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SCIENTIFIC REVIEW

The Use of Prophylactic Somatostatin Therapy Following Pancreaticoduodenectomy: A Meta-analysis of Randomised Controlled Trials

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Abstract

Background Prophylactic administration of somatostatin analogues (SA) to reduce the incidence of post-operative pancreatic fistula (POPF) remains contentious. This meta-analysis evaluated its impact on outcomes following pancreaticoduodenectomy (PD).

Methods The EMBASE, MEDLINE and Cochrane databases were searched for randomised controlled trials (RCTs) investigating prophylactic SA following PD. Comparative effects were summarised as odds ratio and weighted mean difference based on an intention to treat. Quantitative pooling of the effect sizes was derived using the random-effects model.

Main results Twelve RCTs were included involving 1615 patients [SA-treated group (n = 820) and control group (n = 795)]. The SA used included somatostatin-14, pasireotide, vapreotide and octreotide. Pooling of the data showed no significant benefit of its use for the primary outcome measure of all grades of POPF, odds ratio (OR) 0.73 [95% confidence interval (CI), 0.51–1.05, p = 0.09] and clinically relevant POPF, OR 0.48 [95% CI, 0.22–1.06, p = 0.07]. There were no benefits in the secondary outcome measures of delayed gastric emptying, OR 0.98 [95% CI, 0.57–1.69, p = 0.94]; infected abdominal collections, OR 0.80 [95% CI, 0.44–1.43, p = 0.80]; reoperation rates, OR 1.24 [95% CI, 0.73–2.13, p = 0.42]; duration of hospital stay, − 0.23 [95% CI − .59 to 1.13, p = 0.74]; and mortality, 1.78 [95% CI, 0.94–3.39, p = 0.08].

Conclusion SA did not improve the post-operative outcomes following PD, including reducing the incidence of POPF. The routine administration of SA cannot be recommended following PD.

Introduction

Although the overall 5-year survival rate following pancreaticoduodenectomy (PD) for pancreatic cancer has improved over the last decade [1], PD is associated with a morbidity rate of up to 60% and mortality rate of less than 5% [2]. The improvement in post-operative outcomes is thought to be due to the advancement in critical care following surgery and the introduction of post-operative protocols, rather than reduction in complications following PD [3, 4]. Post-operative pancreatic fistula (POPF) following PD remains a major cause of morbidity, with current studies reporting incidence rate of up to 30% [3, 5, 6].

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Table 1 The 2005 International Study Group on Pancreatic Fistulas (ISGPF) classification of post-operative pancreatic fistula (POPF) [8]

Grade	Clinical conditions	Specific treatment[a]	USS/CT (if obtained)	Persistent drainage (after 3 weeks)[b]	Reoperation	POPF-related death	Signs of infection	Sepsis	Readmission
A	Well	–	–	–	–	–	–	–	–
B	Often well	±	±	Usually +	–	–	+	–	±
C	Ill/bad	+	+	+	+	±	+	+	±

+ positive, − negative, *USS* ultrasonography, *CT* computed tomography

[a]Partial (peripheral) or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue and/or minimal invasive drainage

[b]With or without a drain in situ

It has also been reported that developing a POPF is associated with a twofold increased risk of mortality [4–8].

The differences in incidence of POPF may be due to the varying definitions reported in published studies. In 2005, the International Study Group on Pancreatic Fistulas (ISGPF) released a universal classification of fistulae, based on drainage, morbidity and mortality (Table 1) [9]. This classification is composed of Grades A, B and C, with Grade B and C fistulae that are considered clinically relevant [9]. Since POPF influences both short- and long-term outcomes following PD [3–7], various methods have been used in an attempt to reduce this complication, including fibrin sealants; transanastomotic stents; duct-to-mucosa and pancreatico-enteric anastomosis; and somatostatin analogues (SA) [10].

The use of hormone somatostatin or its synthetic analogues, despite the inconsistent evidence of its clinical benefit [2], is the most commonly used method to reduce the incidence of POPF. Klempa et al. [11] first reported that somatostatin reduced the incidence of complications following PD. Since then, the efficacy of somatostatin has been investigated, but the published data have been conflicting. Furthermore, most of these studies predate the initial ISGPF classification [9], where studies did not differentiate between biochemical and clinically relevant POPF. The aim of this systematic review and meta-analysis of randomised controlled trials (RCTs) was to determine the outcome of the prophylactic use of SA on morbidity and mortality following PD.

Methods

This study was conducted according to the recommendations laid out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [12].

Identification and selection of studies

The review and quantitative analysis was restricted to the classic Whipple's procedure (PD) and pylorus-preserving PD (PPPD). All placebo-controlled randomised trials, conducted to appraise the efficacy of the prophylactic use of somatostatin or its analogues following PD since year 2000, were considered.

Prior to the International Study Group on Pancreatic Fistulas (ISGPF) classification introduced in 2005, there was no standardised definition or classification of POPF [9]. However, even after this date, variability in its definition persists. Hence, studies were considered if a reasonable definition of POPF was included in the methodology. Quasi-randomised trials, review articles, retrospective analysis, abstracts only, observational studies and letters were excluded.

Search

A systematic and comprehensive electronic literature search of MEDLINE, EMBASE and Cochrane databases to identify trials evaluating the prophylactic use of SA following PD and PPPD was performed. The detailed search strategy is included in 'Appendix' section. The search encompassed the relevant pancreatic surgery of interest, the SA used and outcomes. This included 'Pancreatico-duodenectomy', 'PD', 'Pylorus preserving pancreatico-duodenectomy', 'somatostatin', 'somatostatin analogue', 'octreotide', 'pasireotide', 'lanreotide', 'vapreotide', 'pancreatic leak', 'pancreatic fistula' mapped to corresponding Medline Subject Headings (MeSH). The use of the Scottish Intercollegiate Guidelines Network (SIGN) methodological filters [13] allowed restriction and identification of articles that specifically described RCTs. The search was further magnified by exploring the 'Related Articles' section and the reference list of the preliminary search.

