis and a Disproportionality Analysis

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***Background.*** There is a growing concern about the association between the combined use of daptomycin (DAP) and statins and the occurrence of musculoskeletal adverse events (MAEs), but this remains controversial. This study aimed to clarify the association between statin use and DAP-related MAEs.

***Methods.*** We used a mixed approach that combines 2 methodologies. First, we conducted a meta-analysis to examine the effects of statin use on DAP-related MAEs. Second, we conducted a disproportionality analysis using the US Food and Drug Administration Adverse Events Reporting System (FAERS) to further confirm the results of the meta-analysis and to examine the effect of each type of statin on DAP-related MAEs in a large population.

***Results.*** In the meta-analysis, statin use significantly increased the incidence of DAP-related rhabdomyolysis (odds ratio [OR]: 3.83; 95% confidence interval [CI]: 1.43–10.26) but not DAP-related myopathy (OR: 1.72; 95% CI: .95–3.12). In the disproportionality analysis using the FAERS, the use of statin significantly increased the reporting OR (ROR) for DAP-related myopathy (ROR: 5.69; 95% CI: 4.31–7.51) and rhabdomyolysis (ROR: 5.77; 95% CI: 4.33–7.68). Atorvastatin, rosuvastatin, and simvastatin all increased the incidence of DAP-related myopathy and rhabdomyolysis.

***Conclusion.*** The mixed approach combining a meta-analysis and disproportionality analysis showed that statin use was associated with the occurrence of DAP-related rhabdomyolysis. The appropriate use of statins and DAP should be performed with careful consideration of its safety.

**Keywords.** daptomycin; statin; musculoskeletal adverse event; meta-analysis; disproportionality analysis.

Daptomycin (DAP) is a cyclic lipopeptide antibiotic widely used for patients with methicillin-resistant *Staphylococcus aureus* infection [1, 2]. DAP increases the risk of elevated creatine phosphokinase (CPK) caused by muscle injury, leading to myopathy and rhabdomyolysis in 2%–13% and 5% of the patients,

respectively [3–6]. Therefore, weekly monitoring of CPK levels is recommended to prevent the occurrence of musculoskeletal adverse events (MAEs) such as myopathy and rhabdomyolysis [7].

Statins, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors, are used to reduce cholesterol and triglycerides by blocking the formation of cholesterol in the liver. Similar to DAP, statins also cause the development of MAEs [8]. In patients using statins, myopathy is observed in 5%–10% and rhabdomyolysis only in 0.01%–0.1% [8, 9]. Rhabdomyolysis leads to a high mortality rate of approximately 10%; therefore, even the occurrence of mild and moderate MAEs in some cases requires statin therapy to be discontinued [10, 11]. Several studies have investigated the concerning increased incidence of MAEs following the combined use of DAP and statins [5, 6, 12–14]. An observational study that analyzed 128 cases of DAP-related MAEs revealed that statin use was associated with an increased incidence of DAP-related MAEs [13]. Conversely,

other studies did not show an association between statin use and the occurrence of DAP-related MAEs [5, 6, 12, 14]. The inconsistent results remain controversial and thus need to be clarified to optimize pharmacotherapy using DAP and statins. Despite limited supporting data, the manufacturer of DAP recommends discontinuation of statin therapy to prevent potential drug–drug interactions [7]. In contrast, based on the clinical practice guidelines for methicillin-resistant *S aureus* treatment, there is no need to withdraw statins [15]. Discontinuing statin therapy may worsen neurological, cardiac, and survival outcomes in patients with acute stroke or myocardial infarction [16, 17]. Therefore, to develop safer and more effective pharmacotherapy, it is important to elucidate if the combined use of DAP and statins potentiate the occurrence of MAEs.

This study aimed to clarify, using a mixed approach, whether statins increase the incidence of DAP-related MAEs. To improve the quality of evidence on the association between statin use and DAP-related MAEs, we first performed a meta-analysis and then analyzed a database of spontaneous reports of adverse events. This mixed approach was successful in identifying other adverse events in recent articles because both methods complemented each other and improved the quality of evidence [18, 19].

