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Dupilumab safety and efficacy in uncontrolled asthma: a systematic review and meta-analysis of randomized clinical trials

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ABSTRACT

Objective: We aimed to perform a meta-analysis evaluating the efficacy and safety of dupilumab in patients with uncontrolled asthma. **Data source:** A search of electronic databases was performed using PubMed, Cochrane library and Embase. **Study selection:** The literature search was conducted independently by two reviewers. Only randomized controlled trials (RCTs) that compared between placebo and dupilumab in patients with uncontrolled asthma were included in this analysis. Pooled risk ratios (RRs) and mean differences (MDs) with their corresponding 95% confidence intervals (CIs) were calculated for dichotomous and continuous data, respectively. **Results:** A total of four RCTs representing 2,992 patients were included. Pooled analysis showed significant reductions of the annualized rate of severe asthma exacerbation in the dupilumab group compared with placebo (RR 0.44; 95% CI 0.35–0.55; $P < 0.01$; $I^2 = 42\%$). In addition, the absolute forced expiratory volume at 1 s (FEV1) changes were significantly increased for the dupilumab group (MD 0.14; 95% CI: 0.12–0.17; $P < 0.01$; $I^2 = 0\%$). Finally, there were no significant differences between both groups in the development of any adverse event, serious adverse events, adverse events leading to death, discontinuation of medication due to adverse event or the occurrence of upper respiratory tract, influenza or bronchitis infections. However, dupilumab was associated with an increased risk of injection site reactions compared with placebo (RR 1.91; 95% CI 1.41, 2.59; $P < 0.01$; $I^2 = 24\%$). **Conclusion:** Among patients with uncontrolled asthma, the addition of dupilumab was associated with a reduced risk of severe asthma exacerbations and improvement in FEV1 without an increased risk of adverse events apart from injection site reactions with dupilumab.

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Introduction

Asthma is a common disease affecting about 250 million people worldwide, of whom 20% have poor control of their symptoms or moderate to severe exacerbations that require frequent hospitalization despite maximal medical therapy [1–3]. Severe persistent uncontrolled asthma is characterized by uncontrolled symptoms despite use of medium to high doses of inhaled glucocorticoids in addition to a second line therapy or by use of continuous or near continuous oral glucocorticoids [4].

T-helper2 (Th-2) lymphocytes, in conjunction with multiple interactions between the innate and adaptive immune system, mediate the Th-2 immune response that precipitates asthma. The process involves the

initial stimulation of Th-2 lymphocytes by several upregulated inflammatory cytokines, culminating in the expression of the CCR-4 chemokine receptor and eventual secretion of other inflammatory interleukins, including IL-4, IL-5, IL-9 and IL-13. As Th-2 lymphocytes migrate from surrounding lymph nodes to the airways, they promote chemotaxis and activation of inflammatory cells, such as mast cells and eosinophils, that ultimately are responsible for the symptoms of asthma [5,6]. In addition, IL-4 and IL-13 serve to activate B cells and promote “class switching” of immunoglobulins (Ig) into the IgE class from IgM antibodies [7]. Furthermore, those interleukins innately enhance smooth muscle contractility [8].

Many monoclonal antibodies have been developed to target and interrupt these inflammatory processes in an effort to control asthma symptoms in

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uncontrolled patients. Dupilumab, a fully human-derived monoclonal antibody directed against the alpha subunit of the IL-4 receptor, functions by blocking the early signal transduction of the Th-2 mediated immune response [9].

Several randomized controlled trials (RCTs) have been conducted to investigate the effectiveness of dupilumab in uncontrolled asthma. Therefore, we performed a meta-analysis of all RCTs comparing dupilumab to placebo in patients with uncontrolled asthma.

Methods

Literature search and data source

We conducted our meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) Statement 2015 [10]. An electronic literature search was performed independently and separately by two investigators

(M.B. and A.A) using PubMed, Embase and Cochrane library from inception through May 24, 2018. Any disagreement was resolved by a discussion with a third investigator (Y.Z.). No language restrictions were applied. In addition, references of the relevant studies and previous meta-analyses were reviewed for possible eligibility.

Studies were first screened by their titles and abstracts for eligibility. The full texts of eligible studies were reviewed in the second step before exclusion. The search process is detailed in Figure 1. The electronic search was archived through the Mendeley program and is available on request.

Study selection

We have included RCTs that compare the efficacy and safety of dupilumab with placebo in patients with uncontrolled asthma on inhaled glucocorticoids and

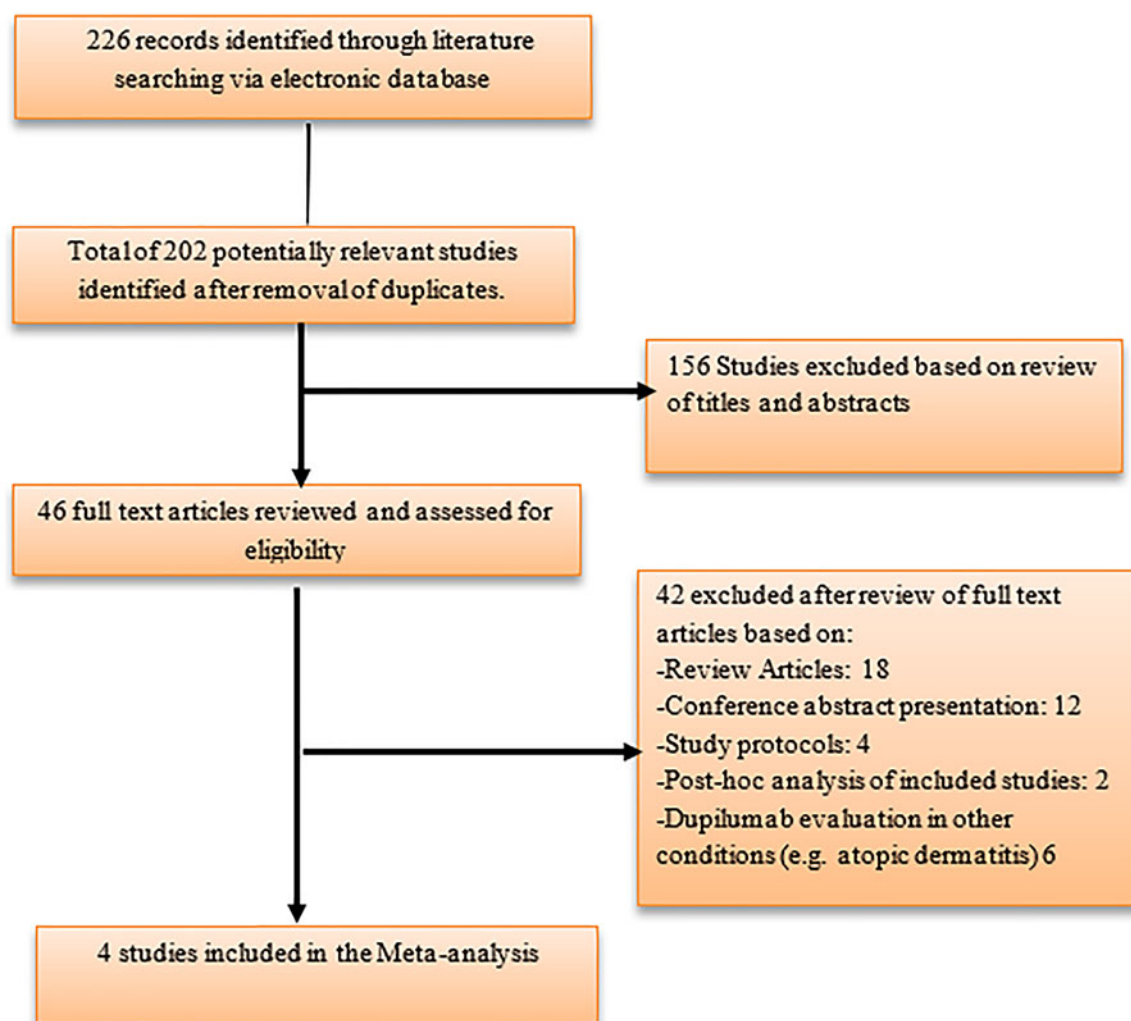


Figure 1. Flow diagram of literature search and study selection based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) recommendation.

