

Selective COX-2 inhibitor versus non-selective COX-2 inhibitor for the prevention of heterotopic ossification after total hip arthroplasty

A meta-analysis

Xi-Tian Zhu, MD*, Lei Chen, MD, Jian-Hua Lin, MM

Abstract

Background: Whether selective non-steroidal anti-inflammatory drugs (NSAIDs) has equally efficacy with non-selective NSAIDs in preventing heterotopic ossification (HO) after total hip arthroplasty (THA) was controversial. The purpose of this meta-analysis was to assess the efficacy and safety of selective NSAID versus non-selective NSAIDs for the prevention of HO after THA.

Methods: PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science, Google Search Engine, and China National Knowledge Infrastructure databases was searched for randomized controlled trials (RCTs) were comparing selective NSAID versus non-selective NSAIDs for preventing HO after THA. The primary outcomes were overall HO incidence, Brooker classification HO incidence, gastrointestinal side effects, the occurrence of excessive bleeding and discontinuation caused by gastrointestinal side effects (DGSE). Data were analyzed using Stata 12.0.

Results: A total of 8 RCTs involving 1636 patients were included in the meta-analysis. There was no significant difference between the nonselective NSAIDs group and the selective NSAIDs group in the overall incidence of HO (relative risk, RR=0.91, 95% confidence intervals, CI 0.78–1.06, $P=.203$), Brooker I HO (RR=1.02, 95% CI 0.85–1.23, $P=.794$), Brooker II HO (RR=1.00, 95% CI 0.66–1.52, $P=.996$), Brooker III HO (RR=0.98, 95% CI 0.37–2.62, $P=.971$). And the occurrence of excessive bleeding (RR=0.67, 95% CI 0.24–1.92, $P=.458$). The selective NSAIDs group was associated with a significant decrease in gastrointestinal side effects (RR=0.35, 95% CI 0.18–0.71, $P=.004$) and discontinuation caused by gastrointestinal side effects compared with the nonselective NSAIDs group (RR=0.28, 95% CI 0.11–0.66, $P=.004$).

Conclusion: The available evidence indicates selective NSAIDs were as effective as non-selective NSAIDs in preventing HO after THA. And selective NSAIDs were associated with less gastrointestinal side effects than non-selective NSAIDs. Considering the limitation of current meta-analysis, more RCTs need to identify the optimal NSAIDs drug for HO after THA.

Abbreviations: CIs = confidence intervals, DGSE = discontinuation caused by gastrointestinal side effects, HO = heterotopic ossification, Mesh = medical subject heading, NSAIDs = non-steroidal anti-inflammatory drugs, RCT = randomized controlled trials, RR = relative risk, THA = total hip arthroplasty.

Keywords: heterotopic ossification, meta-analysis, non-selective, non-steroidal anti-inflammatory drugs, selective

1. Introduction

Heterotopic ossification (HO) is a common complication after total hip arthroplasty (THA), arthroscopy or the trauma of the hip.^[1,2] The incidence of HO after THA was ranged from 30% to

40%.^[3,4] Among the HO patients, 15% of these HO patients suffer from pain and limited range of motion of the hip.^[5] What's more, the satisfaction rate of patients with severe HO after THA can decrease to only 30% compared to 90% satisfaction among patients without HO.^[6] Prevention of HO is therefore important for patients undergoing elective THA.

Oral non-steroidal anti-inflammatory drugs (NSAIDs), diphosphonates and prophylactic with low dose irradiation were currently 2 main therapy methods.^[7,8] Among them, NSAIDs have been recommended as a general prophylaxis therapy after THA.^[9] Most NSAIDs are nonselective inhibitors of both COX-1 and COX-2. The common gastrointestinal side effects of nonselective COX-2 inhibitors trouble the patients and limit their application. There have been several clinical trials of selective COX-2 inhibitor for HO control in THA. However, the effectiveness of the use of selective COX-2 inhibitors in THA patients was controversial in several studies.^[10–12] And whether selective COX-2 inhibitor was as effective as non-selective COX inhibitor was unknown.

The aim of this meta-analysis of randomized controlled trials was to investigate whether a selective COX-2 inhibitor, would be as effective and safety as non-selective COX inhibitor, in the prevention of HO in patients undergoing THA.

Editor: Robert L. Barkin.

The authors declare no conflict of interest.

Supplemental Digital Content is available for this article.

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Medicine (2018) 97:31(e11649)

Received: 23 November 2017 / Accepted: 2 July 2018

<http://dx.doi.org/10.1097/MD.00000000000011649>

2. Material and methods

2.1. Search strategy

Electronic databases, including PubMed, Embase, the Cochrane Central Register of Controlled Trials, Chinese Wanfang databases, and Web of Science, were searched for relevant studies published from the time of the establishment of these databases up to November 2017. In addition, Google was searched for additional literature. The reference lists of all the full-text studies were reviewed to identify any initially omitted studies, and there was no restriction on the language of the publication. The search keywords were selective COX-2 inhibitor, non-selective COX-2 inhibitor, and total hip arthroplasty.

The relevant medical subject heading (Mesh) terms were used to maximize the specificity and sensitivity of the search. These keywords and mesh terms were combined with the Boolean operators AND or OR. Since this is a meta-analysis, no ethics committee or institutional review board approval was necessary for the study.

2.2. Eligibility criteria and study quality

Study selection was performed according to the following inclusion criteria: published randomized controlled trials (RCTs) of patients who underwent THA; employed interventions that included selective NSAIDs versus non-selective NSAID for HO formation; and reported overall HO incidence, Brooker classification HO incidence, gastrointestinal side effects, the occurrence of excessive bleeding, and discontinuation caused by gastrointestinal side effects (DGSE) as outcomes.

Two reviewers independently scanned the quality of the eligible studies, and discrepancies were solved by a senior reviewer. A risk of bias assessment was conducted and recorded in the corresponding tables for each involved RCT according to the Cochrane Handbook for Systematic Reviews of Interventions. The assessment items included the randomization method; allocation concealment; blinding of participant, personnel, and assessor; and complete outcome data and other bias.

2.3. Data extraction

The following data were extracted and recorded: demographic data about the patients, author names, publication date, drug dose, and interval in the selective COX-2 inhibitor group and non-selective COX-2 inhibitor group, the number of male patients in the 2 groups; study type and duration of follow-up; and outcomes (overall HO incidence, Brooker classification HO incidence, gastrointestinal side effects, the occurrence of excessive bleeding, and DGSE as outcomes.).