Data collection and analysis

Data extraction was performed independently by two reviewers (AA and ZA), using a data extraction template. In cases of discordance, a third reviewer (DG) adjudicated. For the review process, the details of the author, date of publication, country of origin and number of patients in

each study were extracted. Additionally, demographic data, type of surgery, dose and the variant of SA used and administration method were also extracted.

Outcomes

The primary outcome assessed was POPF following PD. The primary outcome was further examined in the subgroup of studies published after 2005 to reflect the implementation of the ISGPF classification. The secondary outcomes included: length of hospital stay, delayed gastric emptying, infected abdominal collections, reoperation and mortality.

Quality assessment of included studies

Risk of bias in studies is noted to result in overstating or understating of treatment effects. The Cochrane risk of bias domains was used to assess the risk of bias of the included studies [14]. The domains assessed include selection bias, allocation bias, attrition bias, detection bias, performance bias and reporting bias.

Statistical analysis

Meta-analyses of the pooled data were performed using the Review Manager (RevMan) [computer program], version 5.3 [15]. The quantitative analysis assumed an 'intention-to-treat' basis for all the included studies. For dichotomous outcomes, the odds ratio (OR) was calculated with their respective 95% confidence interval (CI). For continuous outcomes, the weighted mean difference (WMD) was calculated with its 95% confidence intervals (CI). A random-effects model was used in the pooling of data. The degree of heterogeneity was measured by Chi-squared test with significance set at a p value of <0.05, and the quantity of heterogeneity was measured by the I^2 statistic, with an I^2 value $>50\%$ considered to represent statistically significant heterogeneity. Publication bias was assessed with a funnel plot based on the primary outcome.

Results

Description of included studies

Participants

Twelve RCTs were included (Fig. 1a) which consisted of 1615 patients [SA-treated group ($n = 820$) and control group ($n = 795$)] [16–27]. There were 784 patients in RCTs comparing octreotide to placebo; 256 patients in trials comparing somatostatin-14 to placebo; 275 patients in trials comparing vapreotide to placebo; and 300 patients in trials comparing pasireotide to placebo [16–27]. The majority of the study population were male ($n = 921$, 57%), and the median age was 61.5 years (interquartile range 58.2–65.5 years). All trials reported no difference in baseline characteristics between the intervention and control groups. The study characteristics, demographics and risk of bias are summarised in Tables 2 and 3 and Fig. 1b.

Results of meta-analyses

Primary outcomes

POPF There were 320 POPF reported in the studies included (320/1615, 19.8%). Of these cases, 143 (143/820, 17.4%) patients with POPF occurred in the somatostatin-treated group and 177 (177/795, 22.3%) patients had POPF reported in the control group, respectively. The pooled OR was 0.73 [95% CI 0.51–1.05; $p = 0.09$]. For the six studies [16, 17, 20–22, 26] reported after the 2005 ISGPF classification, the number of cases in the SA group was 68 (68/339, 20.1%) and 99 (99/326, 30.4%) in the control group, respectively. The pooled OR was 0.57 [95% CI, 0.30–1.10, $p = 0.09$] (Fig. 2a, b). The pooled results of those studies [16, 17, 22–24, 26] that specifically reported clinically relevant POPF were also not significant, OR 0.48 [95% CI, 0.22–1.06, $p = 0.07$] (Fig. 3a).

Secondary outcomes

1. Delayed gastric emptying was reported as dichotomous data in six studies [17, 20–22, 24, 26]. One study reported this complication as continuous data of duration of the delayed gastric emptying, but provided no data on the number of study participants with this complication [16]. The pooled OR was 0.98 [95% CI 0.57–1.69, $p = 0.94$] (Fig. 3b).
2. Seven studies reported on infected abdominal collections [17, 18, 20, 22, 24, 25, 27]. This complication was present in 24 (24/413, 5.8%) patients treated with SA and 29 (29/395, 7.3%) patients in the control group. The OR was 0.80 [95% CI 0.44–1.43, $p = 0.80$] (Fig. 4a).
3. Reoperation rates were reported by seven studies [18, 21, 22, 24–27] for the first 30 days after the index operation. The pooled OR was 1.24 [95% CI 0.73–2.13, $p = 0.42$] (Fig. 4b).
4. Duration of hospital stay was reported fully in six studies [16, 19, 21, 22, 24, 27]. Two other studies reported mean duration of stay without the standard deviations [17, 18]. The pooled WMD of the duration of hospital stay was − 0.23 [95% CI − 1.59–1.13, $p = 0.74$] between the two groups (Fig. 5a).

