NOVEL THERAPEUTIC OPTIONS IN THE TREATMENT OF ACUTE PANCREATITIS

Ph.D. Thesis

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" Nature uses only the longest threads to weave her patterns so that each small piece of her fabric reveals the organization of the entire tapestry."

Richard Feynman

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1. LIST OF ABBREVIATIONS

AKI	acute kidney injury
ARDS	acute respiratory distress syndrome
AP	acute pancreatitis
APR	abdominal pain relief
CI	confidence intervals
COH	cohort study
CRP	C-reactive protein
ERCP	endoscopic retrograde cholangiopancreatography
GI	gastrointestinal
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HA	hyperamylasemia
IL	interleukin
LOHS	length of hospital stay
MD	mean differences
MODS	multiple organ dysfunction syndrome
N/A	no data available
OR	odds ratio
PEP	post-ERCP pancreatitis
PPI	proton pump inhibitor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
RCT	randomized controlled trial
ROB2	revised Cochrane Risk-of-Bias tool
ROBINS-I	Risk Of Bias in Non-randomized Studies-of Intervention
SD	standard deviation
SoC	standard of care
SR	symptom reduction
TNF	tumor necrosis factor

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

Pharmacists have a special knowledge of medications' pharmacokinetics and pharmacodynamics, which places them in a unique position in the medical team. My vision is to have a dedicated pharmacist in every ward to provide and support evidence-based medicine. I would like to advocate for this vision with my PhD thesis as a mission statement, in which our team investigated several aspects of evidence-based medicine related to acute pancreatitis (AP) treatment. My specific goals in my doctoral studies were to investigate ulinastatin and proton pump inhibitors (PPIs) in the treatment of AP and to investigate nafamostat in the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis.

2.2. Scientometrics

Number of all publications:	5
Cumulative IF:	23.3
Av IF/publication:	4.66
Ranking (Sci Mago):	D1:4, Q1:1, Q2: -
Number of publications related to the subject of the thesis:	3
Cumulative IF:	14.7
Av IF/publication:	4.9
Ranking (Sci Mago):	D1: 3, Q1: -, Q2: -
Number of citations on Google Scholar:	27
Number of citations on MTMT (independent):	17
H-index:	3

The detailed bibliography of the student can be found on page 58.

2.3. Future plans

My future plans are to continue exploring therapeutic options in the treatment of AP and to expand my expertise to other fields.

I believe that clinical pharmacists are essential in a modern healthcare system. Clinical pharmacy has great opportunities both in patient care and in research. I would like to share the knowledge gained throughout my doctoral studies with my colleagues to build better care for our patients. Every relationship between the medical staff or between the medical staff and the patient could benefit from their knowledge and viewpoint.

3. SUMMARY OF THE PH.D.

Management of AP is challenging. The key challenges are the sudden onset of the disease, the lack of specific treatment available, and the condition of the patients.

To improve the rational pharmacotherapy of AP, we investigated different therapeutic options in three systematic reviews and meta-analyses.

Ulinastatin, a protease inhibitor, could suppress the activation of inflammatory mediators, thus might prevent the autoactivation sequence in AP. In our meta-analysis, we found that then added to the standard of care (SoC) (somatostatin or octreotide), the complication rate of acute respiratory distress syndrome (ARDS), acute kidney injury (AKI) and multiple organ dysfunction syndrome (MODS) was significantly lower than in case of standard therapy alone.

Nafamostat is also a protease inhibitor with theoretical effects similar to ulinastatin and it is commonly used to prevent post-ERCP pancreatitis (PEP). However, there were conflicting results in the literature on its efficacy. Based on our results, nafamostat significantly reduced the overall incidence rate of PEP, although in the subgroup analysis of different severity of PEP, it prevented only mild PEP.

In theory, PPIs could decrease exocrine secretion of the pancreas by inhibiting the activity of hydrogen potassium ATPases within the pancreatic ducts, thus alleviating the severity of AP. Both experimental studies and human trials show controversial effects of PPIs in the treatment of AP. Our analysis suggests that there are no significant effects on mortality, length of hospital stay (LOHS), or complication rate of ARDS, but the available evidence is scarce.

Our analyses showed statistically beneficial effects of ulinastatin in the treatment of AP; and nafamostat in the prevention of PEP. Furthermore, our results suggest that there is no evidence for the use of PPIs in the treatment of AP.

4. GRAPHICAL ABSTRACT

[1] Horváth, István László et al. *Scientific reports* vol. 12,1 17979.
[2] Horváth, István László et al. *Clinical pharmacology and therapeutics* vol. 115,2 (2024): 206-212
[3] Horváth, István László et al. *Scientific reports* vol. 13,1 2791

5. INTRODUCTION

5.1. Overview of the topic

5.1.1. What is the topic?

The investigations focused on the evaluation of different therapeutic options in the treatment of AP.

5.1.2. What is the problem to solve?

There is no disease-specific treatment for AP, which targets pathophysiological pathways, so prompt and effective therapy is needed.

5.1.3. What is the importance of the topic?

AP is the sudden inflammation of the pancreas of various etiologies, mainly alcohol and gallstones (1). The incidence rate of AP ranges between 4.6 and 100 cases per 100,000 patients; however, its frequency has steadily increased in the past decade, especially in Western countries (2, 3). The overall mortality rate is approximately 5%, but it is highly dependent on the severity of the disease (4). Based on the Atlanta classification, AP can be classified as mild, moderate, or severe according to local and systemic complications (5). Mild cases are primarily self-limiting and resolve within a week, but in severe cases, mortality can reach 20–40% (6). Early identification and management of AP are crucial to achieve better patient outcomes. Treatment delay could lead to life-threatening complications even in cases of mild AP at onset.

ERCP is used in the diagnosis and treatment of patients with pancreatobiliary diseases. The procedure is minimally invasive, but not without risks. Although the overall mortality rate for ERCP is around 1%, it is highly dependent on the underlying disease, particularly cancer (7). The leading complications of ERCP are bleeding, perforation, and PEP (8, 9). The overall incidence of PEP ranges from 3.5 to 9.7% (10), with a mortality rate of around 0.7%. Of all cases of ERCP, the incidences of mild, moderate and severe PEP are 6.0%, 3.3%, and 0.7%, respectively (11).

5.1.4. What would be the impact of our research results?

We evaluated a possible specific and preventive therapy that are little known in western countries. Based on our statistical analyses, both therapies can be used effectively in the treatment of disease, thus supporting better patient outcomes. In addition, we highlight the potential misuse of PPI in the treatment of AP, thereby improving patient safety and reducing health care costs.

5.2. Acute pancreatitis

Based on complications arising and the severity and occurrence of organ failure, AP can be classified as 'mild', 'moderately severe', and ‘severe’ according to the revised Atlanta classification system (4). A common definition for PEP is based on the consensus of Cotton et al. (12) and the revised Atlanta classification for AP (5). However, the latest European guideline suggests a definition of the condition as “new or worsened abdominal pain combined with > 3 times the normal value of amylase or lipase at more than 24 hours after ERCP and requirement of admission or prolongation of a planned admission.” (10) Both diseases have common characteristics, but we have to distinguish the two from each other.

The development of AP is initiated by excessive Ca^{2+} signal generation, leading to decreased mitochondrial ATP generation in acinar cells, thus promoting trypsin activation. The resulting necrosis releases further trypsin, kallikrein, and other pro-inflammatory mediators, which further damage the acinar cells, creating an inflammatory cascade (13).

The precise pathophysiology of PEP is not fully understood; however, several risk factors have been identified. Physical factors (mechanical, thermal, and hydrostatic), chemical (contrast agent and enzymatic), and patient-related factors (female sex, history of PEP, and Oddi dysfunction) factors can contribute to the development of PEP (14). Physical damage can occur during the procedure, for example, prolonged manipulation of the papillary orifice, or difficult cannulation, causing papillary edema. This process inhibits the outflow of pancreatic juice and thus leads to pancreatitis (14). The type of contrast

agent could cause osmolality-induced and ionic toxicity; however, a recent analysis did not find significant differences between the types of agents (15).

5.3. Theoretical mechanisms of action of ulinastatin, nafamostat and PPIs in pancreatitis

Somatostatin or its analogue octreotide is part of standard AP care, although international guidelines do not recommend its use. They are commonly used in the therapy of AP, especially in Asian countries (16). In theory, they reduce pancreatic enzyme secretion, allowing the pancreas to rest and avoiding further autodigestion (17). However, clinical studies show no statistical difference in patient outcomes when comparing octreotide or somatostatin with placebo (18).

If given in the early stage of AP, the trypsin inhibitor ulinastatin may suppress the trypsin autoactivation sequence. An *in vitro* study by Kanayama (19) suggests that ulinastatin might inhibit Ca^{2+} influx or mobilization; however, this effect has not been studied further. Furthermore, it also inhibits chymotrypsin, thrombin, kallikrein, neutrophil elastase, and cathepsin, thus regulating systemic inflammation by reducing the release of pro-inflammatory cytokines (20). This complex mechanism of action could complement those of somatostatin analogues, explaining the increased efficacy of combination treatment in AP. In hereditary pancreatitis, trypsinogen activation plays a pathogenic role in the development of chronic pancreatitis after an acute episode of AP (21, 22). Further investigation is needed to determine the precise mechanism of action.

Acute gastric mucosal lesions caused by stress are more likely to occur in patients with severe AP (23), increasing the risk of gastrointestinal (GI) bleeding and ulceration. Therefore, protecting the gastric mucosa appears to be a crucial therapeutic objective. The pillars of acid secretion suppression are H_2-receptor inhibitors and PPIs. Theoretically, PPIs could also decrease pancreatic exocrine secretion by inhibiting the activity of H^+/K^+ ATPases within pancreatic ducts similar to gastric ATPases (24). Experimental studies had controversial results regarding their ability to reduce pancreatic amylase secretion (25, 26). Furthermore, in experimentally induced pancreatitis, pantoprazole reduced inflammation and necrosis (26). Theoretically, PPI administration can be a good therapeutic option for protecting the upper GI mucosa and resting the inflamed pancreas.

Nafamostat is also a serine protease inhibitor that suppresses trypsin and kallikrein in experimental models of pancreatitis (27, 28). In theory, the effects of nafamostat reduce circulating mediators of AP, thus preventing the escalation of inflammation. However, the exact mechanism of nafamostat in the prevention of PEP is not yet known. Nafamostat also inhibits other proteolytic enzymes, for example, thrombin and plasmin (27).

AP research is currently dominated by studies on risk factors for pancreatitis (29-31), with a decreasing number of articles on therapeutic options (32). Only a few supportive therapies are recommended in the current guidelines, which consist of early nutrition, pain relief, and fluid management (4, 33-35), therefore, there is a great need for a disease specific treatment.

6. OBJECTIVES

6.1. Study I. – Investigating the effects of ulinastatin-somatostatin analogue combination therapy in acute pancreatitis

There are several clinical trials (36-44) in the literature that report on the effectiveness of ulinastatin combination therapy in AP, showing promising results. We aimed to conduct a systematic review and meta-analysis to summarize the available data on therapy.