2.4. Outcome measures and statistical analysis

The main outcomes were overall HO incidence, Brooker classification HO incidence, gastrointestinal side effects, the occurrence of excessive bleeding, and DGSE. Dichotomous outcomes (overall HO incidence, Brooker classification HO incidence, gastrointestinal side effects, the occurrence of excessive bleeding, and DGSE) were expressed as relative risks (RR) with 95% confidence intervals (CIs). Statistical significance was set at $P < .05$ to summarize findings across the trials. The meta-analysis was performed using Stata software, version 12.0 (Stata Corp.,

College Station, TX). Statistical heterogeneity was tested using the χ^2 test and I^2 statistic. When there was no statistical evidence of heterogeneity ($I^2 < 50\%$, $P > .1$), a fixed-effects model was adopted; otherwise, a random-effects model was chosen. If the heterogeneity was large, a sensitivity analysis was conducted to further seek out the source of heterogeneity. Publication bias was assessed by a funnel plot and quantitatively assessed by Begg test. There was considered no publication bias if the funnel plot was symmetrical and the P value drawn from Begg test was greater than .05.

3. Results

3.1. Search results

A summary of the study selection process are presented in Figure 1. Based on the search strategies and inclusion criteria, a total of 305 references were generated. Of these, we included 8 clinical trials with 1636 patients (719 patients in the selective COX-2 inhibitor group, and 917 patients in non-selective COX-2 inhibitors group).^[10–17] The general characteristic of the included RCTs can be seen in Table 1. The selective COX-2 inhibitors including celecoxib, etoricoxib, meloxicam, and rofecoxib. Non-selective COX-2 inhibitors including indomethacin, ketoprofen, diclofenac, and ibuprofen. The duration of follow-up was ranged from 3 months to 12 months.

3.2. Quality of the included studies

The risk of bias summary and risk of bias graph can be seen in Figures 2 and 3 respectively. All of the 8 included RCTs were described as randomized. However, only 4 of studies comprehensively described the generation method of a randomized sequence, and the remaining studies did not demonstrate the randomization method. Blinding of participants and personnel was performed in 4 studies. Blinding of the outcome assessment was performed in 6 RCTs and attrition bias was with low in 7 studies. Other biases were low in 5 of the studies. Kappa value between reviewers was 0.715.

3.3. Results of meta-analysis

3.3.1. Overall incidence of HO. Eight studies, including 1636 patients, provided data for the overall incidence of HO between the nonselective NSAIDs group and the selective NSAIDs group. There was no significant difference between the nonselective NSAIDs group and the selective NSAIDs group in the overall incidence of HO (RR=0.91, 95% CI 0.78–1.06, $P = .203$, Fig. 4). We then performed a subgroup analysis according to the drug of the selective COX-2 inhibitor and non-selective COX-2 inhibitor. Results shown that when compared with ibuprofen, celecoxib was associated with a reduction of the overall incidence of HO (RR=0.62, 95% CI=0.52–0.89, $P = .004$) (Fig. 5). Indomethacin was associated with a reduction of the overall incidence of HO when compared with meloxicam (RR=1.86, 95% CI=1.27–2.72, $P = .001$, Fig. 5). Next, we performed a subgroup analysis according to the dose of meloxicam (7.5 mg or 15 mg). Results shown that the overall incidence of 7.5 mg meloxicam was less than 15 mg meloxicam (Supplement S1, <http://links.lww.com/MD/C359>).

A funnel plot was then obtained and indicated that there is no publication bias between the included studies (Fig. 6). The P value obtained from Begg test (0.494) (Fig. 7) is greater than .05; this outcome also indicated that there is no publication bias between the studies.

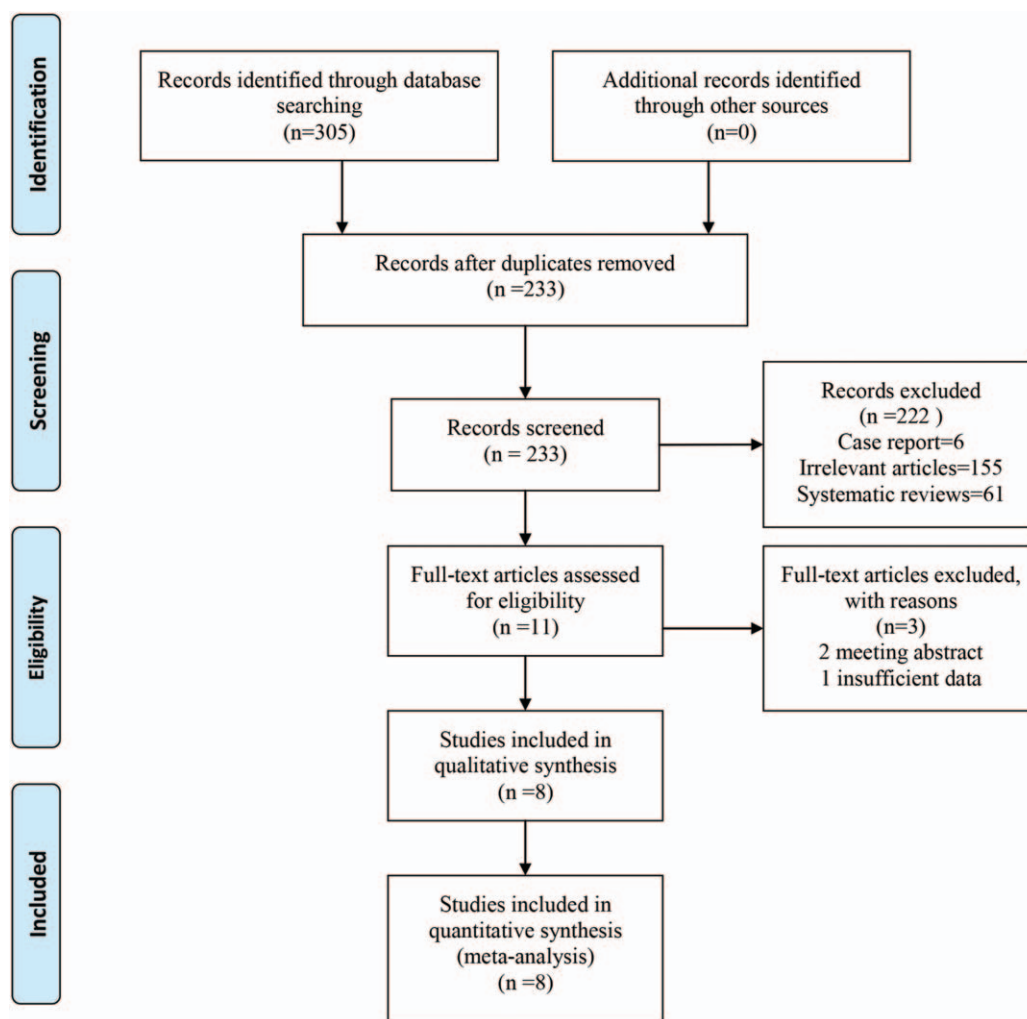


Figure 1. Flow diagram for study selection.

