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ORIGINAL ARTICLE

Comparing the efficacy and safety of low, medium, and high dosages of selexipag for treating pulmonary hypertension: A systematic review and meta-analysis

Shang Wang[1] | Yi Yan[2] | Jian Zhang[3] | Ping Yuan[1] | Ci-Jun Luo[1] | Hong-Ling Qiu[1] | Hui-Ting Li[1] | Jian Xu[1] | Lan Wang[1] | Tian-Lan Li[4] | Rong Jiang[1]

[1]Department of Cardio-Pulmonary Circulation, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, China

[2]Heart Center and Shanghai Institute of Pediatric Congenital Heart Disease, Shanghai Children's Medical Center, National Children's Medical Center, Shanghai Jiaotong University School of Medicine, Shanghai, China

[3]Department of Respiratory and Critical Care Medicine, The 416 Hospital of Nuclear Industry, The Second Affiliated Hospital of Chengdu Medical College, Chengdu, China

[4]Department of Hematology, The Affiliated Hospital of Qingdao University, Qingdao, China

Correspondence
Lan Wang and Rong Jiang, Department of Cardio-Pulmonary Circulation, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, No. 507 Zhengmin Road, Yangpu District, Shanghai 200433, China.
Email: lanwang@tongji.edu.cn and listening39@163.com

Tian-Lan Li, Department of Hematology, The Affiliated Hospital of Qingdao University, Qingdao 266003, China.
Email: tianlan0919@163.com

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Abstract

Background: The maintenance dosage of selexipag is categorized as low, medium or high. In order to assess the efficacy and safety of different dosages of selexipag for the risk stratification of pulmonary arterial hypertension (PAH), we performed a systematic review and meta-analysis.

Methods: Studies assessing PAH risk stratification indices, such as the World Health Organization functional class (WHO-FC), six-minute walk distance (6MWD), N-terminal pro-B-type natriuretic peptide (NT-proBNP) level, right atrial pressure (RAP), cardiac index (CI) and mixed venous oxygen saturation (SvO_2), were included.

Results: Thirteen studies were included. Selexipag led to improvements in the 6MWD (MD: 24.20 m, 95% CI: 10.74–37.67), NT-proBNP (SMD: −0.41, 95% CI: −0.79–0.04), CI (MD: 0.47 L/min/m^2, 95% CI: 0.17–0.77) and WHO-FC (OR: 0.564, 95% CI: 0.457–0.697). Subgroup analysis demonstrated that all three dosages improved the 6MWD. A moderate dosage led to improvements in the CI (MD: 0.30 L/min/m^2, 95% CI: 0.15–0.46) and WHO-FC (OR: 0.589, 95% CI: 0.376–0.922). Within 6 months of treatment, only the WHO-FC and CI were significantly improved (OR: 0.614, 95% CI: 0.380–0.993; MD: 0.30 L/min/m^2, 95% CI: 0.16–0.45, respectively). More than 6 months of treatment significantly improved the 6MWD, WHO-FC and NT-proBNP (MD: 40.87 m, 95% CI: 10.97–70.77; OR: 0.557, 95% CI: 0.440–0.705; SMD: −0.61, 95% CI: −1.17–0.05, respectively).

Shang Wang, Yi Yan and Jian Zhang contributed equally to the article.

Conclusions: Low, medium, and high dosages of selexipag all exhibited good effects. When treatment lasted for more than 6 months, selexipag exerted obvious effects, even in the low-dosage group. This finding is important for guiding individualized treatments.

KEYWORDS
individualized treatments, meta-analysis, prostacyclin receptor agonist, risk stratification, systematic review

1 | INTRODUCTION

Progressive increase of pulmonary artery pressure (PAP) due to pulmonary artery bed remodeling in pulmonary arterial hypertension (PAH) patients can eventually lead to right heart failure, suggesting that PAH is a deadly disease.[1] Along with the therapeutic advances in the field of PAH, it has become increasingly important to recognize clinically relevant treatment goals that are associated with long-term outcomes. The basis for current treatment strategy is the severity of newly diagnosed PAH, which is evaluated by a multiparametric risk stratification tool and patients are divided as low-, intermediate- or high-risk according to their expected 1-year mortality.[2,3] This multiparametric risk-assessment tool includes six-minute walk distance (6MWD), the World Health Organization functional class (WHO-FC), N-terminal pro-B-type natriuretic peptide (NT-proBNP) level, cardiac index (CI), right atrial pressure (RAP) and mixed venous oxygen saturation (SvO_2). A simplified low-risk treatment goal includes WHO-FC I or II, 6MWD > 380 m, a decrease in or normalization of the NT-proBNP level, and hemodynamics with a RAP <8 mmHg and CI >2.5 L/min/min^2. In terms of the diagnosis and treatment of PH, the ESC/ERS Guidelines suggest using a three-level model to classify patients as being at a low, intermediate, or high risk of death, based on a multiparametric approach.[3,4]

Currently, in addition to classic PAH-targeted drugs, including prostacyclin and its derivatives, endothelin receptor antagonists and phosphodiesterase inhibitors are used. As the first orally administered prostacyclin receptor (IP receptor) agonist, selexipag has a nonprostanoid structure. The GRIPHON study, a placebo-controlled double-blind international phase III study of selexipag, and many other real-world studies have demonstrated that targeting the IP receptor leads to long-term efficacy with respect to clinical outcomes.[5–10] The recommended initial dose of selexipag is 200 μg twice daily, which is then increased by 200 μg twice daily weekly until the onset of associated unmanageable adverse effects, such as headache or gastrointestinal reaction, or until the maximum approved dose (1600 μg twice daily) is reached. Each twice-daily dosage is then decreased by 200 μg, and this reduced dosage is considered the maximum tolerated dosage for individual patients. In the GRIPHON study, the selexipag treated cohort was divided into low (200 and 400 μg b.i.d.), medium (600, 800 and 1000 μg b.i.d.) and high (1200, 1400 and 1600 μg b.i.d.) dosage groups. Low, medium and high dosages seem to have similar effects on long-term prognosis.[5] In other real-world studies, treatment intensity is more complex, with individualized maintenance including low, medium and high dosages, due to substantial individual heterogeneity. However, few studies have evaluated the effects of different doses of selexipag on risk stratification of PAH. Therefore, it remains unclear whether low-, moderate-, or high-dosage selexipag treatments can achieve or maintain a low-risk profile and yield beneficial treatment outcomes in patients with PAH.[3,4]

We therefore carried out a systematic review and meta-analysis to assess (i) the efficacy and safety of selexipag in the treatment of PAH patients and (ii) the efficacy of low, medium or high dosages of selexipag on the determinants of prognosis that are used to calculate the risk-assessment tool.

2 | METHODS

We acted according to a prespecified protocol (PROSPERO: CRD420022297798) and the PRISMA guidelines for reporting systematic reviews (Table S1).[11]

2.1 | Search strategy and selection criteria

From databases established before October 31, 2021, we retrieved 141, 179, 94 and 83 publications from the PubMed, Embase, Cochrane Library and Web of Science databases, respectively, for a total of 497 studies published in English. We excluded clinical trials that were published as abstracts or congress proceedings. Free text words and MeSH subject words were used as search terms. We used the standard Boolean operators (AND, OR) to link search terms, e.g., the search formula of PubMed was as follows: ((selexipag [Title/Abstract]) AND (pulmonary arterial hypertension [Text Word]) OR (pulmonary hypertension [Text Word])), and we also tracked the references for inclusion in the literature and related reviews. The inclusion criteria were as follows: (1) patients with pulmonary arterial hypertension who had not used selexipag before the study; and (2) observational studies comparing clinical data between the baseline and follow-up and randomized controlled trials (RCTs) comparing changes in clinical data between cases and controls or between experimental groups and control groups under the same conditions. We also used the following exclusion criteria: (1) case

reports, reviews, animal studies and pharmacological studies; and (2) analyses of data extracted from a large study.