6.2. Study II. – Investigating the effects of proton pump inhibitors in acute pancreatitis

Previous studies (45-53) had contradictory findings on the impact of PPIs on the prognosis of patients with AP, our aim was to investigate the associations between PPIs in AP and various clinical outcomes in a systematic review and meta-analysis.

6.3. Study III. – Investigating the effects of nafamostat in the prevention of post-ERCP pancreatitis

A former network meta-analysis showed no beneficial effect of nafamostat (54), however, several trials (55-61) have been published since. Therefore, our objective was to investigate the current evidence for nafamostat in the prevention of PEP in a systematic review and meta-analysis.

7. METHODS

7.1. Search and selection strategy

The recommendations of the Cochrane Collaboration (62) and the statements of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA 2020) (63) were followed in reporting the findings of this systematic review and meta-analysis. We registered the review protocol in the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: Study I.: CRD42021282614; Study II.: CRD42022303136; and Study III.: CRD42022367988). We used the PICO (Patient/Population, Intervention, Comparison and Outcomes) framework to formulate the research question, and to define eligibility criteria:

- Study I. – The population consisted of adult patients (> 18 years old) with AP; the intervention group included patients who received the combination treatment (ulinastatin therapy with somatostatin or octreotide) besides other supportive measures; the control or comparator group included cases treated with somatostatin or octreotide monotherapy besides other supportive measures. The primary outcomes were mortality, complications (ARDS, shock, AKI, MODS), and LOHS. As secondary outcomes, we evaluated symptom reduction (SR) rate, changes in laboratory parameters, and adverse events of the intervention.
- Study II. – We investigated adult patients with AP, who were treated with PPIs in addition to SoC (I). The control group did not receive PPI, and we investigated outcomes including mortality, LOHS, complications, and change in laboratory parameters.
- Study III. – The patient population consisted of adult patients who underwent the ERCP procedure. We investigated the effects of nafamostat as a preventive treatment compared to placebo. The primary outcome was the incidence of PEP. Secondary outcomes were PEP severity, complication rates, adverse reactions, and laboratory parameters. Only randomized clinical trials (RCTs) were eligible for inclusion.

The systematic searches were performed in six databases (Cochrane Central Register of Controlled Trials, Embase, MEDLINE, Scilit, Scopus, Web of Science). The reference lists of the identified eligible studies were screened for further reports.

7.2. Selection and data collection

The systematic search results were exported to the EndNote X9 citation manager (Clarivate Analytics, Philadelphia, PA, USA). After the automatic and manual duplicate removal, the title and abstract, and full-text selection processes were done by two independent authors according to the inclusion criteria. A third author made the final decision in case of disagreements. Cohen's kappa coefficient was calculated at each selection step to evaluate the level of agreement between the authors.

We used Google Translate® for the translation of articles in languages other than English or German. Plot Digitizer (2015) was used to transform graphical values into numerical form. Additionally, we searched the reference list of the included studies.

Two independent investigators manually extracted the data from the eligible articles and cross-checked each other's datasets to ensure precision. Microsoft Excel (Microsoft, Office 365, Redmond, WA, USA) was used for data collection.

7.3. Statistics

Only outcomes reported in at least three studies were considered for including in the meta-analysis. The pooled results were reported as ORs (odds ratios) for binary outcomes calculated with the Mantel–Haenszel method, and as mean differences (MDs) for continuous outcomes and the corresponding 95% confidence intervals (CI). For binary outcomes, ORs were used for the effect measure, while for continuous outcomes, MDs with corresponding standard deviations (SDs) were used. In the latter case when only before-and-after treatment group means and SDs were reported, we used the difference in means, and the sum of within-group before-and-after SDs as a conservative estimate for SDs of the differences. Random models were used for pooling in the case of both outcome types. Subgroup comparisons were carried out following the description in Harrer et al. (64). To estimate τ^2 we used the Paule-Mandel method and the Q profile

method to calculate the CI of τ^2 (64, 65). A funnel plot of the logarithm of effect size and comparison with the standard error for each trial was used to evaluate publication bias. Statistical heterogeneity between trials was assessed by the Cochrane Q test and the I^2 statistic values (66). I^2 values of 25, 50, and 75% were identified as low, moderate, and high estimates, respectively. Outlier and influence analyses were carried out following the recommendations of Harrer et al. and Viechtbauer and Cheung (64, 67). Forest plots were used to graphically summarize the results (68, 69). Where applicable, we reported the prediction intervals (i.e., the expected range of effects of future studies) of the results following the recommendations of IntHout et al. (69). All analyses were carried out in R version 4.1.3 (R Core Team, Vienna, Austria) using the meta (70) and dmetar (64) packages.

7.4. Risk of bias assessment and certainty of evidence assessment

Two authors independently evaluated the risk of bias for each included by utilizing the revised Cochrane Risk-of-Bias tool (RoB2) (71). In case of disagreements, a third author resolved were involved. The domains evaluate the bias arising from the randomization process, deviations from the intended intervention, missing data, the measurement of the outcome, and the selection of the reported results. Cohort studies were evaluated by Risk Of Bias in Non-randomized Studies-of Intervention (ROBINS-I) tool (72). The final conclusion of the risk assessment could be characterized as ‘low’, ‘some concerns’, or ‘high’.

The framework Grading of Recommendations, Assessment, Development and Evaluations (GRADE) and the corresponding tool (73) were used to evaluate each outcome for the certainty of evidence. Each outcome was rated for risk of bias, inconsistency, indirectness, imprecision, publication bias, and the presence of a large effect, dose-dependent response, and plausible confounders as ‘not serious’, ‘serious’, or ‘very serious’. The final certainty of the evidence was categorized as ‘very low’, ‘low’, ‘moderate’, or ‘high’.

8. RESULTS

8.1. Study I. – Investigating the effects of ulinastatin-somatostatin analogue combination therapy in acute pancreatitis

8.1.1. Description of included studies

The database search identified 60 records. After duplicate removal, and title and abstract selection (Cohen's Kappa 0.93), we identified 9 eligible articles during the full-text article analysis (Cohen's Kappa 1.00). All included reports were available as peer reviewed journal articles. The search results and the selection process are summarized in **Figure 1.**

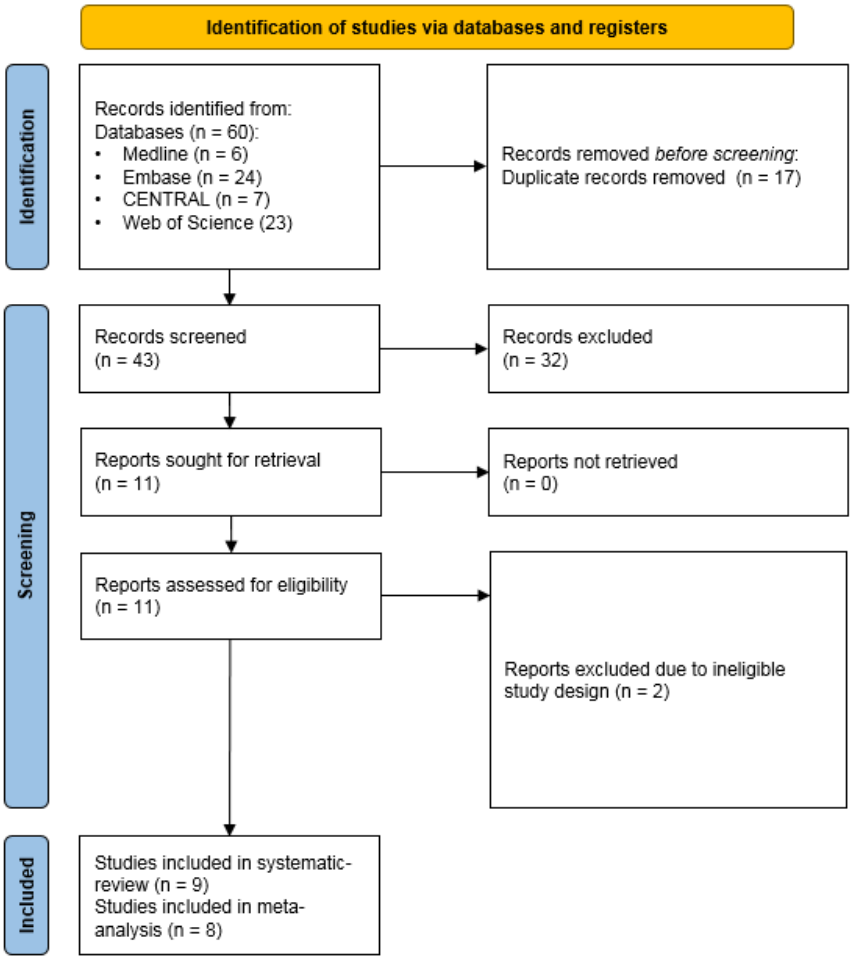

Figure 1. *PRISMA flowchart for Study I. (74)*

Overall, 9 studies were included in our systematic review. There were no overlapping populations in the meta-analyses. All studies were single centre. Treatment arm allocation ratios were 1:1 in each study. The baseline characteristics of the eligible studies are summarized in **Table 1**. The posology for each therapeutic regimen is detailed in **Table 2.**

Table 1. Baseline characteristics of the trials included in Study I. (74)

Study	Country	Population	Sample size (% female)	Intervention group	Sample size [intervention group] (% female)	Mean age (years) ± SD [intervention group]	Control group	Sample size [control group] (% female)	Mean age (years) ± SD [control group]	Outcomes
Wang, 2013	China	Severe acute pancreatitis	123 (49.6)	ulinastatin + somatostatin	62 (50.0)	41.8 ± 13.9	somatostatin	61 (49.2)	42.6 ± 12.6	mortality; MODS
Tu, 2014	China	Acute pancreatitis	110 (47.3)	ulinastatin + octreotide	55 (45.5)	37.3 ± 6.1	octreotide	55 (49.1)	38.7 ± 5.8	LOHS; SR; APR
Guo, 2015	China	Severe acute pancreatitis	120 (46.7)	ulinastatin + octreotide	60 (48.3)	46.6 ± 4.1	octreotide	60 (45.0)	46.3 ± 4.3	mortality; LOHS; MODS; ARDS AKI; shock; SR; APR
Wang, 2016	China	Severe acute pancreatitis	246 (48.8)	ulinastatin + somatostatin	124 (49.2)	40.8 ± 11.6	somatostatin	122 (48.4)	41.9 ± 12.8	mortality; LOHS; MODS; SR; APR
Wang, 2017	China	Moderately severe and severe acute pancreatitis	42 (40.5)	ulinastatin + somatostatin	21 (42.9)	47.3 ± 11.1	somatostatin	21 (38.1)	48.6 ± 10.0	ARDS; AKI; shock; APR
Yang, 2017	China	Severe acute pancreatitis	88 (39.8)	ulinastatin + octreotide	44 (40.9)	42.1 ± 9.8	octreotide	44 (38.6)	43.2 ± 9.2	N/A
Yang, 2018	China	Severe acute pancreatitis	94 (37.2)	ulinastatin + octreotide	46 (41.3)	46.2 ± 10.6	octreotide	48 (33.3)	47.7 ± 11.8	mortality; LOHS; ARDS; AKI; shock; SR; APR
Meng, 2019	China	Acute pancreatitis	108 (45.4)	ulinastatin + octreotide	54 (N/A)	N/A	octreotide	54 (N/A)	N/A	SR
Xu, 2019	China	Severe acute pancreatitis	106 (49.1)	ulinastatin + somatostatin	53 (50.9)	57.0 ± 6.9	somatostatin	53 (47.2)	57.5 ± 7.4	LOHS; SR