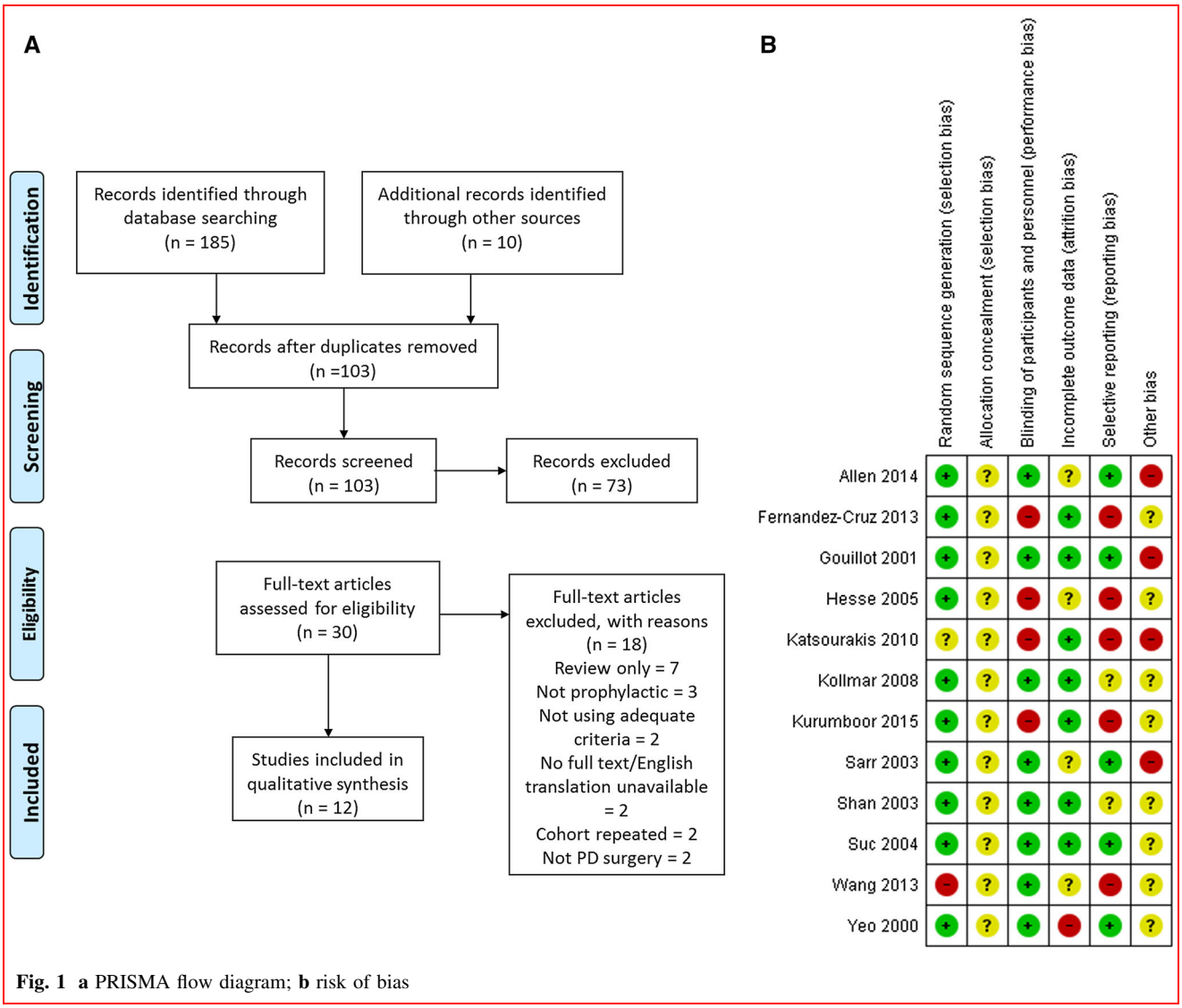

Fig. 1 **a** PRISMA flow diagram; **b** risk of bias

5. Mortality was reported by all the included studies; it was 2.6% (42/1615) [16–27]. The mortality rate in the SA group was 3.4% (28/820) and 1.8% (14/795) in the control group, respectively. Pooled OR of mortality was 1.78 [95% CI 0.94–3.39, $p = 0.08$] (Fig. 5b).

There were no significant differences in the primary and secondary outcomes between the SA group and the placebo group.

Publication bias

In this analysis, publication bias was assessed using funnel plots based on the primary outcome of POPF and significant POPF. Asymmetry of the plot as demonstrated in Fig. 6 favoured trials with positive outcomes and raises the plausibility of publication bias.

Heterogeneity

The studies included in this analysis were all RCTs and investigated the prophylactic administration of SA following PD. Heterogeneity for all of the parameters in the primary and secondary outcomes was assessed. There was a varying degree of statistical heterogeneity in the outcomes measured as reported in the individual figures (Figs. 2a, 3, 4, 5b) ranging from an I^2 of 0% in clinically significant POPF, reoperation rates and DGE, to an I^2 of 89% in duration of hospital stay. This suggested the presence of clinical and statistical heterogeneity in the individual included studies and influenced the decision to employ the random-effects model for this present meta-analysis.

