Proton Pump Inhibitors Reduce Survival Outcomes in Patients Treated with Capecitabine: Meta-analysis

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Research Article

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Abstract

Background

Proton pump inhibitors (PPIs) are widely-used over-the-counter drugs. However, possible, and quite ambiguous, interaction has been suggested between capecitabine and PPIs; with some discrepancy still being present within the literature regarding the possible risks, or even benefits, of their concomitant use. This meta-analysis therefore aims to analyze data from the literature regarding both the risk of PPIs on survival in patients treated with capecitabine, as well as their benefit regarding the incidence of hand foot syndrome (HFS).

Methods

A total of 17 studies were included after searching Pubmed, Medline, and Cochrane until October 2022 for the effect of PPIs on the treatment efficacy and pharmacokinetics, and incidence of HFS. Revman Ver. 5.3 was used for all statistical analyses.

Results

Our data showed a significant HFS reduction at a relative risk of 0.77 (95% CI: 0.70–0.85; p < 0.00001) in the PPI-using groups compared to control. Meta-analysis of studies assessing survival; however, showed reduction in almost all survival aspects, most notably within the recurrence-free survival, with a hazard ratio of 1.75; 95% CI: 1.21–2.53; p = 0.003.

Conclusion

Individual data incriminating the use of PPIs with capecitabine is quite limited; however, our robust survival data on around 30,000 patients gave significant worse survival outcomes, particularly in the (neo)adjuvant setting.

Background

Capecitabine is an oral fluoropyrimidine chemotherapeutic drug which is converted to 5-fluorouracil (5FU) through a three-step cascade beginning in the liver, and ending within the tumor microenvironment; where the final step takes place, allowing 5FU to exert its anti-tumorigenic effect while sparing the normal tissues [1]. Oral chemotherapy has been emerging as a possible alternative for the conventional IV route drugs without diminishing the possible clinical benefit of IV agents [2, 3].

Hand-foot syndrome, or palmar-plantar erythrodysesthesia, is an adverse event commonly seen with capecitabine, as well as other antineoplastic drugs. It occurs in more than half of the patients taking this
treatment and is characterized by distal skin changes ranging from as little as minor edema and erythema, and up to more severe symptoms like blistering; desquamation; and debilitating pain. In such severe forms, HFS can cause premature treatment discontinuation [4, 5].

Although still not completely understood, multiple theories have been implicated in HFS, including the inflammatory pathway, there is no definitive treatment for HFS, and therapy relies mainly on supportive measures. This includes constant hydration, moisturization, and limb elevation. Local creams containing steroids or anti-histaminic formulas can also be used. When it comes to systemic treatments, pyridoxine; steroids; and anti-cox2 drugs are usually used. Most of these treatments exert their effects through their anti-inflammatory properties, with the use of COX2 inhibitors having prophylactic effects in preventing HFS in up to half of the patients [4–7].

Acid-suppressing drugs are commonly used with capecitabine due to its direct irritating effect on the gastric mucosa; with up to half of oncology patients using one form or another of acid-suppressing therapy [8]. One group of these acid-suppressing drugs is proton pump inhibitors (PPIs). In addition to its widely-known anti-acid secretion use in patients with gastritis – which usually occurs with cepcitabine [8, 9] – proton pump inhibitors have complementary anti-inflammatory effect through inhibiting the lysosomal influx of H+ ions. This lack of lysosomal acidification can reduce the phagocytic function as well as decrease the adhesion molecule expression, and therefore, the chemotactic abilities of immune cells. Proton pump inhibitors also reduce the production of endothelial and tissue chemotactic cytokines resulting in possible anti-inflammatory effects [10, 11].

A recent study by Hiromoto et al. has tested this theory in particular as its primary outcome on capecitabine-induced HFS in mice, and reported significant reduction in the severity of the HFS (p < 0.05), with it possibly being due to the reduction in the tumor necrosis factor (TNF)-α in the mice limbs (p < 0.01). This study also had a retrospective patient-based arm that was also included in the meta-analysis data of HFS on around 60,000 patients [4].