## METHODS

### Study Design

A mixed approach combining 2 methodologies, a meta-analysis and a disproportionality analysis using the US Food and Drug Administration (FDA) Adverse Events Reporting System (FAERS), was applied to clarify the association between statin use and DAP-related MAEs (Figure 1). First, we conducted a meta-analysis to examine the effects of statin use on DAP-related MAEs. Based on the results of the meta-analysis, we examined the effects of each type of statin on DAP-related MAEs using the FAERS, which has a large-scale spontaneous reporting database for adverse events related to drugs.
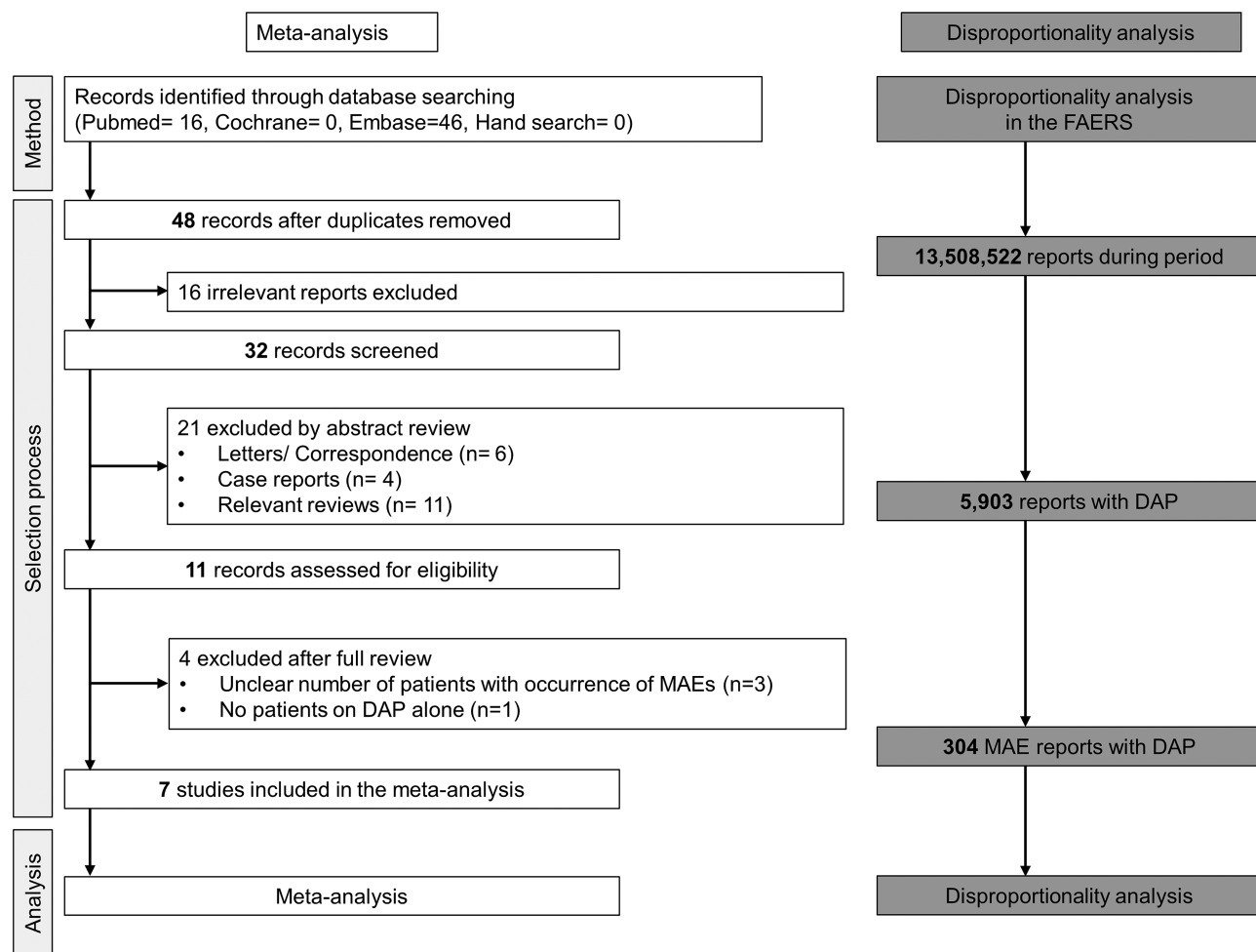


**Figure 1.** Flow diagram of the study design.
FAERS, US Food and Drug Administration Adverse Events Reporting System; DAP, daptomycin; MAE, musculoskeletal adverse event.