Table 2 Study characteristics

References	Country	Definition of POPF	Aim of study	Numbers SA: somatostatin CC: control	Funding	*p* values, confidence intervals and/or risk ratio of POPF and CR-POPF	Initiation time and length of treatment (day 0 = op)
Allen et al. [16]	USA	MSKCC Surgical Secondary Events System	To evaluate the use of pasireotide in preventing POPF	300 SA: 152 CC: 148	Novartis Pharmaceuticals	$p = 0.006$ RR 0.44 95% CI 0.24–0.78	900 µg pasireotide BD from day 0 to 14
Fernandez-Cruz et al. [17]	Spain	ISGPF definition	To evaluate octreotide's role in reducing pancreatic output	62 SA: 32 CC: 30	Not available	Grade B POPF: $p = 0.819$	100 µg octreotide S/C TDS day 0–10
Gouillat et al. [18]	France	Drainage of amylase-rich fluid > 100 mL/day	Evaluating somatostatin-14's role in preventing post-operative complications	75 SA: 38 CC: 37	Grant from UBC Pharma SA, Nanterre, France	POPF: 0.24 (0.06, 1.07)	Somatostatin infusion day 0–14
Hesse et al. [19]	Belgium	Drainage > 100 mL/day of amylase-rich fluid 5 limits above normal	To evaluate the role of octreotide in preventing pancreatic complications post-surgery	80 SA: 41 CC: 39	Not available	CR-POPF: RR 1.09 (0.31, 3.85) 95%	100 µg octreotide TDS day 0–7
Katsourakis et al. [20]	Greece	ISGPF definition	To evaluate the role of somatostatin in preventing pancreatic complications	67 SA: 35 CC: 32	Supported in part by a grant from Faran Laboratories SA, Athens, Greece	POPF: 0.18 (0.02, 1.48)	Somatostatin 3.5 µg/kg/h from 30 min before surgery to day 7
Kollmar et al. [21]	Switzerland	ISGPF definition	To evaluate prophylactic octreotide's role in preventing DGE	67 SA: 35 CC: 32	None declared	POPF: 1.37 (0.55, 3.42) CR-POPF: 1.14 (0.34, 3.89)	100 µg octreotide TDS from day 0 to 7
Khurumboor et al. [22]	India	ISGPF definition	To evaluate the role of octreotide in preventing pancreatic fistulae	109 SA: 55 CC: 54	Not available	POPF: 0.98 (0.71, 1.37) CR-POPF: 0.7 (0.22, 2.27)	100 µg octreotide S/C
Sarr et al. [23]	USA	Drainage fluid (on or after day 5 post-op) of 30 mL/day; amylase and lipase activity > 5 × UL of normal	To evaluate the role of vapreotide in preventing pancreas-specific complications post-operatively	275 SA: 135 CC: 140	Financial support from Debiopharm SA	POPF: 1.04 (0.68, 1.59)	Vapreotide 600 µg S/C 2 h pre-operatively, and up to day 7 BD
Shan et al. [24]	Taiwan	Amylase-rich fluid > 10 mL/day, persistent elevation of drain amylase and 3x over serum for > 7 days	To evaluate the role of somatostatin in preventing pancreatic stump-related morbidity	54 SA: 27 CC: 27	Not available	POPF: 1 (0.15, 6.59)	250 µg/h Somatostatin day 0–7 IV
Suc et al. [25]	France	Chemical evidence (serum amylase 4x normal for 3 days) or radiological evidence of anastomotic leaks	Role of octreotide in preventing post-operative intra-abdominal complications	230 SA: 122 CC: 108	Not available	POPF: 0.93 (0.53, 1.62)	100 µg octreotide TDS from day 0 to 7

Table 2 continued

References	Country	Definition of POPF	Aim of study	Numbers SA: somatostatin CC: control	Funding	*p* values, confidence intervals and/or risk ratio of POPF and CR-POPF	Initiation time and length of treatment (day 0 = op)
Wang et al. [26]		ISGPF definition	To evaluate the efficacy of pre-operative somatostatin in reducing complications post-operatively	67 SA: 35 CC: 32	Not available		
Yeo et al. [27]	USA	Drainage > 50 mL of amylase-rich fluid per day on or after post-op day 10, or radiological evidence	To evaluate octreotide's role in preventing pancreatic complications post-operatively	211 SA: 107 CC: 104	NIH grants RO1-CA56130 & P50-CA62924	POPF: 1.07 (0.47, 2.41)	100 µg octreotide TDS from day 0 to 7 starting at least 1 h pre-operatively

Discussion

Background of use of somatostatin therapy following pancreaticoduodenectomy

POPF is known to occur in about 30% of cases following PD and is associated with a twofold risk of mortality [4–8]. It is therefore unsurprising that several methods have been utilised to reduce the risk of its occurrence such as the prophylactic administration of SA. Brazeau et al. [28] were the first to report on somatostatin, the polypeptide isolated from ovine hypothalamus that was capable of inhibiting the secretion of pituitary growth hormone. The possibility of its role in the pancreas was identified in animal studies by Klempa et al. [11], who reported suppression of pancreatic exocrine secretion, reduction in serum amylase and histological improvement in pancreatic cellular architecture [11]. Following these findings, the authors subsequently demonstrated that the administration of somatostatin led to the reduction in serum amylase following PD in ten patients. This landmark finding engendered the development of other studies with investigators aiming to exploit somatostatin's function in reducing pancreatic exocrine secretion as a means of reducing the incidence of POPF. Somatostatin has a short half-life, thereby requiring a continuous infusion to achieve a steady state for its effect. SA such as octreotide, lanreotide, vapreotide and pasireotide have a much longer half-life and hence are preferred for ease of administration [2, 16].

Results of meta-analysis

The current analysis showed that the overall incidence of POPF was 19.8% (320/1615, 19.8%), which is consistent with the current published literature with respect to the risk of POPF following PD. The rate of clinically relevant POPF was 18%, in the studies that reported it as an outcome (159/881, 18.05%). Four different SA were used in the studies included: somatostatin-14, octreotide, vapreotide and pasireotide. There are no current experimental studies directly comparing the efficacy of these different analogues in reducing pancreatic exocrine secretions, and as such, the SA are treated as equivalent.

This meta-analysis showed no significant difference in the primary outcomes of POPF and in the secondary outcomes of interest including delayed gastric emptying, infected abdominal collections, duration of hospital stay and mortality. Considering the ISGPF classification was established in 2005 [9], analysis of the post-2005 studies where definitions were more likely to be consistent still showed no benefit in reducing the incidence of POPF. Due to the limited number of studies in each of the different