2.2 | Data extraction and quality assessment

Independently, investigators (S.W. and Y.Y.) collected data, including the first author, year of publication, sample size, follow-up time, main outcome and adverse events. The pooled efficacy outcomes included parameters that are included in the simple risk stratification of PAH,[4] which included 6MWD, the WHO-FC, NT-proBNP, CI, RAP and SvO_2. We also evaluated other hemodynamic and echocardiographic parameters, such as pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (mPAP) and right atrial area (RAA). Subgroup analysis was performed based on the clinical classification of PAH, dosages [low (200 and 400 μg b.i.d.), medium (600, 800 and 1000 μg b.i.d.) or high (1200, 1400 and 1600 μg b.i.d.)] and treatment time. To avoid double-counting data, when patients in an included study were also described in the GRIPHON study, we used their data from the GRIPHON study.[5] If we could not extract the relevant data from the GRIPHON study,[5] we used articles derived from GRIPHON studies.[8,12,13] As for quality assessments, the Newcastle–Ottawa quality assessment scale was used for cohort studies and the Cochrane collaboration tool was used for RCTs.

2.3 | Data analysis

The risk ratio (RR) with a 95% confidence interval (CI) was used to evaluate dichotomous data, and weighted mean differences (WMDs or MDs) or standardized mean differences (SMDs) were used to study continuous variables. Fixed effects models were used to calculate the results of pooled analyses, while random effects models were used where there was a considerable amount of study heterogeneity. 0.5 was added to both trial arms when there were no occurrences seen. Statistical heterogeneity was evaluated using the I^2 statistic. STATA software 10.0 (StataCorp, College Station, TX, USA) and RevMan 5.2 (The Cochrane Collaboration, Copenhagen, Denmark) were used to conduct the statistical analyses. All *P* values were two-tailed, and $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Eligible studies

497 potentially relevant studies were identified, including 179 from Embase, 141 from PubMed, 83 from Web of Science and 94 from the Cochrane Library. After removing 216 duplicate studies, 281 studies remained for further analysis. 188 studies were excluded (37 pathological studies, 20 conference/meeting abstracts, 47 case reports, 59 reviews, 5 comments and letters, 22 cell/animal studies, 2 editorials/letters, and 1 protocol) after screening the titles and abstracts. Ultimately, 13 studies were recruited in the meta-analysis, including 7 RCTs[5,8,12–16] and 6 cohort studies[10,17–21] (Figure 1).

Figure S2 shows the quality assessments of the RCTs. The Cochrane Bias Risk Assessment showed that all RCTs were graded as A and had a small risk of various biases, thus indicating high-quality study designs. The Newcastle–Ottawa Quality Assessment Scale (NOS) was used to assess the risk of bias in the included cohort studies (Table S2).[22] The NOS evaluates the quality of studies across 3 parameters: selection, comparability, and exposure/outcome. A score of ≥7, 4–6 and <4 are defined as high quality, moderate quality, and low quality, respectively.[22] The characteristics of the recruited studies are showed in Table 1.

3.2 | Risk stratification for pulmonary arterial hypertension

3.2.1 | 6MWD

In 10 studies that compared 6MWD results between baseline and post treatment,[8,10,14–21] selexipag therapy was found to improve 6MWD results (MD: 24.20 m, $p = 0.0004$), and there was a small amount of heterogeneity ($I^2 = 10\%$, $p = 0.35$) (Figure 2A). With regard to different dosages, Jae Yong Choi's study found that low dosages of selexipag improved the 6MWD results by 64.60 m (95% CI: 6.24–122.96 m, $p = 0.03$).[21] Pooled analysis showed that moderate and high dosages of selexipag improved the 6MWD results by 16.38 m (95% CI: 2.68–30.08 m, $p = 0.02$, $I^2 = 0\%$) and 58.46 m (95% CI: 16.06–100.86 m, $p = 0.007$, $I^2 = 53\%$), respectively (Figure 2B). With regard to treatment time, selexipag therapy did not improve the 6MWD results within 6 months ($p = 0.11$); after more than 6 months of treatment, selexipag therapy led to a significant improvement in 6MWD results, and there was moderate heterogeneity (MD: 40.87 m, 95% CI: 10.97–70.77 m, $p = 0.007$, $I^2 = 55\%$) (Figure 2C). Subgroup analysis based on the clinical classification of PH showed that selexipag therapy improved the 6MWD results by 25.31 m (95% CI: 7.82–42.79, $p = 0.005$) in Group 1 PAH, 22.72 m in both Group 1 PAH and Group 4 PH (95% CI: −1.25–46.68, $p = 0.06$), and 14.08 m in Group 4 PH (95% CI: −15.20–43.36, $p = 0.35$). Mild or no heterogeneity was observed across these subgroup analyses ($I^2 = 49\%$, $p = 0.005$; $I^2 = 0\%$, $p = 0.06$; $I^2 = 0\%$, $p = 0.74$, respectively) (Figure S3A). In RCTs,[8,14–16] compared with placebo, selexipag led to significant improvements in 6MWD results by 41.18 m; there was no heterogeneity (95% CI: 15.59–66.77 m, $p = 0.002$) (Figure S3B). Our analysis showed that low, moderate and high selexipag all improved 6MWD, as did a therapy duration of more than 6 months.

3.2.2 | WHO-FC

Selexipag improved the WHO-FC in eight studies.[5,10,15–19,21] Ordered logistic regression showed that the odds ratio (OR) of the WHO-FC was significantly reduced by 0.564 after treatment (95%

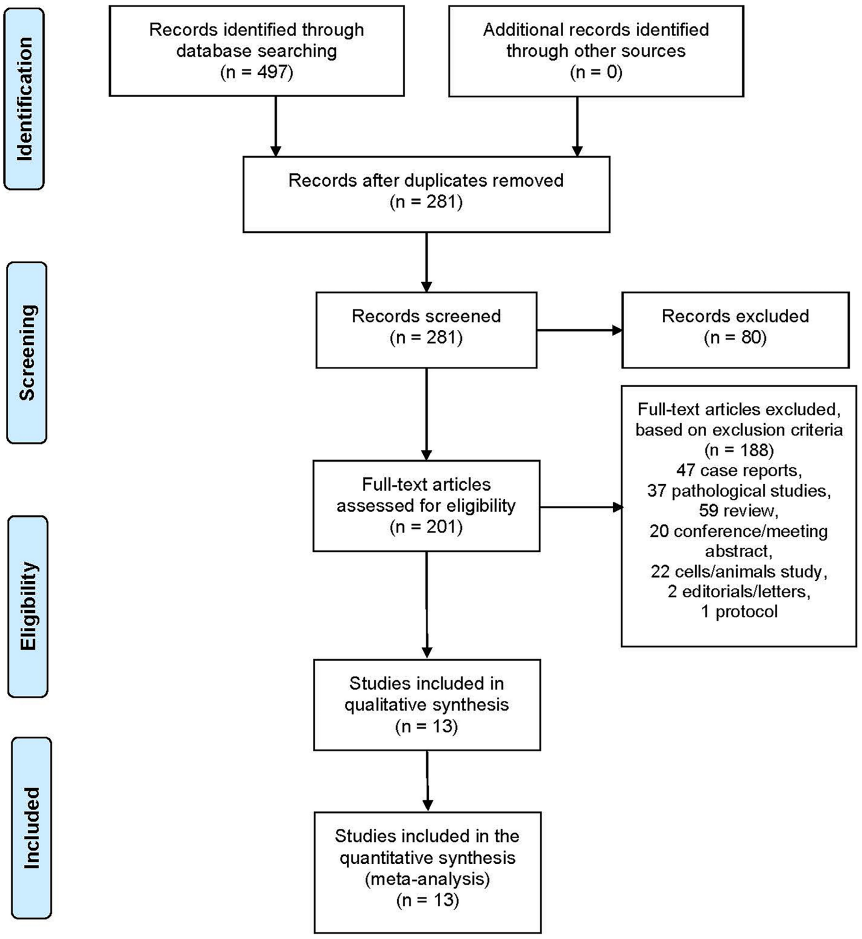

FIGURE 1 Search flow diagram for studies included in the meta-analysis.