## Meta-analysis

### Literature Search and Study Selection

In the meta-analysis, we identified studies that evaluated the incidence of MAEs in patients who received DAP with or without statins (DAP + statin group vs DAP group). An electronic literature search was performed on PubMed, Cochrane databases, and Embase using prespecified search terms through November 2019 (Table 1). Handsearching in the reference lists of the identified studies was also conducted to increase the comprehensiveness of the search process according to the Preferred Reporting Items for Systematic and Meta-Analysis guidelines [20]. Two researchers (M. C. and A. N.) independently checked the titles and abstracts and then reviewed the full text of the articles to determine eligibility for the meta-analysis. All case reports, case series, review articles, and studies published in languages other than English were excluded. This meta-analysis was registered in the University Hospital Medical Information Network Clinical Trial Registry (UMIN 000046414).

### Quality Assessment

The methodological quality of the selected studies was assessed and scored using the risk of bias assessment tool for nonrandomized studies (RoBANS) [21]. This tool rates the risk of bias based on 6 domains: (1) selection of participants; (2) confounding variables; (3) measurement of exposure; (4) blinding of outcome assessments; (5) incomplete outcome data; and (6) selective outcome reporting, with each domain evaluated as either having low, high, or unclear risk of bias. The RoBANS score was determined independently by 2 researchers (M. C. and A. N.). Differences in results of assessments were discussed and settled between the 2 researchers.

### Data Synthesis and Statistical Analysis

To assess the association between statin use and DAP-related MAEs, we calculated the odds ratio (OR) and corresponding 95% confidence interval (CI) using the DerSimonian–Laird random-effects model. This model was chosen because of differences in the population, definition of MAEs, and duration of the studies [22]. Heterogeneity of the selected studies was examined using the estimated Cochrane $\chi^2$ test, Tau$^2$, and $I^2$ statistics ($I^2$ >50% indicated severe heterogeneity). If heterogeneity

### Table 1. Search Terms

| Number | Search Terms |
|---|---|
| 1 | Daptomycin |
| 2 | Hydroxymethylglutaryl-CoA reductase inhibitors |
| 3 | Statin |
| 4 | Creatine phosphokinase |
| 5 | Myopathy OR rhabdomyolysis |
| Total | 1 AND (2 OR 3) AND (4 OR 5) |

was identified, post hoc subgroup analyses were performed. All statistical analyses were conducted using EZR software [23].

## Disproportionality Analysis Using the FAERS

### Data Collection and Definition

Adverse event reports were downloaded from the FDA website. In the FAERS analysis, data from the first quarter of 2004 to the second quarter of 2020 were used [24]. In line with the FDA recommendations and because the FAERS includes duplicate reports, only the latest reports of patients and those with complete information on age were used. The description of adverse events in the FAERS conforms to the Medical Dictionary for Regulatory Activities (MedDRA) developed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; and as such, in our study, adverse event names were based on MedDRA version 23.0. Myopathy was defined by 11 preferred terms including "rhabdomyolysis/myopathy" (standardized MedDRA query, narrow: 20000002) and rhabdomyolysis as "rhabdomyolysis" (preferred term: 10039020). Statins were defined as the following 8 drugs: (1) atorvastatin; (2) cerivastatin; (3) fluvastatin; (4) simvastatin; (5) lovastatin; (6) pitavastatin; (7) pravastatin; and (8) rosuvastatin, which are all listed in the FAERS. Relationship between dose of DAP and DAP-related MAE were evaluated in cases with reported dose, body weight, and interval.