Abbreviations: SD: Standard deviation; N/A: no data available; MODS: multiple organ dysfunction syndrome; LOHS: length of hospital stay; SR: symptom reduction; APR: abdominal pain relief; ARDS: acute respiratory distress syndrome; AKI: acute kidney injury

Table 2. Summary of the applied therapies as reported in each eligible article for Study I. (74)

Study	Intervention group	Dose	Regime	Duration (days)	Control group	Dose	Regime	Duration (days)
Wang, 2013	ulinastatin + somatostatin	100000 U	q12h	10	somatostatin	250 mcg/h	continuous	10
Tu, 2014	ulinastatin + octreotide	200000 U	qd	14	octreotide	0.5 g/(kg x h)	N/A	14
Guo, 2015	ulinastatin + octreotide	1. 100000 U 2. 50000 U	1. q12h 2. q12h	1. for 3 2. then 7–14	octreotide	0.1 mg	q8h	7-14
Wang, 2016	ulinastatin + somatostatin	100000 U	q12h	10	somatostatin	3 mg	continuous	10
Wang, 2017	ulinastatin + somatostatin	100000U	1. q12h 2. q24h	1. for 3 2. then 7	somatostatin	6 mg	continuous	10
Yang, 2017	ulinastatin + octreotide	100000 U	q12h	10	octreotide	0.1 mg	q6h	7
Yang, 2018	ulinastatin + octreotide	200000 U	qd	14	octreotide	0.1 mg bolus + 25 mcg/h	continuous	14
Meng, 2019	ulinastatin + octreotide	100000U	q12h	7	octreotide	0.6 mg	continuous	7
Xu, 2019	ulinastatin + somatostatin	100000 U	q24h	7	somatostatin	6 mg	continuous	7

Abbreviations: U: unit; q: every; h: hour; d: day; mcg: microgram; mg: milligram, N/A: no data available

8.1.2. Statistical analysis

Our pooled results revealed decreased complication rates in the intervention group (**Figure 2**). With combination therapy, the rates of ARDS [OR 0.27; 95% CI 0.13–0.60; I^2=28%] and AKI [OR 0.29; 95% CI 0.09–0.97; I^2=49%] were reduced by approximately 70%, while MODS could be prevented in around 60% of cases [OR 0.39; 95% CI 0.20–0.75; I^2=0]. Reduction of shock incidence was not statistically significant [OR 0.46; 95% CI 0.20–1.07; I^2=39%]. The associated heterogeneity for the results was not important or moderate; however, due to the low number of trials, interpretation has to be treated with caution.

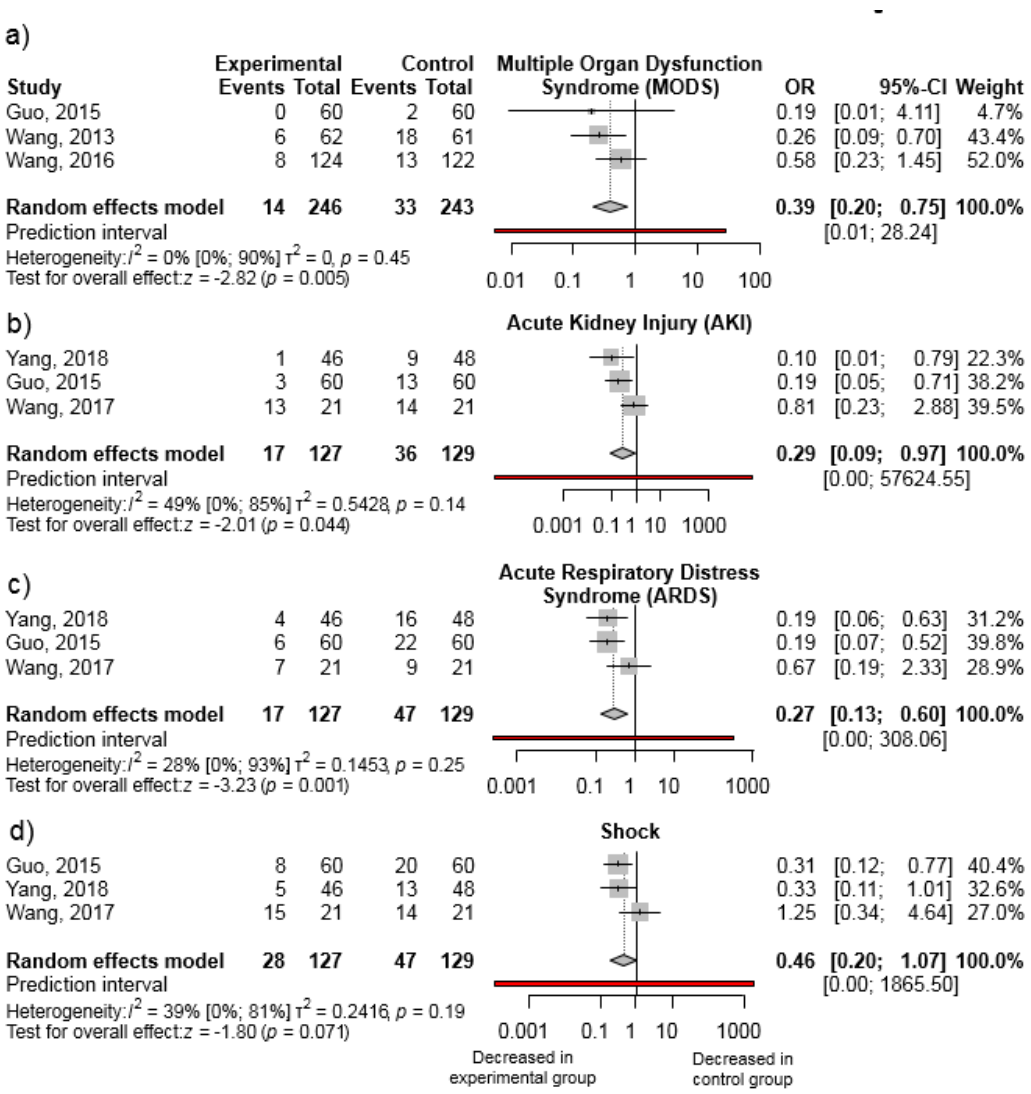

Figure 2. *Ulinastatin in combination with somatostatin analogue decreases rates of: a) MODS, b) AKI, and c) ARDS, but not of d) shock, compared to somatostatin analogue monotherapy when administered besides standard of care in acute pancreatitis (74)*

Analysis of pooled data from four trials, including 583 patients, shows a trend for a decreased mortality rate with combination therapy [OR 0.55; 95% CI 0.29–1.07; I^2=0%]; however, the result was not statistically significant (**Figure 3**). These studies yielded homogenous results. All studies reported on in-hospital mortality.

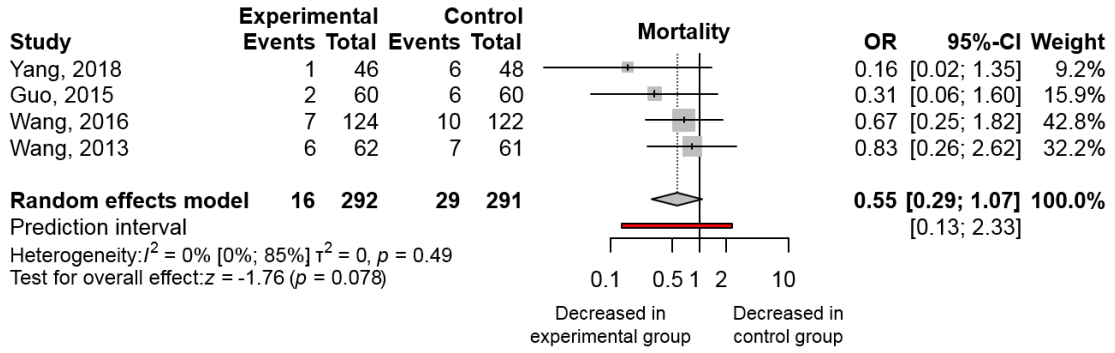

Figure 3*. Ulinastatin in combination with the somatostatin analogue is associated with decreasing trends in mortality compared to somatostatin analogue monotherapy (74)*

Four studies reported the LOHS, measured in days. In the intervention group, admission duration was shortened by 9.43 days [95% CI (-12.55)–(-6.31); I^2=97%] by comparison with the control group (**Figure 4**). The results showed substantial heterogeneity. The effect was similar for severe AP cases [MD (-8.10); 95% CI (-11.64)–(-4.56); I^2=99%].

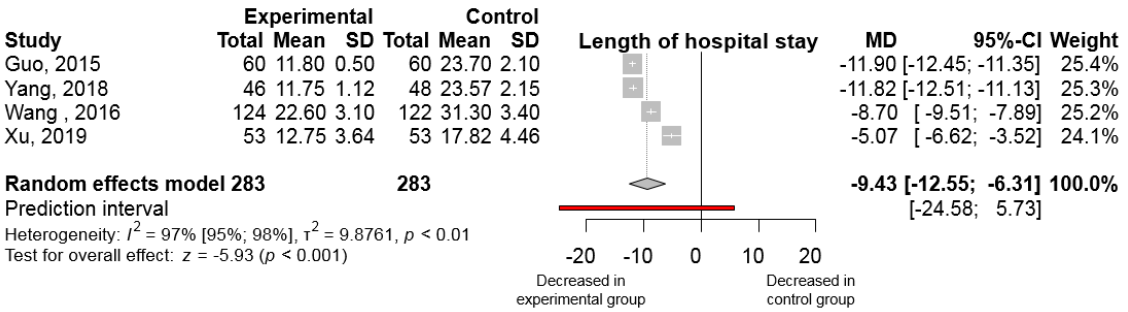

Figure 4. *Ulinastatin combination with somatostatin analogue administered besides standard of care decreases the length of hospital stay in severe acute pancreatitis cases by comparison with somatostatin alone (74)*

Six trials, including 651 patients, reported SR. Among the assessed symptoms were gastrointestinal manifestations and abdominal pain, as well as laboratory parameters. They were evaluated at 7-17 days from treatment start. Pooled analysis shows 3.51 times higher odds of SR in the combined therapy group than in the monotherapy group [OR 3.51; 95% CI 2.30–5.37; I^2=0%]. This effect is similar in the subgroup analysis of severe cases [OR 3.32; 95% CI 2.07–5.33; I^2=0%].

Duration until abdominal pain relief (APR) was specifically reported in five trials, including 612 patients. It was measured as the number of days patients reported abdominal pain. Ulinastatin combined with somatostatin analogue led to significantly faster pain relief than somatostatin derivates monotherapy. The MD is -1.72 days [95% CI (-2.23)–(-1.21); I^2=88%, **Figure 5**]. The results were similar in the severe form of AP [MD -1.68; 95% CI (-1.86)–(-1.50); I^2=60%; **Figure 5**].