Table 1. Summary of included studies.

First author and year	Study design	Follow-up period	Inclusion criteria	Dupilumab dose/frequency	Total patients number
Castro (2018)	Multicenter Double-blind Phase 3 trial 2:2:1:1 randomization	64 weeks	– Uncontrolled moderate-to-severe asthma – Use of inhaled glucocorticoids plus up to two additional controllers (e.g. LABA, leukotriene antagonist)	Dupilumab 200 mg every 2 weeks Dupilumab 300 mg every 2 weeks	1902
Rabe (2018)	Multicenter Double-blind Phase 3 trial 1:1 randomization	36 weeks	Oral glucocorticoid-dependent severe asthma	Dupilumab 300 mg every 2 weeks	210
Wenzel (2016)	Multicenter Double-blind Phase 2b clinical 1:1:1:1:1 randomization	40 weeks	– Uncontrolled persistent asthma despite – Use of medium-to-high-dose inhaled corticosteroids plus LABA	Dupilumab 200 mg every 2 weeks Dupilumab 300 mg every 3 weeks Dupilumab 200 mg every 4 weeks Dupilumab 300 mg every 4 weeks	776
Wenzel (2013)	Multicenter Double-blind Phase 2A study, 1:1 randomization	20 weeks	– Uncontrolled persistent, moderate-to-severe asthma – Elevated blood eosinophil count (≥ 300 cells per microliter) or an elevated sputum eosinophil level ($\geq 3\%$)	Dupilumab 300 mg every week	104

LABA: Long Acting β_2 agonist.**Table 2.** Baseline characteristics of study population reported for overall population in each study.

	Castro (2018)	Rabe (2018)	Wenzel (2016)	Wenzel (2013)
Total patient's number	1902	210	776	102
Age (mean $\pm$ SD)	47.9 $\pm$ 15.3	51.3 $\pm$ 12.6	48.6 $\pm$ 13.0	39.7 $\pm$ 13.2
Female No. (%)	1197 (62.9)	127 (60)	490 (63)	52 (50)
Former smoker – no. (%)	368 (19.3)	41 (20)	174/775 (22%)	–
Prebronchodilator FEV1 (L) mean $\pm$ SD	1.78 $\pm$ 0.60	1.58 $\pm$ 0.57	1.84 $\pm$ 0.54	2.5 $\pm$ 0.65
Prebronchodilator FEV1 – % of predicted value mean $\pm$ SD	58.43 $\pm$ 13.52	52.18 $\pm$ 15.18	60.77 $\pm$ 10.72	72 $\pm$ 12.58
No. of severe asthma exacerbations in previous year mean $\pm$ SD	2.09 $\pm$ 2.15	2.09 $\pm$ 2.16	2.17 $\pm$ 2.14	–
Blood eosinophil count – cells/mm ³ mean $\pm$ SD	360 $\pm$ 366	347 $\pm$ 307	347.46 $\pm$ 427.59	510 $\pm$ 203
ACQ-5 score mean $\pm$ SD	2.76 $\pm$ 0.77	2.50 $\pm$ 1.16	2.74 $\pm$ 0.81	2.1 $\pm$ 0.49

SD: Standard deviation; FEV1: forced expiratory volume at 1 s; L: liters; No: number; ACQ-5: The 5-item Asthma Control Questionnaire.

long-acting β_2 agonists (LABAs) or who require oral glucocorticoids to control their symptoms.

We performed a quality assessment for the included RCTs using the Cochrane collaboration's tool for assessing risk of bias in RCTs. We assessed the included RCTs for random sequence generation, allocation concealment, blindness of participants and health-care personnel, blindness of outcome assessment, incomplete outcome data, selective reporting and other biases.

Data extraction

Two reviewers (M.B. and Y.Z.) independently and separately extracted the data into a predesigned form from the included RCTs. Any disagreements were resolved via a third investigator (A.A.).

Outcomes

The primary efficacy outcome was the annualized rate of severe asthma exacerbations defined as

exacerbations leading to hospitalization, treatment for three or more days with oral glucocorticoids, emergency department visit leading to systemic steroid or ≥ 2 times increase in the current oral steroid dose. Other efficacy outcomes were: the absolute change in forced expiratory volume at 1 s (FEV1) between baseline and the longest follow-up duration (12–24 weeks). Safety outcomes were any or serious adverse events defined as per each included RCT, adverse events leading to death, discontinuation of medication due to adverse event, injection site reactions and the occurrence of upper respiratory tract, influenza and bronchitis infections as reported according to the preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA).

Statistical analysis

We calculated pooled risk ratios (RRs) and 95% confidence intervals (CIs) using the Mantel-Haenszel