### Statistical Analysis

Signal detection for the risk of adverse events was assessed via a disproportionality analysis using the reported odds ratio (ROR) and 95% CI. A risk signal was considered significant when the ROR and the lower limit of the corresponding 95% CI was >1 [25, 26]. All data analyses were performed independently by 2 or more authors. All statistical analyses were conducted using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

### Meta-analysis

#### Description of Selected Studies

Of the 48 articles from the database search, we included 7 in this review. The article selection process is illustrated in Figure 1. Of the 32 extracted articles, 21 were letters/correspondence, case reports, or relevant reviews and therefore were excluded. The study design and outcomes of the other 11 articles were reviewed, and only 7 studies were found eligible for a detailed analysis and quality assessment [5, 6, 12–14, 27, 28]. The characteristics of the included studies are summarized in Table 2. Overall, 4548 patients were included in the meta-analysis, 3489 patients in the DAP group and 1059 patients in the DAP + statin group. The number of participants in each study ranged from

**Table 2. Summary of Included Studies**

| Source/Year | Country | Design | Total (DAP-G vs DAP + statin-G) | Definition of MAEs | DAP Dose (Median, DAP-G vs DAP + statin-G) |
|---|---|---|---|---|---|
| Lehman/2019 | USA | Cohort | 3658 (2787 vs 871) | CPK elevation, CPK ≥1000 | Not shown |
| Dare/2018 | USA | Case control | 256 (210 vs 46) | Myopathy, CPK ≥200 | 6.1 vs 6.3 (mean, with vs without myopathy) |
| | | | | Rhabdomyolysis, CPK ≥1000 | 6.1 vs 6.3 (mean, with vs without rhabdomyolysis) |
| McConnell/2014 | USA | Cohort | 233 (180 vs 53) | Myopathy, CPK ≥696 (if CPK <232 at baseline) | 5.9 vs 6.0 |
| | | | | Myopathy, CPK ≥1160 (if CPK ≥232 at baseline) | |
| Bland/2014 | USA | Cohort | 220 (171 vs 49) | Myopathy, CPK ≥1000 | 6.8 vs 6.8 |
| Jugun/2013 | Switzerland | Cohort | 16 (14 vs 2) | CPK elevation, CPK ≥188 | 8.1 vs 8.5 (mean) |
| Lai/2013 | Taiwan | Cohort | 61 (59 vs 2) | CPK elevation, CPK ≥480 on 2 serial measurements, and 1 of 2 CPK ≥480 (baseline CPK <160) | 6.8 vs 6.8 |
| | | | | CPK ≥800 on 2 serial measurements (baseline CPK ≥160) | |
| Ruiz/2012 | Spain | Cohort | 104 (68 vs 36) | Myopathy, CPK ≥1000 | 7.8 vs 8.1 |

Abbreviations: CPK, creatine phosphokinase; DAP, daptomycin; DAP-G, daptomycin group; DAP + statin-G, daptomycin + statin group; MAE, musculoskeletal adverse event.

16 to 3658. The definition of MAEs based on CPK values differed among the studies.

### Quality Assessment
Seven studies were assessed and scored according to the RoBANS guideline (Table 3) [21]. There was a high risk of bias associated with participant selection for 5 of 7 studies because patients who have been treated with statins before DAP administration were not excluded. Four of the 7 studies were found to have a high risk of bias linked to confounding variables because these factors were not considered in the analysis [5, 6, 27, 28]. The 2 studies were evaluated to have a high risk of bias related to incomplete outcome data because patients with incomplete CPK data were excluded [27, 28].

### Meta-analysis
Figure 2 shows the forest plot for each study on myopathy. Myopathy was observed in 210 of 3489 patients (6.0%) among the DAP group and 70 of 1059 patients (6.6%) among the DAP + statin group. There was no significant difference in the incidence of myopathy between the DAP and

DAP + statin groups (OR: 1.72; 95% CI: .95–3.12). Because heterogeneity among studies was observed ($I^2$ = 46.0%, $P$ = .09), subgroup analysis was conducted for comparison of rhabdomyolysis incidence between the DAP and DAP + statin groups. Rhabdomyolysis was observed in 17 (6.2%) and 9 patients (13.0%) in the DAP (n = 276) and DAP + statin (n = 69) groups, respectively (Figure 3). The rhabdomyolysis incidence in the DAP + statin group was significantly higher than that in the DAP group (OR: 3.83; 95% CI: 1.43–10.26). Heterogeneity of rhabdomyolysis incidence was not observed ($I^2$ = 0.0%, $P$ = .5142) among the studies.