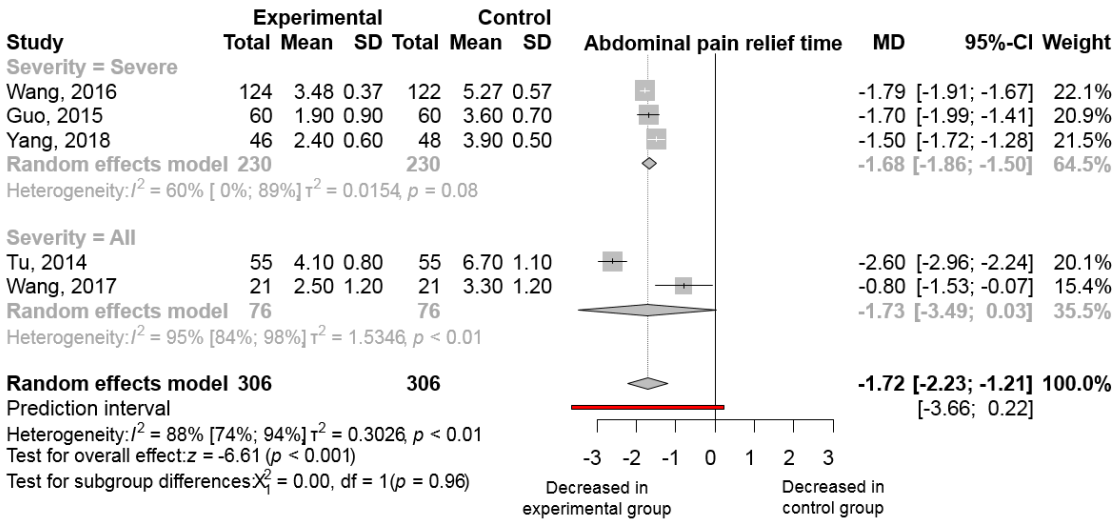

Figure 5. *Ulinastatin in combination with somatostatin analogue decreases the time to abdominal pain relief (74)*

Some of the studies reported variations from baseline in several laboratory parameters, of which we were able to meta-analyse the results for C-reactive protein (CRP). There was a significant difference between the two groups in terms of the reduction in CRP values from baseline to the end of treatment [MD=13.73 mmol/L, 95% CI 4.44–23.02; I^2=73%], favouring the intervention group. Although we could not meta-analyse the results for other laboratory parameters (amylase, white blood cell count, tumor necrosis factor (TNF) α, interleukins (IL-6, -8, -10), diamine oxidase), the identified trends favoured combination therapy.

8.1.3. Quality assessment

The overall risk of bias was moderate, mainly due to inaccurate reporting of blinding, imprecise measure reporting, and lack of available study protocols. The quality of the evidence was low to moderate due to the small sample sizes and the overall moderate bias. Publication bias could not be assessed due to an insufficient number of studies.

8.2. Study II. – Investigating the effects of proton pump inhibitors in acute pancreatitis

8.2.1. Description of included studies

The systematic search resulted in 4864 records. We discarded 2,141 records in the manual and automatic duplicate removal process. After title and abstract and full text selection (Cohen's kappa 0.95 and 1.00, respectively), we found nine eligible studies to include in the systematic review, comprising 28,834 patients. The detailed identification process and the patient characteristics are summarized in **Figure 6**. and **Table 3**., respectively.

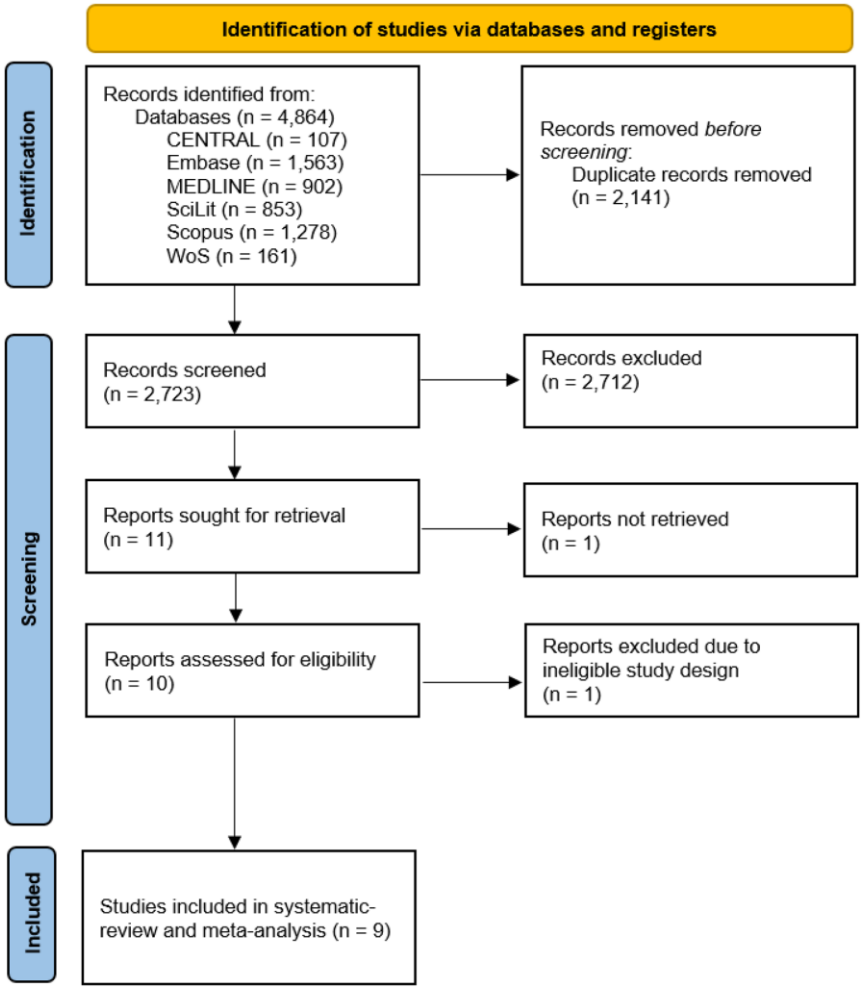

Figure 6. *PRISMA flowchart for Study II. (75)*

Table 3. Baseline characteristics of included articles in Study II. (75)

Study	Type	Origin	Sample size (female %)	Mean age ± SD (years)	Acute pancreatitis severity	Experimental group	Experimental group sample size (female %)	Experimental mean age ± SD (years)	Control group	Control group sample size (female %)	Control group mean age ± SD (years)	Outcome
Demcsák, 2020	cohort	Inter-national	17,422 (43.6%)	56.5 ± 17.9	All form	dexlansoprazole, esomeprazole, ilaprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	12,764 (43.6%)	56.8 ± 17.9	SoC	4,658 (44.2%)	55.6 ± 17.6	GI bleeding
Hong, 2021	RCT	China	96 (53.1%)	N/A*	Severe	3 mg somatostatin + 40 mg IV omeprazole q24h for 7d then 3 mg somatostatin + 40 mg IV omeprazole q12h for 7d	48 (54.2%)	N/A*	SoC	48 (52.1%)	N/A*	ARDS GI bleeding Pancreatic pseudocyst
Ma, 2017	RCT	China	45 (40.0%)	45.4 ± N/A	Severe	octreotide 50 mcg/h for 72h then 25mcg/h for 96h + esomeprazole 40 mg IV for 7d	24 (33.3%)	44.8 ± 10.6	octreotide 50 mcg/h for 72h then 25mcg/h for 96h SoC	21 (47.6%)	46.0 ± 11.7	GI bleeding Laboratory parameters
Ma, 2020	RCT	China	66 (34.8%)	45.3 ± N/A	Severe	esomeprazole 40mg q24h	33 (30.3%)	46.1 ± 11.1	SoC	33 (39.4%)	44.6 ± 9.3	Mortality (7d)
Murata, 2015	cohort	Japan	10.400	N/A**	Severe	lansoprazole or omeprazole	3,879 (33.1%)	N/A**	SoC	6521 (34.8%)	N/A**	Mortality (7d)
Wang, 2020	RCT	China	160 (46.3%)	63.4 ± N/A	Severe	3 mg somatostatin + 40 mg IV esomeprazole q24h for 7d then 6 mg somatostatin + 40 mg IV esomeprazole q12h for 14d	80 (45.0%)	63.4 ± 8.0	SoC	80 (47.5%)	63.3 ± 8.5	LOHS
Xia, 2014	RCT	China	140 (34.3%)	42.8 ± N/A	Severe	3 mg somatostatin + 40 omeprazole IV q24h for 7d	70 (37.1%)	41.67 ± 22.56	SoC	70 (31.4%)	43.85 ± 19.71	ARDS Mortality (7d) LOHS Pancreatic pseudocyst
Yoo, 2021	RCT	South Korea	40 (20.0%)	48.5 ± N/A	All form	pantoprazole IV or PO q12h	20 (15.0%)	49.3 ± 16.5	SoC	20 (25.0%)	47.6 ± 18.3	LOHS
Zhang, 2021	cohort	China	858 (37.9%)	56.0 ± N/A	All form	esomeprazole, omeprazole, or pantoprazole	336 (45.5%)	56.59 ± 17.17	SoC	174 (47.7%)	55.4 ± 17.03	ARDS LOHS Mortality (7d) Pancreatic pseudocyst

Abbreviations: SD: standard deviation; RCT: randomized controlled trial; PPI: proton pump inhibitor; SoC: standard of care; N/A: no data available; mg: milligram; mcg: microgram; IV: intravenous; PO: per os; q: every; h: hour; d: day; GI: gastrointestinal; ARDS: acute respiratory distress syndrome; AKI: acute kidney injury; LOHS: length of hospital stay; * Min-max age was reported; ** Age groups were reported

8.2.2. Statistical analysis

The analysis of the pooled results from three studies including 746 patients, showed that in the intervention group the rate of pseudocyst development decreased by 61% compared to the control group [OR 0.39; 95% CI 0.18–0.87; I^2 = 0%; **Figure 7A**]. The incidence of ARDS was reported in three studies (746 patients), and there was no significant difference between the two groups in this concern [OR 0.56; 95% CI 0.04–8.59; I^2 = 59%; **Figure 7B**]. Regarding GI bleeding, our pooled results from four studies, including 27,963 patients, revealed a higher probability of occurrence in PPI administration cases [OR 1.81; 95% CI 1.41–2.33; I^2 = 17%; **Figure 7C**].