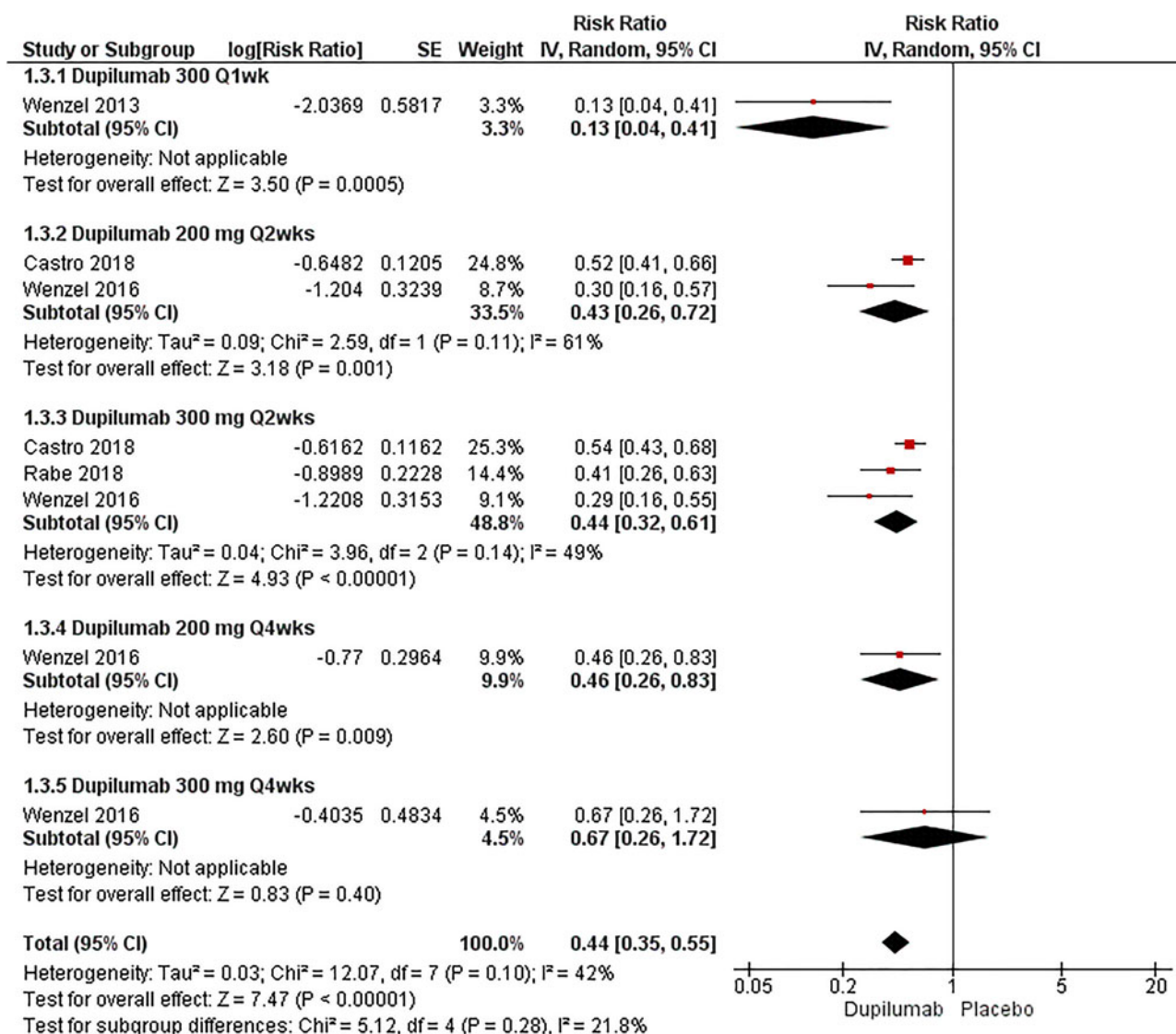


Figure 2. Forest plot for annualized severe asthma exacerbations.

method for dichotomous data. For continuous data, we reported the weighted mean differences (MDs) and 95% CIs using the inverse variance (IV) test. A random-effects model was used to account for the between-study heterogeneity. Heterogeneity was measured using the Cochrane's Q statistics and I² test. Publication bias was assessed with visual inspection of the funnel plot. Furthermore, we explained any heterogeneity by performing subgroup analyses according to the dupilumab dosages. In addition, sensitivity analysis was performed by removing trials sequentially. Data were analyzed using RevMan v5.3 Windows.

Results

Summary of the studies

A thorough literature search of electronic databases revealed 226 studies. After review, four RCTs that

compared dupilumab with placebo in patients with uncontrolled asthma were included [11–14]. The selection process used for identifying the included RCTs are detailed in Figure 1. Table 1 explains the summary characteristics of the included studies. The included studies have low risk of bias based on the quality assessment performed by the reviewers.

The total number of included patients were 2,992 patients. There were 2,037 patients in the dupilumab group and 955 patients in the placebo group. All trials were double-blinded. Different dupilumab dosages were used in the included clinical trials; 200–300 mg every 2 weeks were the most frequently used doses; other dosages included 300 mg every week and 200–300 mg every 4 weeks. Follow-up period ranged from 20 to 64 weeks. The baseline characteristics of the included patients are detailed in Table 2.

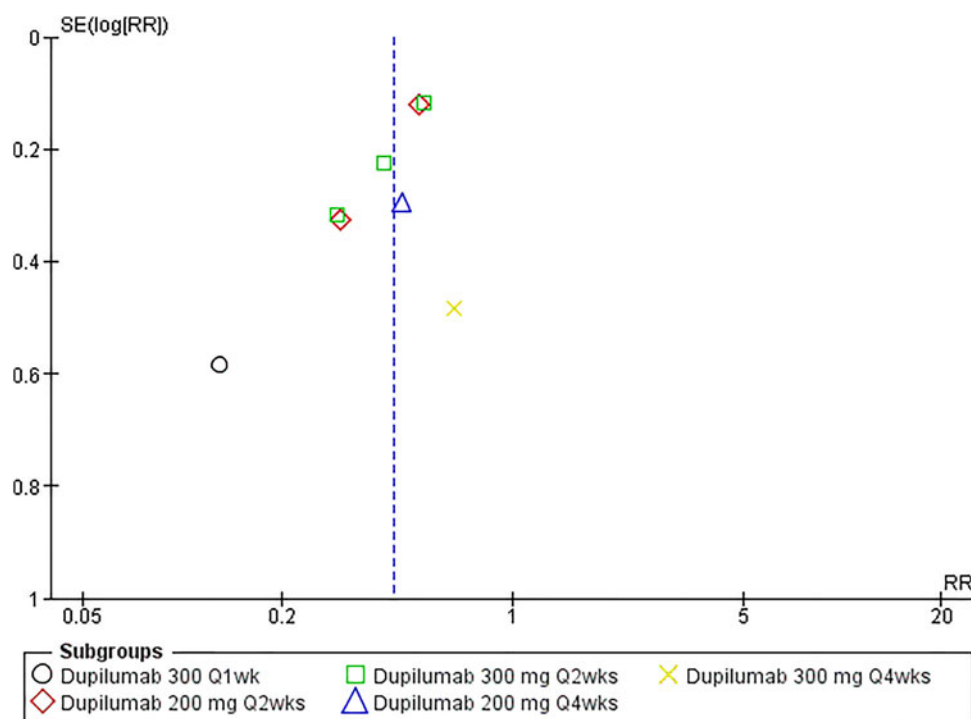


Figure 3. Funnel plot for primary outcome.

Efficacy measures

Severe asthma exacerbations

Pooled analysis showed significant reductions in annualized severe asthma exacerbations in the dupilumab group compared with the placebo group (RR 0.44; 95% CI 0.35–0.55; $P < 0.01$; $I^2 = 42\%$) (Figure 2). Examination of the funnel plot did not suggest any publication bias (Figure 3). Furthermore, there were significant reductions of the severe asthma exacerbation rates with dupilumab compared with placebo (12.8% vs 27.3%, respectively) (Figure 4).

Furthermore, sensitivity analysis by removing trials sequentially were consistent with the primary analysis. Subgroup analysis of the different dupilumab doses did not show any P interaction ($P = 0.28$) (Figure 2). In addition, subgroup analysis of patients with eosinophils >300 cells/mm³ (RR 0.33; 95% CI: 0.27–0.40; $P < 0.01$, $I^2 = 0\%$) and eosinophils <300 cells/mm³ (RR 0.50; 95% CI: 0.37–0.68; $P < 0.01$, $I^2 = 0\%$) showed persistent significant reductions of the annualized severe asthma exacerbations with dupilumab (Supplementary Figures 1–2). In a subset of patients with an eosinophil count <150 cells/mm³, the difference in annualized severe asthma exacerbations between those taking dupilumab and those taking placebo was not statistically significant (RR 0.85, 95% CI: 0.52–1.38, $P = 0.51$, $I^2 = 57\%$) (Supplementary Figure 3).

Mean difference of the absolute FEV1 change

Pooled analysis showed significant improvements in the absolute FEV1 measured in liters from baseline to the longest follow-up period with dupilumab-treated patients (MD 0.14; 95% CI: 0.12 – 0.17; $P < 0.01$; $I^2 = 0\%$). Subgroup analysis of the different dupilumab doses did not show any significant P interaction ($P = 0.49$) (Figure 5). Furthermore, subgroup analyses of patients with eosinophil count >300 cells/mm³ (MD 0.21; 95% CI: 0.17–0.25; $P < 0.01$; $I^2 = 0\%$), eosinophil count <300 cells/mm³ (MD 0.12; 95% CI 0.07 – 0.17; $P < 0.01$, $I^2 = 0\%$), and eosinophil count <150 cell/mm³ (MD 0.10, 95% CI 0.02–0.18, $P = 0.01$, $I^2 = 26\%$) showed significant improvements in the absolute FEV1 from baseline in those treated with dupilumab (Supplementary Figures 4–6).