### Disproportionality Analysis Using the FAERS
Among 13 508 522 reports submitted during the study period, the number of cases related to administration of DAP and statins was 5903 and 329 778, respectively (Supplemental Table 1). An increase in reports of myopathy and rhabdomyolysis was observed in cases treated with DAP and statins, regardless of age and sex (Supplemental Tables 1–6). Increased incidence of DAP-related MAE was not observed in patients with higher DAP dosing (≥8 mg/kg/d) compared with those with standard DAP dosing

**Table 3. Summary of Risk of Bias Using RoBANS**

| | Risk of Bias | | | | | |
|---|---|---|---|---|---|---|
| Author/Year | Selection of Participants | Confounding Variables | Measurement of Exposure | Blinding of Outcome Assessments | Incomplete Outcome Data | Selective Outcome Reporting |
| Lehman/2019 | High | Low | Low | Low | Unclear | Unclear |
| Dare/2018 | High | Low | Low | Low | Unclear | Unclear |
| McConnell/2014 | High | High | Low | Low | Unclear | Unclear |
| Bland/2014 | Unclear | Low | Low | Low | Unclear | Unclear |
| Jugun/2013 | High | High | High | High | High | Unclear |
| Lai/2013 | Unclear | High | Low | Low | High | Unclear |
| Ruiz/2012 | High | High | Low | Low | Low | Unclear |

Abbreviation: RoBANS, Risk of Bias Assessment for Nonrandomized Studies.

| Study | DAP Events | DAP Total | DAP+statin Events | DAP+statin Total | Odds Ratio | OR | 95%-CI | Weight (fixed) | Weight (random) |
|---|---|---|---|---|---|---|---|---|---|
| Bethany 2019 | 90 | 2787 | 26 | 871 | | 0.92 | [0.59; 1.44] | 67.5% | 31.7% |
| Dare 2018 | 96 | 210 | 32 | 46 | | 2.71 | [1.37; 5.38] | 17.0% | 25.5% |
| McConnell 2014 | 2 | 180 | 3 | 53 | | 5.34 | [0.87; 32.84] | 1.4% | 8.4% |
| Bland 2014 | 9 | 171 | 5 | 49 | | 2.05 | [0.65; 6.41] | 5.8% | 15.9% |
| Jugun 2013 | 2 | 14 | 1 | 2 | | 6.00 | [0.26; 140.04] | 0.4% | 3.3% |
| Lai 2013 | 4 | 59 | 0 | 2 | | 2.47 | [0.10; 59.60] | 0.6% | 3.2% |
| Parra-Ruiz 2012 | 7 | 68 | 3 | 36 | | 0.79 | [0.19; 3.27] | 7.2% | 12.1% |
| **Fixed effect model** | | 3489 | | 1059 | | 1.38 | [1.00; 1.89] | 100.0% | -- |
| **Random effects model** | | | | | | 1.72 | [0.95; 3.12] | -- | 100.0% |