CI: 0.457–0.697, $p < 0.0001$) (number of observations = 1404, LR chi^2 (1) = 28.55, prob > chi^2 = 0.0000, log likelihood = −1102.75). Within 6 months of selexipag treatment, the OR of the WHO-FC was significantly reduced by 0.614 (95% CI: 0.380–0.993, $p < 0.047$); after 6 months of treatment, the OR of the WHO-FC was significantly reduced by 0.557 (95% CI: 0.440–0.705, $p < 0.0001$). Jae Young Choi 2021[21] showed that before selexipag treatment, there were 0, 7, 5, and 0 patients with WHO-FC I, II, III and IV, respectively; after low-dosage treatment, there were 4, 4, 4, and 0 patients with WHO-FC I, II, III and IV, respectively. In addition, Katrin Milger[17] found that before selexipag treatment, there were 0, 9, 11, and 0 patients with WHO-FC I, II, III and IV, respectively. However, after low-dosage treatment, there were 0, 15, 4, and 1 patients with WHO-FC I, II, III and IV, respectively. At moderate dosages of selexipag, ordered logistic regression showed that the OR of the WHO-FC was 0.589 (95% CI: 0.376–0.922, $p < 0.0001$).

3.2.3 | NT-proBNP

Across 7 studies,[5,15–19,21] selexipag therapy was found to reduce NT-proBNP levels (SMD: −0.41, 95% CI: −0.79–0.04, $p = 0.03$) with a high level of heterogeneity ($I^2 = 77\%$, $p = 0.0002$) (Figure 3A). According to the subgroup analysis based on dosages, the low, medium and high dosage groups did not show significant reductions in the level of NT-proBNP[13,15–19,21] (Figure 3B). Compared with baseline, the NT-proBNP level within 6 months of selexipag therapy was not reduced significantly (SMD: −0.08, 95% CI: −0.35–0.20 pg/mL, $p = 0.60$); after more than 6 months (median: 9.5 months, interquartile range [7.3 months, 16.5 months]), the NT-proBNP level significantly improved, with a moderate level of heterogeneity (SMD: −0.61, 95% CI: −1.17–0.05, $p = 0.03$, $I^2 = 85\%$) (Figure 3C). Across 3 RCTs,[5,15,16] compared with placebo, selexipag treatment significantly improved the NT-proBNP level; there was no heterogeneity (SMD: −0.23, 95% CI: −0.35–0.11, $p = 0.0003$, $I^2 = 0\%$) (Figure 3D). Based on the above results, we conclude that NT-proBNP is improved by long-term treatment with selexipag.

3.2.4 | Cardiac index (CI)

In 6 studies,[10,14–17,20] selexipag therapy was found to improve the CI (MD: 0.47 L/min/m^2, $p = 0.002$), and there was a moderate level of heterogeneity ($I^2 = 76\%$, $p = 0.0009$) (Figure 4A). With regard to different dosages, a moderate dosage of selexipag treatment improved the CI by 0.30 L/min/m^2, and there was no heterogeneity (95% CI: 0.15–0.46 L/min/m^2, $p = 0.0001$). In a pooled analysis of two studies, high-dosage

TABLE 1 Basic characteristics of the included literature.

Author year	Design type	Follow-up	Outcome measures	Results
Georg[19] 2020	$n=15$; Group 1[a], 3[b], 5[d]; CSS	4.5–20 w	WHO-FC, 6MWD, NT-proBNP, hemodynamics	↑ 6MWD, NT-proBNP, mRAP, mPAP/mSAP, etc.
Jae[21] 2021	$n=13$; Group 1[a] (CHD); CSS	12.3 ± 2.8 m	WHO-FC, 6MWD, echo, NT-proBNP, etc.	↑ 6MWD, TPG, etc. * NT-proBNP, etc.
Katrin[17] 2019	$n=26$; Group 1[a], 4[c]; CSS	149 ± 80 d	WHO-FC, 6MWD, pro-BNP, hemodynamics, echo, etc.	↑ pro-BNP, mRAP, etc. * 6MWD, TAPSE, RAA, mPAP, PAWP, CI, etc.
Masaharu[20] 2021	$n=26$; Group 1; CSS	72 w	WHO-FC, 6MWD, BNP, hemodynamics, echo, etc.	↑ 6MWD, BNP, mRAP, mPAP, CO, CI, PVR, TAPSE, RVS', RVESA. * PAWP, RAA, RVEDA, etc.
Maurice[8] 2019	$n=110$; Group 1[a] (CHD); RCT	26 w	WHO-FC, 6MWD, NT-proBNP, etc.	* 6MWD, NT-proBNP, etc.
Nobuhiro[10] 2017	$n=37$; Group 1[a]; CSS	16 w	WHO-FC, 6MWD, NT-proBNP, hemodynamics	↑ 6MWD, PVR, mPAP, CO, CI, etc. * mRAP, SvO_2, NT-proBNP, etc.
Silvia[18] 2019	$n=23$; Group 1[a], 4[c]; CSS	2–4 m & 221 d	WHO-FC, 6MWD, CPET, NT-proBNP, echo, QoL	↑ 6MWD, QoL, etc. * NT-proBNP, peak VO_2, TPG, LVEF, etc.
Vallerie[5] 2015	$n=1156$; Group 1[a]; RCT	26 w	Death or complications related to PAH	↑ Death or complications related to PAH.
Ge'rald[14] 2012	$n=43$; Group 1[a]; RCT	17 w	WHO-FC, 6MWD, NT-proBNP, hemodynamics	↑ mPVR, CI, RAP, SVR, etc. * NT-proBNP, Borg score, mPAP, PCWP, etc.
Nobuhiro[15] 2020	$n=28$; Group 4[c]; RCT	17 w	WHO-FC, 6MWD, NT-proBNP, hemodynamics	* 6MWD, PVR, CI, mPAP, TPR, etc.
Sean[12] 2018	$n=376$; Group 1[a]; RCT	26 w	WHO-FC, 6MWD, morbidity/mortality, etc.	↑ The risk of morbidity/mortality.
Sean[13] 2017	$n=334$; Group 1[a] (CTD); RCT	26 w	Morbidity/mortality, etc.	↑ The risk of morbidity/mortality
Takeshi[16] 2021	$n=78$; Group 4[c]; RCT	20 w	WHO-FC, 6MWD, NT-proBNP, Borg score, hemodynamics, etc.	↑ PVR, CI, TPR, SvO_2, Borg score, etc. * 6MWD, NT-proBNP, mPAP, mRAP, etc.

Note: ↑ represents a significant improvement in the measure compared with baseline or placebo. * represents no significant improvement in the measure compared with baseline or placebo.

[a]Group 1: pulmonary arterial hypertension.

[b]Group 3: pulmonary hypertension due to pulmonary disease and/or hypoxia.

[c]Group 4: chronic thromboembolic pulmonary hypertension.

[d]Group 5: unknown and/or multifactorial pulmonary hypertension.

Abbreviations: 6MWD, six-minute walk distance; BNP, brain natriuretic peptide; CHD, pulmonary arterial hypertension associated with congenital heart disease; CI, cardiac index; CO, cardiac output; CPET, cardiopulmonary exercise test; CSS, cross-sectional studies; CTD, pulmonary arterial hypertension associated with connective tissue disease; echo, echocardiography; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; QoL, Quality of life questionnaires, RAA, right atrial area; RCT, randomized controlled trial; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVS', right ventricular systolic excursion velocity; SvO_2, mixed venous oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; TPG, tricuspid pressure gradient; TPR, total pulmonary resistance; WHO-FC, World Health Organization functional class.

