Systematic Review

Hemodynamic Influences of Remimazolam Versus Propofol During the Induction Period of General Anesthesia: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Background: Remimazolam is a novel ultrashort-effect benzodiazepine. In 2020, the US Food and Drug Administration approved it for procedural sedation. Remimazolam is beneficial for consistent sedation and quick recovery in painless gastrointestinal endoscopy. Propofol is one of the most commonly used intravenous anesthetics in clinical practice. Recently, only a few studies have compared propofol with remimazolam for general anesthesia induction.

Objectives: The purpose of our systematic review and meta-analysis was to compare the hemodynamic effects of remimazolam and propofol during the induction of general anesthesia.

Study Design: Systematic review and meta-analysis of randomized, controlled trials.

Methods: The authors retrieved the PubMed, Embase, Cochrane Library, and Web of Science databases for studies published through September 30, 2022, which reported relevant prospective randomized controlled trials (RCTs) comparing remimazolam with propofol for general anesthesia.
The primary outcome was hemodynamic changes, including the absolute value of fluctuation of mean arterial pressure (Δ MAP) and heart rate (Δ HR). The secondary outcomes were the following 2 indicators: the occurrence of total adverse events and the quality of recovery from general anesthesia at 24 hours postsurgery. RevMan 5.4.1 (The Nordic Cochrane Centre for The Cochrane Collaboration) and trial sequential analysis were used to execute the statistical analyses. The different domains of bias were judged by the Cochrane risk of the bias assessment tool.

Results: The authors identified 189 papers in PubMed, Embase, Cochrane Library, and Web of Science. Eight articles with 964 patients were selected. The included studies had moderate quality. For primary outcomes, the lower ΔHR (mean difference [MD] = -4.99; 95% CI, -7.97 to -2.00; I^2 = 41.6%; P = 0.001] and ΔMAP (MD = -5.91; 95% CI. -8.57 to -3.24; I^2 = 0%; P < 0.0001) represent more stable hemodynamic characteristics in the remimazolam group. Regarding secondary outcomes, a considerably lower incidence of total adverse events was noted in the remimazolam group than that for the propofol group (odds ratio [OR] = 0.40; 95% CI, 0.28 to 0.58; I^2 = 63%; P < 0.00001). In comparison to the propofol group, remimazolam achieved an advantage score of quality of recovery -15 in 24 hours postsurgery (MD = 5.31, 95% CI, 1.51 to 9.12; I^2 = 87%; P = 0.006).

Limitation: Firstly, there are only a handful of published RCTs on the administration of remimazolam in general anesthesia. In addition, due to patient privacy, we could not extract individual patient data, therefore we could not combine and assess any variations in patient characteristics.

Conclusion: Evidence suggests that remimazolam has a lower hemodynamic effect during general anesthesia and fewer perioperative adverse effects after general anesthesia than propofol; however, which agent is superior regarding quality benefit in postoperative recovery based on the

studies included here remains inconclusive. Additional RCTs with updated meta-analyses to enlarge the sample size and properly analyze the benefit-to-risk ratio to patients are needed to determine the evidence for such a relatively new medicine.

Key words: Remimazolam, propofol, general anesthesia, hemodynamic, adult

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Despite careful administration of anesthetics, the induction period of general anesthesia is characterized by easily occurring hemodynamic fluctuations, which primarily include bradycardia and hypotension (1). Postinduction hypotension can potentially lead to significant anesthesia-related adverse outcomes, such as ischemic stroke and myocardial ischemia (2,3). An ideal induction drug should maintain adequate depth of anesthesia and provide stable hemodynamics to ensure patient safety during anesthesia.

Propofol, the most popular sedative, has high lipophilicity and can cross the blood-brain barrier to promptly achieve a deep sedative effect (4). However, propofol-based general anesthesia has certain cardiopulmonary side effects, including hypoxia, hypotension, arrhythmia, respiratory depression, and other adverse reactions, such as injection pain and fatal metabolic derangement (5). Remimazolam, a novel ultrashort-effect benzodiazepine sedative, acts as a full agonist at the benzodiazepine-binding site of the gamma-aminobutyric acid (GABA) A receptor, which has a chemical structure parallel to that of midazolam (6). Remimazolam's short onset of action, low active metabolites, minimal effects on the circulatory system, and the fact that it can be easily antagonized by flumazenil, like other benzodiazepines, makes it a preferable drug for general anesthesia management.

Unlike propofol, remimazolam is only metabolized by esterases in tissues, and its major metabolite (CNS 7054) has very low pharmacological activity (7,8). Compared with midazolam or propofol, numerous published clinical experiments have shown the safety and efficacy of remimazolam as an anesthetic during sedative procedures and general anesthesia (9,10). In contrast to propofol, however, information regarding its hemodynamic effects during general anesthesia, a factor that anesthesiologists are increasingly considering when judging the safety and effectiveness of anesthetic agents in intraoperative situations, remains limited. Comparing remimazolam with propofol is inevitable, as propofol has predominantly been used in total intravenous anesthesia and procedural sedation domains. Remimazolam has exhibited similar or superior quality in many prior studies investigating its safety and effectiveness, demonstrating its capacity to improve hemodynamic stability during induction and maintenance during general anesthesia.

Consequently, we hypothesized that compared with propofol, remimazolam might provide more stable hemodynamics during the induction period of general anesthesia. Therefore, based on previously published relevant data, we aimed to explore the hemodynamic changes induced by remimazolam and propofol during general anesthesia and whether remimazolam could be an alternative to propofol.

Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42022365975).

Search Strategy

We conducted a comprehensive search for numerous types of terms using MeSH and free-text, such as "remimazolam," OR "CNS 7056," OR "ONO 2745," OR "Propofol," OR "ICI 35868," OR "Disoprofol" OR "Randomized Controlled Trial." We did not limit the search to intervention patients to avoid missing the general anesthesia literature linked to remimazolam. These electronic databases were searched for relevant literature: PubMed, Embase, Cochrane Library, and Web of Science from their inception through September 30, 2022. A "snowballing" method was used in order to search each article's references for additional studies. All articles published in various languages were included in this study.

Study Selection

Two collaborators (XP and XZ) evaluated the inclu-

sion criteria fulfillment in 3 stages: first by title, then by abstract review, and finally by full text review. A consensus was reached during disagreements on whether a study fulfilled the inclusion standards through conversations between the 2 collaborators performing the screening or consultation with the corresponding author, who resolved any discrepancies to eliminate bias.

The inclusion criteria were: 1) population: patients (adults undergoing surgery aged ≥ 18 years) undergoing general anesthesia in various surgery types; 2) intervention: induction and maintenance with remimazolam (no restrictions on dosage or administration method); 3) control: induction and maintenance with propofol (no restrictions on dosage or administration method); 4) design: prospective randomized controlled trial; 5) outcomes: studies that qualified had to contain at least one predefined endpoint; and 6) not restricted to the American Society of Anesthesiologists Physical Status Classification, sample size, date of publication, muscarinic drugs, analgesics, or other drugs.