The heterogeneity between the studies was high, thus a random-effects model was adopted to analyze the final results. To further analyze the large heterogeneity, a sensitivity analysis was conducted to analyze the source of heterogeneity (Fig. 8). The results indicated that none of the studies affected the heterogeneity.

3.3.2. Incidence of Brooker I HO. Eight studies, including 1636 patients, provided data for the incidence of Brooker I HO between the nonselective NSAIDs group and the selective NSAIDs group. There was no significant difference between the nonselective NSAIDs group and the selective NSAIDs group

Table 1

The general characteristic of the included studies.

Study	Country	Control Group			Intervention group			Study	Outcomes	Follow-up, mos
		Drug and dose	Age, ys	Male patients, %	Drug and dose	Age, ys	Male patients, %			
Romano 2004	Italy	Indomethacin (2 × 50 mg/d) for 20 ds	62.3	28.0	Celecoxib (2 × 200 mg/d) for 20 ds	59.3	26.5	RCTs	1,2,3,4,5,6,7	12
Vastel 2005	French	Ketoprofen (iv, 1 × 200 mg/d) for 2 ds and 300mg oral for 5 ds	58.4	22.6	Celecoxib (2 × 200 mg/d) for 7 ds	55.6	25.4	RCTs	1,2,3,4,5,6,7	12
Winkler 2016	Germany	Diclofenac(2 × 75 mg/d) for 9 ds	60.2	53.2	Etoricoxib (1 × 90 mg/d) for 9 ds	61.9	54.2	RCTs	1,2,3,4,5	6
Legenstein 2003	Australia	Indomethacin (2 × 50 mg/d) for 12 ds	68	41.4	Meloxicam (1 × 7.5 mg/d) for 12 ds	65	25.9	RCTs	1,2,3,4,5	6
van der Heide 2004	Netherlands	Indomethacin (3 × 50 mg/d) for 7 ds	NS	NS	Rofecoxib (2 × 25 mg/d) for 7 ds	NS	NS	RCTs	1,2,3,4,5,6,7	6
Barthel 2002	Germany	Indomethacin (2 × 50 mg/d) for 14 ds	63.2	41.2	Meloxicam (7.5 mg/d or 15 mg/d) for 14 ds	61.5	38.6	RCTs	1,2,3,4,5,6,7	6
Grohs 2007	Austria	Indomethacin (2 × 25 mg/d and 1 × 50 mg/d) for 14 ds	60.1	55.1	Rofecoxib (1 × 25 mg/d) for 7 ds	58.5	47.2	RCTs	1,2,3,4,5,	12
Saudan 2007	Switzerland	Ibuprofen (3 × 400 mg/d) for 10 ds	65.2	40.1	Celecoxib (2 × 200 mg/d) for 10 ds	62.5	43.4	RCTs	1,2,3,4,5	3

Note: This includes overall HO incidence, incidence of Brooker I HO, incidence of Brooker II HO, incidence of Brooker III HO, gastrointestinal side effects, the occurrence of excessive bleeding, and discontinuation caused by gastrointestinal side effects.

Ho = heterotopic ossification, NS = not stated, RCT = randomized controlled trials.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Barthel 2002	?	+	+	+	+	+	+
Grohs 2007	+	+	+	+	+	+	+
Legenstein 2003	+	+	+	+	+	+	?
Romano 2004	?	?	?	+	+	+	+
Saudan 2007	+	?	?	+	+	+	+
van der Heide 2004	?	?	?	?	+	+	+
Vastel 2005	?	?	?	?	?	?	?
Winkler 2016	+	+	+	+	+	+	+

Figure 2. Risk of bias summary.

in the incidence of Brooker I HO (RR = 1.02, 95% CI 0.85–1.23, $P = .794$) (Fig. 9).

3.3.3. Incidence of Brooker II HO. Eight studies, including 1636 patients, provided data for the overall incidence of Brooker II HO between the nonselective NSAIDs group and the selective NSAIDs group. There was no significant difference between the nonselective NSAIDs group and the selective NSAIDs group in the incidence of Brooker II HO (RR = 1.00, 95% CI 0.66–1.52, $P = .996$) (Fig. 10).

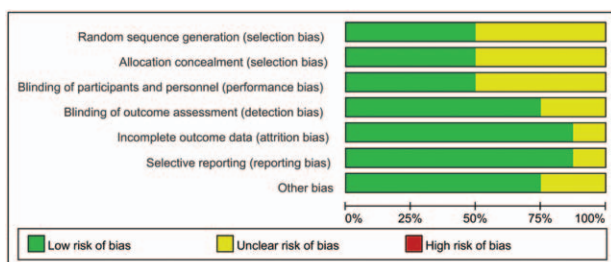


Figure 3. Risk of bias graph.

3.3.4. Incidence of Brooker III HO. Eight studies, including 1636 patients, provided data for the overall incidence of Brooker III HO between the nonselective NSAIDs group and the selective NSAIDs group. There was no significant difference between the nonselective NSAIDs group and the selective NSAIDs group in the incidence of Brooker III HO (RR = 0.98, 95% CI 0.37–2.62, $P = .971$) (Fig. 11).

3.3.5. Gastrointestinal side effects. Six studies, including 646 patients, provided data for the gastrointestinal side effects between the nonselective NSAIDs group and the selective NSAIDs group. The selective NSAIDs group was associated with a significant decrease in gastrointestinal side effects compared with the nonselective NSAIDs group (RR = 0.35, 95% CI 0.18–0.71, $P = .004$) (Fig. 12).

3.3.6. The occurrence of excessive bleeding. Four studies, including 577 patients, provided data for the occurrence of excessive bleeding between the nonselective NSAIDs group and the selective NSAIDs group. There was no significant difference between selective NSAIDs group and nonselective NSAIDs group in terms of the occurrence of excessive bleeding (RR = 0.67, 95% CI 0.24–1.92, $P = .458$) (Fig. 13).