Heterogeneity: $I^2 = 46\%$, $\tau^2 = 0.2403$, $p = 0.09$
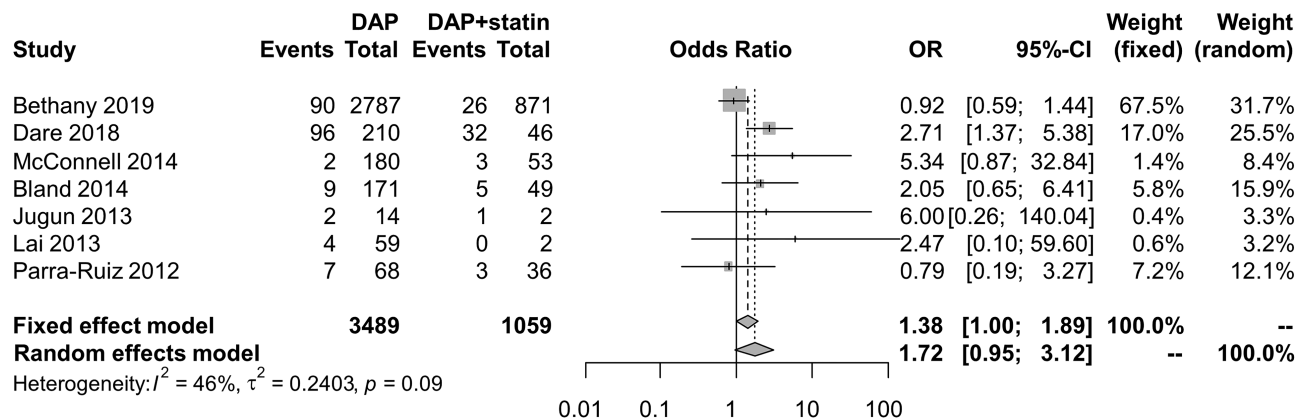
0.01  0.1  1  10  100

**Figure 2.** Forest plot comparing the incidence of myopathy between DAP and DAP + statin groups. CI, confidence interval; DAP, daptomycin; OR, odds ratio.

(<8 mg/kg/d) (data not shown). Data for daily dose of DAP were available in 568 (9.6%) of 5903 reports with DAP therapy. Among the reports of DAP therapy, the incidence of myopathy and rhabdomyolysis were 5.15% (304/5903) and 4.68% (276/5903), respectively (Supplemental Tables 1 and 2). In patients using statins, incidence rates of DAP-related myopathy (19.42%) and rhabdomyolysis (17.99%) were significantly higher than those in patients not on statins (myopathy: 4.06%; rhabdomyolysis: 3.66%) (Table 4). The combination of statin and DAP significantly increased the ROR for DAP-related myopathy ($P < .001$) and rhabdomyolysis ($P < .001$). The incidence of DAP-related MAEs in cases using simvastatin, atorvastatin, or rosuvastatin was significantly higher than that in cases not on these statins (Table 5). The effect of the other four statins on DAP-related MAEs could not be evaluated because of limited reports available, with no reports on the combination of DAP and cerivastatin.

## DISCUSSION

To our knowledge, this is the first study to clearly demonstrate the association between statin use and DAP-related rhabdomyolysis through a mixed approach using 2 methodologies. The meta-analysis showed that the incidence of DAP-related rhabdomyolysis was significantly higher in patients using statins than in patients not on statins. Disproportionality analysis using the FAERS showed an association between statin use and increased incidence of DAP-related rhabdomyolysis. This relationship was observed for all commonly used statins in clinical settings, such as atorvastatin, rosuvastatin, and simvastatin. The novel findings of the present study provide useful information on the safety of the combined use of statins and DAP. It is important to carefully decide on the use of DAP and statin combination; sufficient monitoring to prevent the occurrence of DAP-related rhabdomyolysis may be necessary. Frequent CPK monitoring at least once a week is required if the combined use is unavoidable. Many of the populations in the meta-analysis and FAERS in the present study were of Western descent. Our results were consistent with that of a very recent report that concomitant use of statins is associated with a risk of increased CPK during DAP therapy using a large Japanese electronic medical record database [29]. The present study may be applicable to populations other than those of Western descent; further detailed study for verification is needed.