The exclusion criteria were as follows: 1) patients undergoing general anesthesia with no included agents; 2) duplicated literature; 3) a review or meta-analysis; 4) basic research; 5) articles published as an abstract, editorial, case report, letter, note, conference article, animal studies, pediatric studies, bench studies, or protocol, and 6) publications in non-English languages.

Outcome Measures

Primary Outcomes

The primary outcome was hemodynamic changes (i.e., absolute value of fluctuation of the mean arterial pressure [ΔMAP] and heart rate [ΔHR]) in the general anesthesia induction stage.

Secondary Outcomes

The Secondary outcomes included the occurance of total adverse events (AEs) and a decrease in the Quality of Recovery-15 (QoR-15) scores at 24 hours postsurgery after general anesthesia. Total AEs included hypotension, bradycardia, nausea and vomiting, injection pain, fever, somnolence, emergency delirium, intraoperative awareness, and hypoxemia.

Quality of Recovery 24 Hours Postsurgery Using the QoR-15 Scale

The QoR-15 questionnaire includes 5 dimensions of recovery: physical comfort, physical independence, emotional state, psychological support, and pain. The total score ranges from 0 (poorest recovery quality) to 150 (best recovery quality) (11,12).

Data Extraction (Table 1)

XP and XZ were independently responsible for extracting information. The following data were extracted from individual studies: 1) reference details (first author, clinic registration number, publication year); 2) country/centers; 3) study design; 4) number of patients in each study; 5) American Society of Anesthesiologists Physical Status Classification; 6) demographic characteristics (age, gender, body mass index); 7) surgery type; 8) specific interventions and comparisons, including name and dose of drug, and method of administration; and 9) results with only outcomes prespecified in the protocol were extracted from the studies.

Quality Assessment of Included Studies

CL and YZ independently assessed the risk of bias using the Cochrane Collaboration Risk of Bias Tool (The Nordic Cochrane Centre for The Cochrane Collaboration). It includes the following 7 predefined criteria: 1) random sequence generation; 2) allocation concealment; 3) blinding of patients and personnel; 4) blinding of outcome assessment; 5) completeness of outcome data; 6) selectivity of reporting; 7) other biases (including baseline imbalance, protocol deviations, and inappropriate influence of funders).

Each study was compared for consistency, and any disagreement was resolved by discussion between the 2 reviewers or mediated by the corresponding author. According to Cochrane Collaboration's definitions, each domain should be rated as low (bias is unlikely to seriously alter the results), high (bias is likely to seriously weaken confidence in results), or unclear. Unclear or missing information was obtained from the original trial investigators.

Statistical Analysis

This meta-analysis was applied with RevMan 5.4.1 (The Nordic Cochrane Centre for The Cochrane Collaboration). The number of occurrences and patients were used to generate the Mantel-Haenszel odds ratio (OR) and 95% CI for dichotomous outcomes. The mean difference (MD) was calculated using the mean and standard deviation for continuous outcomes. We adopted a 2-tailed test and a P value of < 0.05 for the overall effect observed, indicating significant differences. Between-study heterogeneity was investigated

Table 1. *Data extraction*.

Rank	Trails	Country/ centers	Study design	Sample size	ASA	Surgery type	Participant characteristics		Remimazlolam	Propofol	Outcomes
							Intervention group	Control group			
1	Zhang et al. 2022 (15) (ChiCTR2100055039)	China/ single-center	RCT double blind	59	II, III	Elective hip replacement	Age (74.31±10.6) F/M (19/11) BMI (24.07±2.17)	Age (75.04±9.98) F/M (17/12) BMI (23.99±2.11)	(IV) Induction: 0.2–0.4 mg/kg Maintenance: 0.3–0.5 mg/kg/h	(IV) Induction: 1.5–2 mg/kg Maintenance: 4–8 mg/kg/h	①③
2	Lee et al. 2022 (19) (NCT05215834)	Korea/ single-center	RCT double blind	90	I, II, III	RARP/LRP	Age (66.8 ± 4.0) F/M (0/40) BMI (26.2 ± 1.6)	Age (66.4 ± 4.0) F/M (0/39) BMI (26.1 ± 1.4)	(IV) Induction: 6 mg/ kg/h Maintenance: 1–3 mg/kg/h	(TCI) Induction: 6.0 μg/mL Maintenance: 2–4 μg/mL	①
3	Choi et al. 2022 (20) (NCT05016518)	Korea/ single-center	RCT double blind	140	I, II	Thyroidectomy	Age (40.2 ± 11.35) F/M (70/0)	Age (41.7 ± 7.57) F/M (69/0)	(IV) Induction: 6 mg/ kg/h Maintenance: 1–2 mg/kg/h	(TCI) Induction: 5.0 μg/mL Maintenance: 2 - 6 μg/mL	①②③
4	Hasegawa et al. 2022 (16) (UMIN000043447)	Japan/ single-center	RCT open lable	32	I, II	Elective surgery	Age (35 ± 18) F/M (7/8)	Age (42 ± 17) F/M (7/8)	(IV) Induction: 12 mg/ kg/h Maintenance: 1 mg/kg/h	(IV) Induction: 0.5 mg/kg/10s Maintenance: 10 mg/kg/h	①③
5	Liu et al. 2022 (21) (ChiCTR2000040650)	China/ single-center	RCT double blind	60	III	Heart valve replacement surgery	Age (54.9 ± 11.3) F/M (16/14)	Age (50.6 ± 10.5) F/M (13/17)	(IV) Induction: 1.8 mg/ kg/h	(TCI) Induction 2.5 μg/mL	①③
6	Doi et al. 2020 (17) (CTI121973)	Japan/ multicenter	RCT single blind	375	I, II	Elective surgery	6mg/kg/h: Age (57.7±14.7) F/M (70/80) BMI (23.5 ±3.0) 12mg/kg/h: Age (56.2±16.0) F/M (74/76) BMI (23.0±3.1)	Age (56.3 ±17.6) F/M (33/42) BMI (23.3 ±3.4)	(IV) Induction: 6 or 12mg/kg/h Maintenance: 1 mg/kg/h	(IV) Induction: 2.0–2.5 mg/kg Maintenance: 4–10 mg/kg/h	①③
7	Tang et al. 2021 (18) (CHCTR2020BL-015-10)	China/ single-center	RCT single blind	80	I, II, III	Heart valve replacement surgery	Age (54.9 ± 8.5) F/M (15/25) BMI (24.1 ± 2.4)	Age (52.7 ± 7.0) F/M (20/20) BMI (23.9 ± 2.2)	(IV) Induction: 0.3 mg/kg	(IV) Induction: 1.5 mg/kg Maintenance: 4–10 mg/kg/h	①③
8	Mao et al. 2022 (22) (ChiCTR2100041986)	China/ single-center	RCT double blind	128	I, II, III	Urologic Surgery	Age (52.5±17.5) F/M (23/41) BMI (25.2±3.9)	Age (50.0±25.8) F/M (19/45) BMI (23.9 ± 2.3)	(IV) Induction: 0.2–0.3 mg/kg Maintenance: 1-2 mg/kg/h	(IV) Induction:2-3 mg/kg Maintenance: 4-10 mg/kg/h	①②③