Safety outcomes

There were no significant differences between treatment groups with regard to risk of the following adverse safety outcomes: any adverse events (RR 0.99; 95% CI: 0.95–1.02; $P = 0.46$; $I^2 = 0\%$), serious adverse event (RR 1.05; 95% CI: 0.8–1.38; $P = 0.76$; $I^2 = 0\%$), adverse events leading to death (RR 0.84; 95% CI: 0.2–3.49; $P = 0.81$), discontinuation of medication due to adverse events (RR 1.08; 95% CI: 0.74–1.57; $P = 0.68$; $I^2 = 0\%$), the occurrence of upper respiratory tract infections (RR 0.82; 95% CI: 0.67–1.01; $P = 0.06$; $I^2 = 0\%$), influenza infections (RR 0.92; 95% CI:

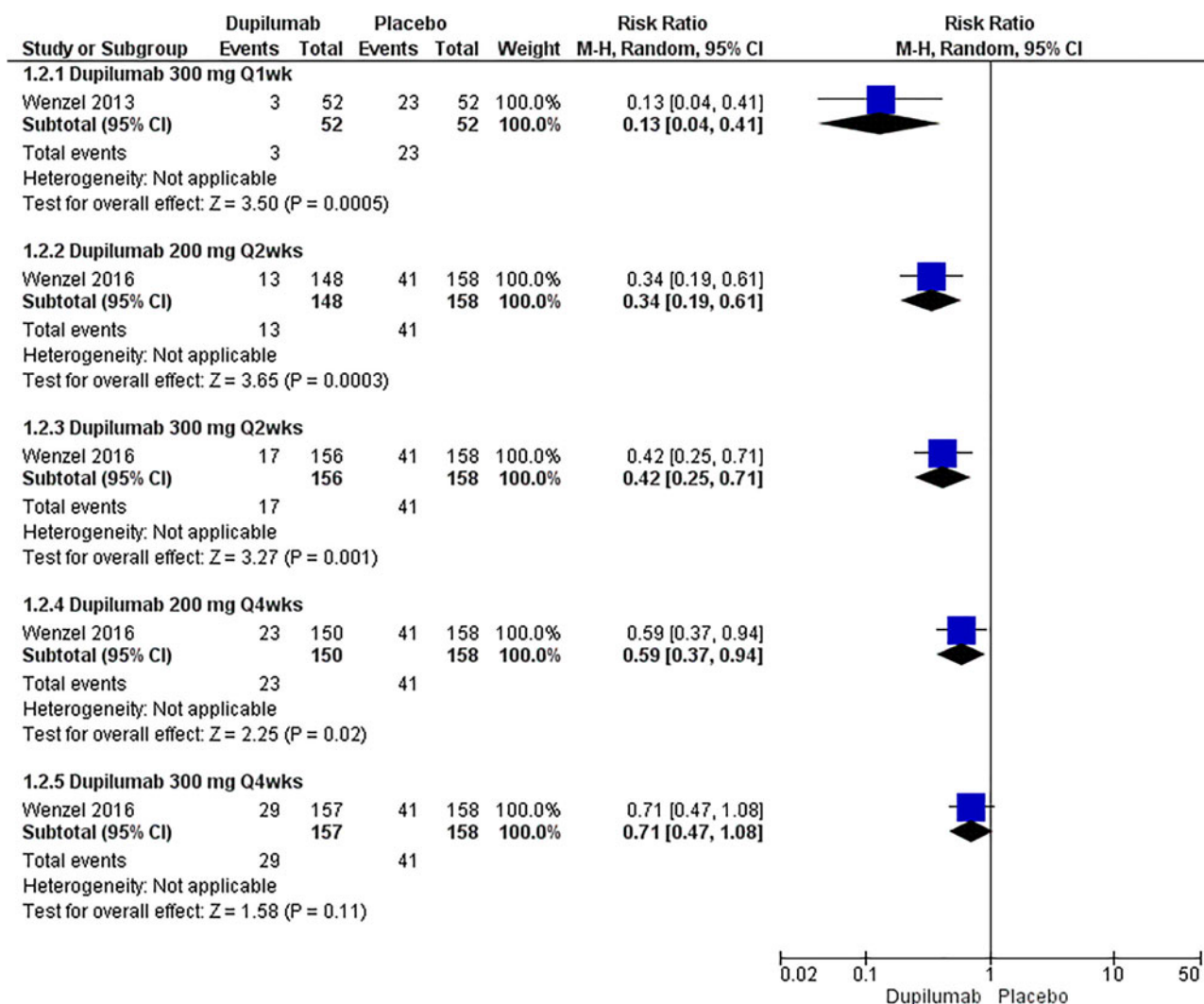


Figure 4. Forest plot for rate of severe asthma exacerbations.

0.46–1.84; $P = 0.81$; $I^2 = 55\%$), and bronchitis infections (RR 0.83; 95% CI: 0.67–1.03; $P = 0.09$; $I^2 = 0\%$). Dupilumab was associated with increased risks for injection site reactions when compared to placebo (RR 1.91; 95% CI 1.41, 2.59; $P < 0.01$; $I^2 = 24\%$) (Figure 6).

Discussion

Our meta-analysis revealed the following key findings. First, dupilumab was associated with reduced risk of severe asthma exacerbations. Second, absolute FEV1 improved with dupilumab when compared to placebo. Third, there were no significant differences between both groups with regard to safety outcomes, apart from injection site reactions, which occurred more with dupilumab. Fourth, subgroup analysis revealed that a reduced rate of annualized severe asthma exacerbations and an improved absolute FEV1 occur with eosinophil counts >150 cells/mm³ in those taking

dupilumab. The rate reduction of severe asthma exacerbations in those taking dupilumab fails to be significant in patients with <150 cells/mm³, despite continued improvement in FEV1.

Our results were consistent with the findings of the included RCTs [11–14]. In the LIBERTY ASTHMA QUEST trial, there was a significant reduction of the annualized rate of severe asthma exacerbations when dupilumab was added to inhaled glucocorticoids and at least two other disease controller medications, such as LABAs or leukotriene antagonists, in comparison to placebo (46.7% lower rate with dupilumab than placebo) [11]. As we demonstrated, several RCTs have shown that FEV1 improves in patients taking dupilumab, with the effect starting as early as after just 2 weeks of therapy and lasting at least 52 [11]. We lacked patient-level data in the present study and were therefore unable to perform similar time-course analyses.