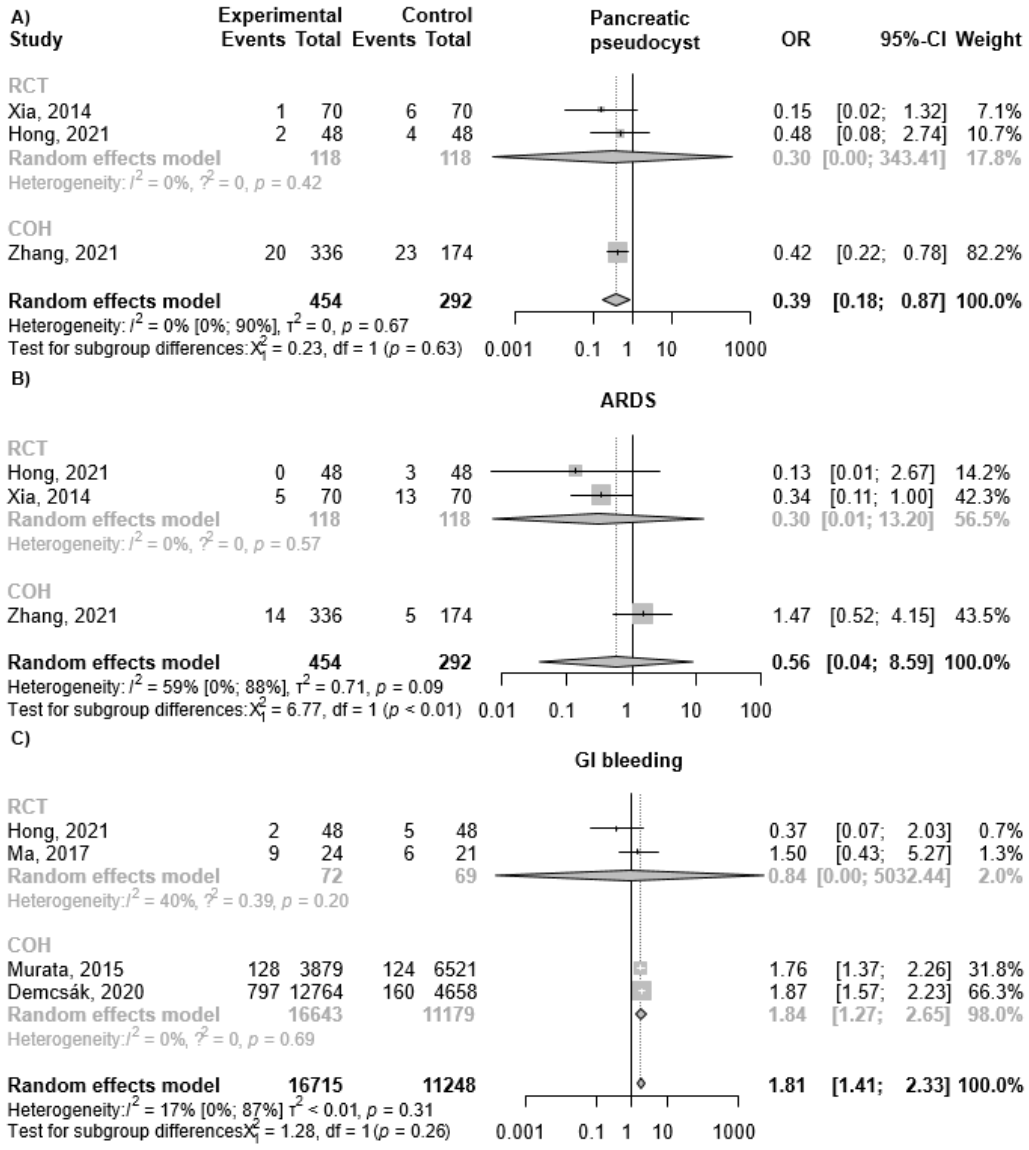

Figure 7. *The addition of proton pump inhibitor treatment to standard of care in acute pancreatitis was associated with:*

(A) Decreased pancreatic pseudocyst development rate;

(B) No significant difference regarding development of ARDS;

(C) Increased odds of GI bleeding (75)

Abbreviations: OR: odds ratio; CI: confidence interval; RCT: randomized controlled trial; COH: cohort study; ARDS: Acute Respiratory Distress Syndrome; GI: gastrointestinal

The pooled results from three trials (690 patients), including all severity forms of AP, did not show statistically significant differences between the groups regarding the LOHS [MD -3.47; 95% CI (-12.32)–5.39; I^2 = 91%; **Figure 8**]. Wang et al. (52) have reported on the length of hospital stay; however, we had to exclude the result from the analysis due to a contradiction between the written and graphical results.

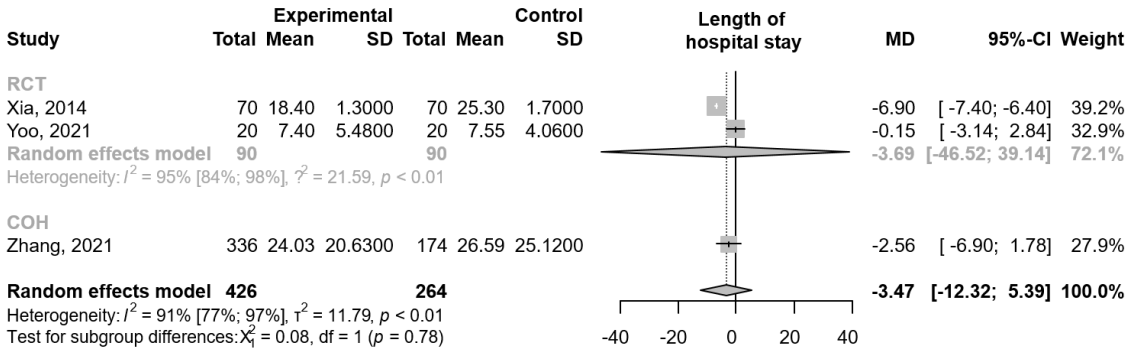

Figure 8. *The addition of proton pump inhibitor treatment to standard of care in acute pancreatitis was not associated with a significant change in hospital stay compared to standard of care alone (75)*

Abbreviations: MD: mean difference; CI: confidence interval; RCT: randomized controlled trial; COH: cohort study

Mortality rates were variously reported in eligible studies, in terms of moment of evaluation. We were able to perform a meta-analysis for mortality at seven days after diagnosis. In three studies, including 10,607 patients, there were no significant differences between the experimental and control groups [OR 0.77; 95% CI 0.05–10.65; I^2=63%; **Figure 9**].

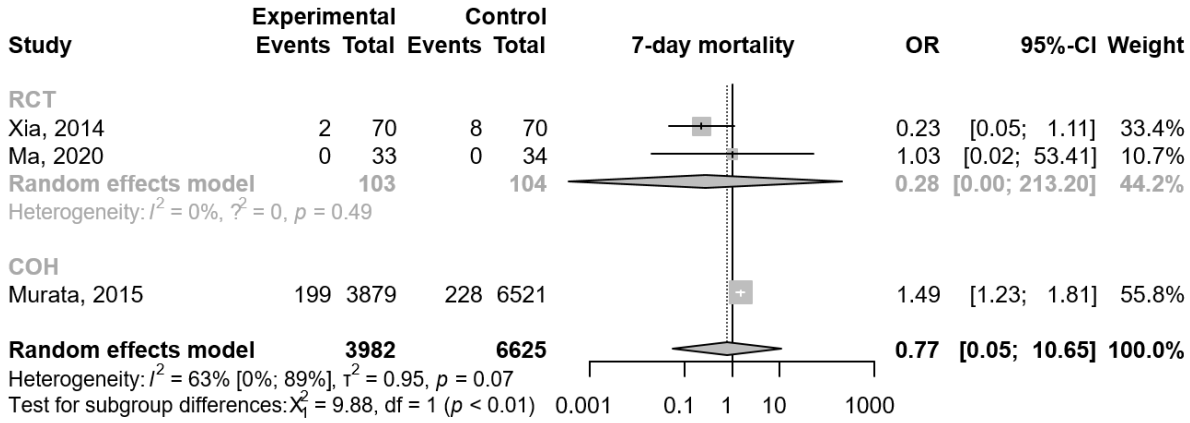

Figure 9. *The addition of proton pump inhibitor treatment to standard of care in acute pancreatitis was not associated with a significant change in mortality compared to standard of care alone (75)*

Abbreviations: OR: odds ratio; CI: confidence interval; RCT: randomized controlled trial; COH: cohort study

8.2.3. Quality assessment

Most of the included RCTs were evaluated as having some concerns. Potential biases emerged from the inappropriate reporting of the randomization process, the maintenance of blinding, and the measurement of outcomes. There were no accessible study protocols to investigate the selection of the reported results, except for the study by Ma et al. (53).

The studies by Demcsák et al. (45) and Murata et al. (47) were well designed and with low risk of bias in all the investigated domains, except for the selection of the reported results, where prior protocols were missing. In the cohort study conducted by Zhang (46), we found a critical level of bias in the selection of the participants: they selected patients by PPI intake after the start of the intervention. Furthermore, we found a moderate risk in the classification of intervention – they defined the intervention group after the start of the intervention, and in the measurement of outcomes. The outcome assessors were probably aware of the invention, yet reported strong objective outcomes, which were unlikely to be influenced by knowing the group to which the patients were assigned.

On the basis of the GRADE framework, the evidence level was very low in each investigated outcome.

8.3. Study III. – Investigating the effects of nafamostat in the prevention of post-ERCP pancreatitis

8.3.1. Description of included studies

After a systematic search in the databases, we found 133 articles. The manual and automatic duplication removal discarded 80 records. After title-abstract selection (Cohen's coefficient 1.00) and full-text selection (Cohen's coefficient 1.00), six reports from the database searches were found suitable for inclusion in the systematic review. We also screened the references of the included articles and found one additional study. Both independent authors agreed to include it in the review, resulting in a final article pool of seven articles (**Figure 10**). The characteristics of the included studies are summarized in **Table 4**.

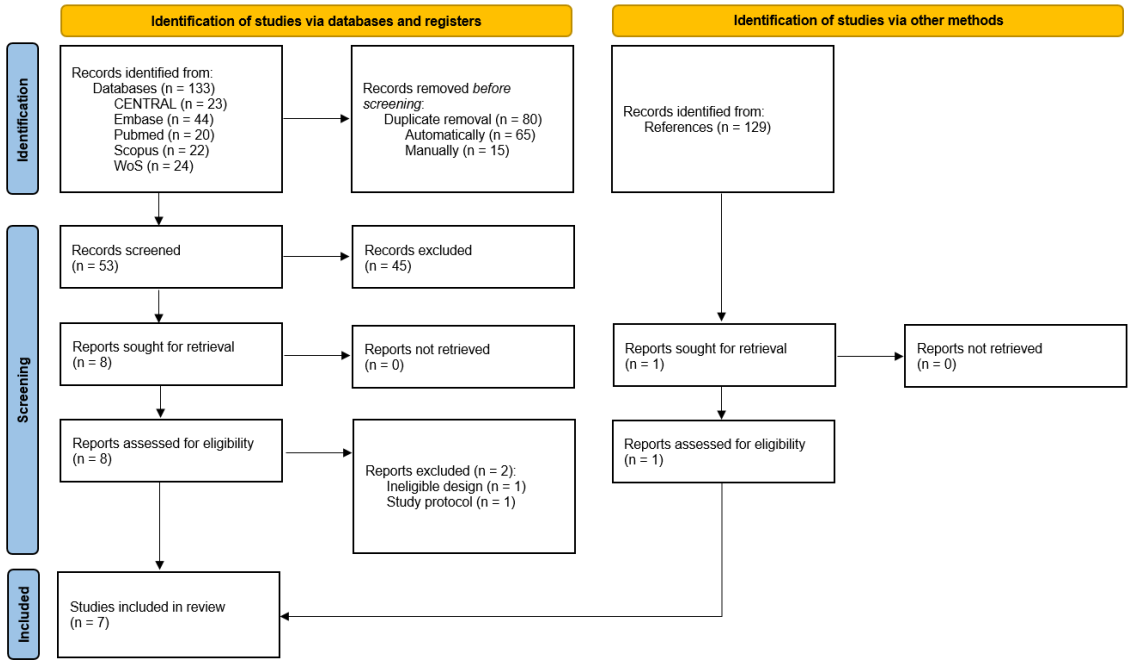

Figure 10. *PRISMA flowchart for Study III. (76)*

Table 4. Baseline characteristics of the articles included for Study III. (76)