Despite the possible benefits of PPIs on the adverse event profile of capecitabine, a possible interaction has long been suggested between PPIs and capecitabine, mostly due to the pre-notion that the increase in the gastric PH by the PPIs could possibly affect the gastric fragmentation of the tablet, therefore affecting its rate of absorption [8, 12]. However, multiple pharmacokinetic studies have revoked this theory; as assessed in a narrative review assessing this interaction in particular [13].

Multiple studies have retrospectively assessed the effect of PPIs on the efficacy of capecitabine, as analysed in this study. However, the present literature of systematic reviews only assess the effect of PPIs on the treatment efficacy using multiple parameters; which is of course the major factor to consider in this relationship [14, 15]. None of the reviews however, to our current knowledge, has done a quantitativ meta-analysis or concurrently assessed the effect of PPIs on the incidence of HFS or other AE; despite multiple studies reporting such benefits.
In 2019, a systematic review was done by Viñal et al. specifically to assess the effect of PPIs on the efficacy on capecitabine [14], with most of the studies in the original review till 2019 being included – save for one study that was excluded due to the non-specification of the type of acid-suppression therapy used. In addition, when it comes to the studies in the review reported to show significant results, one of the studies included as a conference [16], released the full trial paper in 2020 with additional study subjects [17]. This discrepancy in the results of the studies included in this review, the publishing of newer studies after that, as well as the absence of any meta-analysis studies on this particular interaction between both drugs has created a need for a wholesome review assessing not only the risks; but also the benefits of PPIs on the use of capecitabine, has led to the birth of this systematic review and meta-analysis.

**Methods**

In this systematic review and meta-analysis, we aimed to systematically select our included studies through screening some of the major online libraries including Pubmed, Medline, and the Cochrane Libraries were all searched until October 2022. The search engines were searched for the following keywords “((proton pump”) OR (omeprazole) OR (lansoprazole) OR (esomeprazole) OR (rabeprazole) OR (pantoprazole)) AND (capecitabine)”

Our meta-analysis adheres to the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses report (PRISMA guidelines). All studies, whether observational or interventional and of any date, with quantitative data regarding the effect of PPI administration on different survival outcome, and/or capecitabine adverse-event incidence, and/or different pharmacokinetic data were all included in the qualitative and quantitative meta-analysis; assuming the present data is sufficient for at least one aspect of comparison. Study abstracts that lacked a complementary full article were included in case they included sufficient data; while those that had a follow-up published article were dismissed for the sake of the main article. None of the articles were in non-English languages, and therefore no translations were required. Secondary analysis studies were included, provided that the National Clinical Trial (NCT) number was checked prior to inclusion to avoid overlap in case of multiple studies analysing the same primary clinical trial.

The primary outcome of this review and meta-analysis was the different survival outcomes in the PPI group versus the control group. Different survival outcomes include overall survival (OS) and progression-free survival in metastatic setting, and OS and recurrence-free survival (RFS) or disease-free survival (DFS) in the non-metastatic setting. The secondary outcomes include the incidence of HFS and diarrhea, as well as the pharmacokinetic differences between both the PPI and control groups.

In this systematic review, we have included a total of 17 studies out of the original 96 studies brought up from our searching keywords [4, 8, 12, 17–30]. These 17 studies were relevant and had sufficient data, and were hence included in the review and meta-analysis. Fourteen of the included studies had data concerning survival – with eight being in the metastatic setting and six in the non-metastatic setting –
nine had information regarding the effect on HFS incidence; and three regarding the effect on pharmacokinetics.

Regarding the meta-analysis, 12 out of the 14 studies included detailed data regarding the hazard ratios of PPIs on the efficacy of capecitabine, and were therefore included in the meta-analysis of the effect of PPI on the OS, RFS, PFS, and disease-free survival (DFS) (Fig. 1).

**Statistical Analysis**

We performed our meta-analysis on the data extracted from the included studies through Revman Ver. 5.3. All of the included forest plots were standardized to favour the PPI arm of the included studies on the left; and favour the control group on the right. In some cases where the sample was heterogeneous – p value of heterogeneity > 0.05 and I^2 > 50% – then the statistical was changed to “Random Model” to account for this heterogeneity.