There was a difference in the results between the meta-analysis and the FAERS disproportionality analysis in our mixed approach. The increased incidence of DAP-related myopathy with statin use was only observed in the FAERS disproportionality
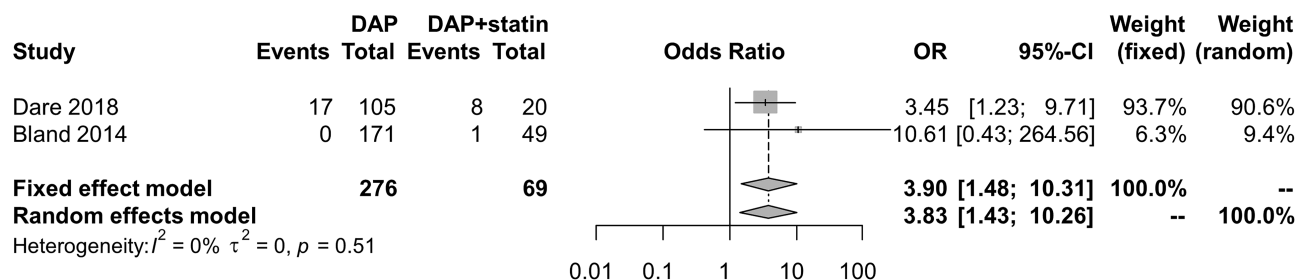
| Study | DAP Events | DAP Total | DAP+statin Events | DAP+statin Total | Odds Ratio | OR | 95%-CI | Weight (fixed) | Weight (random) |
|---|---|---|---|---|---|---|---|---|---|
| Dare 2018 | 17 | 105 | 8 | 20 | | 3.45 | [1.23; 9.71] | 93.7% | 90.6% |
| Bland 2014 | 0 | 171 | 1 | 49 | | 10.61 | [0.43; 264.56] | 6.3% | 9.4% |
| **Fixed effect model** | | 276 | | 69 | | 3.90 | [1.48; 10.31] | 100.0% | -- |
| **Random effects model** | | | | | | 3.83 | [1.43; 10.26] | -- | 100.0% |

Heterogeneity: $I^2 = 0\%$ $\tau^2 = 0$, $p = 0.51$

0.01  0.1  1  10  100

**Figure 3.** Forest plot comparing the incidence of rhabdomyolysis between DAP and DAP + statin groups. CI, confidence interval; DAP, daptomycin; OR, odds ratio.

**Table 4.  Effect of Statin Combination on the Incidence of Daptomycin-related MAEs**

| Adverse Event | Reporting Rate of Daptomycin-associated MAEs (No. of Reports) | | ROR (95% CI) | P |
|---|---|---|---|---|
| | Without statins | With statins | | |
| Myopathy | 4.06% (223/5486) | 19.42% (81/417) | 5.69 (4.31–7.51) | <.001 |
| Rhabdomyolysis | 3.66% (201/5486) | 17.99% (75/417) | 5.77 (4.33–7.68) | <.001 |

Abbreviations: CI, confidence interval; MAE, musculoskeletal adverse event; ROR, reporting odds ratio.

analysis and not in the meta-analysis. In most studies in the meta-analysis, the median DAP dose for enrolled patients was above 6 mg/kg. High dosing (≥6 mg/kg) of DAP, which has been widely used recently, leads to the development of MAEs [12]. Therefore, the combined use of DAP and statins should be with careful consideration and sufficient monitoring of parameters such as frequent CPK to avoid developing DAP-induced rhabdomyolysis. The difference between the FAERS analysis and the meta-analysis of DAP-related myopathy and statin use may also be explained by the distinct definitions of myopathy in each study included in the meta-analysis. Meta-analysis carries a higher level of evidence than studies of other design. Reportedly, the results obtained from the analysis of real-world data are consistent with those of randomized controlled trials (RCTs) [30]. Nonetheless, a mixed approach using a meta-analysis and using a spontaneous adverse event reporting database is particularly useful because it is difficult to conduct RCTs to investigate adverse events with drug–drug interactions.

The FAERS disproportionality analysis suggests that careful pharmacovigilance is required if DAP is combined with clinically recommended statins (atorvastatin, rosuvastatin, and simvastatin). In contrast, Imai et al recently reported that the use of rosuvastatin, a hydrophobic statin, was not associated with an increased incidence of DAP-related MAEs in a large Japanese population [29]. We propose that the inconsistency in results is

from differences between study populations; however, additional investigation is required to determine the details. Furthermore, the mechanism behind the effect of statins on DAP-related MAEs remains unclear and additional studies are needed to investigate its etiology and occurrence in various populations. The positive association between the dose of DAP and DAP-related MAE was not observed in the present study. In our analysis, only 9.6% reported on DAP therapy with sufficient information on the daily dose of DAP; therefore, the relationship between dosage and incidence of adverse event in spontaneous adverse event database may need to be evaluated carefully. Our result is consistent with a previous report on patients with DAP in the Japanese spontaneous adverse event database [31]. Further studies are needed to clarify the dose effect of DAP on DAP-related MAEs.