Study	Origin	Sample size	Intervention	Intervention group, sample size	Intervention group, female (%)	Intervention group, mean age SD ± (years)	Control	Control group, sample size	Control group, female (%)	Control group, mean age ± SD (years)	Outcome
Choi, 2009	South Korea	704	nafamostat 20 mg IV for 24 h; starting 1 h before ERCP	354	171 (48.3)	64.4 ± 12.6	5% dextrose	350	168 (48.0)	65.6 ± 12.1	PEP, HA
Kwon 2012	South Korea	169	nafamostat 50 mg IV for 12 h; starting 0.5 h before ERCP	88	49 (55.7)	66.6 ± 12.8	5% dextrose	81	50 (61.7)	64.4 ± 13.8	PEP
Matsumoto 2020	Japan	293	nafamostat 20 mg for 6 h; starting 0.5-2 h before ERCP	144	50 (34.7)	75*	5% dextrose	149	48 (32.2)	71*	PEP
Ohuchida 2015	Japan	809	nafamostat 20 mg IV for 2 h; starting with ERCP	405	147 (36.3)	68.4 ± 12.1	5% dextrose	404	160 (39.6)	69.3 ± 11.2	PEP, HA
Park 2011 20 mg	South Korea	398	nafamostat 20 mg for 24 h; starting 1 h before ERCP	198	94 (47.5)	64.1 ± 10.6	5% dextrose	200	91 (45.5)	62.7 ± 12.4	PEP, HA
Park 2011 50 mg	South Korea	397	nafamostat 50 mg for 24 h; starting 1 h before ERCP	197	91 (46.2)	63.3 13.8	5% dextrose	200	91 (45.5)	62.7 ± 12.4	PEP, HA
Park 2014	South Korea	106	nafamostat 10 mg IV; starting 2-4 h before ERCP + nafamostat 10 mg IV; starting 6-8 h after ERCP	53	24 (45.3)	58.6 ± 17.1	5% dextrose	53	24 (45.3)	60.5 ± 16.2	PEP, HA
Yoo 2011	South Korea	286	nafamostat 50 mg IV for 6 h; starting 1 h before ERCP	143	74 (51.7)	61.9 ± 15.7	5% dextrose	143	69 (48.3)	63.2 ± 15.4	PEP, HA

Abbreviations: SD: standard deviation; mg: milligram; IV: intravenous; h: hour; PEP: post endoscopic retrograde cholangiopancreatography pancreatitis; HA: hyperamylasemia; * SD was not reported

8.3.2. Statistical analysis

Seven studies reported on PEP using 20 mg and 50 mg of nafamostat. The overall incidence of PEP was lower in both nafamostat groups compared to SoC [20 mg: OR: 0.50, 95% CI 0.30–0.82; and 50 mg: OR: 0.48, 95% CI: 0.24–0.96; **Figure 11**].

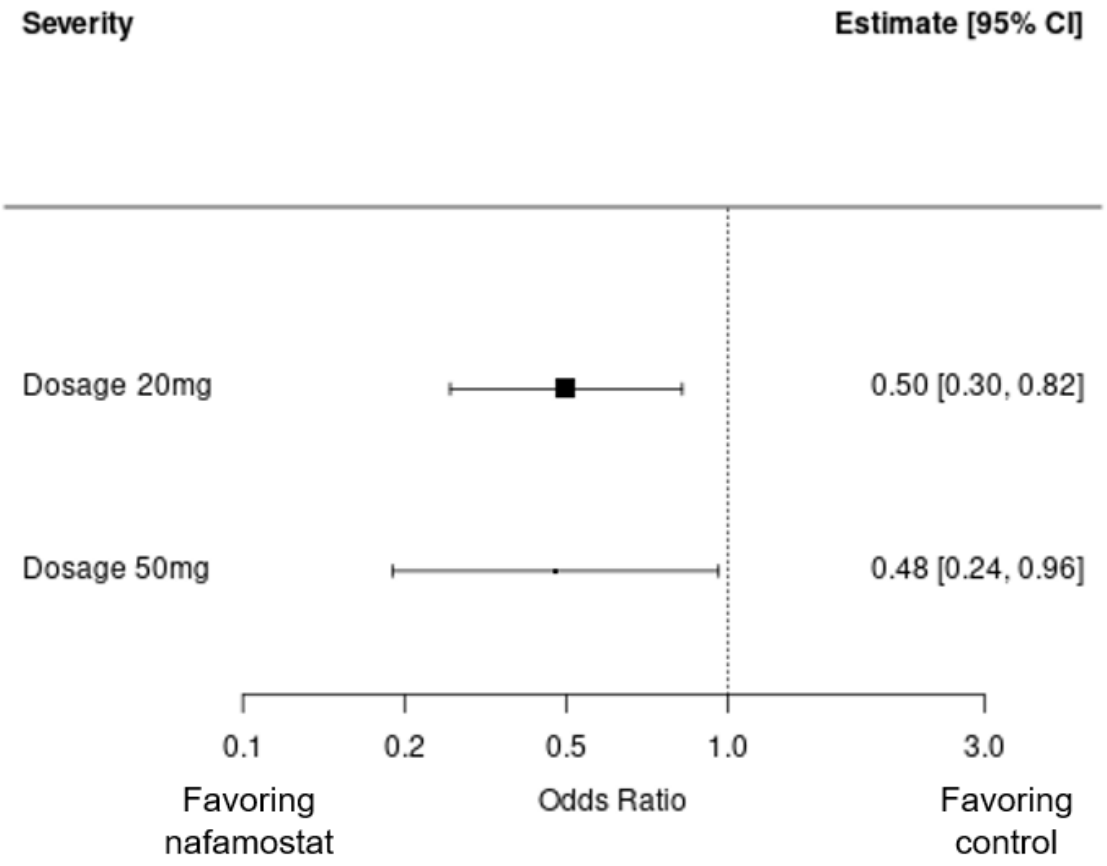

Figure 11. *Multilevel model results on the overall effect of nafamostat therapy in the prevention of post-ERCP pancreatitis (PEP) (76)*

However, in the subgroup analysis, we found statistically significant prevention of mild PEP only in the 20 mg subgroup [OR: 0.49, 95% CI: 0.31–0.77]. We found no statistical differences in other severity groups (mild, moderate, and severe) investigating 20 mg and 50 mg doses of nafamostat compared to SoC (**Figure 12**).

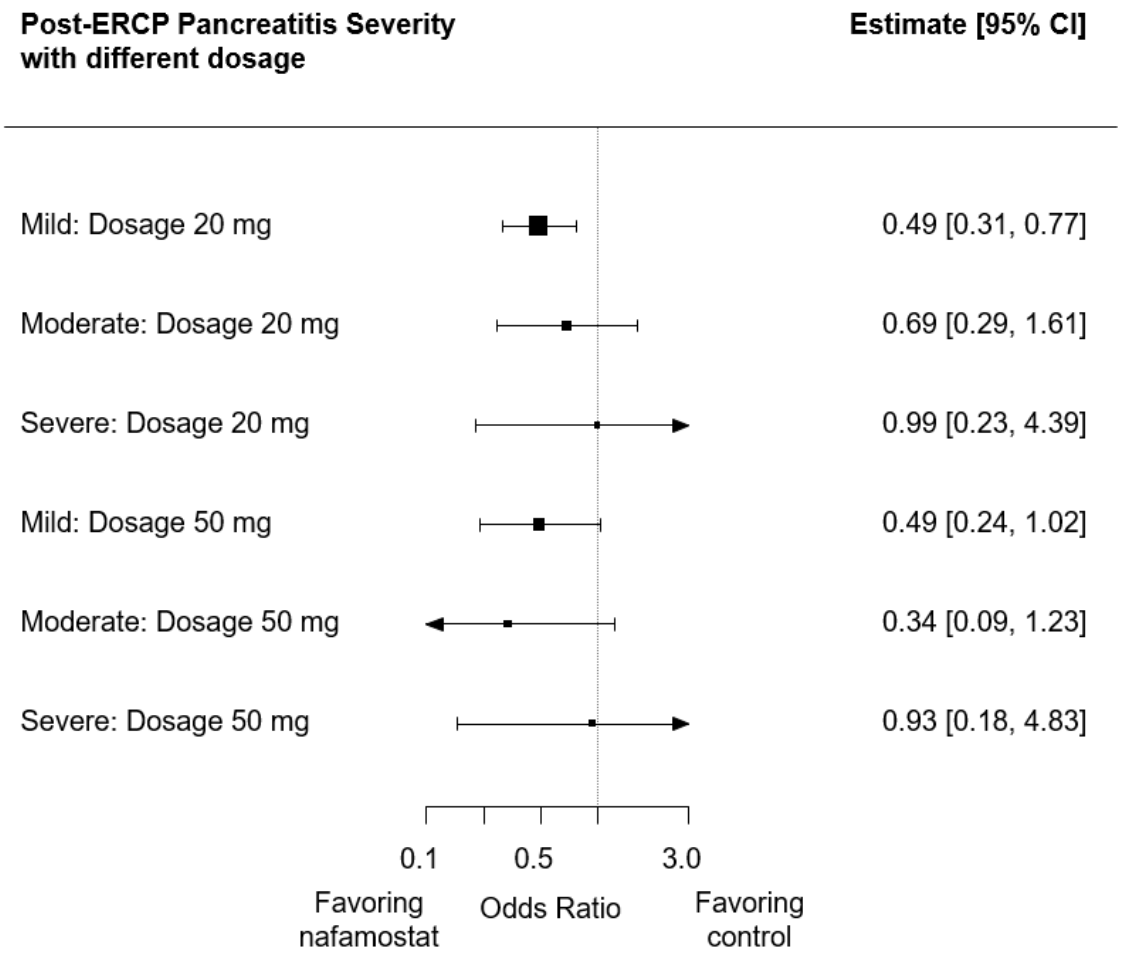

Figure 12. *Multilevel model results on the nafamostat therapy in the prevention of post-ERCP pancreatitis (PEP) (76)*

We analyzed PEP severity in high- and low-risk patients. The overall use of nafamostat therapy could reduce moderate PEP in high-risk patients [OR: 0.18, 95% CI: 0.0.4–0.84]; and mild PEP in low-risk patients [OR: 0.32, 95% CI: 0.17–0.61; **Figure 13**].