Given the presence of some discrepancy in the units used to assess the different pharmacokinetic parameters, conversion measures were needed to standardize the data in order to be able to analyse correctly. The AUC was standardized to µM h/L, with standard deviation (SD) as the measure of data dispersion. Therefore, the ng h/mL unit – in the van Doorn study – was converted to µM h/L by dividing the AUC (ng h/mL) by the molecular weight of the measured compound [31] [Given the molecular weight of capecitabine is 359.35; of 5’ DFUR is 246.19; and of 5FU is 130.078; [32–35]]. The coefficient of variation (CV %) of that AUC was then converted to an SD through multiplying the CV% by the mean, and dividing the resulting number by 100.

The Cmax was standardized to µM/L. Therefore the Cmax in the study by Roberto et al. was converted from its original unit of µg/mL using the molarity and concentration calculator provided by “Novus Biologicals” [36]; through multiplying the given Cmax by 1000, setting the volume to Liters, and adding the molecular weight of the corresponding molecule as previously stated [32–35]. The standard deviation could then be easily calculated.

Both the Tmax and the T1/2 parameters in the study by van Doorn et al. were supplied as medians and inter-quartile ranges (IQR). Therefore they were converted to the standard mean and SD through a personal excel tool made based on the equations provided by Wan et al [37].

**Results**

4.1 Individual Qualitative Study Assessment of the Effect of PPI on PFS/RFS and OS

A total of fourteen studies addressed this issue [in breast of gastrointestinal malignancies or both], eight of which were retrospective studies; three that were secondary analyses; and three were clinical trials – either animal or human studies. Out of these studies, eight assessed patients with metastatic cancer on
capcitabine (Supplementary File 1 Table 1; [12, 17–23]), and six assessed non-metastatic patients in the neo- or adjuvant settings (Supplementary File 1 Table 2; [8, 24–28]).

Out of the fourteen studies comparing treatment efficacy with the concomitant use of PPIs versus control, only three studies showed significant differences between both groups [8, 12, 25]. These three studies were either in the retrospective analyses [8, 25] or the secondary analysis category [12] – none were clinical trials. The first one of these three was the study done by Chu et al. [12], where there appeared to be significant difference in the hazard ratios for both PFS (HR = 1.55, 95% CI: 1.29–1.81, p < 0.001) and OS (HR = 1.34, 95% CI: 1.06–1.62, p = 0.04) in the Capeox only arms, with the lapatinib arms showing no significant difference (Fig. 2).

The second study, showing significant differences between both groups, was the study done by Sun et al. which showed statistically significant lower RFS in the PPI group (HR = 1.89, 95% CI: 1.07–3.35, p = 0.03; [8]). Additionally, the study by Wong et al. has also shown statistically significant double the RFS in the control group (HR 2.03; 95% CI 1.06–3.88; p = 0.033; Figure 3; [25]).

It is also worthy of mention that in Wang et al.’s study [9], which is later included in the meta-analysis of the effect of PPIs on the incidence of HFS, the authors reported additional information regarding the possible interaction between PPIs and capcitabine in the Capeox arm; and reported no significant differences in either the PFS (p = 0.52) or the OS (p = 0.98) – with no detailed data regarding the exact hazard ratios included. This study was not included in the qualitative or meta-analysis figures, and was only included in the supplementary File 1 Table 1 provided.

4.2 Meta-analysis of the Effect of PPIs on the Efficacy of Capecitabine

A complementary meta-analysis for the OS, PFS and/or RFS was done individually for studies including hazard ratios of such outcomes, using inverse variance (Supplementary File 2 Figs. 1–10). In regards to overall survival, 11 studies were included using the unadjusted HRs (Fig. 4). The analysis found a statistically significant effect on the OS; with a pooled HR of 1.12; 95% CI 1.00–1.25, p = 0.05; Fig. 4a. On using the adjusted HR for analysis, the pooled HR became 1.23; with a 95% CI of 1.08, 1.39; p = 0.001.