3.4. DGSE

Three studies, including 750 patients, provided data for the discontinuation caused by gastrointestinal side effects between the nonselective NSAIDs group and the selective NSAIDs group. The selective NSAIDs group was associated with a significant decrease in discontinuation caused by gastrointestinal side effects compared with the nonselective NSAIDs group (RR = 0.28, 95% CI 0.11–0.66, $P = .004$) (Fig. 14).

4. Discussion

This meta-analysis aimed to assess whether selective COX-2 inhibitor were equally effective compared to nonselective NSAIDs for the prevention of HO after THA. Main finding of current meta-analysis was that there was no significant difference between the overall incidence of HO and any grade of Brooker classification. And, selective COX-2 inhibitor was associated with a reduction of the occurrence of the gastrointestinal side effects and discontinuation caused by gastrointestinal side effects. A major strength of current meta-analysis was that we comprehensively searched the electronic database and calculated with the final outcomes strictly. We performed sensitivity analysis and subgroup analysis to improve the robust of the finding.

One systematic review revealed that selective COX-2 inhibitor was superior than non-selective COX inhibitor in prevention HO after THA. But that analysis did not include all available RCTs and thus a selective bias was existed in that meta-analysis. The current meta-analysis included all available RCTs in comparisons at all Brooker classification HO, avoiding the weakness of small sample size and illustrating the effect of selective COX-2 inhibitor for preventing different classification HO after THA.

The efficacy of COX-2 inhibitor for preventing heterotopic bone formation after hip arthroplasty was identified by several studies.^[18,19] However, Neal et al^[9] revealed that no effect of low-dose aspirin for the prevention of HO after THA. Current meta-analysis revealed that selective COX-2 inhibitor has similar efficacy in preventing HO after THA. And then we use Brooker classification to identify there was any difference between the classification. Results shown that there was no significant

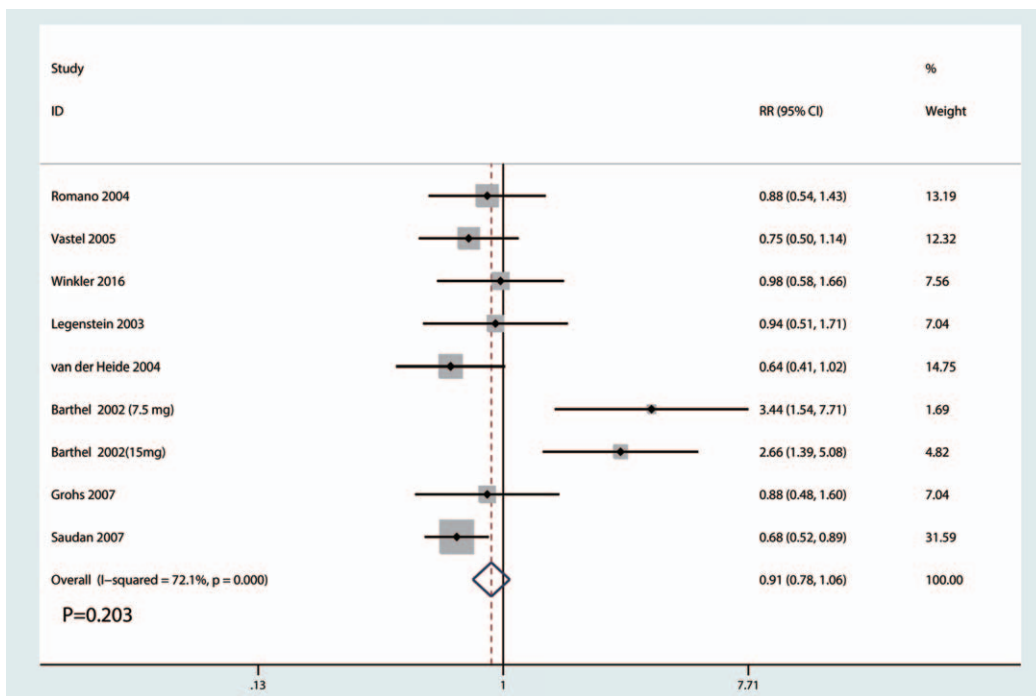


Figure 4. Forest plots comparing overall incidence of HO between the 2 groups.

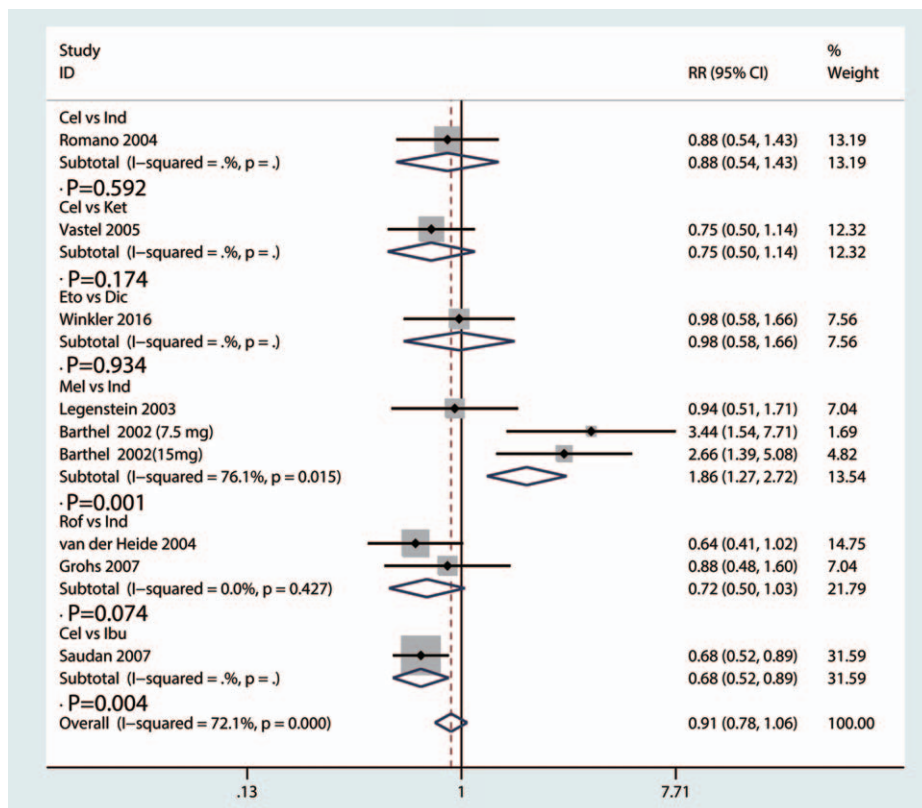


Figure 5. Subgroup analysis of the overall incidence of HO.