Table 3 Demographics and key findings

Reference	Number in study	Incidence of POPF	Age (median)	Male %	Somatostatin/analogue dosage	Mortality % (*n*)	Severity measure
Allen et al. [16]	300	12.3% (37)	65	55	900 μg pasireotide	0.7 (2)	MSKCC Surgical Secondary Events and 2005 ISGPF criteria
Fernandez-Cruz et al. [17]	62	8% (5)	69	54.8	100 μg octreotide	0 (0)	ISGPF criteria
Gouillat et al. [18]	75	18.7% (14)	60.3	68	6 mg somatostatin day 1–6 3 mg per 24 h day 7	4 (3)	Drainage of amylase-rich fluid > 100 mL/day
Hesse et al. [19]	80	10% (8)	59.4	73.3	100 μg octreotide	0.95 (1)	Drainage > 100 mL/day of amylase-rich fluid 5 limits above normal
Katsourakis et al. [20]	67	8.95% (6)	61.1	58.2	3000 μg somatostatin 3x	4.4% (3)	ISGPF criteria
Kollmar et al. [21]	67	21.5% (14)	62.4	61.2	100 μg octreotide	4.5 (3)	ISGPF criteria
Khurumboor et al. [22]	109	61.5% (67)	57	60.6	100 μg octreotide	2.98% (2)	ISGPF criteria
Sarr et al. [23]	275	23.3% (64)	62	52.5	Vapreotide (0.6 mg) 2 h pre-op, and BDS for 7 days post-op	0.73% (2)	Drainage fluid (on or after day 5 post-op) of 30 mL/day; amylase and lipase activity > 5x UL of normal
Shan et al. [24]	54	7.4% (4)	67	51.9	250 μg/hour somatostatin for 7 days	3.7 (2)	Amylase-rich fluid > 10 mL/day, persistent elevation of drain amylase and 3x over serum for > 7 days
Suc et al. [25]	230	17.8% (41)	56.5	57	100 μg octreotide TDS 10 days	10 (23)	Chemical evidence (serum amylase 4x normal for 3 days) or radiological evidence of anastomotic leaks
Wang et al. [26]	60	41.7% (25)	51	63.3	6 mg somatostatin daily	0 (0)	ISGPF criteria
Yeo et al. [27]	211	9.95% (21)	66	53	250 μg octreotide 2 h pre-op and 7 days post-op TDS	0.47 (1)	Drainage > 50 mL of amylase-rich fluid per day on or after post-op day 10, or radiological evidence

classes of SA, subgroup analysis was not performed. However, there was one study that used pasireotide, and this showed a significant benefit in all the outcomes measured. Although this trial was well designed and powered, it reported a higher-than-expected withdrawal rate of 17% within the pasireotide group. This was the highest withdrawal rate of all the studies included in this analysis. In addition, the rate of all grade 3 or grade 4 complications that would require intervention or reoperation was 21% in the placebo group, which was considered higher than expected for a tertiary high-volume centre [29]. Furthermore, since the publication of this trial that was funded by the manufacturer, no further validation studies have been reported.

Current evidence

Previously, a meta-analysis of four studies by Rosenberg and co-workers [30] showed that the use of octreotide prevented POPF following all pancreatic surgery. However, a subsequent high-powered RCT by Yeo et al. [27] showed no clinically significant benefit in the use of prophylactic octreotide following PD. The differences in results observed could be related to the definition of POPF. Previously published studies did not differentiate between clinically relevant fistulae and biochemical leaks following pancreatic surgery. In addition, the type of pancreatic surgery may have also influenced the findings as well as some trials being sponsored by pharmaceutical companies.

Montorsi et al. [31] did account for the difference between surgical procedures and showed that octreotide administration reduced the incidence of POPF after distal pancreatectomy and local resection but did not influence the rate of POPF following PD. However, this report was prior to the standardised POPF classification introduced in 2005 [9]. The meta-analysis by Jin et al. [32] showed no significant difference of SA in reducing POPF following pancreatic surgery. The authors also observed a similarly non-significant increased risk of mortality in the somatostatin group compared to placebo group. Furthermore, the