Unfortunately, our meta-analysis was underpowered to determine differences in outcomes based on

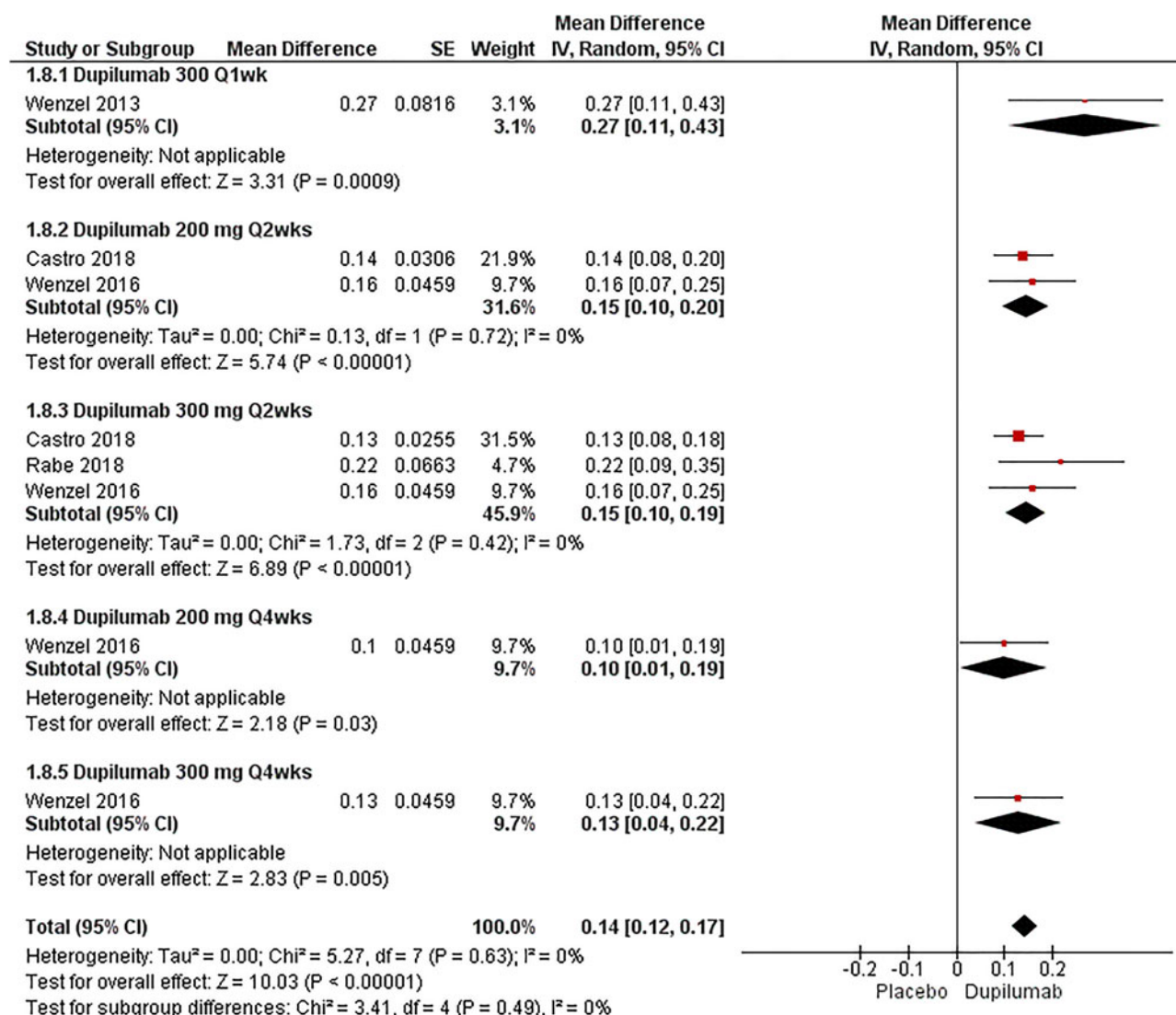


Figure 5. Forest plot for absolute mean difference changes in the forced expiratory volume at 1 s (FEV1) measured by liters.

specific dupilumab dose, which will be an area for future study. Previous RCTs have hinted at the idea that effect of dupilumab may be dose-dependent. For instance, Castro et al. demonstrated that higher doses of dupilumab (300 mg every 2 weeks vs 200 mg every 2 weeks) are needed to achieve significant improvement in the annualized rate of severe asthma exacerbation for patients with baseline eosinophil count between 150–300 cells/mm³ [11]. Wenzel et al. also showed that higher doses and more frequent doses of dupilumab (200–300 mg every 2 weeks vs every 4 weeks) achieve more significant reduction in severe asthma exacerbations in patients with baseline eosinophil count <300 cells/mm³ [13].

The effect dupilumab has on reducing severe asthma exacerbations is likely complex and related to eosinophil count, among other factors. In our

subgroup analysis of patients with eosinophil counts <150 cells/mm³, the annualized rate of severe asthma exacerbations in those taking dupilumab did not significantly differ from those taking placebo, despite the significant improvements in FEV1. This finding may indicate a potential role of dupilumab in suppressing eosinophilia-related asthma exacerbations only in patients with higher baseline eosinophilia (i.e. >150 cell/mm³). The elevated eosinophil counts may potentiate a dual-blocking effect of dupilumab on both IL-4 and IL-13. Perhaps higher doses of dupilumab may result in symptomatic improvement for those with low eosinophil counts (<150 cells/mm³), but this has yet to be studied. The improved FEV1 observed in our analysis despite the low baseline eosinophil count (<150 cell/mm³) may suggest a potential effect of dupilumab on airway remodeling and reduced mucous production induced by IL-13,

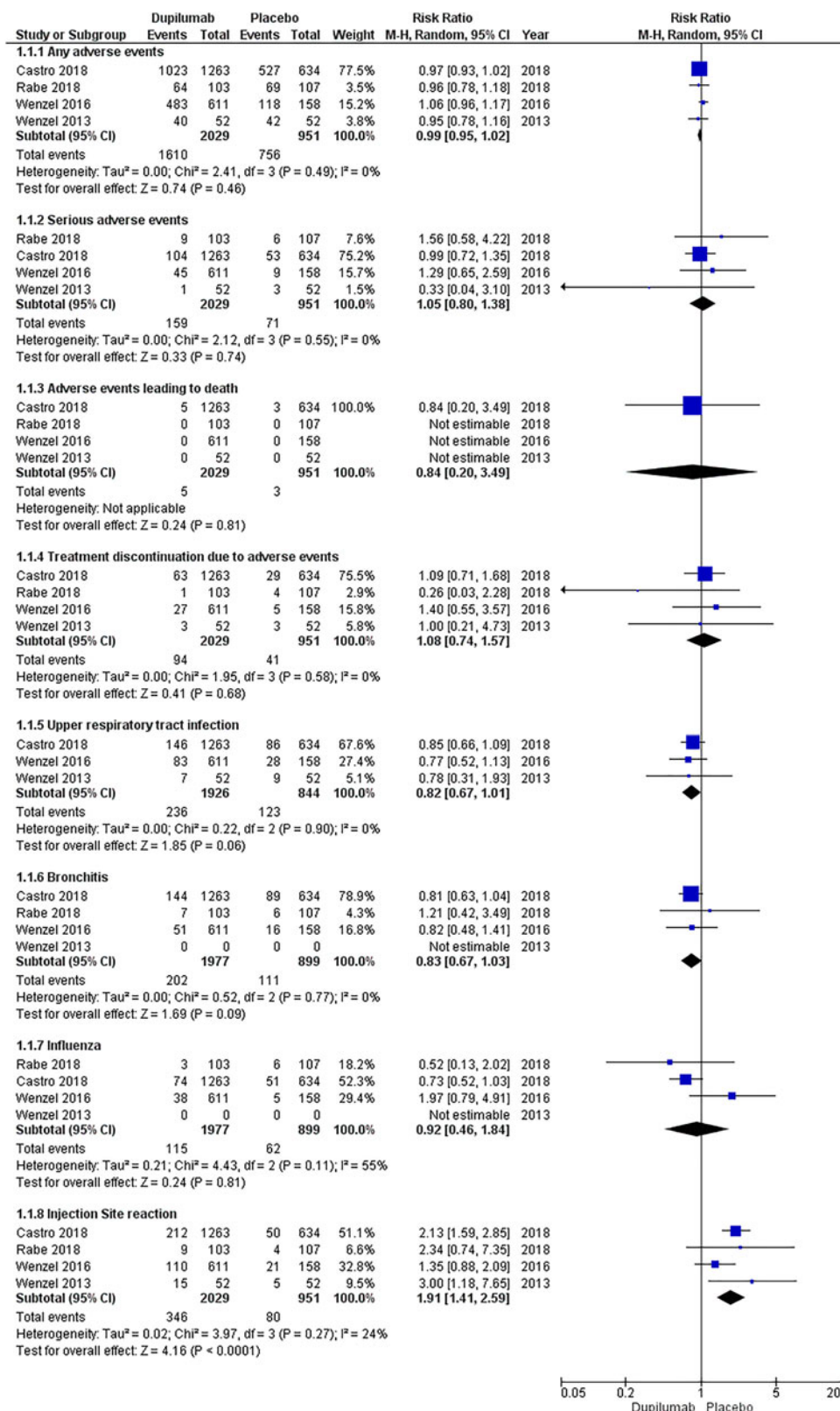


Figure 6. Forest plot for adverse events.

which is unrelated to the eosinophilia-associated Th-2 response.