Continuous datas are mean ± SD; Outcomes: ① The hemodynamic parameters. ② Adverse events(AEs). ③ Quality of recovery in 24h after surgery

using standard measures (Q test, I^2 index), and a fixed-effect model was initially constructed. Fixed- and random-effects models were compared to assess model robustness. Heterogeneity was considered low, medium, or high if the I^2 index level was < 25%, < 50%, or < 75%, respectively. If a strong heterogeneity ($I^2 \geq$ 50% or a *P* value for heterogeneity < 0.1) was found, a leave-one-out sensitivity analysis was employed to evaluate the single comparison-driven conclusion. The random-effect models were used when the source of heterogeneity could not be found.

Trial Sequential Analysis (TSA)

Since Type-I error and Type-II error exist for multiple comparisons and sequential analyses in meta-analyses, TSA is frequently applied to resolve and evaluate the statistical dependability of data by repeated and accumulated testing (13). Therefore, we performed statistical analyses using the TSA program (Copenhagen Trial Unit, Center for Clinical Intervention Research). The sample size's determined information value took into account the percentage of experimental and comparison events as well as the heterogeneity variance of meta-analysis. We fixed the anticipated required information size (RIS) to 0.05 for Type I and 0.2 for Type II errors. For testing hypotheses, the O'Brien-Fleming monitoring boundaries and Sidik-Jonkman's random-effects model were utilized. Further, we chose between relative risk, risk difference, OR, and Peto OR when the data type was dichotomous.

The "empirical" item or minimal difference was defined for MD and variance, and the "model-based variance" item was employed when the data type was continuous. When the Z-curve breached the O'Brien-Fleming monitoring boundaries it was deemed a true positive. When the Z-curve crossed the region of futility, it was deemed a true negative. Underpower was defined as the total sample size that failed to attain the RIS. However, in case the Z-curve remained outside the monitoring boundaries and did not surpass the RIS, the results were deemed to be robust (14).

Results

Study Selection

We identified 189 articles in PubMed, Embase, Cochrane Library, and Web of Science. Thereafter, we excluded 70 papers because of repetition and 110 articles based on their title and abstract. One of the 9 remaining articles was also excluded following a full-text review because it was a nonprospective randomized clinical trial. According to PRISMA guidance, 8 studies fulfilled the inclusion criteria. Eventually, we used 8 articles with 964 patients for the gathered data meta-analysis (Fig. 1).

Assessment of Risk of Bias (Risk of Bias 2)

All studies were rated as having a low risk of bias in the domains of random sequence generation and allocation concealment. The risk of bias was rated as high in 2 trials and moderate in 2 trials for the domain of patients and personnel blinding (15-18). Only one study was assessed as high-risk in the domain of publication bias because it did not report its pooled HR values (17). The risk of bias was rated as moderate in 5 papers for the domain of other biases because of their singular gender or type of surgery (15,19-22). Among these trials, 5 were regarded high-quality (18-22) (Figs. 2, 3).

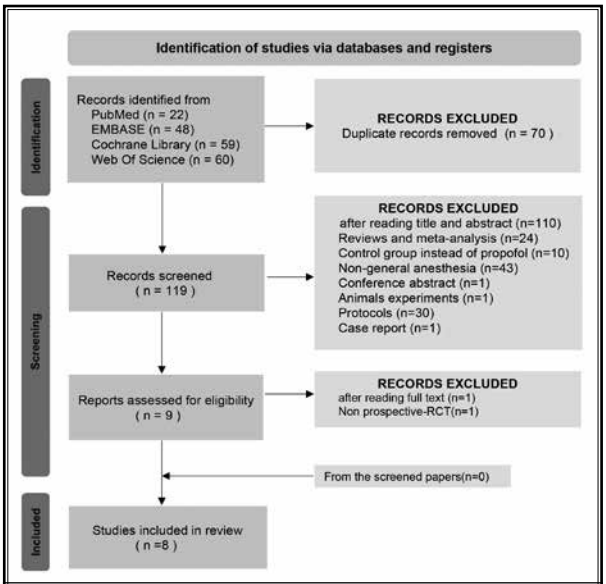

Fig. 1. *PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.*

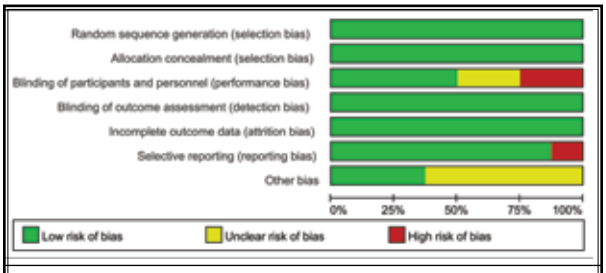

Fig. 2. *Risk of bias as assessed by the Cochrane Collaboration Risk of Bias Assessment Instrument.*

Studies and Patients' Characteristics

Eight trials involved 964 patients, all were randomized controlled trials (RCTs) published from August 2020 through May 2022. Two trials involved 218 patients undergoing urologic surgery, 2 involved 140 patients undergoing cardiac surgery, one involved 59 patients undergoing hip replacement surgery, one involved 59 patients undergoing open thyroidectomy, and 2 involved no restriction on the type of surgery. The patients were aged between 18 and 90 years and 42.84% were men. According to the type of sedatives used in anesthesia induction, we separated the patients into 2 groups: remimazolam and propofol (control group) (Table 1).

Outcomes

Primary Outcomes

The primary outcome was absolute values of hemodynamic changes between baseline and postinduction. Despite included RCTs having hemodynamic outcome indicators, only 4 recorded the HR or MAP after induction.

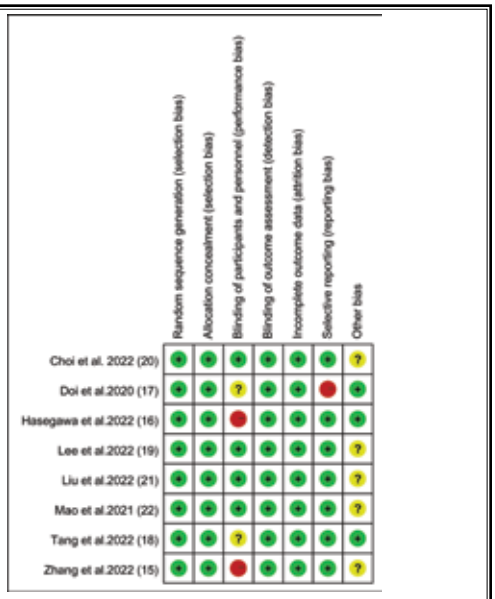

Fig. 3. *Risk of bias assessment for each included studies.*

Changes in Heart Rate

Four trials with 277 patients measured HR changes (15,16,21,22). Our statistical analysis revealed significant discrepancies between the 2 groups, wherein the remimazolam group having a lower ΔHR (MD = -4.99; 95% CI, -7.97 to -2.00; I^2 = 42%; P = 0.001) (Fig. 4).