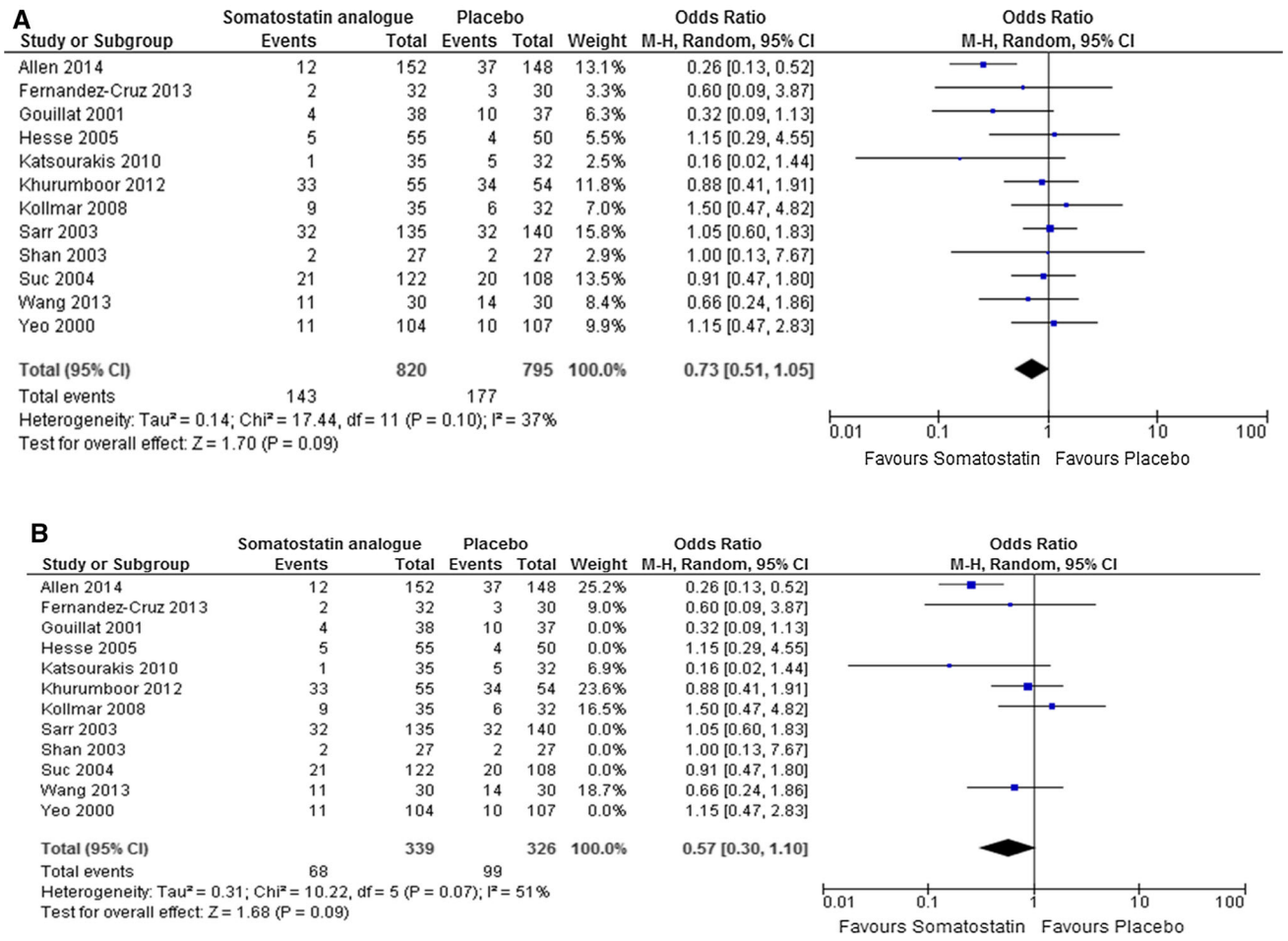

Fig. 2 **a** All POPF overall, **b** POPF post-2005 ISGPF classification

authors did not identify any difference in their secondary outcomes. Nevertheless, the authors did perform a subgroup analysis and concluded that the use of prophylactic somatostatin and pasireotide but not octreotide or vapreotide may have beneficial effects with respect to clinically significant fistulas. In this present meta-analysis, pooled synthesis of the different studies showed no benefit for all grades of POPF and no benefit for clinically significant POPF (Figs. 2a, b, 3a) after PD in agreement with the findings by Jin et al. [32].

In 2013, a Cochrane review [2] reported that SA did not reduce perioperative mortality, risk of reoperation or the occurrence of clinically significant POPF. The authors also found no difference in duration of hospital stay following the prophylactic use of somatostatin therapy, all consistent with our findings [2]. Nevertheless, the authors concluded that SA should still be given due to its low cost and theoretical benefit (Table 4).

Recent studies have suggested a potential increased risk of mortality, increased delayed gastric emptying and higher risk of bleeding in patients treated with prophylactic somatostatin therapy following pancreatic surgery compared to controls [17, 22], making theoretical benefit alone difficult to justify. In a retrospective study by McMillan et al. [35], that included a risk-adjusted analysis of 1018 PDs, the authors demonstrated that the prophylactic administration of octreotide led to no clinical benefit and was associated with an increase in clinically relevant POPF, particularly in a subgroup of patients that had moderate to high pancreatic fistula risk.

Somatostatin analogues are implicated in a reduction in tissue perfusion in several studies evaluating regional blood flow to the gastroduodenal mucosa and to the pancreas [36–38]. This reduction selectively affects the splanchnic circulation without altering the systemic circulation [36]. It has been hypothesised that the reduction in pancreatic exocrine secretion owing to prophylactic somatostatin analogue use is outweighed by the decreased splanchnic blood flow [35]. This alteration in tissue perfusion results in a reduction in anastomotic perfusion,