In case of studies assessing metastatic malignancies, the pooled HR of the PFS from six studies showed statistically significant difference at 1.14; 95% CI 1.04–1.26, p = 0.008; Fig. 4b. However, on accounting for the present sample heterogeneity – $I^2$ 61% and p-value of heterogeneity 0.03 – through using a random model analysis, this significance was lost; HR = 1.10; 95% CI 0.93–1.30; p = 0.26; Supplementary File 2 Fig. 3. The adjusted pooled HR for PFS was also significant at 1.43; 95% CI 1.25, 1.63; p < 0.00001. Yet, on doing random model analysis to account for sample heterogeneity, $I^2$ 79%; the significance of the effect on the adjusted PFS was once again lost (HR = 1.30; 95% CI 0.92–1.82; p = 0.13; Supplementary File 2 Fig. 8).
While, in studies assessing patients in the (neo)adjuvant setting, six studies were assessed, and the four studies assessing RFS showed the strongest association at a pooled HR of 1.75; 95% CI: 1.21–2.53; p = 0.003; Fig. 4c, and a pooled adjusted HR of 1.87; 95% CI 1.21–2.89; p = 0.005. A meta-analysis was also done on DFS; yet no significant difference was found in the unadjusted (HR: 1.31; 95% CI: 0.94–1.83; p = 0.12; Fig. 4d) or confounder-adjusted setting (HR: 1.46; 95% CI: 0.94–2.27; p = 0.10).

4.3 Met-analysis of the effect of PPIs on the incidence of HFS

A total of nine studies, three of which were clinical trials, were included in the meta-analysis assessing the relationship between the concomitant administration of PPI with capecitabine and the incidence of HFS [4, 9, 12, 17, 20, 26, 29, 30]. The analysis showed statistically significant lower relative risk by around 23% in the PPI group when compared to the control group (RR: 0.77, 95% CI: 0.70, 0.85, p < 0.00001; Fig. 5). There was no statistical significance; however, regarding the use of PPI and the incidence of diarrhea after analysing six of the included studies (RR: 0.95; 95% CI: 0.65, 1.26, p 0.56; Supplementary File 2 Fig. 12; [9, 12, 17, 26, 29, 30]).

The study done by Takemura et al. has also reported additional data regarding HFS; where they found a greater difference between both groups regarding the incidence of HFS when the HFS grade was adjusted to ≥ Grade 2, with significantly lower HFS events reported in the PPI group (18% vs. 43% in the PPI vs. non-PPI groups respectively, p = 0.001; [18]). Additionally, the PPI group reported a lack of pre-mature capecitabine termination due to HFS; compared to the non-PPI group (14%), as well as longer time of onset to HFS (reaching up to 20 months in the PPI group with a median of 1.4 months; compared to up to 9 months in the non-PPI using group with a median of 2.2 months).

4.4 Pharmacokinetics

On assessing the effect of PPIs on the pharmacokinetics – including the AUC, Cmax, Tmax, and T1/2 – of capecitabine, three studies were included [17, 29, 30]. However, none of the assessed parameters showed statistically significant results on doing individual meta-analysis for each parameter (Supplementary File 2 Figs. 13–20).

Discussion

Capecitabine is an oral 5-fluorouracil pro-drug fluoropyrimidine chemotherapeutic agent. [1] Oral chemotherapy has been emerging as a more convenient alternative for the conventional IV route drugs without diminishing the possible clinical benefit achieved by the IV agents [2] [38, 39]. In a questionnaire done on around 400 patients who have previously received both oral and IV chemotherapy regimens, a major preference for the oral route was seen in around three-fourth of the patients. This preference is mostly due to the lower alteration of daily life routine, less hospital waiting time, less IV-related complications, and less worry about IV access-related difficulties [38].
One of the most commonly associated adverse events associated with capecitabine is gastrointestinal upset; commonly treated with PPIs or other forms of acid-suppressing drugs [9]. However, PPIs have long been avoided with capecitabine due to some evidence of interference with its pharmacokinetics and efficacy [6, 7]. However, a review recently done by Cheng et al. has reported lack of evidence regarding this notion [13]. The suggested interaction between PPI and capecitabine is mostly due to the pre-notion that the increase in the gastric PH by the PPIs could possibly affect the gastric fragmentation of the tablet, and therefore affect its rate of absorption [8, 12]. However, capecitabine tablets can dissolve over multiple PH degrees ranging from the highly acidic spectrum up to an almost neutral environment [13], and therefore the average gastric pH while on PPI – around 4 – is not sufficient to significantly affect the ionization, and absorption, of capecitabine.