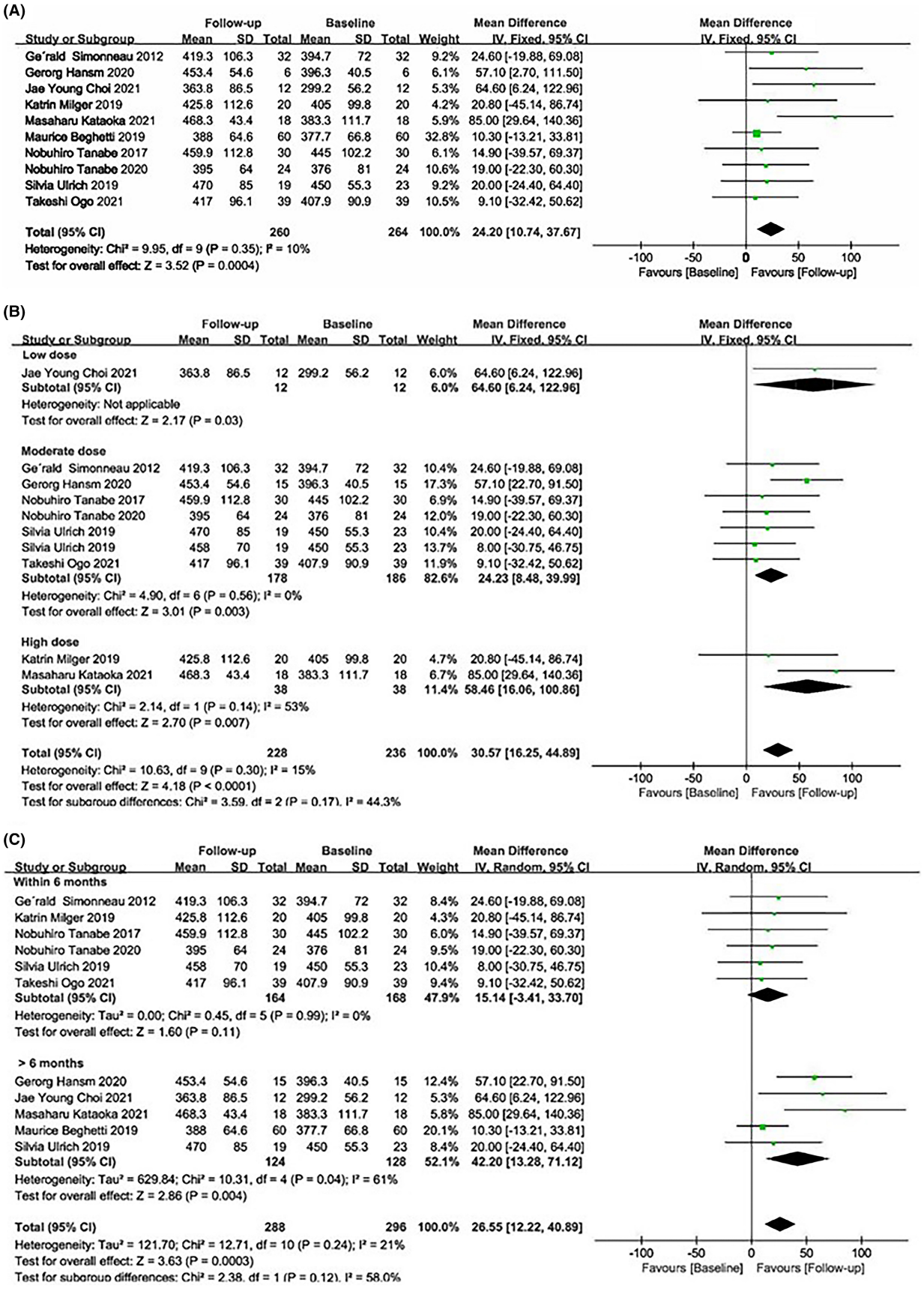

FIGURE 2 Changes in the 6MWD. (A), The effect of added selexipag on the 6MWD compared with baseline. (B), The effect of different dosages of selexipag on the 6MWD compared with baseline. (C), The effect of added selexipag on the 6MWD compared with baseline at different treatment times. 6MWD, six-minute walk distance.

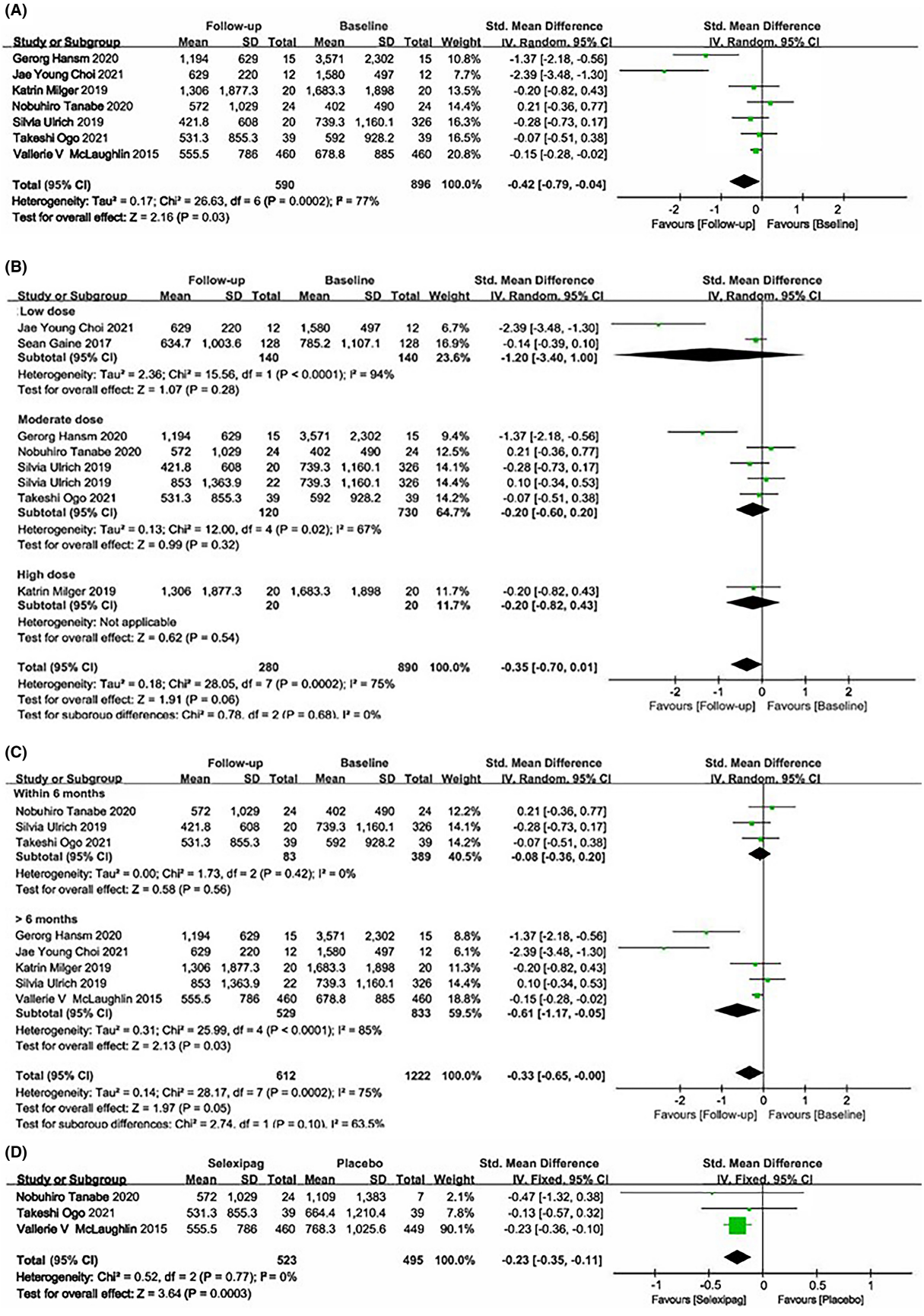

FIGURE 3 Changes in NT-proBNP levels. (A), The effect of added selexipag on NT-proBNP compared with baseline. (B), The effect of different dosages of selexipag on NT-proBNP compared with baseline. (C), The effect of added selexipag on NT-proBNP compared with baseline at different treatment times. (D), The effect of added selexipag on NT-proBNP compared with placebo. NT-proBNP, N-terminal pro-B-type natriuretic peptide.