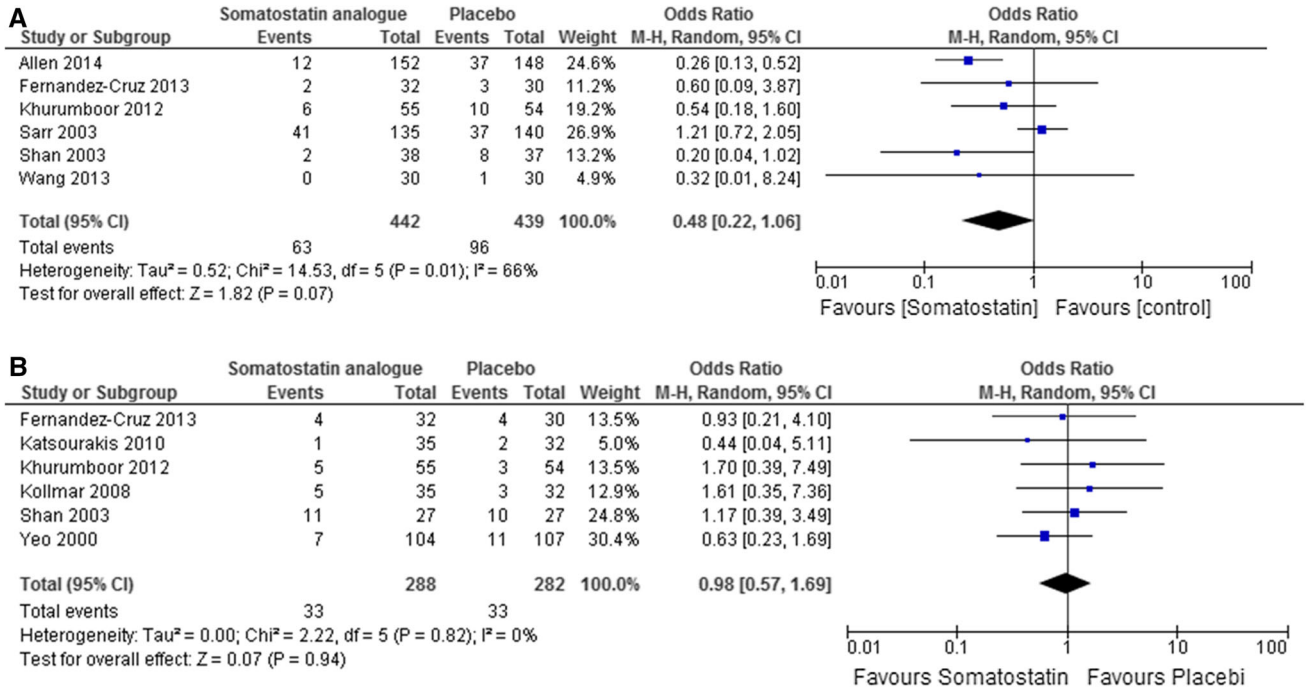

Fig. 3 **a** Clinically significant POPF; **b** delayed gastric emptying

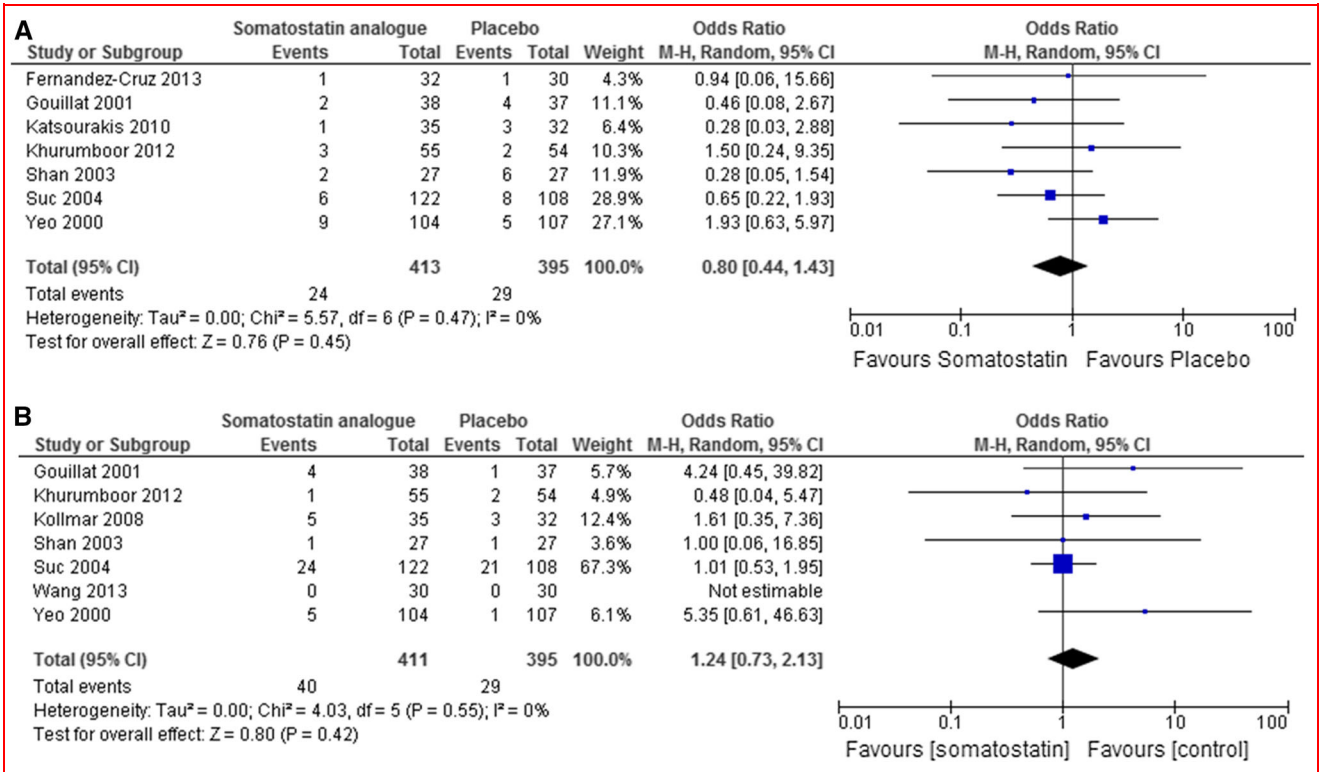

Fig. 4 **a** Infected intra-abdominal collections; **b** reoperations

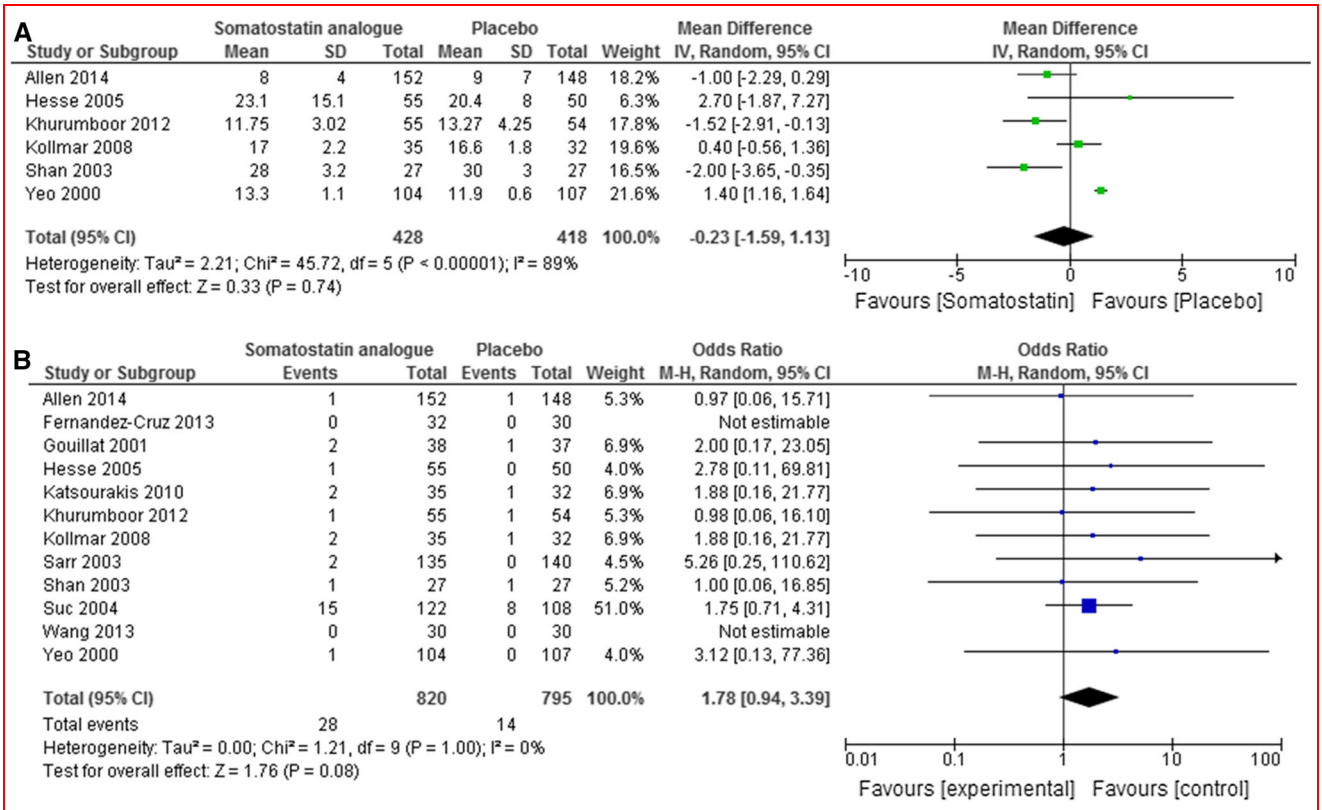

Fig. 5 **a** Hospital stay; **b** mortality

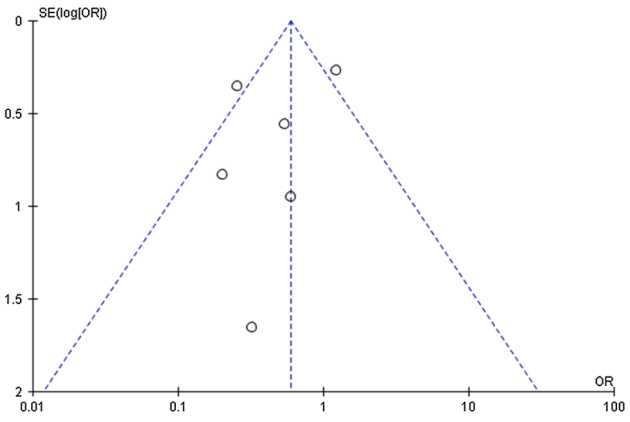

Fig. 6 Publication bias—assessed on significant POPF

promoting ischaemia and congestion at the sites of anastomosis, thereby increasing the risk of POPF.

In addition, the inhibitory effects of somatostatin analogues on hormonal pathways are exploited in conditions such as acromegaly where its inhibition of the pituitary growth hormone is desirable [39]. In the post-surgical phase, suppression of important hormonal mediators of tissue healing such as epidermal growth factor and insulin-like growth factor 1 could impair the rate of healing at the pancreatic anastomotic sites and potentiate the risk of anastomotic leak [35]. However, further work is required to delineate the exact pathophysiological mechanism that underlies the possible detrimental effects of SA in patients undergoing PD with a moderate to high fistula risk.

The present review and meta-analysis, in agreement with recent contemporary evidence, illustrates that somatostatin and its analogues have no statistically significant beneficial effect on the risk of morbidity and mortality following PD.

Strengths and limitations of the current analysis

This comprehensive systematic review of contemporary studies published since the year 2000 evaluated the prophylactic use of somatostatin therapy following PD or PPPD. Subgroup analysis by patient characteristics, underlying pathophysiology of the pancreas gland or type of SA was not undertaken as this was not consistently reported. With respect to the type of SA, there have been no experimental studies [16] that have shown or quantified