Due to the moderate heterogeneity observed among the included studies, we conducted a leave-one-out analysis. Upon removal of the study by Liu et al (21), a substantial dissimilarity in ΔHR between the 2 study arms persisted, thereby bolstering the position of the remimazolam group (MD = -6.03, 95% CI: -9.22 to -2.85, I^2 = 0%, P = 0.0002). It is noteworthy that the baseline HR and coefficient of variation in this study were higher than in prior investigations. Furthermore, when employing a random-effects model and excluding this particular study, there remained no significant alteration in the results.

To further validate our findings, we conducted a thorough assessment using TSA (Fig.5). Notably, the final point in the Z-curve lay outside the monitoring boundaries, signifying entry into the 'Area of Benefit.' This occurred despite the sample size being insufficient, which suggests a true positive result. This finding indicates that remimazolam induces a subtle variation in heart rate compared to propofol following induction.

Changes in Mean Arterial Pressure

Four trials with 277 patients measured MAP changes (15,16,21,22). Our analysis revealed a statistically significant difference in MAP with low heterogeneity (I^2 = 0%; P < 0.0001) (Fig. 6) between the use of remimazolam and propofol (MD = -5.91; 95% CI, -8.57 to -3.24). In addition, the heterogeneity findings obtained with the random-effects model were equal to

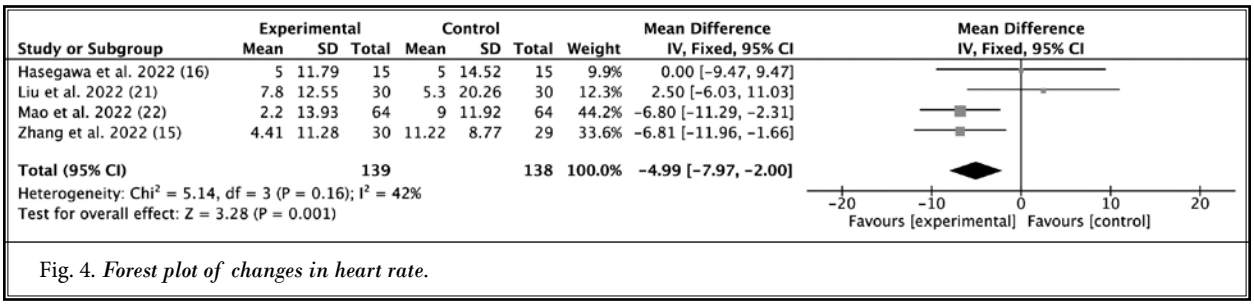

Fig. 4. *Forest plot of changes in heart rate.*

those obtained with the fixed-effects model. Figure 7 shows the sample size was sufficient, and the cumulative Z-curve breached the monitoring boundaries to reach the "Area of Benefit"; therefore, certain positive results were obtained. Minor hemodynamic changes were noted in the remimazolam group.

Secondary Outcomes

Incidence of Adverse Events

Seven trials with 921 patients reported adverse events (15,17-22). The pooled results demonstrated that the number of AEs was significantly reduced when remimazolam was compared to propofol (OR = 0.40; 95% CI, 0.28 to 0.58; $I^2 = 63\%$; $P < 0.00001$) (Fig. 8).

Owing to the significant heterogeneity between the included studies ($I^2 = 63\%$), a leave-one-out analysis was performed. When Mao, et al's study (22) was excluded from the analysis, ΔMAP still showed a significant difference between the 2 groups (OR = 0.29; 95% CI, 0.19 to 0.45; $I^2 = 0\%$; $P < 0.00001$). Since the sample size was adequate, the cumulative Z-curve crossed the O'Brien-Fleming boundaries, and the result was truly positive. Figure 9 shows that the result favored the remimazolam group.

To obtain more information on AEs, we performed further subgroup analyses. Based on the incidences of hypotension, the pooled data from the hypotension subgroup indicated considerable variation between the remimazolam and propofol treatments (OR = 0.29; 95% CI, 0.18 to 0.46; $I^2 = 0\%$; $P < 0.00001$) (Fig. 10); the remimazolam group had better outcomes (17-19,21,22).

Both fixed- and random-effects specifications also suggested a decreased incidence of AEs in the remimazolam group. The cumulative Z-curve shows the sample size was sufficient, demonstrating a true positive result (Fig. 11). Based on the fixed-effects model, the OR of remimazolam to propofol in the subgroup of nausea and vomiting was 1.32 95% CI, 0.73 to 2.39; $I^2 = 33\%$) (Fig. 12), indicating that there existed no statistical conspicuous discrepancy in the prevalence of nausea and vomiting between the 2 arms. No meaningful change in the results was obtained when the sensitivity analysis and the random-effects model were used (15,17,18,20,22). The last point of the Z-curve neither get through the inner wedge of futility borders nor the O'Brien-Fleming monitoring boundaries, and as such, no positive or negative conclusion could be drawn yet (Fig. 13).

Likewise, there was no record of AEs with "injection pain" in the remimazolam group; the prevalence of injection pain in the propofol group was 9.72%.

There was no difference when the prevalence of bradycardia between the 2 groups was compared (17,19). However, one of the studies showed that compared to the propofol group, the remimazolam group had more somnolence and emergency delirium.

Quality of Recovery

Two trials with 267 patients reported a decrease in QoR-15 scores at 24 hours postsurgery (20,22).The pooled result based on only 2 trials with 267 patients conducted with the fixed-effects model yielded a high heterogeneity result (MD = 5.31; 95% CI, 1.51 to 9.12; $I^2 = 87\%$; $P = 0.006$] (Fig. 14). Thus, we performed a ran-