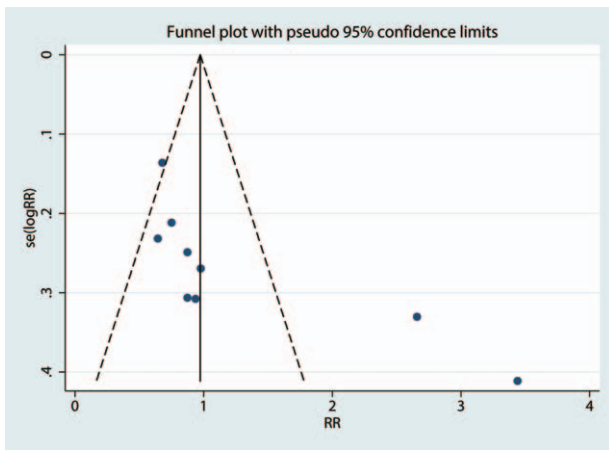


Figure 6. Funnel plot for overall incidence of HO between the 2 groups.

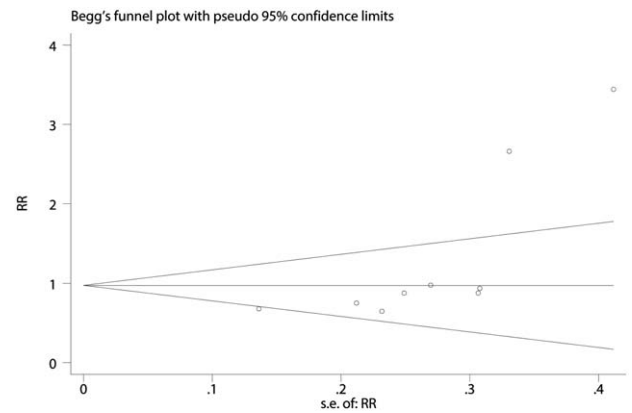


Figure 7. Begg's test for overall incidence of HO between the 2 groups.

difference between the overall incidence of HO, any Brooker classification HO incidence. All of the included RCTs found that 0% of patients suffered from Brooker IV HO. Diclofenac was highly with COX2 events otherwise COX 1 events.^[14]

Gastrointestinal side effects and excessive bleeding were 2 main problems of traditional nonselective NSAIDs. Tözün et al^[20] found that the 2 patients were excluded in the study due to the gastrointestinal bleeding and recovered after withdrawal of the drug. Current meta-analysis revealed that selective COX-2 inhibitor was associated with a reduction of the gastrointestinal side effects with significantly difference. However, there was no significant difference between the excessive bleeding between the selective COX-2 inhibitor versus non-selective COX-2 inhibitor. As for these complications, more RCTs should be focused on the related complications.

Grohs et al^[17] reported the Harris hip scores between the selective COX-2 inhibitors and non-selective COX-2 inhibitors in the formation of HO after THA. Results shown that there was no significant difference between the hip function. In the future research, studies should be focused on the functional outcome of the hip between the 2 drugs.

There were several limitations in this meta-analysis: only 8 RCTs were included, the relative small number of the eligible studies will affects the final results; the drug administration period in some studies was unclear, and the optimal drugs of selective COX-2 inhibitors was need to identify; there were a total of 10 studies were included and there was a potential publication bias that existed in the meta-analysis; different prosthesis and peri-operative administration may affect the final outcomes; the included studies did not report the hip function (Harris hip scores), and thus we need to identify whether use

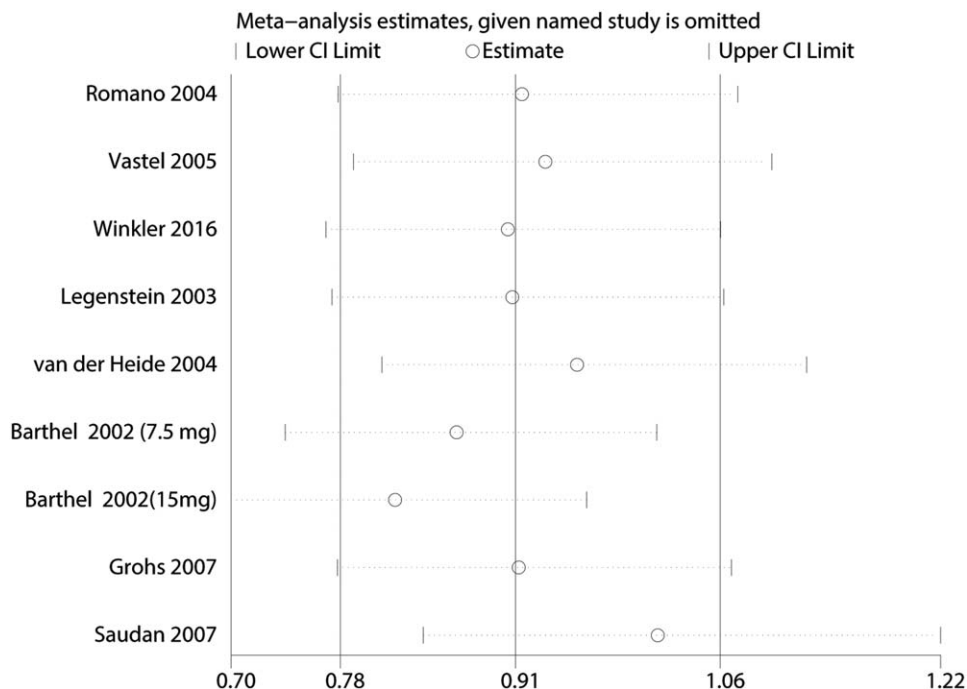


Figure 8. Sensitivity analysis of the overall incidence of HO between the 2 groups.