In this era of personalized medicine, it will be important to determine the effect size of dupilumab

across eosinophil counts and the subsequent dose-adjustments depending on this effect.

In the LIBERTY ASTHMA VENTURE trial, which evaluated the role of dupilumab in glucocorticoid

dependent asthma, there was a reduced use of oral glucocorticoids and severe asthma exacerbations as well as improved FEV1 when dupilumab 300 mg was used every 2 weeks compared to placebo [12]. In contrast to our analysis, the reduction in the annualized rate of severe asthma exacerbations in this trial remained significant regardless of eosinophil count, including patients with eosinophil count <150 cells/mm³. Whether the use of oral (rather than inhaled) glucocorticoids have potentiated the dupilumab blocking effects on IL-4 and IL-13 will also need further assessment.

In addition to dupilumab, multiple monoclonal antibodies targeting various elements of the Th-2-mediated immune response have been approved for the treatment of severe uncontrolled asthma [15]. Reslizumab, mepolizumab and benralizumab are monoclonal antibodies directed toward IL-5 signal transduction by binding IL-5 subunits or its receptor [16–18]. Many RCTs have proven the efficacy of these monoclonal antibodies in asthmatic patients with high eosinophil count [19–25]. In contrast to other biologics, dupilumab has a dual blocking effect on IL-4 and IL-13, which could explain its broader treatment effect. However, further adequately powered RCTs are needed to compare these biologics and to establish the best regimen depending on baseline eosinophil count.

Limitations

There are several limitations in the present meta-analysis. First, there was varied duration of follow-up in the included clinical trials (20–64 weeks). Despite this, subgroup analyses did not show significant P interaction. Second, the inclusion criteria differed among the included studies. One study included only oral glucocorticoid-dependent asthmatics while other studies included uncontrolled asthmatics using only high-dose inhaled glucocorticoids and LABAs. Third, two of the included studies represented phase 3 trials, one was a phase 2 A trial and one was a pivotal phase 2B trial. Fourth, dupilumab was given in different doses and frequencies across the included trials, and not all trials reported their outcomes with mention of respective eosinophil counts. In lieu of these limitations, we found that higher and shorter interval dosing regimens resulted in better outcomes for patients, especially those with lower baseline eosinophil count (150 – 300 cells/mm³).

Conclusions

In patients with uncontrolled asthma on inhaled glucocorticoids and LABAs and in those patients who require oral glucocorticoids despite inhaler therapy to control their symptoms; the addition of dupilumab is associated with a reduced rate of severe asthma exacerbations and with improved FEV1 when compared to placebo regardless of baseline eosinophil count (less and more than 300 cell/mm³). The reduction of annualized severe asthma exacerbations between patients taking dupilumab and those taking placebo, however, was not statistically significant in a subset of patients with baseline eosinophil count <150 cells/mm³, despite the significant improvements in their FEV1. There were no significant differences between both groups with regard to adverse events, with the exception being increased injection site reactions in patients taking dupilumab. Further adequately powered RCTs will be needed to establish the best dupilumab dose in relation to baseline eosinophil counts. In addition, future studies should seek to evaluate the efficacy, safety and cost of dupilumab in comparison with other available monoclonal antibodies.

Disclosure statement

No conflicts of interests.

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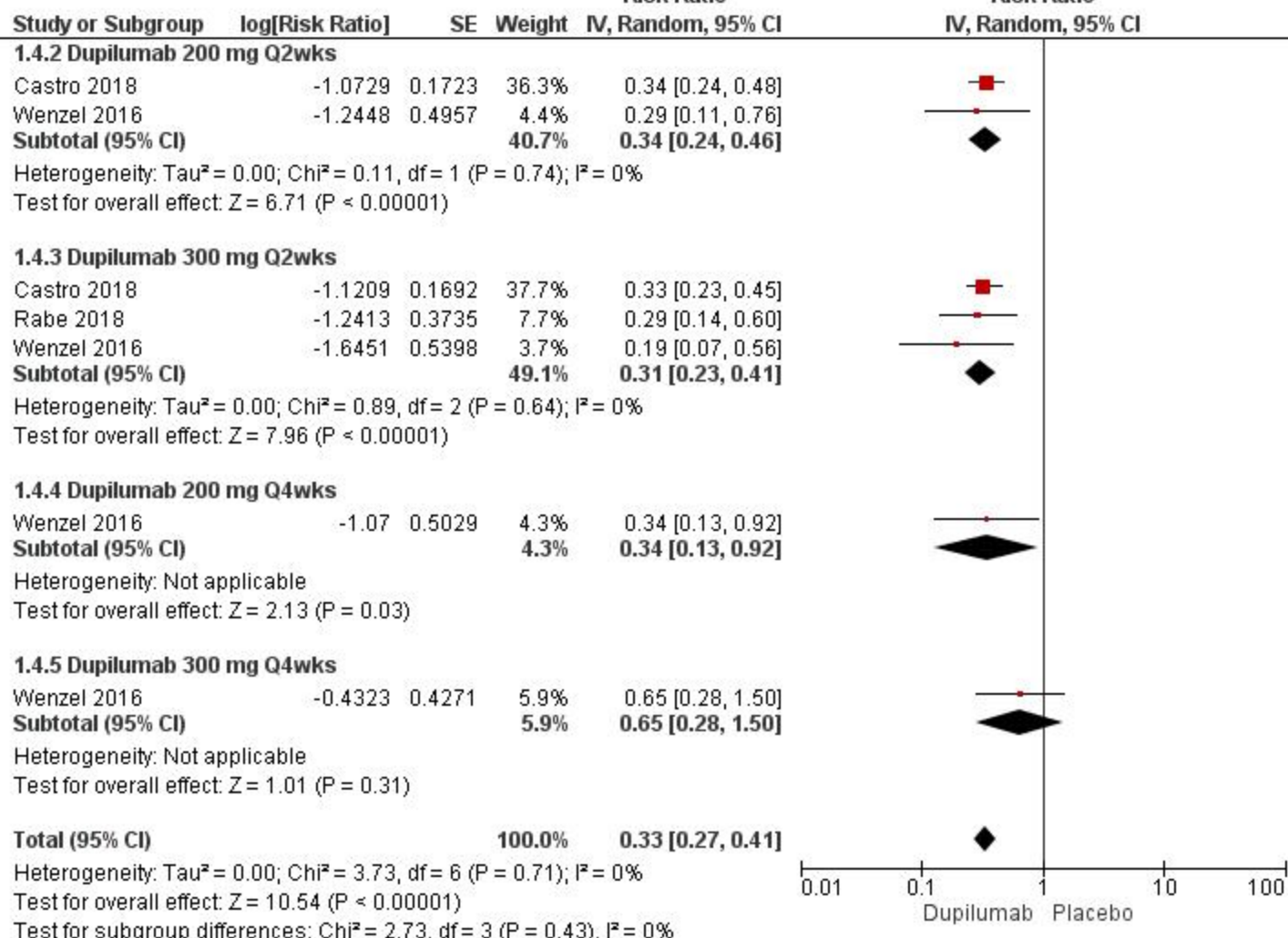
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Risk Ratio