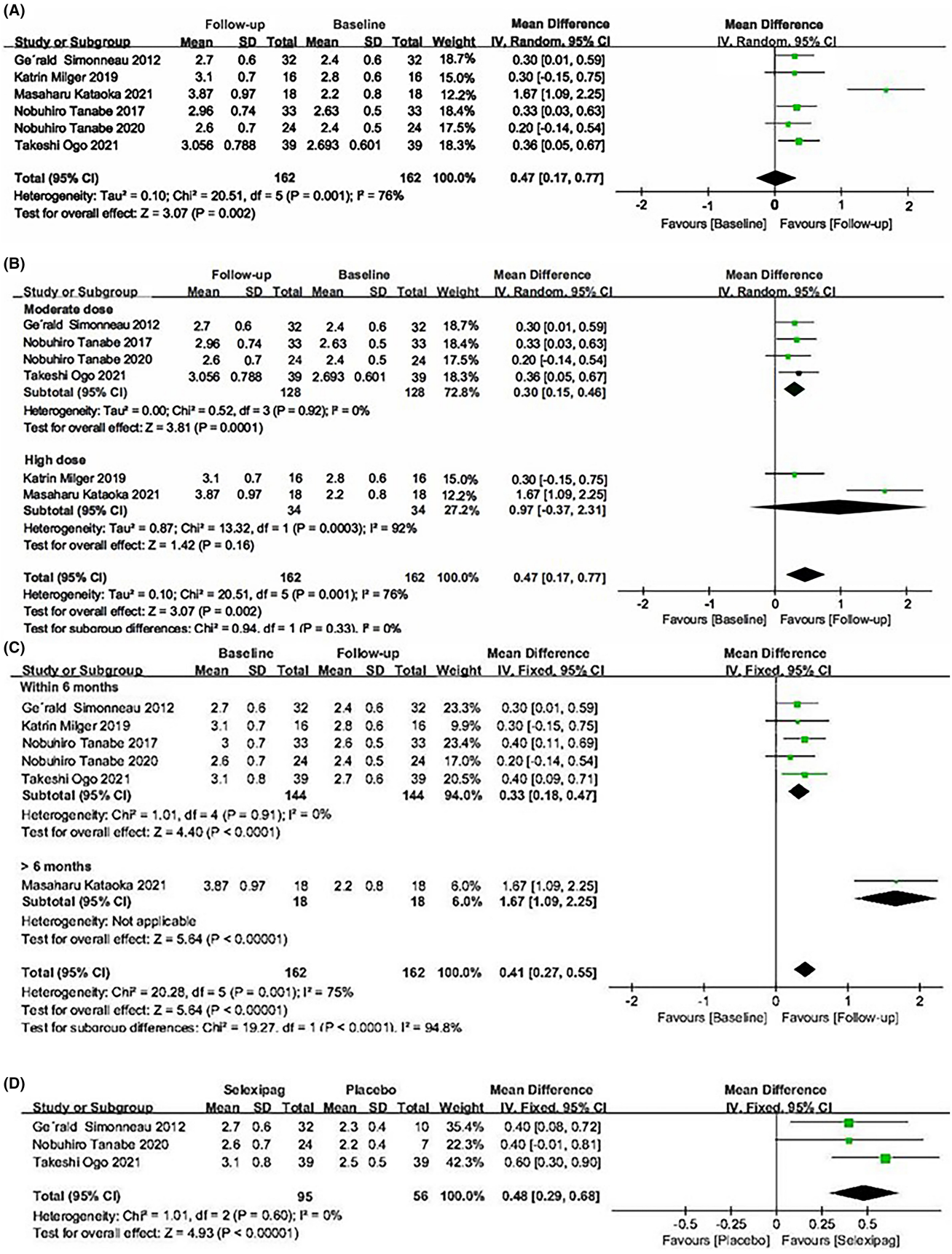

FIGURE 4 Changes in the CI. (A), The effect of added selexipag on the CI compared with baseline. (B), The effect of different dosages of selexipag on the CI compared with baseline. (C), The effect of added selexipag on the CI compared with baseline at different treatment times. (D), The effect of added selexipag on the CI compared with placebo. CI, cardiac index.

selexipag treatment did not significantly improve the CI (MD: 0.99 L/min/m^2, 95% CI: −0.39–2.36 L/min/m^2, $p=0.16$) (Figure 4B). Within 6 months of treatment, selexipag therapy significantly improved the CI by 0.30 L/min/m^2 (95% CI: 0.16–0.45 L/min/m^2, $p<0.0001$, $I^2=0\%$). Only Masaharu Kataoka's study evaluated the effect of long-term selexipag treatment on the CI[20]; after 441 (229–1103) days of treatment, selexipag therapy significantly improved the CI (MD: 1.70 L/min/m^2, 95% CI: 1.11–2.29 L/min/m^2, $p<0.00001$) (Figure 4C). In RCTs,[14–16] compared with placebo, selexipag significantly improved the CI by 0.48 L/min/m^2, and there was no heterogeneity ($p<0.00001$) (Figure 4D). In addition, in a pooled analysis of other parameters that reflect cardiac function, selexipag therapy was not found to improve the cardiac output (CO) or tricuspid annular plane systolic excursion (TAPSE) ($p=0.15$ and 0.38, respectively) (Figure S4A,B). In brief, selexipag therapy, especially at a moderate dosage and with short-term treatment can improve CI. However, whether selexipag improves CO and TAPSE still needs to be further explored.

3.2.5 | Right atrial pressure (RAP) and mixed venous oxygen saturation (SvO_2)

In a pooled analysis of 6 studies,[10,14–17,20] RAP was not significantly reduced after the implementation of selexipag therapy (MD: −0.30 mmHg, 95% CI: −1.01–0.41 pg/mL, $p=0.41$) (Figure 5A). In a subgroup analysis based on the treatment time, selexipag therapy did not improve RAP within 6 months of selexipag treatment. Only Masaharu Kataoka[20] explored the effect of long-term selexipag treatment on RAP. The implementation of selexipag treatment significantly reduced RAP after 441 (229–1103) days of treatment (MD: −2.17 mmHg, 95% CI: −3.83–0.51 pg/mL, $p=0.01$) (Figure 5B). In a pooled analysis of 4 studies,[10,15–17] SvO_2 did not significantly improve after the implementation of selexipag therapy (MD: 0.28%, 95% CI: −1.57%–2.13%, $p=0.77$) (Figure 5C). Therefore, more studies are needed to confirm the impact of selexipag on RAP and SvO_2 in PAH patients.

3.2.6 | Right atrial area (RAA)

In a pooled analysis of two articles,[17,20] the RAA did not significantly improve after the implementation of selexipag treatment ($p=0.91$) (Figure S4C).

3.3 | Other pulmonary hemodynamic parameters

3.3.1 | Mean pulmonary arterial pressure (mPAP)

Low-dosage and longer duration selexipag led to improvements in the mPAP. In 7 studies,[10,14–17,20,21] selexipag therapy was found to reduce the mPAP (MD: −5.27 mmHg, 95% CI: −8.96–1.58 mmHg, $p=0.005$) with a moderate level of heterogeneity ($I^2=60\%$) (Figure 6A). With regard to different dosages, a moderate dosage of selexipag treatment significantly reduced the mPAP by 2.37 mmHg, and there was no heterogeneity ($p=0.03$). Only Jae Young Choi[21] described the effect of low-dosage selexipag treatment on mPAP. Implementing low-dosage selexipag treatment significantly reduced the mPAP (MD: −13.8 mmHg, 95% CI: −21.86–5.74 mmHg, $p=0.0008$) (Figure 6B). Subgroup analysis showed no significant reduction in mPAP with high-dosage selexipag treatment ($p=0.14$) (Figure 6B). Regardless of the treatment length (i.e., less than 6 months or long-term treatment), selexipag therapy significantly reduced the mPAP by 2.41 mmHg (95% CI: −4.44–0.37 mmHg, $p=0.02$) and 15.11 mmHg (95% CI: −21.26–8.95 mmHg, $p<0.00001$), respectively, and no heterogeneity was observed. (Figure 6C).