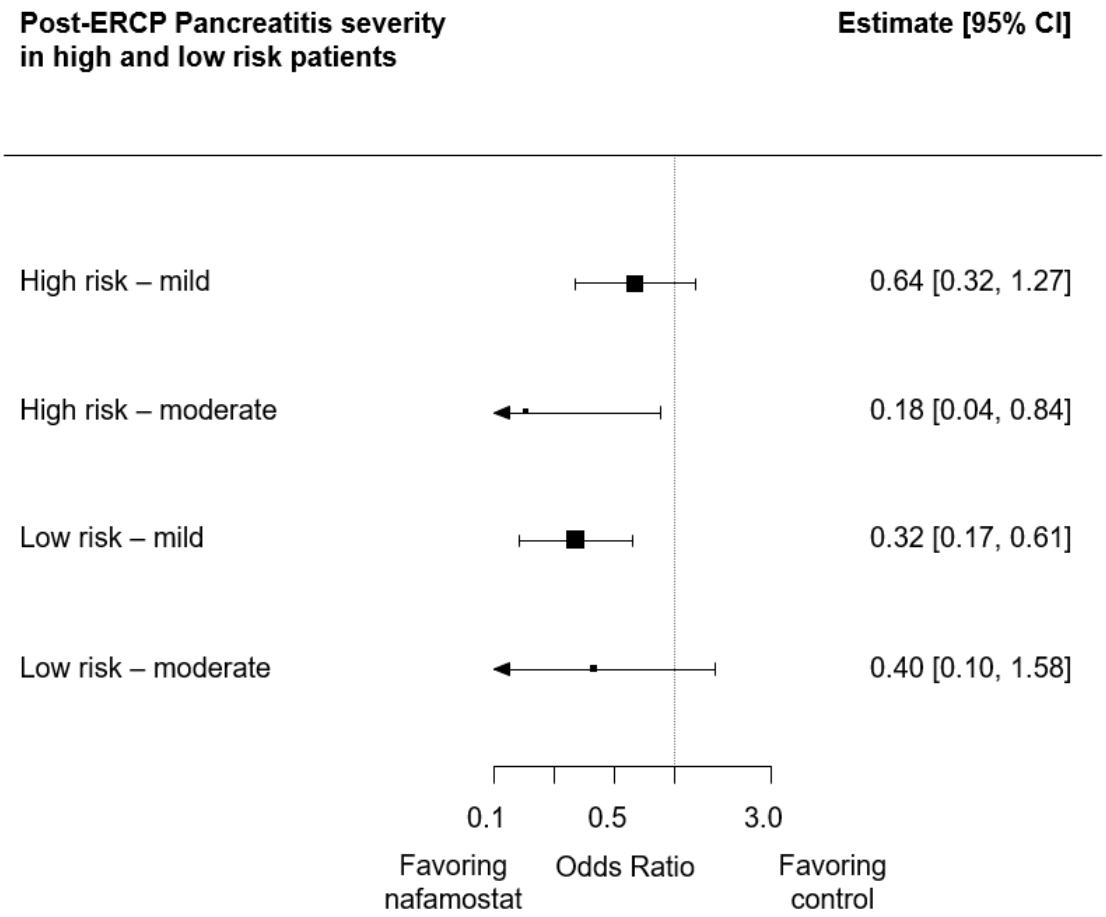

Figure 13. *Multilevel model results on the nafamostat therapy in the treatment prevention of post-ERCP pancreatitis (PEP) in low and high risk patients. There was an overall reduction of moderate PEP in high risk, and of mild PEP in low-risk patients (76)*

There were insufficient reports of severe PEP in high- and low-risk patients. The pooled results of the five studies showed no statistical differences in the ability of nafamostat to reduce post-ERCP hyperamylasemia (HA) compared to placebo. The results of the multilevel analysis are shown in **Figure 14**.

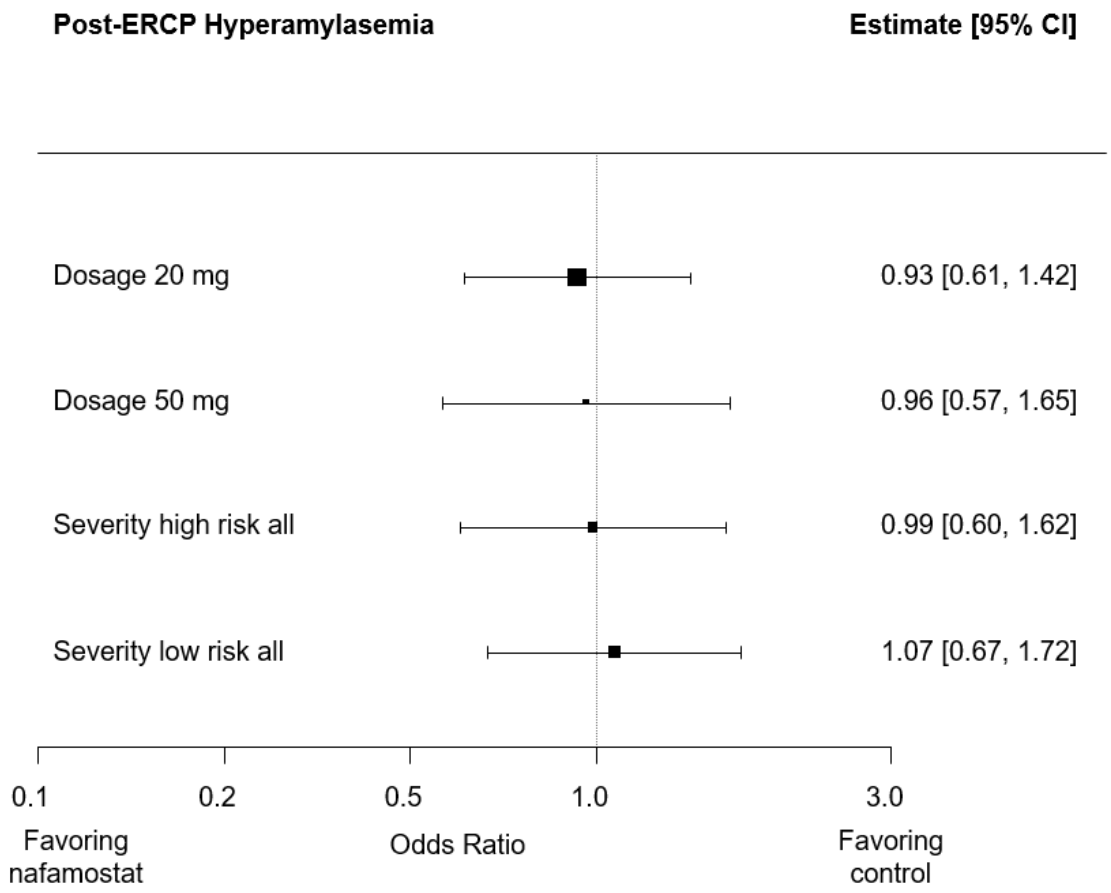

Figure 14. *Multilevel model results on the nafamostat therapy regarding the post-ERCP hyperamylasemia (76)*

8.3.3. Quality assessment

Overall, the trials included had a low risk of bias. In some cases, due to the inaccessible study protocols, we were unable to compare the intended interventions with the published results and therefore marked them with “some concerns.” On the basis of the GRADE assessment, the certainty of evidence is “low.”

9. DISCUSSION

9.1. Summary of findings, international comparisons

9.1.1. Study I. – Investigating the effects of ulinastatin-somatostatin analogue combination therapy in acute pancreatitis

Our meta-analysis assessed the clinical advantage of the combination therapy of ulinastatin with somatostatin analogues compared to somatostatin alone besides SoC in AP. Ulinastatin combined with somatostatin or octreotide therapy significantly reduced the complication rates of MODS, AKI, and ARDS, which might be a contributing factor in the reduced hospitalization time. Data on mortality and shock rates are limited, however, the combination therapy shows beneficial results in both outcomes.

Our results indicate that the intervention determines a three-fold reduction in symptoms compared to monotherapy, which is consistent in severe AP. The better response rate, the decreased APR time, and the less frequent complications might be a contributing factor to faster recovery and avoid complications. It could alleviate abdominal pain almost 2 days earlier than monotherapy. Abdominal pain is the main symptom of AP; proper management has a great impact on the perspectives of patients (77). Furthermore, the combination therapy could significantly reduce CRP, thus decreasing inflammation. With fewer days of hospital stay and lower complication rates, it is a clinically effective therapy. Additional health care expenses could be saved in both short and long terms.

Mortality showed a decreasing trend in the experimental group, but the results were not statistically significant. If we expect a 10% reduction in mortality (from 12% to 2%) within the intervention group (38, 78) an optimal study sample size would be approximately 99 patients in each study arm (80% power, one-sided alpha level of 5% with continuity correction). None of the studies reached this threshold, so our results must be considered with caution, since we cannot strongly confirm the impact of combination therapy on mortality.

In other studies, researchers found that ulinastatin inhibits necrosis by preventing mitochondrial damage, decreases endothelial dysfunction, normalizes coagulation

disturbances, improves perfusion, and thus restores organ functions (20, 79-81). Several meta-analyses revealed positive effects of ulinastatin in many severe clinical scenarios: it can prevent postoperative bleeding in patients undergoing cardiac surgery (82), it protects against ischemia–reperfusion injuries in hepatectomy (83), in ARDS of various aetiologies it decreases the mortality rates (84), after cardiopulmonary bypass it reduces pulmonary injury and improves pulmonary function (85), and decreases the duration of mechanical ventilation (86). The clinical effects of ulinastatin observed in patients suffering from diseases that are associated with a high risk of major complications support its potential in the treatment of AP.

9.1.2. Study II. – Investigating the effects of proton pump inhibitors in acute pancreatitis

We investigated the association between PPIs addition to conventional therapy compared to conventional therapy alone in patients with AP. PPI use in the treatment of AP is associated with a decreased risk of developing pancreatic pseudocysts. However, there were no significant differences between the two groups in terms of 7-day mortality, LOHS, and incidence rate of ARDS. Furthermore, we found an increased risk of bleeding in the PPI group.

Pancreatic pseudocysts in AP are caused by extravasation of pancreatic fluid. They can have a spontaneous evolution to resorption in time or progress with complications such as rupture, bleeding, and infection (87). In theory, PPIs cannot reduce not only gastric acid secretion, but also secretin-stimulated bicarbonate secretion (88). Experimental studies showed contradictory results on inhibition of pancreatic enzyme production. Omeprazole failed to suppress amylase release in isolated pancreatic acini; however, pantoprazole significantly reduced amylase secretion in an experiment with rats (25, 26). One case report showed a decrease in serum amylase level after PPI treatment: a patient had acute necrotizing pancreatitis secondary to 6-mercaptopurine (6-MP) therapy, which was resolved by octreotide therapy. However, when starting 6-MP again, octreotide with 2 mg/kg/day lansoprazole could decrease amylase to the normal level (89). Nevertheless, no trials to date have further evaluated the hypothesis. Furthermore, PPI elevates the gastric pH level, thus reducing secretin release, which further decreases pancreatic

secretion (88). Our results suggest that there may be a link between PPI use and the decreased rate of pancreatic pseudocyst formation in AP.

Furthermore, our analyses showed that PPI treatment during AP does not have a significant effect on 7-day mortality, LOHS, and the complication rate of ARDS, indicating that there are no major benefits in adding them to SoC.