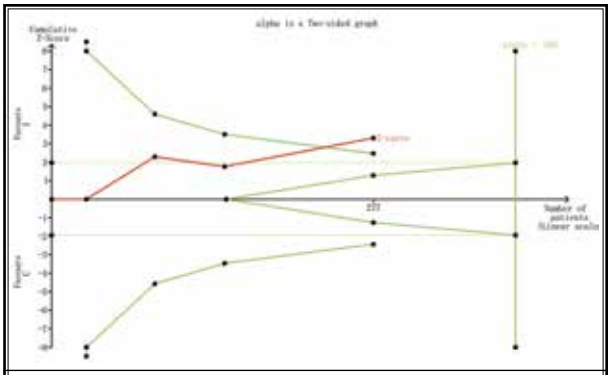

Fig. 5. *Trial sequential analysis of changes in heart rate.*

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Hasegawa et al. 2022 (16)	16	15.13	15	22	11.14	15	7.8%	−6.00 [−15.51, 3.51]
Liu et al. 2022 (21)	18.3	9.63	30	24.6	11.62	30	24.3%	−6.30 [−11.70, −0.90]
Mao et al. 2022 (22)	14.4	12.75	64	18.6	11.7	64	39.4%	−4.20 [−8.44, 0.04]
Zhang et al. 2022 (15)	26.94	9.91	30	34.85	9.67	29	28.4%	−7.91 [−12.91, −2.91]
Total (95% CI)			**139**			**138**	**100.0%**	**−5.91 [−8.57, −3.24]**

Heterogeneity: $Chi^2 = 1.26$, df = 3 (P = 0.74); $I^2 = 0\%$
Test for overall effect: Z = 4.35 (P < 0.0001)

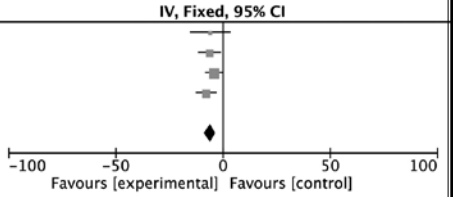

Fig. 6. *Forest plot of changes in mean arterial pressure.*

dom-effects model (MD = 5.22; 95% CI, -5.17 to 15.60,I^2 = 87%; *P* = 0.33. The cumulative Z-curve in TSA did not cross the O'Brien-Fleming monitoring limits, which means that the results between the remimazolam and control groups were not statistically different (Fig. 15). Therefore, we cannot conclude that patients receiving remimazolam showed better postoperative recovery than those receiving propofol.

Discussion

Our study investigated the effects of remimazolam and propofol on hemodynamic characteristics during general anesthesia induction. Our statistical analysis showed that remimazolam had a more stable effect on hemodynamic characteristics during the induction phase than propofol; also relevant was its lower probability of hypotension. However, the incidence of AEs, such as bradycardia, and nausea and vomiting was similar to the propofol group. However, compared with the traditional sedative drug, propofol, a conclusion on the quality of recovery could not be drawn. Therefore, large-sample experiments are required to examine the influence of remimazolam in postoperative recovery quality.

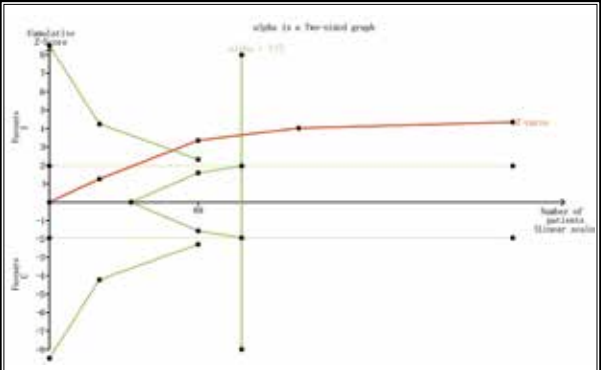

Fig. 7. *Trial sequential analysis of changes in mean arterial pressure.*

Furthermore, our results indicate that remimazolam is safe and allows stable induction of general anesthesia. The promotion of comfort medicine has increased the range of applicability of anesthetic treatment, which has increased the demand for anesthetic medicines. However, common sedative medications have drawbacks. For instance, propofol causes respiratory and circulatory depression, especially in the elderly or critically ill patients; etomidate suppresses adrenal cortical function (15); dexmedetomidine is a widely prescribed shallow sedative prone to causing bradycardia and hypotension; and midazolam is not recommended for the maintenance of general anesthesia because of its accumulation and delayed recovery.

Remimazolam was introduced following the quest for better sedative drugs. Remimazolam, the newest 1.1 benzodiazepine, has an ester-like structure, unlike ordinary benzodiazepines. It acts on the GABA acid receptor subunit (GABA-A). Sedation is achieved by inhibiting neuronal firing in the substantia nigra reticularis of the brain. Remimazolam is predictable and controllable in clinical applications because it has a pharmacokinetic-pharmacodynamic profile that is characterized by quick onset, quick recovery, and mild hemodynamic side effects (23). Remimazolam is hydroxylated by plasma tissue esterase to the inactive metabolite CNS 7054, which does not rely on kidney and liver metabolism (24,25). Long-term infusions or administering massive doses do not result in the accumulation of the drug or its metabolite, making it superior to midazolam and propofol.

Furthermore, flumazenil can be used to completely reverse remimazolam's sedative effect (26,27). According to therapeutic trials, the recommended general

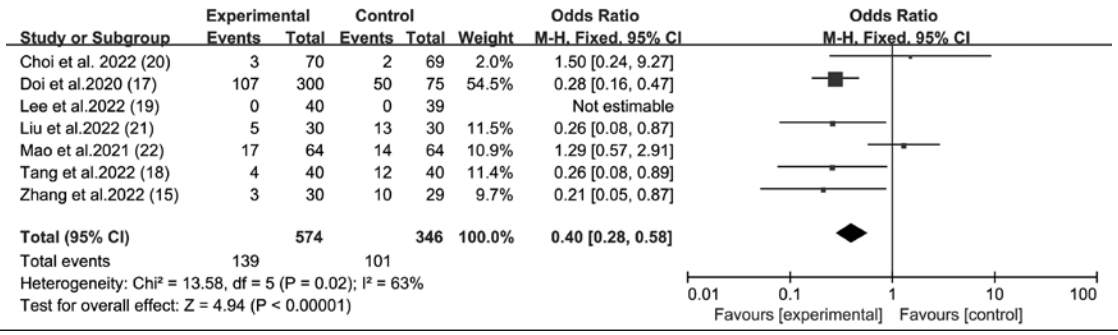

Fig. 8. *Forest plot of incidence of total adverse events.*

anesthesia regimen for induction of remimazolam is 12 mg/kg/h and after that one mg/kg/h for maintenance. In the elderly, a single push dose of 0.3 mg/kg is recommended. The administration can be adjusted according to the depth of anesthesia but must not exceed 2 mg/kg/h (28,29).

Currently, intravenous administration is the most appropriate method of administration for remimazolam. However, when used with Ringer's acetate solution, precipitation may form, leading to an intravenous line obstruction, so precautions may need to be taken (30). Other routes of administration are not recommended because remimazolam is not effective when administered via inhaled/nasal or mucosa/oral routes (31,32). Consequently, further investigation of the safety, utility, and benefits or risks of various methods of administration is required. Remimazolam was not approved until 2020 for general anesthesia in adult patients in Japan, clinical application in general anesthesia in Korea, and procedural sedation in The People's Republic of China, the United States, and the European Union. The application of remimazolam can include outpatient examination, day surgery, general anesthesia, the intensive care unit, pediatric sedation, and anesthesia outside the operating room (33).