Risk Ratio



Risk Ratio

Risk Ratio

Study or Subgroup	log[Risk Ratio]	SE	Weight	IV, Random, 95% CI	Year
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IV, Random, 95% CI

1.5.2 Dupilumab 200 mg Q2wks

Wenzel 2016	-1.127	0.4245	13.4%	0.32 [0.14, 0.74]	2016
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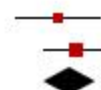
Subtotal (95% CI)

Heterogeneity: Not applicable

Test for overall effect: $Z = 2.65$ ($P = 0.008$)**1.5.3 Dupilumab 300 mg Q2wks**

Wenzel 2016	-0.9138	0.3758	17.2%	0.40 [0.19, 0.84]	2016
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Rabe 2018	-0.607	0.2797	31.0%	0.54 [0.31, 0.94]	2018
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Subtotal (95% CI)Heterogeneity: $\text{Tau}^2 = 0.00$; $\text{Chi}^2 = 0.43$, $df = 1$ ($P = 0.51$); $I^2 = 0\%$ Test for overall effect: $Z = 3.19$ ($P = 0.001$)**1.5.4 Dupilumab 200 mg Q4wks**

Wenzel 2016	-0.5604	0.3618	18.5%	0.57 [0.28, 1.16]	2016
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Subtotal (95% CI)

Heterogeneity: Not applicable

Test for overall effect: $Z = 1.55$ ($P = 0.12$)**1.5.5 Dupilumab 300 mg Q4wks**

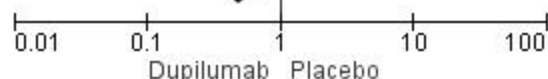
Wenzel 2016	-0.4652	0.3488	19.9%	0.63 [0.32, 1.24]	2016
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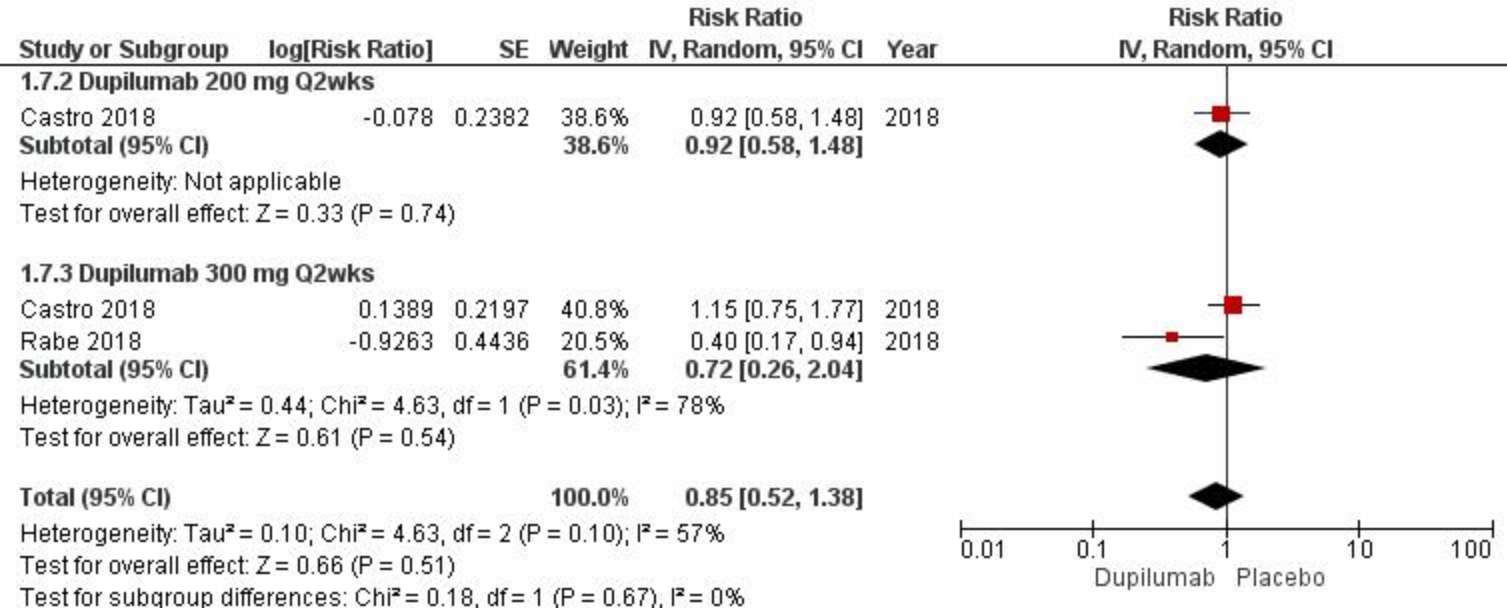
Subtotal (95% CI)

Heterogeneity: Not applicable

Test for overall effect: $Z = 1.33$ ($P = 0.18$)**Total (95% CI)**

100.0% 0.50 [0.37, 0.68]

Heterogeneity: $\text{Tau}^2 = 0.00$; $\text{Chi}^2 = 2.05$, $df = 4$ ($P = 0.73$); $I^2 = 0\%$ Test for overall effect: $Z = 4.45$ ($P < 0.00001$)Test for subgroup differences: $\text{Chi}^2 = 1.62$, $df = 3$ ($P = 0.66$), $I^2 = 0\%$ 



Mean Difference

Mean Difference

IV, Random, 95% CI

IV, Random, 95% CI

Study or Subgroup

Mean Difference

SE

Weight

IV, Random, 95% CI

1.9.2 Dupilumab 200 mg Q2wks

Castro 2018 0.21 0.0408 29.8% 0.21 [0.13, 0.29]

Wenzel 2016 0.16 0.0714 9.7% 0.16 [0.02, 0.30]

Subtotal (95% CI) 39.5% **0.20 [0.13, 0.27]**Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.37$, $df = 1$ ($P = 0.54$); $I^2 = 0\%$ Test for overall effect: $Z = 5.58$ ($P < 0.00001$)**1.9.3 Dupilumab 300 mg Q2wks**

Castro 2018 0.24 0.0408 29.8% 0.24 [0.16, 0.32]

Rabe 2018 0.32 0.1122 3.9% 0.32 [0.10, 0.54]

Wenzel 2016 0.16 0.0765 8.5% 0.16 [0.01, 0.31]

Subtotal (95% CI) 42.2% **0.23 [0.16, 0.30]**Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.54$, $df = 2$ ($P = 0.46$); $I^2 = 0\%$ Test for overall effect: $Z = 6.75$ ($P < 0.00001$)**1.9.4 Dupilumab 200 mg Q4wks**

Wenzel 2016 0.16 0.0765 8.5% 0.16 [0.01, 0.31]