3.3.2 | Pulmonary vascular resistance (PVR)

Across 6 studies,[10,14–17,20] selexipag therapy was found to reduce PVR (SMD: −0.59, 95% CI: −0.81–0.36, $p<0.00001$), and there was a low level of heterogeneity ($I^2=18\%$) (Figure 7A). With regard to different dosages, both moderate and high dosages of selexipag treatment significantly reduced PVR, and there was no heterogeneity (SMD: −0.47, 95% CI: −0.72–0.23, $p=0.0002$; SMD: −1.07, 95% CI: −1.59–0.56, $p<0.0001$, respectively) (Figure 7B). Regardless of the treatment length (i.e., less than 6 months or long-term treatment), selexipag therapy significantly reduced PVR, and there was no heterogeneity (SMD: −0.52, 95% CI: −0.75–0.28, $p<0.0001$; SMD: −1.26, 95% CI: −1.99–0.54, $p=0.0006$, respectively) (Figure 7C). To sum up, selexipag can improve PVR in PAH patients.

3.4 | Survival

In addition, three studies explored the influence of selexipag on the primary composite endpoint of morbidity/mortality[5,12,13]; all of these studies used data from the GRIPHON study. Overall, selexipag exerted a significant treatment effect compared to placebo (HR: 0.60; 95% CI: 0.46–0.78) in the GRIPHON study.[5] Subgroup analysis revealed that compared with placebo, the risk of morbidity/mortality was reduced by 40%, 47% and 37% with low, medium and high doses of selexipag, respectively. In addition, Sean[12] noted that among patients receiving double oral combination therapy, selexipag could reduce the risk of morbidity/mortality by 37% compared with placebo (HR: 0.63; 95% CI: 0.44–0.90).

And similar effects were observed in patients who were classified as WHO-FC II and III. In addition, Sean also examined the influence of selexipag on morbidity/mortality in CTD-PAH patients from the GRIPHON study and selexipag was found to be associated with a 41% reduction in morbidity/mortality compared with placebo (HR: 0.59; 95% CI: 0.41–0.85).[13] Similarly, in patients with PAH-systemic sclerosis and PAH-systematic lupus erythematosus, selexipag also reduced the risk of morbidity/mortality by 46% and 66%,

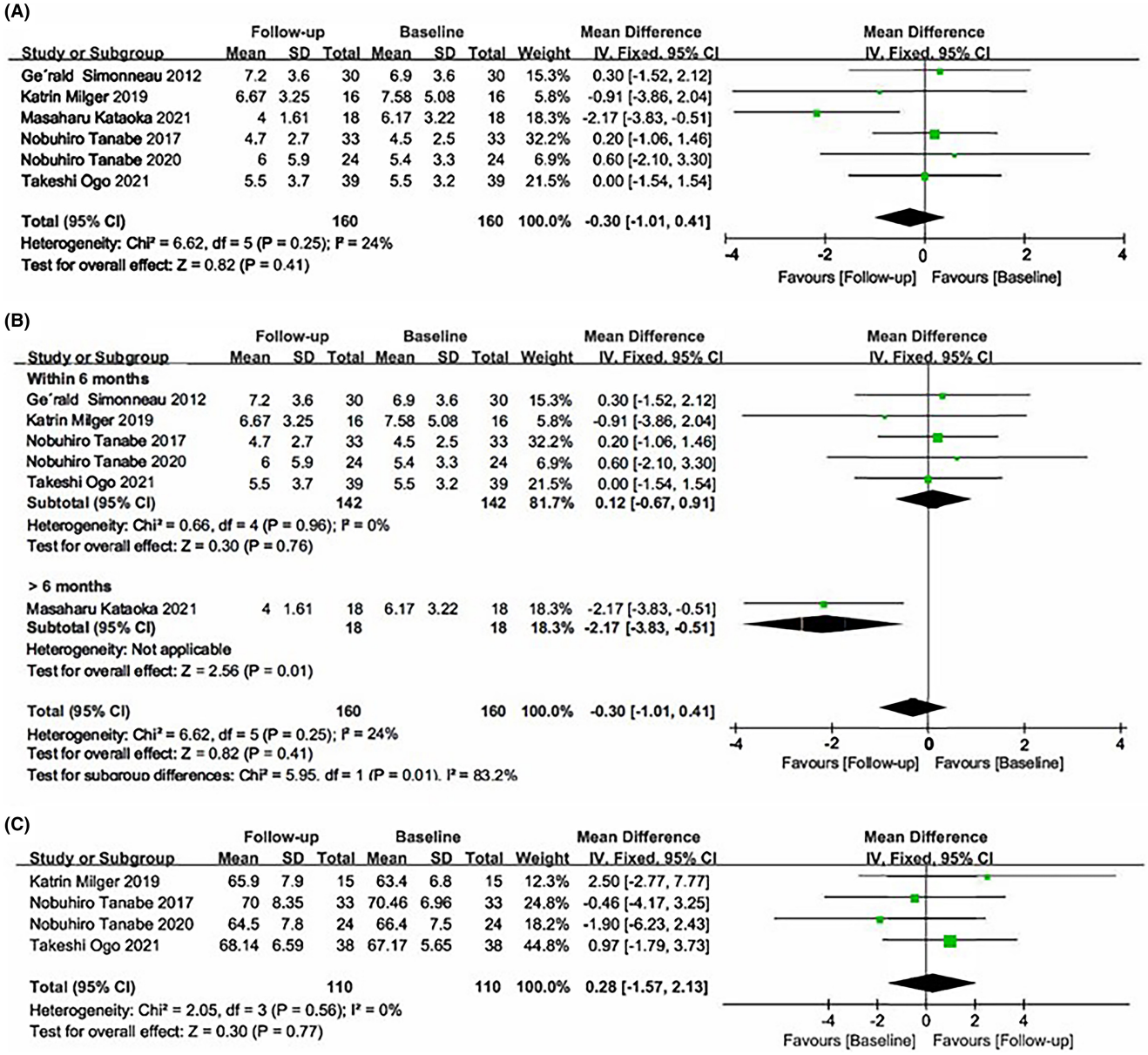

FIGURE 5 Changes in RAP and SvO_2. (A), The effect of added selexipag on RAP compared with baseline. (B), The effect of added selexipag on RAP compared with baseline at different treatment times. (C), The effect of added selexipag on SvO2 compared with baseline. RAP, right atrial pressure; SvO_2, mixed venous oxygen saturation.

respectively, compared with placebo. In total, selexipag can reduce the risk of the primary composite endpoint of morbidity/mortality.

3.5 | Safety

Among the patients taking selexipag, the most common adverse events included headache (64%), diarrhea (41%), nausea (33%), jaw pain (27%), worsening of PAH (22%), vomiting (17%), extremity pain (17%), low appetite (17%), arthralgia (17%), malaise, myalgia, dizziness and other symptoms (Figure S5A). However, except that we could not specify the therapeutic dose in the study of McLaughlin (2015), we found that the remaining included studies which discussed the safety of selexipag focused only on medium dosage treatment. In addition, the incidence of almost all recorded adverse reactions was higher in the selexipag group than in the placebo group, with the main adverse reactions being headache (96% vs. 32%), diarrhea (59% vs. 18%), and nausea (50% vs. 17%) (Figure S5B). Therefore, more evidence is needed to support the effect of selexipag on the safety of PAH patient, whether at medium or other doses.