Some invasive operations can now be completed in a few minutes thanks to recent ultrasonography and other imaging technology advancements. In addition to general anesthesia procedures, remimazolam has uses in interventional analgesia and other types of anesthesia. According to previous research, 3 patients had coexisting medical issues (involving pacemaker [natural or implanted] function or cardiac conduction) that were affecting the medication they received for procedural sedation in a cardiac catheterization suite (34). The results demonstrate that there was no intraoperative influence on hemodynamic or conduction function when remimazolam was administered compared to propofol. All patients recovered quickly, leaving the postanesthesia care unit in less than 60 minutes.

Propofol can affect atrioventricular (AV) node conduction by decreasing sympathetic outflow and raising vagal tone; it may also extend the Wenckebach cycle and AV conduction. It has been associated with a number of deleterious effects on cardiac conduction and pacemaker performance. Following an injection of propofol, it is documented that both adults and children have had incidences of bradycardia, asystole, and all degrees of heart block, including full heart block (AV dissociation) (35,36). Remimazolam may be beneficial as a main drug for procedural sedation with a native airway in the cardiac catheterization suite. Some data suggest that it has little influence on inotropic, dromotropic, or chronotropic function, making it a potentially useful treatment in patients with concurrent electrophysiologic disorders.

A clinical trial of procedural sedation with remimazolam during ultrasound-guided abdominal

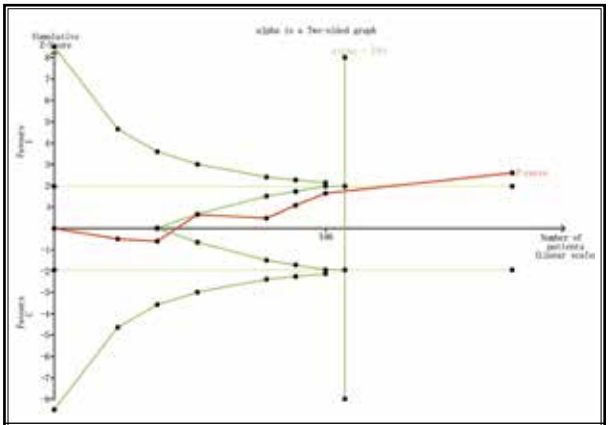

Fig. 9. *Trial sequential analysis of incidence of total adverse events.*

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Doi et al.2020 (17)	66	300	37	75	77.0%	0.29 [0.17, 0.49]
Lee et al.2022 (19)	0	40	0	39		Not estimable
Liu et al.2022 (21)	5	30	13	30	18.1%	0.26 [0.08, 0.87]
Tang et al.2022 (18)	1	40	3	40	4.9%	0.32 [0.03, 3.18]
Total (95% CI)		**410**		**184**	**100.0%**	**0.29 [0.18, 0.46]**
Total events	72		53			

Heterogeneity: Chi² = 0.03, df = 2 (P = 0.98); I² = 0%
Test for overall effect: Z = 5.17 (P < 0.00001)

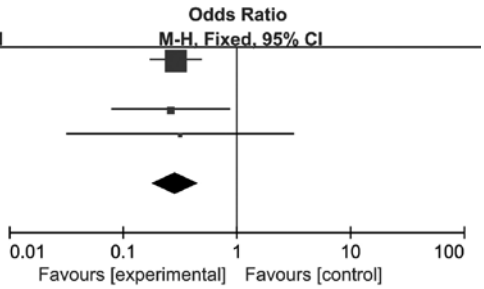

Fig. 10. *Forest plot of incidence of hypotension.*

plane blocks and rectus sheath blocks in patients undergoing abdominal tumor surgery proved its safety and efficacy (37). Remimazolam produced drowsiness faster and more efficiently during nerve blocks than dexmedetomidine and midazolam, with fewer hemodynamic changes. The cause of the increased incidence of hypoxemia with remimazolam may be connected to the augmentation of sufentanil opioid analgesia, but this has to be further investigated and understood. Another study that employed different dosages of remimazolam for sedation in nerve blocks found that 0.08 mg/kg was the most effective for sedation in younger patients. Lowering the dose to 0.04 considerably lowered the incidence of remimazolam-induced respiratory depression, making it an appropriate medication for older patients as well (38). Based on our current literature search, comparative studies of the 2 drugs in interventional pain management are limited. This may be a future research direction.

However, some adverse reactions, such as headache, drowsiness and hypoxia, QT interval prolongation, allergy, tachycardia, and hypertension, have been reported during research trials (25,39,40). More clinical trials should be conducted to investigate the efficacy of remimazolam.

The strengths of our meta-analysis are as follows:

1) First, as the clinical application of remimazolam is limited, most published meta-analyses focused on the safety and efficacy of remimazolam in procedural sedation, such as gastrointestinal endoscopy and hysteroscopy. However, we evaluated the efficacy of remimazolam during general anesthesia. Therefore, our meta-analysis thoroughly analyzed prospective RCTs to determine the efficacy of remimazolam in general anesthesia. The aggregated data demonstrated statistically significant differences in the predicted outcomes.
2) In addition, the primary outcome of our meta-analysis was hemodynamic changes. To reduce confounding bias caused by baseline levels of HR and MAP in the different studies examined, we chose ΔHR and ΔMAP as the primary outcomes, which makes the combined effect results more reliable.

Our study has several limitations.

1) There are few published RCTs on the administration of remimazolam in general anesthesia, most of which are in the registration and trial stages. However, the TSA results certified that some endpoints had sufficient sample sizes and statistical significance.
2) There was no access to individual patient data; therefore, we could not integrate and analyze any variation in patient characteristics. We assume that all these defects might contribute to the heterogeneity observed when we combined their effects.

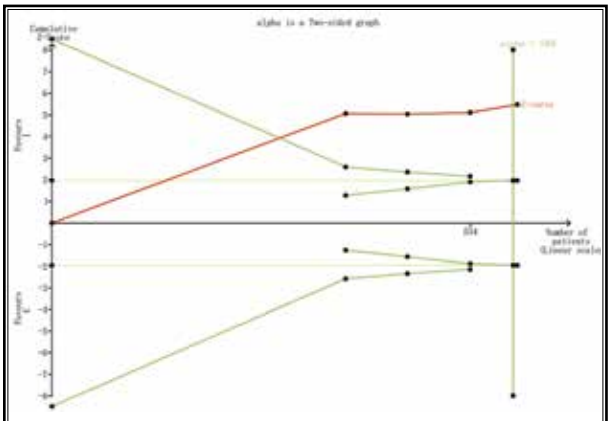

Fig. 11. *Trial sequential analysis of incidence of hypotension.*

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Choi et al. 2022 (20)	3	70	0	69	2.4%	7.21 [0.37, 142.19]
Doi et al.2020 (17)	39	300	7	75	49.4%	1.45 [0.62, 3.39]
Mao et al.2021 (22)	7	64	3	64	13.5%	2.50 [0.62, 10.12]
Tang et al.2022 (18)	1	40	4	40	19.8%	0.23 [0.02, 2.16]
Zhang et al.2022 (15)	1	30	3	29	14.9%	0.30 [0.03, 3.05]
Total (95% CI)		**504**		**277**	**100.0%**	**1.32 [0.73, 2.39]**
Total events	51		17			