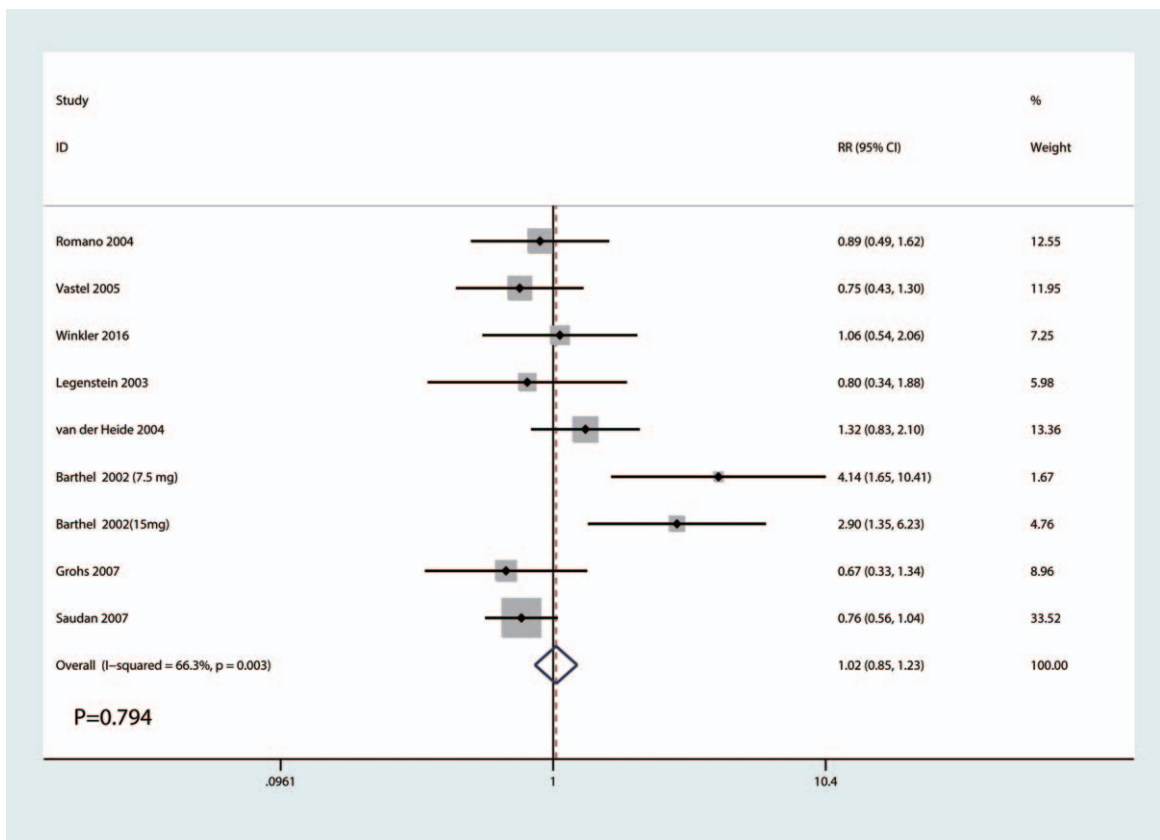


Figure 9. Forest plots comparing incidence of Brooker I HO between 2 groups.

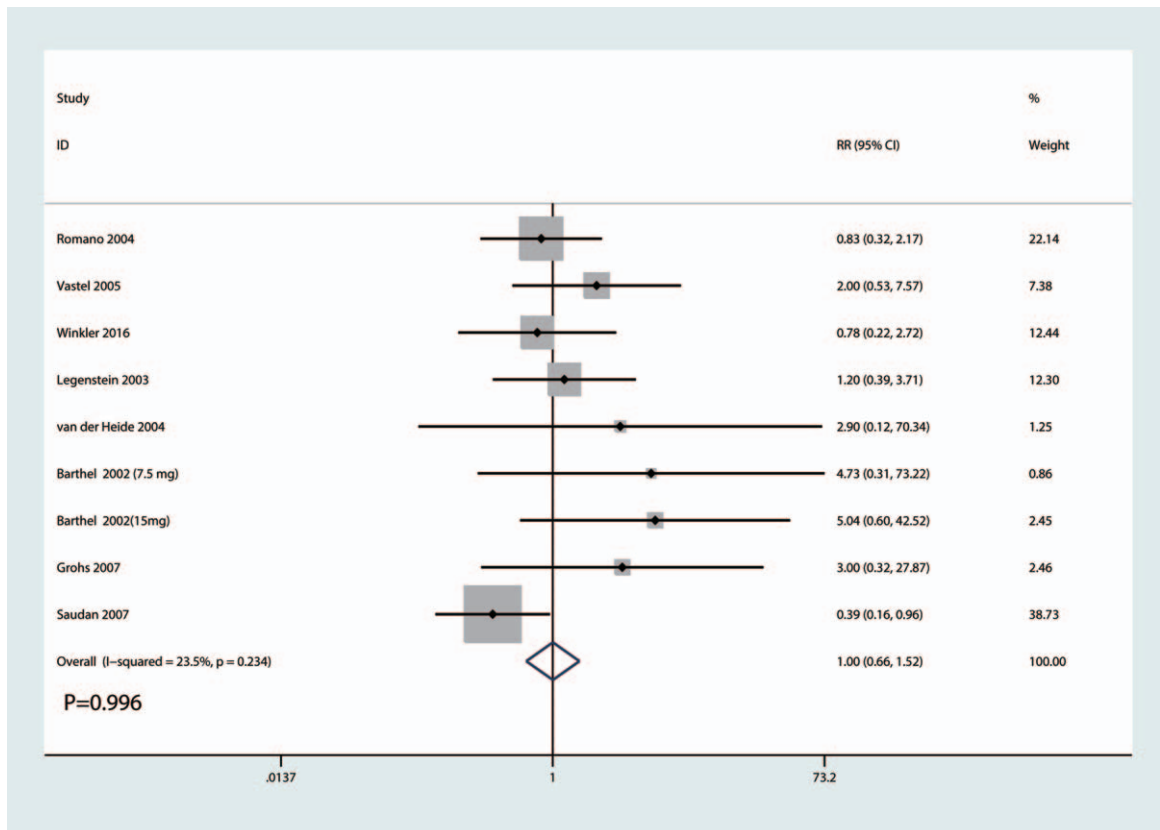


Figure 10. Forest plots comparing Incidence of Brooker III HO between the 2 groups.