4 | DISCUSSION

Our systematic review and meta-analysis further confirmed the efficacy and safety of selexipag for improving clinical,

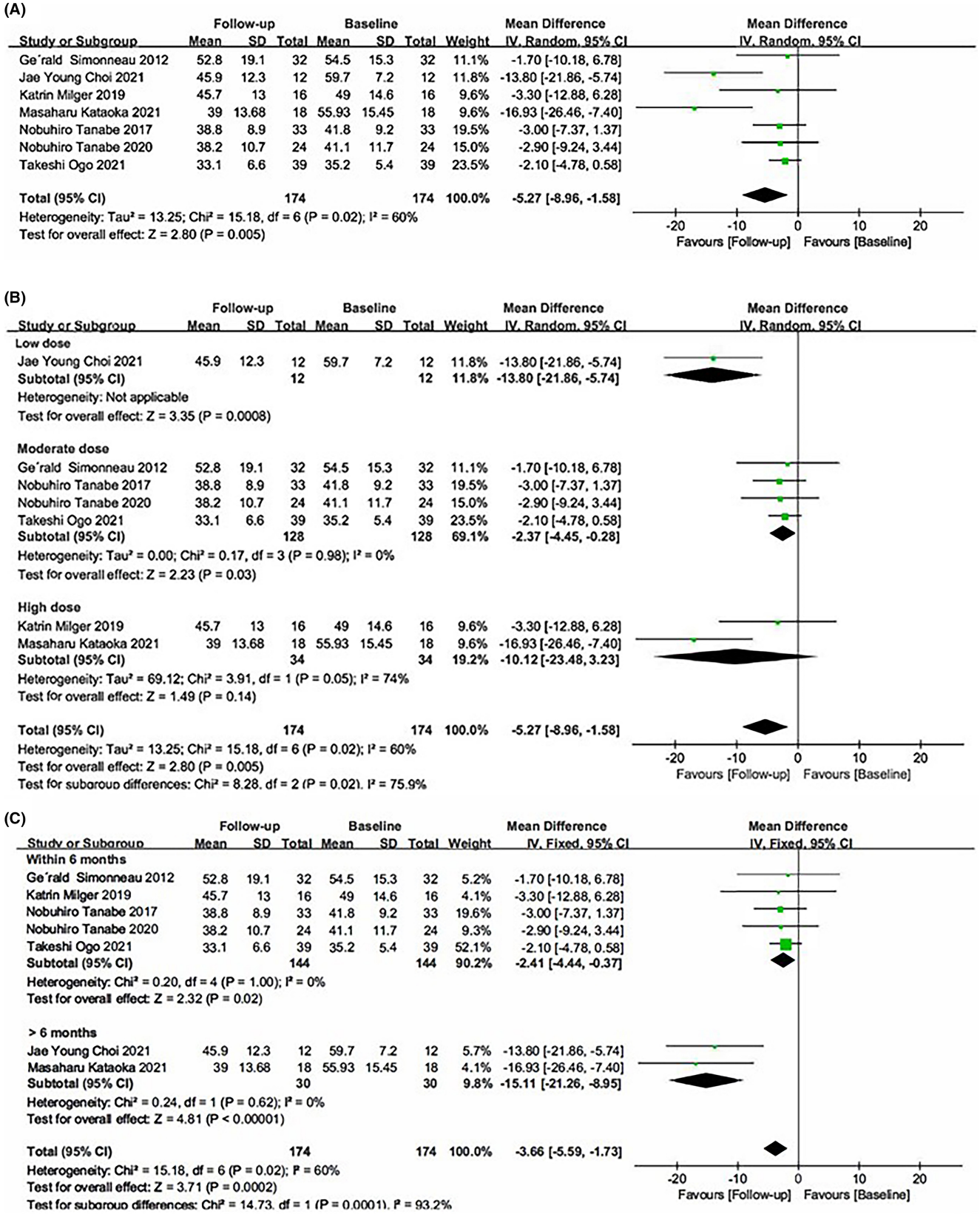

FIGURE 6 Changes in mPAP. (A), The effect of added selexipag on mPAP compared with baseline. (B), The effect of different dosages of selexipag on mPAP compared with baseline. (C), The effect of added selexipag on mPAP compared with baseline at different treatment times. mPAP, mean pulmonary arterial pressure.

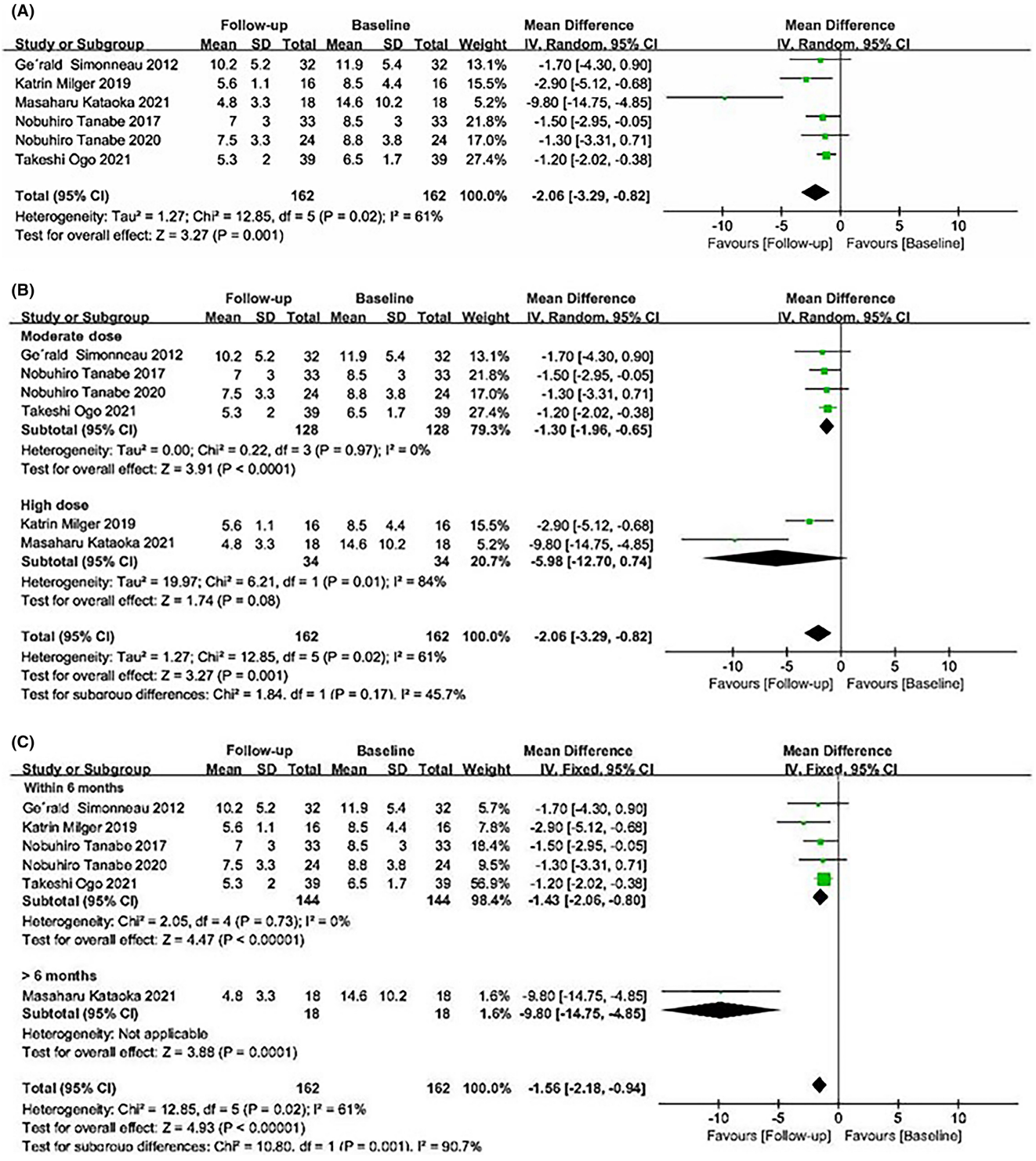

FIGURE 7 Changes in PVR. (A), The effect of added selexipag on PVR compared with baseline. (B), The effect of different dosages of selexipag on PVR compared with baseline. (C), The effect of added selexipag on PVR compared with baseline at different treatment times. PVR, pulmonary vascular resistance.

hemodynamic, and risk stratification parameters in PAH, which is consistent with previous research results. In addition, our research yielded new findings. Different dosages of selexipag can also exert beneficial effects. The efficacy of selexipag in treating PAH depends more on the treatment time than the treatment dosage; after more than 6 months of treatment, selexipag began to exert obvious effects, even in the low-dosage group. The longer the duration of selexipag therapy was, the more obvious the benefit for PAH patients. This finding provides important guidance for individualized clinical treatment.