Subtotal (95% CI) 8.5% **0.16 [0.01, 0.31]**

Heterogeneity: Not applicable

Test for overall effect: $Z = 2.09$ ($P = 0.04$)**1.9.5 Dupilumab 300 mg Q4wks**

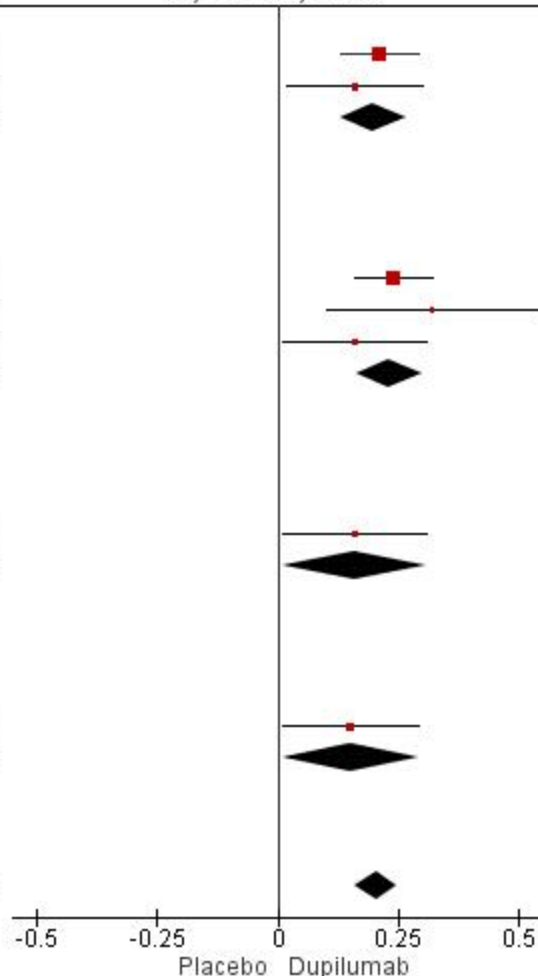
Wenzel 2016 0.15 0.0714 9.7% 0.15 [0.01, 0.29]

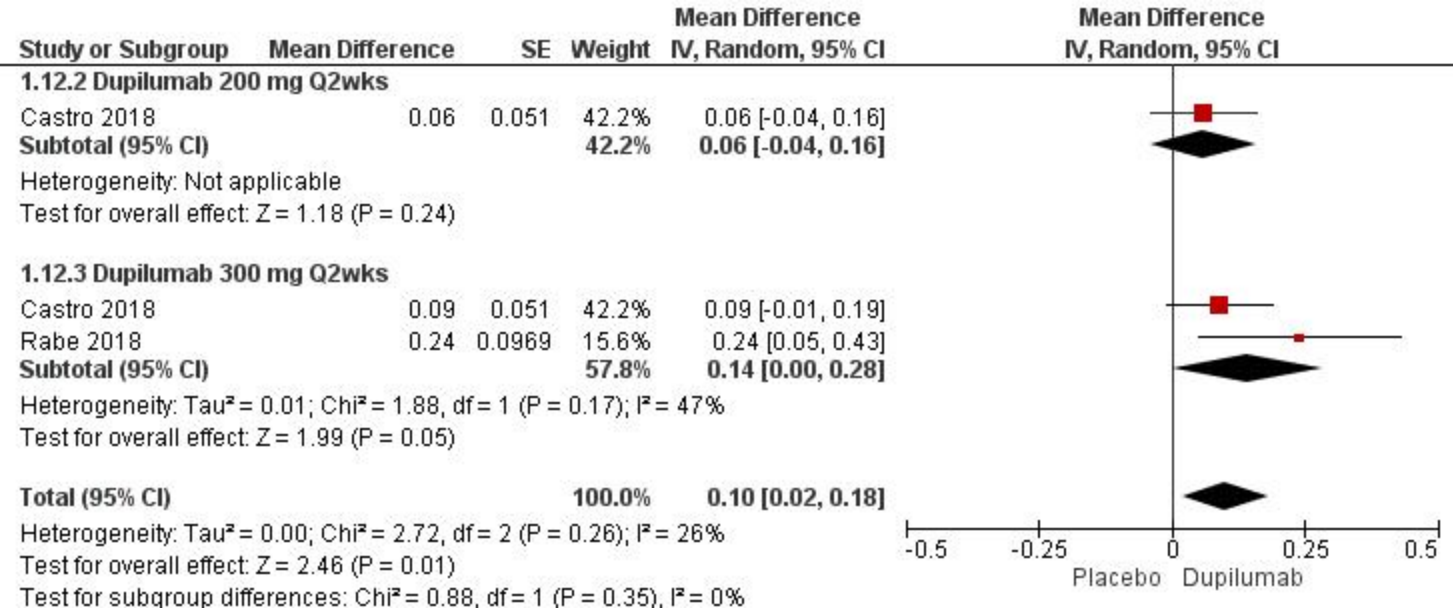
Subtotal (95% CI) 9.7% **0.15 [0.01, 0.29]**

Heterogeneity: Not applicable

Test for overall effect: $Z = 2.10$ ($P = 0.04$)**Total (95% CI)**

100.0%

0.20 [0.16, 0.25]Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.48$, $df = 6$ ($P = 0.75$); $I^2 = 0\%$ Test for overall effect: $Z = 9.16$ ($P < 0.00001$)Test for subgroup differences: $\chi^2 = 1.57$, $df = 3$ ($P = 0.67$), $I^2 = 0\%$ 



Mean Difference

Mean Difference

IV, Random, 95% CI

IV, Random, 95% CI

Study or Subgroup

Mean Difference

SE

Weight

IV, Random, 95% CI

IV, Random, 95% CI

1.10.2 Dupilumab 200 mg Q2wks

Wenzel 2016 0.14 0.0561 21.1% 0.14 [0.03, 0.25]

Subtotal (95% CI) 21.1% **0.14 [0.03, 0.25]**

Heterogeneity: Not applicable

Test for overall effect: $Z = 2.50$ ($P = 0.01$)**1.10.3 Dupilumab 300 mg Q2wks**

Rabe 2018 0.13 0.0765 11.3% 0.13 [-0.02, 0.28]

Wenzel 2016 0.14 0.0561 21.1% 0.14 [0.03, 0.25]

Subtotal (95% CI) 32.4% **0.14 [0.05, 0.23]**Heterogeneity: $\text{Tau}^2 = 0.00$; $\text{Chi}^2 = 0.01$, $df = 1$ ($P = 0.92$); $I^2 = 0\%$ Test for overall effect: $Z = 3.02$ ($P = 0.003$)**1.10.4 Dupilumab 200 mg Q4wks**

Wenzel 2016 0.12 0.0561 21.1% 0.12 [0.01, 0.23]

Subtotal (95% CI) 21.1% **0.12 [0.01, 0.23]**

Heterogeneity: Not applicable

Test for overall effect: $Z = 2.14$ ($P = 0.03$)**1.10.5 Dupilumab 300 mg Q4wks**

Wenzel 2016 0.1 0.051 25.5% 0.10 [0.00, 0.20]

Subtotal (95% CI) 25.5% **0.10 [0.00, 0.20]**

Heterogeneity: Not applicable

Test for overall effect: $Z = 1.96$ ($P = 0.05$)**Total (95% CI)****100.0%****0.12 [0.07, 0.17]**Heterogeneity: $\text{Tau}^2 = 0.00$; $\text{Chi}^2 = 0.40$, $df = 4$ ($P = 0.98$); $I^2 = 0\%$ Test for overall effect: $Z = 4.83$ ($P < 0.00001$)Test for subgroup differences: $\text{Chi}^2 = 0.38$, $df = 3$ ($P = 0.94$), $I^2 = 0\%$ 