The accurate incidence of GI bleeding in AP is not documented well; however, the frequency of excessive GI haemorrhagic complications in AP is reported in 1.2% to 14.5% of the cases, leading to an increased mortality (90). Based on the results, PPI treatment during AP was associated with an increased risk of GI bleeding (45, 47, 49, 50), which could be due to a variety of pancreatic and nonpancreatic conditions, e.g., a history of peptic - and concomitant anticoagulation. In the prevention of upper GI bleeding, PPIs are indisputable, but they might not be as effective against lower GI bleeding, and might even cause small bowel injury by producing dysbiosis in the GI tract, especially when using concomitant warfarin, acetylsalicylic acid, or NSAIDs (91, 92). None of the included articles reported on concomitant medications. Furthermore, the cohort study by Demcsák et al. (45) showed an association between PPI use and the severity of AP: a significant proportion of patients who received acid suppressants had moderate or severe episodes of AP. This finding is also supported by Murata et al. (47).

In severe AP, released inflammatory mediators (IL-1ß, IL-6, and TNFα) may induce gut dysbacteriosis, which could be enhanced by the acid suppressive effect of PPIs (93-95). One RCT comprising 66 patients showed a significant increase in cases of duodenal dysbiosis, duodenal bacterial overgrowth, and candida oesophagitis when using esomeprazole compared to conventional therapy (53). Furthermore, the released inflammatory mediators can cause hyperpermeability of the intestinal mucosa, which, together with bacterial overgrowth, could lead to bacteraemia. This effect can further activate pro-inflammatory cytokines, resulting in an enhancement of the inflammatory processes (95).

On the other hand, PPIs seem to be associated with a decreased pro-inflammatory cytokine release that would disrupt the barrier functions (96). Two studies showed that serum levels of d-lactic acid and diamine oxidase, which rarely get absorbed from the GI

tract in physiological conditions, were lower in the intervention group (which in this case included patients treated with PPI—somatostatin association) compared to the control group, and suggesting a protective effect on the intestinal barrier function (49, 52). However, somatostatin might also have a protective role in the sepsis-induced gut barrier dysfunction according to an animal model study (97); therefore, combining PPI and somatostatin may have an enhanced protective effect. Furthermore, PPIs can show scavenging properties for reactive oxygen species (96). However, somatostatin can express antioxidant effects and decrease cytokine levels; thus, it could also contribute to the anti-inflammatory effect, when administered in combination with PPIs (49). The mechanisms behind these effects have not yet been completely described; further investigations are needed.

PPIs are among the most overused medications, and are generally prescribed without any specific indication (98). Patients with AP receive some kind of acid suppressive drugs in 23.3% of cases on admittance to the hospital, 86.6% of the patients received them during hospitalization, and 57.6% when they were discharged from hospital (45). The prophylactic use of PPIs for stress ulcer prophylaxis in individuals with AP is an off-label indication. PPIs are considered safe medications, with a safe adverse effect profile; however, there are possible adverse reactions in the long term. Drug-induced AP is responsible for 2–5% of the AP cases (99), and PPIs are rarely associated with its onset (100-104). Patients with gastrointestinal reflux disease, peptic ulcer, dyspepsia, or prior GI bleeding are likely to receive PPIs, even at an elevated dose. However, the inappropriate use of PPIs exposes the patient to harm, which could be prevented.

Although PPIs are widely used during AP treatment, this is the first meta-analysis that evaluates their association with various AP related clinical outcomes. However, several limitations should be emphasized. There is a low number of trials available in the topic, and in many cases, they have a moderate to high risk of bias, especially regarding randomization process, deviations from intended intervention, selection of reported results and outcome measurement. In the analyzed trials, different PPIs were used. While the main mechanism of action of these drugs is common, their activity profiles are different, which may influence their clinical effect in AP. For example, omeprazole, in contrast to pantoprazole, does not inhibit amylase release from isolated pancreatic acini

(105). Furthermore, there is no information on the initiation and the duration of PPI therapy in report of AP onset, and follow-up times. Additionally, due to their small sample sizes, the RCTs were assigned low weights in the pooled results by comparison with the cohort studies, which can impact the overall effect measurement. This is important, as they reported opposite results on outcomes such as mortality and GI bleeding. The analysis of the RCT data alone resulted in different results in the case of these two outcomes: no significant differences could be detected between the two treatment groups.

9.1.3. Study III. – Investigating the effects of nafamostat in the prevention of post-ERCP pancreatitis

PEP is the leading adverse event of the ERCP procedure (10). Only supportive therapies are widely available, and for this reason, clinical trials mainly focus on the prevention of PEP with limited success. In this systematic review and meta-analysis, we investigated nafamostat as a prophylactic agent in the prevention of PEP.

Our results suggest that nafamostat can reduce the overall incidence of PEP using 20 and 50 mg doses; however, we found a statistically significant difference only in the 20 mg nafamostat subgroup only for mild PEP. This might suggest that there is no dose-dependent effect of nafamostat on the prevention of PEP, and a lower dose regime is sufficient for prevention. Side effects also did not appear to be dose dependent: only Matsumoto reported hyperkalemia (57); Choi, Park (2011), Park (2014) and Yoo (55, 59-61) did not report any side effects associated with the administration of nafamostat (Kwon (56) did not report any side effect related information). Previous meta-analyses showed controversial results on the effectiveness of nafamostat in the prevention of PEP. Yu et al. (106) showed a significant reduction in overall PEP, including mild and moderate PEP prevention. Their analysis also showed a significant prevention of PEP in both low- and high-risk patients. A later network meta-analysis by Lyu et al. (54), which included four published RCT trials, showed no statistical differences compared with placebo.

The ERCP procedure is generally associated with HA, which is present in 11.2–39% of cases (107-109). The development of HA may be due to patient-related (prior diabetes) and procedure-related factors (difficult cannulation, biliary duct stent placement, and nasobiliary drainage) (108). The underlying disease may also affect the procedure: cases

of acute biliary pancreatitis appear to be more difficult than those of acute cholangitis, due to the increased use of advanced cannulation methods and inadvertent pancreatic cannulation, as well as a longer cannulation time (110). A retrospective analysis of 1.291 patients showed no correlation between HA and the severity of PEP (111).

Several reports investigated the intra-arterial or intravenous administration of nafamostat; however, there are inconsistencies in the results (112-117) Nafamostat also inhibits other proteolytic enzymes, for example, thrombin and plasmin (27), which can be used as an anticoagulant in the treatment of disseminated intravascular coagulopathy (DIC) (118), cardiopulmonary bypass (119-121) or during continuous renal replacement therapy (122, 123). It also emerged in the treatment of coronavirus disease 2019 (COVID-19) because it inhibits viral and human cell fusion (124, 125).

9.2. Strengths

To the best of our knowledge, we provided the first meta-analysis for Study I. and Study II.; and the most up-to-date version for Study III. The strength of our reviews is their rigorous methodology. We strictly followed the Cochrane and PRISMA recommendations and ensured the study's transparency through the prior publication of the review protocol on PROSPERO.

9.3. Limitations

Our results are based on a limited number of trials performed mostly in Far Eastern countries, e.g., China, Japan, and South Korea. The included trials are of low to moderate quality, with the risks of bias resulting from a lack of proper reporting of the study protocols and the blinding. Due to the small sample sizes, interpretations must be made carefully. These factors resulted in high heterogeneity in some cases.

In some cases, we included trials containing somatostatin or octreotide as part of the treatment. Clinical studies (18) show no statistical difference in patient outcomes when comparing octreotide or somatostatin to placebo, therefore, we regarded this modality as placebo.

10. CONCLUSIONS

Our study investigated the rational use of different pharmacologic agents (ulinastatin, nafamostat and PPIs) in AP. Ulinastatin combined with somatostatin analogue significantly decreased complication rates (ARDS, AKI, MODS) in AP in comparison with somatostatin analogue monotherapy. In addition, combination therapy is associated with earlier relief of symptoms and shorter hospital stay.

Our meta-analysis pointed out that even though PPI use in AP treatment reduced the rates of pancreatic pseudocyst formation, it did not show significant effects on other outcomes.

Nafamostat can reduce the overall incidence of PEP compared to placebo and should be considered for use in low-risk patients with mild PEP.

11. IMPLEMENTATION FOR PRACTICE

Translational science is essential to the interpretation of clinical results in daily practice. Every year, more than 1.4 million scientific papers are published, and it is impossible for practitioners to keep up with this amount of data, therefore, a vast majority of the results are not utilized. A prompt reaction to new evidence could be delayed, resulting in inadequate patient care (126, 127).

Somatostatin analogue monotherapy is not sufficiently effective in the management of AP. Our results provide a new insight into a possible drug therapy treatment for AP. This is especially important in severe cases, as there are limited treatment options and mortality is high.

PPIs are one of the most overused medications overall. Despite their safe adverse effect profile, there are some reports of severe reactions, therefore their prescriptions should be validated. PPIs should be recommended only as an addition to the SoC if there is a relevant comorbidity or a higher risk of GI bleeding or the development of pancreatic pseudocyst.

The use of nafamostat as a preventive medication after ERCP showed an overall reduction in PEP. The incidence of mild PEP was significantly reduced in the 20 mg subgroup. In addition, it reduced mild PEP in low-risk and moderate PEP in high-risk patients.

12. IMPLEMENTATION FOR RESEARCH

The results of the ulinastatin combination therapy presented here suggest an improvement of efficacy, but the combination should be further studied e.g., to overcome the limitation that all the available data are available from trials performed in China. The included trials have differences in the applied treatments, outcome measures, and follow-up time, further multicentre, double-blind, RCTs with greater sample sizes and well-defined outcomes are needed to assess the combination therapy's effect in AP. Furthermore, data on the safety of combination therapy in AP are lacking. Due to the shorter hospital stay and the reduced risk of complications, cost effectiveness and the assessment of health technology should be considered. The clinical efficacy and safety of further combination therapies should be systematically evaluated.

Well-designed RCTs are needed to determine which populations would benefit the most from PPI treatment during AP, and most importantly, what are the benefits and drawbacks of PPI use in this disease.

Considering the limited efficacy, researchers should focus on the cost-effectiveness of nafamostat therapy. It should also be investigated compared to the available preventive therapies.

13. IMPLEMENTATION FOR POLICYMAKERS

There are no golden bullet drugs available to treat AP. The key to successful therapy is the optimal and rational use of available drugs. To achieve this, it is key to have up-to-date information on the efficacy of the drugs.

Systematic review and meta-analysis of clinical evidence is therefore of paramount importance. New evidence can justify or oppose an emerging or existing therapy in practice. Translational science should be implemented in the decision-making process to evaluate therapies. It is important that the evidence generated in meta-analyses becomes part of clinical practice and guidelines. It would also be in the interest of patients if drugs that have been shown to be effective but are only available in certain countries were to be made available for therapy worldwide.

14. FUTURE PERSPECTIVES

As a clinical pharmacist with special interest in the pharmacotherapy of AP, I hope that in the future I can support the rational therapy of AP patients as a member of a therapeutic team. Of the agents studied in my doctoral research, ulinastatin appears to be a promising agent for the treatment of AP, but the available evidence is not fully sufficient to judge its efficacy. I had the opportunity to design a protocol for a clinical trial that could fill the missing evidence. I look forward to participating in future research studies with this pharmacon or newer compounds to confirm efficacy and promote rational pharmacotherapy.

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16.2. Publications not related to the thesis

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