Proton pump inhibitors have long been studied for possible extra-acid-suppression benefits. They have proven to bear anti-inflammatory as well as possible anti-resistance benefits in case of multi-drug resistant cancers [10, 18, 40]. However, one of the recently studied benefits includes a recent study by Hiromoto et al. that has reported significant reduction in the severity of the HFS (p < 0.05), possibly being due to the reduction in the TNF-α in the mice limbs (p < 0.01). This study also had a retrospective patient-based arm that was also included in the meta-analysis data of HFS and has reported significant reduction in the HFS in people that were taking concomitant PPI – with an odds ratio of 0.74 in favour of PPI use [4].

Given the contradicting results regarding the benefits and the risks of using PPIs concomitantly with capecitabine; we have tried to meticulously assess both in our meta-analysis, to account for the already-present discrepancy within the literature.

Qualitative assessment of each included study regarding different safety outcomes revealed significant findings in three out of the 14 studies. However most of these studies, eight of the 14, are retrospective in origin, with another three being secondary analyses of prior trials, making their scientific evidence of lower value when compared to actual primary clinical trials with confounder-control [41].

Another possible drawback of the included retrospective studies is that all of the study data were based only on drug dispensal data, with some studies including patients in the PPI group if they received PPIs at any point during treatment [8, 25], therefore exposing these studies to a form of selection bias. Another discrepancy is seen in the study by Chu et al., which showed significant differences only in the incidence within the capeox-only arm [12]; while the capeox/lapatinib arm showed no difference with the use of PPIs. This might raise questions regarding the validity of such results, given that lapatinib does not cause HFS in the first place[42]. Additionally, in the study by Wong et al. [25], confounder adjustment reversed the statistical significance of the effect of PPIs on the RFS (HR: 2.20; 95% CI: 1.14–4.25; p = 0.18). This is not to in any way suspect the validity or credibility of the studies’ methodologies or significant findings, but to point out the common possible limitations, like all of the data obtained from retrospective studies [41, 43].
To this end, the data from our meta-analysis concerning the efficacy has shown that the concomitant use of PPIs was associated with a decline in the OS (HR 1.12; p = 0.05); PFS (HR 1.14; p = 0.008); and RFS (HR 1.75; p = 0.003). Yet, the significance in the PFS effect; both the unadjusted and adjusted hazard ratios, was abolished on using the random effect analysis to account for sample heterogeneity – I² at 61% and 79%, respectively. The RFS was the parameter scoring the highest HR in response to concomitant PPI administration (HR = 1.75; p = 0.003), that was even higher when adjusted for confounding factors; to reach 1.89; p = 0.005; Supplementary File 2 Fig. 9. Disease-free survival reported no significant differences between both groups; Fig. 4d; Supplementary File 2 Figs. 5, 10.

When it comes to safety prognosis, PPIs were associated with lower incidence of HFS; RR 0.77; p < 0.00001; Fig. 5. These findings were in line with the findings of the study by Hiromoto et al. that contributed to the majority of the weight of this analysis at a sample size as large as 60,668 patients with a RR of 0.75 [4].

Finally, when we analysed the pharmacokinetic overlap between both drugs, no significant correlation was found. The lack of significant difference could in our opinion be attributed to the lower number of studies, as well as the different units and times each study measured the PK parameters after the start of therapy, causing high variations in the levels between the studies (Supplementary File 2 Figs. 13–20). On one hand, the study by Sekido et al. measured the plasma levels on the first day of the first cycle [29]; while the study by Roberto et al. measured them at week 4 and week 8 [17], and the study by van Doorn et al. measured them on day 8 of each phase [30]. This could have actually created major discrepancies in the pharmacokinetic comparison across studies.

Despite the possible detrimental effects of PPIs on survival, our findings concerning the incidence of HFS are in our opinion quite promising; even if not directly. The results of our analysis might open the doors for future studies to fully discover and make use of the exact mechanism by which PPIs reduce HFS. Therefore, could this open the doors for the use of anti-TNF agents in patients taking capecitabine? Particularly given the fact that multiple studies have reported the lack of cancer development or progression in patients diagnosed with IBD – with even potential benefits in osseous metastases as well as overcoming treatment resistance to multiple agents [44–47].

Possible limitations in our meta-analysis include different follow-up durations in the studies, and notable discrepancy in the pharmacokinetic data, including the time of assessment since beginning treatment; as well as the measurement units, which required extensive and meticulous conversions as well as using subgroups within each study in order to fully analyse the already-scarce data in the three assessed studies.