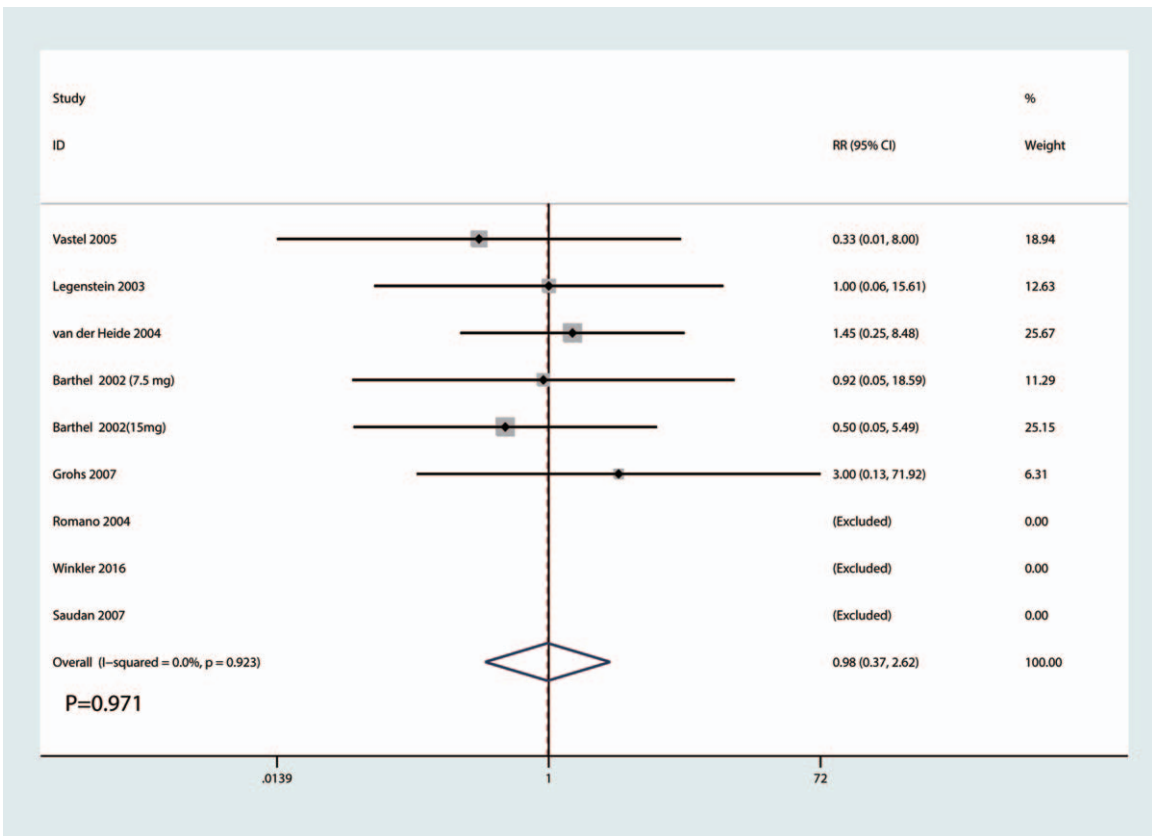


Figure 11. Forest plots comparing gastrointestinal side effects between the 2 groups.

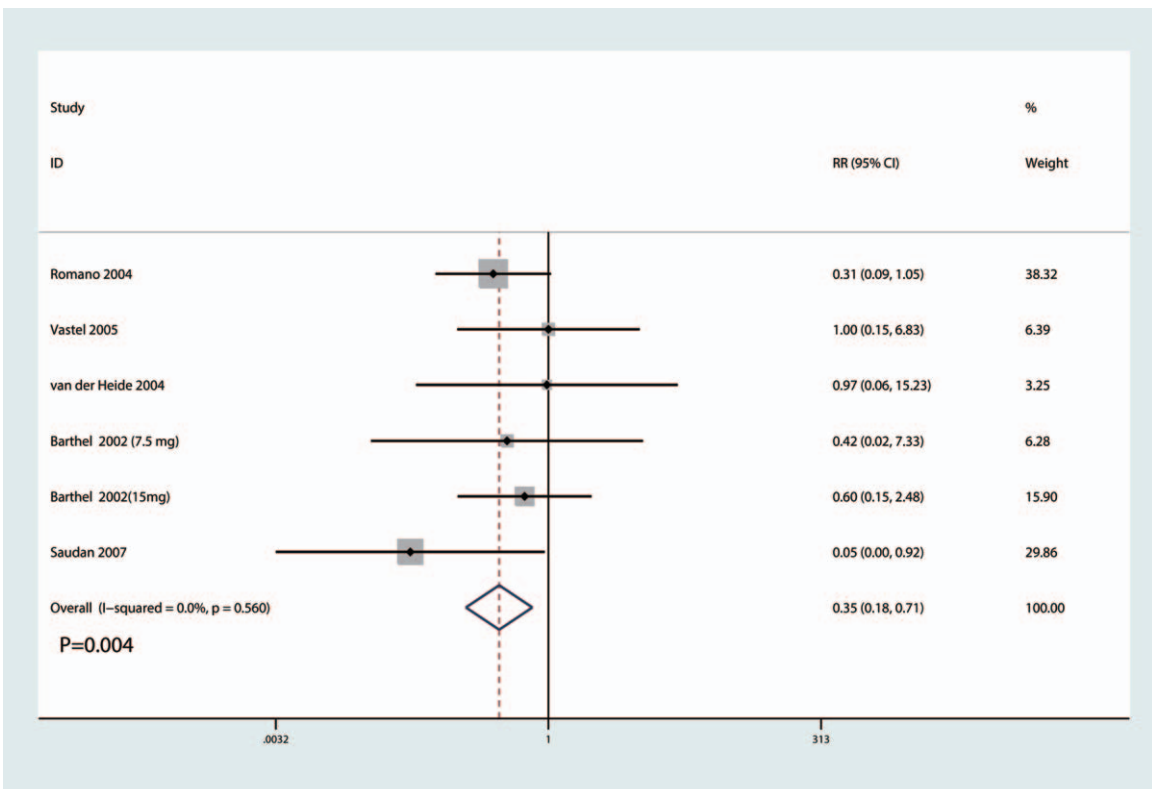


Figure 12. Forest plots comparing the occurrence of excessive bleeding between the 2 groups.