Although the features of the 2 methodologies complemented each other through an integrated study design, there were several limitations inherent to each methodology. First, none of the included studies in the meta-analysis were RCTs and most of them had a high risk of bias. Second, there were only 2 studies about rhabdomyolysis in the meta-analysis, with 25 of the 26 cases with rhabdomyolysis reported by Dare et al, leading to high weight (90.6%) of that report. These factors may have affected the results of the meta-analysis. To address some of these limitations, the FAERS, which has a large claims database, was used in the disproportionality analysis. The association

**Table 5.  Effect of Combination With Each Statin on the Incidence of Daptomycin-related MAEs**

| Adverse Effect | Drug Name | Reporting Rate (No. of Reports) of MAEs | | ROR (95% CI) | P |
|---|---|---|---|---|---|
| | | Without Statins | With Statins | | |
| Myopathy | Atorvastatin | 4.90% (277/5658) | 11.02% (27/245) | 2.41 (1.58–3.65) | <.001 |
| | Simvastatin | 4.46% (254/5692) | 23.70% (50/211) | 6.65 (4.73–9.35) | <.001 |
| | Rosuvastatin | 4.75% (275/5794) | 26.61% (29/109) | 7.28 (4.68–11.32) | <.001 |
| | Lovastatin | 5.14% (303/5891) | 8.33% (1/12) | 1.68(0.22–13.03) | .470 |
| | Pravastatin | 5.13% (300/5847) | 7.14% (4/56) | 1.42 (0.51–3.96) | .533 |
| | Fluvastatin | 5.15% (304/5900) | 0% (0/3) | NA | NA |
| | Pitavastatin | 5.15% (304/5901) | 0% (0/2) | NA | NA |
| Rhabdomyolysis | Atorvastatin | 4.49% (254/5658) | 8.98% (22/245) | 2.10 (1.33–3.31) | .002 |
| | Simvastatin | 4.04% (230/5692) | 21.80% (46/211) | 6.62 (4.65–9.42) | <.001 |
| | Rosuvastatin | 4.28% (248/5794) | 25.69% (28/109) | 7.73 (4.94–12.10) | <.001 |
| | Lovastatin | 4.67% (275/5891) | 8.33% (1/12) | 1.86 (0.24–14.43) | .437 |
| | Pravastatin | 4.65% (272/5847) | 7.14% (4/56) | 1.58 (0.57–4.39) | .333 |
| | Fluvastatin | 4.68% (276/5900) | 0% (0/3) | NA | NA |
| | Pitavastatin | 4.68% (276/5901) | 0% (0/2) | NA | NA |

Abbreviations: CI: confidence interval; MAE, musculoskeletal adverse event; ROR, reporting odds ratio.

indicated by the meta-analysis between statin combination and DAP-related MAEs was confirmed by a disproportionality analysis using the FAERS. However, in the FAERS data, there is no definitive proof of causality between combined DAP and statin use and the occurrence of MAEs. The reported MAEs may have also been owing to other reasons aside from the administration of DAP or statins. Last, the FAERS data are known to have duplicate reports and significant amounts of missing data. To address this, duplicate reports were removed and only cases with complete information were selected. The generalizability of our results may be limited and needs to be verified by further studies in a larger population.

## CONCLUSION

A mixed approach combining a meta-analysis and a disproportionality analysis using the FAERS demonstrated a significant association between statin combination therapy and DAP-related rhabdomyolysis. Disproportionality analysis using the FAERS suggested a relationship regardless of the statin agent. The appropriate use of statins and DAP should be performed with careful consideration of its safety.

### Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors; therefore, questions or comments should be addressed to the corresponding author.

### Notes

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