Individual data incriminating the use of PPIs with capecitabine is quite limited – with possible confounders and validity threats in multiple studies seen during our qualitative assessment, due to study design issues, as previously mentioned. However, given the present fear of conducting a clinical trial in
case of a positive association, this only leaves us with the possibility of doing a meta-analysis in order to get a better insight on these contradictory findings, as done in this paper.

In conclusion, our meta-analysis on this large population – reaching as much as 3303 patients in the survival analyses and reaching 62,173 patients in the HFS incidence assessment – has reported both beneficial as well as detrimental interactions with capecitabine. Proton pump inhibitors are associated with lower incidence of HFS compared to the control group; with 33% relative risk reduction in the incidence of HFS. However, regarding possible survival risk, PPIs have shown statistically significant worse treatment outcomes in all aspects, save for the DFS, with a much greater impact on the RFS in non-metastatic cases with up to 75% higher relative risk of recurrence at a HR of 1.75; p = 0.003; and increasing to up to 87% increased risk when adjusted for confounders. This should in turn warrant caution and awareness on the possible risks of concurrent use of PPIs along with capecitabine, with extra-caution and meticulous history taking in patients taking capecitabine in the (neo)adjuvant setting due to the much higher impact on patient survival.

**Declarations**

**Data Availability**

All collected data can be found in the supplementary files included with the articles – if not included within the main article. Full extracted data included in the qualitative data analysis can be found in Supplementary File 1; while all forest plot data can be found in the Supplementary File 2 – with all data from the included studies being present in the forest plots even if not statistically significant.

**Conflict of Interest**

We report no conflict of interest for this meta-analysis.

**Ethical Approval and Consent to Participate**

Not applicable

**Consent to Publication**

Not applicable

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**Authors’ Contributions**
DM has collected data from the included studies in both the qualitative analysis and the meta-analysis. DM was also a major contributor to the writing of the manuscript. WA has revised the data collected as well as the written manuscript for writing style and fine errors. Both DM and WA have contributed to the meta-analysis portion of the paper. All authors have read and approved of the publication of the final version of the manuscript.

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**Figures**
Figure 1

Prisma flow chart in search for studies assessing the relationship between PPIs and capecitabine
[Legend: PPIs=Proton pump inhibitors; HFS=Hand-foot syndrome; PRISMA=preferred reporting items for systematic reviews and meta-analyses]
Figure 2

Statistical effect of PPIs on metastatic disease; red studies indicate non-significant differences; while blue studies indicate significant differences; PFS = progression-free survival, OS = overall survival, * = Capeox arm in Chu et al’s study, ** = Capeox and Lapatinib arm in Chu et al’s study, *** = Gastrointestinal cancer arm in yang et al’s study, **** = Breast cancer arm in Yang et al’s study; (a) Median PFS in PPI versus Control group; (b) Median OS in PPI versus Control group; (c) Median PFS hazard ratios for PPI versus control group; (d) Median OS hazard ratios for PPI versus control group
Figure 3

Statistical effect of PPIs on metastatic disease; red studies indicate non-significant differences; while blue studies indicate significant differences; RFS = recurrence-free survival, DFS = disease-free survival, OS = overall survival, * = Wong et al's OS rates are at 3 years, ** = Wong et al's significant results were lost when the study accounted for different confounders; (a) DFS/RFS rates at 5 years in PPI versus Control group; (b) OS rates at 5 years in PPI versus Control group; (c) RFS/DFS hazard ratios for PPI versus control group; (d) OS hazard ratios for PPI versus control group
Figure 4

Forest plot of the effect of proton pump inhibitors on three survival outcomes as predicted by the risk ratio (significance at p-value < 0.05). a) Assessment of the overall survival (OS); b) Assessment of the progression-free survival; and c) Assessment of the recurrence-free survival
Figure 5
Forest plot of the effect of proton pump inhibitors on the incidence of capecitabine-induced hand-foot syndrome as predicted by the risk ratio (significance at p-value < 0.05)

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFile1QualitativeDataAnalysisEfficacyTables.docx
- SupplementaryFile2ForestPlotsofMetaanalysis.docx