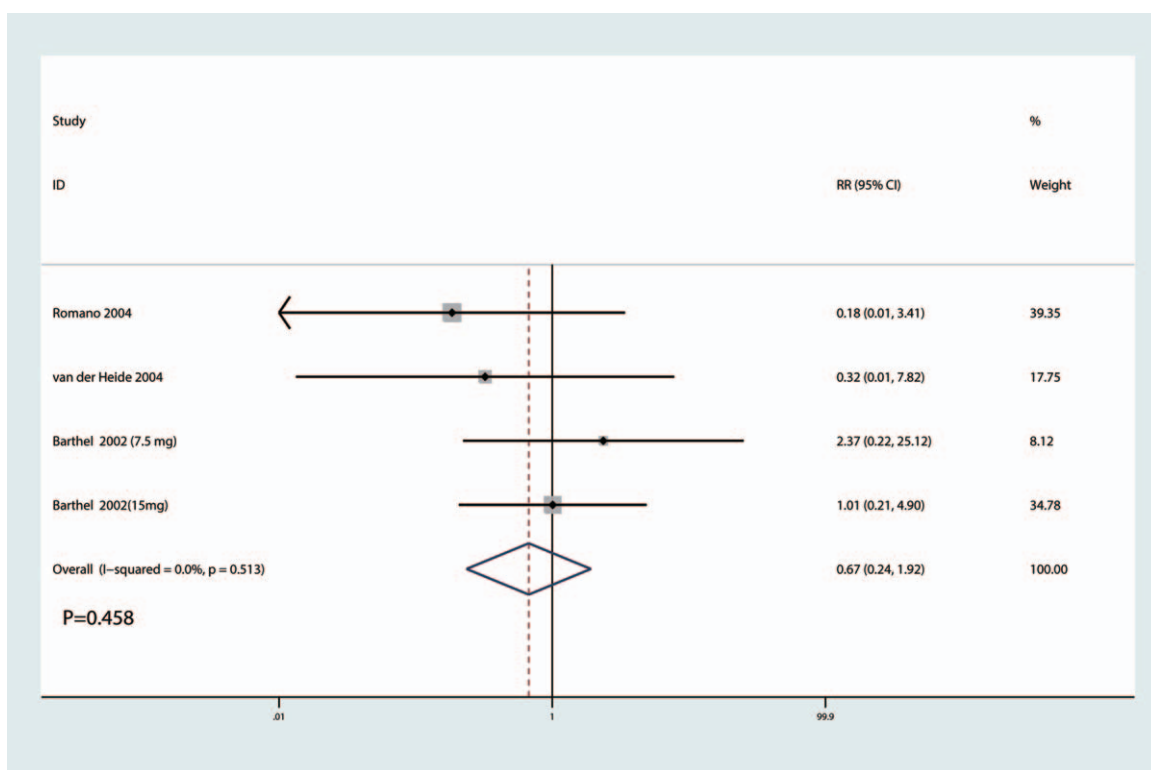


Figure 13. Forest plots comparing the discontinuation caused by gastrointestinal side effects between the 2 groups.

selective COX-2 inhibitors has a beneficial role in improving the hip function; and the heterogeneity among the studies will also affect the final conclusion, although we tried to use subgroup analysis to solve it.

In conclusion, the selective COX-2 inhibitors are equally effective as nonselective NSAIDs for the prevention of HO after THA. However, selective COX-2 inhibitors were associated with a reduction of the gastrointestinal side effects and DGSE. Thus,

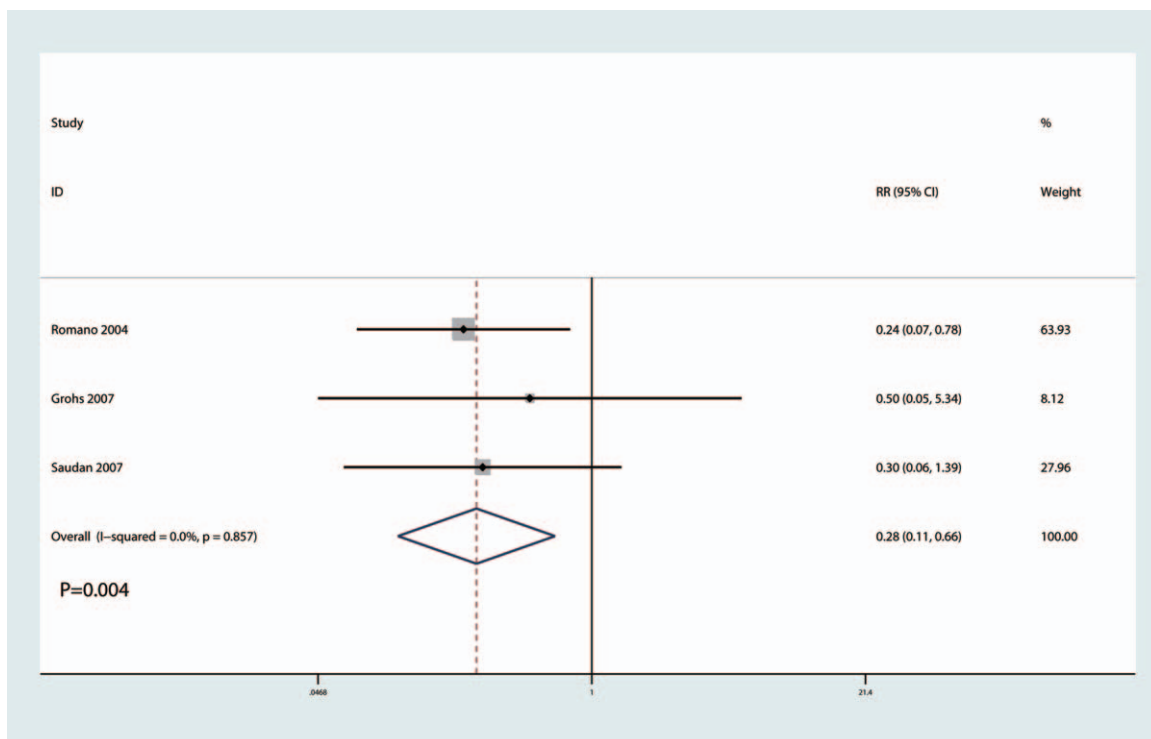


Figure 14. Forest plots comparing DGSE between the 2 groups.

we recommend selective COX-2 inhibitors for the prevention of HO after THA. Considering the limitation of the current meta-analysis, more high quality RCTs are need to identify the optimal selective COX-2 inhibitor and dosage of the drugs in future.

Author contributions

Software: Lei Chen.

Validation: Xi-Tian Zhu.

Visualization: Xi-Tian Zhu.

Writing – original draft: Xi-Tian Zhu, Jian-Hua Lin.

Writing – review & editing: Jian-Hua Lin.

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