As a supplement to Chen's meta-analysis of selexipag for treating PAH,[3] our study further confirmed that selexipag can lead to

improvements in the 6MWD, WHO-FC and PVR. However, in contrast to Chen's study,[3] more updated literature was included in the current meta-analysis. We also performed more detailed subgroup analyses, which focused on the impact of different doses (low, medium and high dosages) and treatment durations on the risk stratification of PAH. In the GRIPHON study, the low-, medium- and high-dosage groups showed similar effects on long-term prognosis. With regard to the primary endpoints, the high-dosage group seemed better than the low-dosage group.[5] In our meta-analysis, low-dosage selexipag led to improvements in the 6MWD and mPAP; moderate-dosage selexipag led to improvements in the 6MWD, WHO-FC, CI, mPAP and PVR; and high-dosage selexipag led to improvements in the 6MWD and PVR. We suggest that these differences are due to the following reasons: 1. Most of the included studies focused on a moderate dosage, and few studies examined low- or high-dosage groups. For example, in the low-dosage selexipag subgroup, only Jae Young Choi's study evaluated mPAP.[21] 2. Not all of the parameters for risk stratification, namely, 6MWD, the WHO-FC, NT-proBNP level, CI, RAP and SvO_2, could be sufficiently pooled for analysis. For example, for the moderate-dosage subgroup, only Katrin Milger's study evaluated the WHO-FC.[17]

We tried to conduct a subgroup analysis based on different treatment durations. The outcomes of selexipag therapy are significantly better when the therapy lasts for more than 6 months; this longer duration can lead to improvements not only in WHO-FC, CI, mPAP, and PVR, but also in NT-proBNP and RAP. Our findings indicate that the WHO-FC, CI, mPAP and PVR can improve within 6 months of selexipag therapy, but the 6MWD, NT-proBNP and RAP only improve after 6 months of selexipag therapy. There was no heterogeneity for any of the above-mentioned outcomes except the 6MWD after more than 6 months treatment of selexipag, which showed moderate heterogeneity. This was the highlight of our study, and this finding provides useful guidance for clinical practice. For example, some patients have good tolerance and can quickly reach high dosages, and some need more time to adapt to upregulation of selexipag's dosage, with dosage adjustments of 100 μg b.i.d. or q.d. or adjustment intervals of more than 1 week or even several months to reach a medium or high dosage. Moreover, some patients with PAH can tolerate only a low dosage. Our meta-analysis indicates that for patients with a poor tolerance who can only maintain a low dose of selexipag, a treatment time of more than 6 months can still lead to beneficial effects on PAH risk assessment. However, these findings should be interpreted with caution. Only Masaharu Kataoka examined the effect of long-term selexipag treatment on RAP and CI.[20] Therefore, the effects of long-term selexipag therapy on RAP and CI require further study.

As a multicenter, randomized, double-blind, parallel group, placebo-controlled, event-driven, phase III trial, the GRIPHON study also has its limitation. For example, we could not extract comprehensive clinical data from it, especially for subgroup analysis. To obtain sufficient data for analysis, we carried out a meta-analysis and systematic review of 6WMD, NT-ProBNP and survival data obtained from other studies that were derived from the GRIPHON study.[8,12,13]

One of the proven effective ways to treat PAH is to target prostaglandin I_2 (PGI_2); epoprostenol and PGI_2 derivatives with a prostanoid structure (treprostinil, beraprost, and iloprost) are used for this approach. Most other drugs have the disadvantages of short half-lives, requiring continuous infusion, subcutaneous injection, or frequent inhalation, but selexipag (Uptravi®) was developed as a selective prostacyclin IP receptor agonist with a long half-life. After oral administration of selexipag, it can be rapidly absorbed and hydrolyzed into the active metabolite MRE-269, which has a high binding affinity. The licensed GRIPHON trials and many real-world studies have revealed the clinical outcomes of selexipag in PAH patients, such as vasodilation, vascular smooth muscle cell proliferation inhibition, and a decreased risk of the composite endpoint of all-cause death or PAH-related complications (titrated combination therapy).[5,8,10,14,18,20,23] However, as an IP receptor agonist, selexipag has the common adverse effects of prostacyclin analogs, such as diarrhea, nausea, myalgia, and jaw pain. These typical side effects occurred frequently during dosage titration of selexipag. Consequently, we performed the dosage titration as recommended, starting with 200 μg twice daily and then increasing in 200 μg twice-daily increments every week until there was an intolerable adverse reaction. In the process of dosage titration, dosages are uptitrated or downtitrated until all side effects respectively increase or subside with supportive therapy, such as antiemetic, antidiarrheal, or analgesic drugs, or until the maximum tolerated dose is reached (the maximum maintenance dosage is 1600 μg twice daily). In the GRIPHON study individualized titration of selexipag was performed based on tolerability in patients with PAH. Compared with placebo, the hazard ratios of selexipag for the primary endpoint were 0.60 (95% CI 0.41–0.88; $p=0.0038$), 0.53 (95% CI 0.38–0.72; $p<0.0001$) and 0.64 (95% CI 0.49–0.82; $p=0.0002$) in the low, medium and high maintenance dosage groups, respectively. It seems that the low-, medium- and high-dosage groups showed similar effects on long-term prognosis. The high-dosage group also exhibited stronger improvements in the primary outcomes than the low-dosage group. Selexipag is usually uptitrated unless there are intolerable side effects. The nonevidence-based rationale for this approach is the assumption that side effects may predict a higher circulating dose of the drug and therefore be related to a beneficial treatment response. Katrin Milger's study[17] favors this assumption because the researchers found that patients who did not experience any side effects responded less significantly to selexipag treatment than those who did.

Although the indication for selexipag is WHO Group 1 PH, there are also exploratory studies on other PHs, such as CTEPH. Therefore, in our meta-analysis, we also performed a subgroup analysis based on different PH groups, which revealed that selexipag can improve the 6MWD results of not only WHO Group 1 PH patients but also WHO Group 4 PH patients.

However, this study also has several limitations. The number of included studies was small, especially in the subgroup analyses, which may influence the reliability of the results. The selexipag

treatment dosage affects the 6MWD, PVR, CI, mPAP and WHO-FC. However, few studies have compared low-dose groups and high-dose groups; therefore, these differential impacts require further study. Similarly, there is a need for further research to confirm the differential effects of various durations of selexipag treatment.

In summary, we conclude that low, medium and high dosages of selexipag have similar effects. The efficacy of selexipag for the treatment of PAH depends more on the treatment time than on the treatment dosage. After more than 6 months of treatment, selexipag began to exert obvious effects, even in the low-dosage group. A longer course of selexipag treatment was associated with stronger benefits for PAH patients. This finding provides important guidance for individualized clinical treatment.

AUTHOR CONTRIBUTIONS

Lan Wang, Tian-Lan Li and Rong Jiang conceived and designed the study. Shang Wang, Yi Yan, Jian Zhang and Ping Yuan analyzed the data. Shang Wang, Yi Yan and Jian Zhang wrote the paper. Ci-Jun Luo, Hong-Ling Qiu, Hui-Ting Li and Jian Xu edited the paper. All authors have read and agreed to the published version of the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest. Yi Yan is an Editorial Board member of AMEM and a co-author of this article. To minimize bias, she was excluded from all editorial decision-making related to the acceptance of this article for publication.

DATA AVAILABILITY STATEMENT

The data and materials are available from the corresponding author upon request.

ETHICS STATEMENT

This article does not contain any studies with human or animal subjects.

PATIENT CONSENT STATEMENT

Not applicable.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

CLINICAL TRIAL REGISTRATION

Not applicable.

ORCID

Yi Yan https://orcid.org/0000-0003-2860-3252
Ping Yuan https://orcid.org/0000-0001-5096-4850
Rong Jiang https://orcid.org/0000-0003-4062-5550

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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