Heterogeneity: Chi² = 5.99, df = 4 (P = 0.20); I² = 33%
Test for overall effect: Z = 0.91 (P = 0.36)

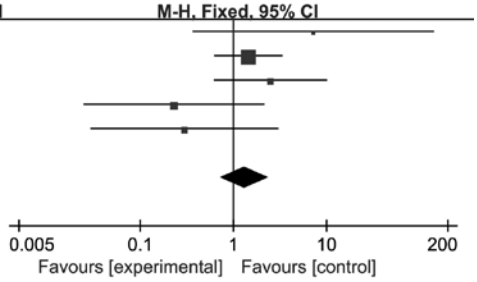

Fig. 12. *Forest plot of incidence of postoperative nausea and vomiting.*

Conclusion

This systematic review and meta-analysis demonstrates that remimazolam has more stable hemodynamics during general anesthesia induction and fewer perioperative adverse effects compared to those during anesthesia using propofol; however, which is superior regarding quality benefit in postoperative recovery remains inconclusive based on the studies included here. To determine the evidence for such a new drug, additional RCTs with updated meta-analyses to expand the sample size in order to better assess the benefits or risks to patients are warranted.

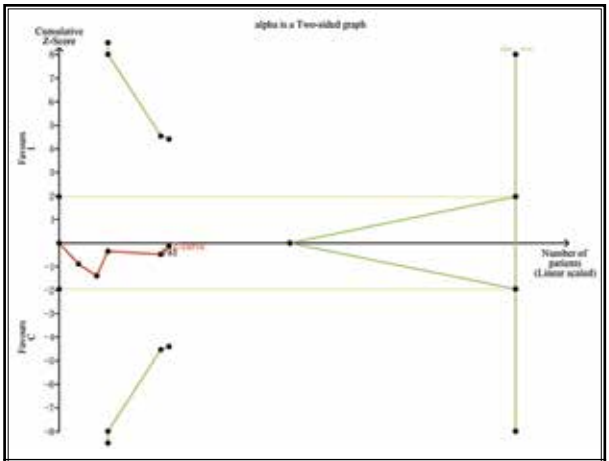

Fig. 13. *Trail sequential analysis of incidence of postoperative nausea and vomiting.*

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Choi et al. 2022 (20)	22.8	16.31	70	22.9	16.38	69	49.9%	-0.10 [-5.53, 5.33]
Mao et al. 2022 (22)	27.5	13.4	64	17	17.08	64	50.1%	10.50 [5.18, 15.82]
Total (95% CI)			**134**			**133**	**100.0%**	**5.22 [-5.17, 15.60]**

Heterogeneity: $Tau^2 = 48.65$; $Chi^2 = 7.46$, df = 1 (P = 0.006); $I^2 = 87\%$
Test for overall effect: Z = 0.98 (P = 0.33)

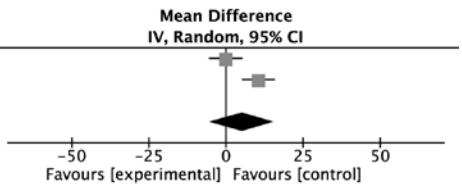

Fig. 14. *Forest plot of quality of recovery 24h after surgery.*

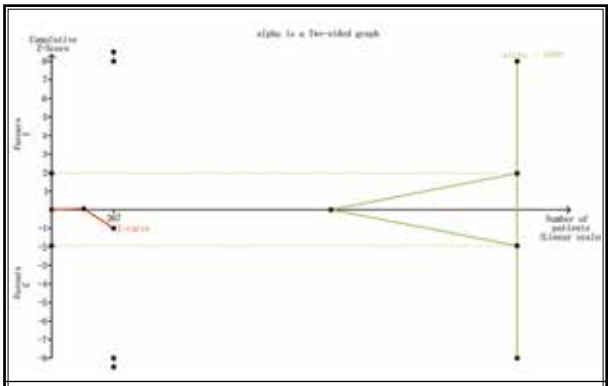

Fig. 15. *Trail sequential analysis of quality of recovery 24h after surgery.*

References

1. Kawasaki S, Kiyohara C, Tokunaga S, Hoka S. Prediction of hemodynamic fluctuations after induction of general anesthesia using propofol in non-cardiac surgery: A retrospective cohort study. *BMC Anesthesiol* 2018; 18:167.
2. Bijker JB, Persoon S, Peelen LM, et al. Intraoperative hypotension and perioperative ischemic stroke after general surgery: A nested case-control study. *Anesthesiology* 2012; 116:658-664.
3. Walsh M, Devereaux PJ, Garg AX, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology* 2013; 119:507-515.
4. Chen B, Pang QY, An R, Liu HL. A systematic review of risk factors for postinduction hypotension in

surgical patients undergoing general anesthesia. *Eur Rev Med Pharmacol Sci* 2021; 25:7044-7050.

5. Ogawa T, Tomoda T, Kato H, Akimoto Y, Tanaka S, Okada H. Propofol sedation with a target-controlled infusion pump in elderly patients undergoing ERCP. *Gastrointest Endosc* 2020; 92:301-307.
6. Kilpatrick GJ, McIntyre MS, Cox RF, et al. CNS 7056. *Anesthesiology* 2007; 107:60-66.
7. Upton RN, Somogyi AA, Martinez AM, Colvill J, Grant C. Pharmacokinetics and pharmacodynamics of the short-acting sedative CNS 7056 in sheep. *Brit J Anaesth* 2010; 105:798-809.
8. Worthington MT, Antonik LJ, Goldwater DR, et al. A Phase Ib, Dose-finding study of multiple doses of remimazolam (CNS 7056) in volunteers undergoing colonoscopy. *Anesth Analg* 2013; 117:1093-1100.
9. Zhu X, Wang H, Yuan S, et al. Efficacy and safety of remimazolam in endoscopic sedation—A systematic review and meta-analysis. *Front Med* 2021; 8:655042.
10. Doi M, Hirata N, Suzuki T, Morisaki H, Morimatsu H, Sakamoto A. Safety and efficacy of remimazolam in induction and maintenance of general anesthesia in high-risk surgical patients (ASA Class III): Results of a multicenter, randomized, double-blind, parallel-group comparative trial. *J Anesth* 2020; 34:491-501.
11. Yoon S, Joo H, Oh YM, Lee J, Bahk JH, Lee HJ. Validation and clinical utility of the Korean version of the Quality of Recovery-15 with enhanced recovery after surgery: A prospective observational cohort study. *Brit J Anaesth* 2020; 125:614-621.
12. Kleif J, Waage J, Christensen KB, Gögenur I. Systematic review of the QoR-15 score, a patient- reported outcome measure measuring quality of recovery after surgery and anaesthesia. *Brit J Anaesth* 2018; 120:28-36.
13. Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive—Trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *Inter J Epidemiol* 2009; 38:287-298.
14. Kang H. Trial sequential analysis: Novel approach for meta-analysis. *Anesth Pain Med* 2021; 16:138-150.
15. Zhang J, Wang X, Zhang Q, Wang Z, Zhu S. Application effects of remimazolam and propofol on elderly patients undergoing hip replacement. *BMC Anesthesiol* 2022; 22:118.
16. Hasegawa G, Hirata N, Yoshikawa Y, Yamakage M. Differential effects of remimazolam and propofol on heart rate variability during anesthesia induction. *J Anesth* 2022; 36:239-245.
17. Doi M, Morita K, Takeda J, Sakamoto A, Yamakage M, Suzuki T. Efficacy and safety of remimazolam versus propofol for general anesthesia: A multicenter, single-blind, randomized, parallel-group, phase IIb/III trial. *J Anesth* 2020; 34:543-553.
18. Tang F, Yi JM, Gong HY, et al. Remimazolam benzenesulfonate anesthesia effectiveness in cardiac surgery patients under general anesthesia. *World J Clin Cases* 2021; 9:10595-10603.
19. Lee C, Lee C, Lee J, Jang G, Kim B, Park S. Comparison of core body temperatures in patients administered remimazolam or propofol during robotic-assisted and laparoscopic radical prostatectomy. *Medicina* 2022; 58:690.
20. Choi JY, Lee HS, Kim JY, et al. Comparison of remimazolam-based and propofol-based total intravenous anesthesia on postoperative quality of recovery: A randomized non-inferiority trial. *J Clin Anesth* 2022; 82:110955.
21. Liu T, Lai T, Chen J, et al. Effect of remimazolam induction on hemodynamics in patients undergoing valve replacement surgery: A randomized, double-blind, controlled trial. *Pharmacol Res Perspec* 2021; 9: e00851.
22. Mao Y, Guo J, Yuan J, Zhao E, Yang J. Quality of recovery after general anesthesia with remimazolam in patients' undergoing urologic surgery: A randomized controlled trial comparing remimazolam with propofol. *Drug Des Devel Ther* 2022; 16:1199-1209.
23. Schüttler J, Eisenried A, Lerch M, Fechner J, Jeleazcov C, Ihmsen H. Pharmacokinetics and pharmacodynamics of remimazolam (CNS 7056) after continuous infusion in healthy male volunteers. *Anesthesiology* 2020; 132:636-651.
24. Hu K, Xiang Q, Wang Z, et al. Effects of vitamin D receptor, cytochrome P450 3A, and cytochrome P450 oxidoreductase genetic polymorphisms on the pharmacokinetics of remimazolam in healthy Chinese volunteers. *Clinical Pharm in Drug Dev* 2021; 10:22-29.
25. Wiltshire HR, Kilpatrick GJ, Tilbrook GS, Borkett KM. A placebo- and midazolam-controlled Phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): Part II. Population pharmacokinetic and pharmacodynamic modeling and simulation. *Anesth Analg* 2012; 115:284-296.
26. Zhou Y, Hu P, Jiang J. Metabolite characterization of a novel sedative drug, remimazolam in human plasma and urine using ultra high-performance liquid chromatography coupled with synapt high-definition mass spectrometry. *J Pharm Biomed Analysis* 2017; 137:78-83.
27. Chen X, Sang N, Song K, et al. Psychomotor recovery following remimazolam-induced sedation and the effectiveness of flumazenil as an antidote. Clin Ther 2020; 42:614-624.
28. Keam SJ. Remimazolam: First Approval. *Drugs* 2020; 80:625-633.
29. Lohmer LL, Schippers F, Petersen KU, Stoehr T, Schmith VD. Time-to-event modeling for remimazolam for the indication of induction and maintenance of general anesthesia. *J Clin Pharma* 2020; 60:505-514.
30. Yoshida K, Tanaka S, Watanabe K. A case of intravenous line occlusion when using Acetated Ringer's solution and remimazolam. *J Clin Anesth* 2021; 70:110190.
31. Pesic M, Schippers F, Saunders R, Webster L, Donsbach M, Stoehr T. Pharmacokinetics and pharmacodynamics of intranasal remimazolam—A randomized controlled clinical trial. *Eur J Clin Pharmacol* 2020; 76:1505-1516.
32. Pesic M, Stöhr T, Ossig J, et al. Remimazolam has low oral bioavailability and no potential for misuse in drug-facilitated sexual assaults, with or without alcohol: results from two randomised clinical trials. *Drugs R D* 2020; 20:267-277.
33. Kleiman RB, Darpo B, Thorn M, Stoehr T, Schippers F. Potential strategy for assessing QT/QTc interval for drugs that produce rapid changes in heart rate: Electrocardiographic assessment of the effects of intravenous remimazolam on cardiac repolarization. *Brit J Clinical Pharma* 2020; 86:1600-1609.
34. Kalsotra S, Khan S, McKee C, Tobias JD. Remimazolam as the primary agent for sedation during cardiac catheterization in three patients with comorbid cardiac

conduction abnormalities. *Cardiol Res* 2023; 14:86-90.

35. Noh JI, Lee JH, Woo SY, et al. Complete atrioventricular nodal block after propofol administration in an elderly patient undergoing total knee replacement arthroplasty -A case report. *Korean J Anesthesiol* 2013; 64:363-366.
36. Morozowich ST, Saslow SB. Progression of asymptomatic bifascicular block to complete heart block during upper gastrointestinal endoscopy with propofol sedation. *Can J Anesth/J Can Anesth* 2009; 56:83-84.
37. Xiao Y, Wei R, Chen L, Chen Y, Kong L. Efficacy and safety of remimazolam for procedural sedation during ultrasound-guided transversus abdominis plane block and rectus sheath block in patients undergoing abdominal tumor surgery: A single-center randomized controlled trial. *BMC Anesthesiol* 2022; 22:381.
38. Li X, Bu T, Li YT, et al. Sedation efficacy of different dose of remimazolam with sufentanil for nerve block in young and elderly patients: A randomized, controlled study. *J Anesth* 2023; 37:177-185.
39. Tsurumi K, Takahashi S, Hiramoto Y, Nagumo K, Takazawa T, Kamiyama Y. Remimazolam anaphylaxis during anesthesia induction. *J Anesth* 2021; 35:571-575.
40. Sato T, Ohno S, Maeda M, Sawashita Y, Hirata N, Yamakage M. Unexpected tachycardia and hypertension during anesthetic induction with remimazolam in cardiac surgery: A case report. *JA Clin Rep* 2021; 7:58.