Table 4 Other meta-analyses on SA in pancreatic surgery

References	Number included	SA used	Pancreas surgery	Clinically relevant POPF	Mortality	Review conclusion
Zeng et al. [33]	–	Somatostatin Octreotide Vapreotide	PD or PPPD	(OR 95% CI (0.64–1.37)	(OR 95% CI, 0.59–7.72)	The use of somatostatin and its analogues does not significantly reduce post-operative complications after PD
Gurusamy et al. [2]	2348	Vapreotide, Pasireotide, Octreotide Somatostatin	All pancreatic surgery	RR 0.69; (95% CI 0.38 – 1.28)	RR 0.80 (95% CI 0.56 to 1.16)	Based on currently available evidence, somatostatin and its analogues are recommended for routine use in people undergoing pancreatic resection
Jin et al. [32]	1352	Octreotide Somatostatin Vapreotide Pasireotide	PD or PPPD	0.70 (95% CI 0.47–1.05)	1.42 (95% CI 0.76–2.65)	The current best evidence suggests prophylactic treatment with somatostatin or pasireotide has a potential role in reducing the incidence of pancreatic fistulas, while octreotide had no influence on the incidence of pancreatic fistulas
Han et al. [34]	1703	Vapreotide, pasireotide, Octreotide Somatostatin	PD and DP	RR 0.60 (95% CI 0.55–0.98)	RR 1.34 (95% CI 0.75–2.40)	SA appears to reduce the overall incidence of clinical pancreatic fistulas and decreases post-operative hospital stay after pancreatic surgery

Other than Han et al., who had a significant finding for 'clinically relevant POPF,' all the other reviews demonstrated no benefit for clinically relevant POPF or for Mortality

OR odds ratio, *RR* relative risk, *PD* pancreaticoduodenectomy, *PPPD* pylorus-preserving pancreaticoduodenectomy, *DP* distal pancreatectomy, *95% CI* 95% confidence interval

the volume of reduction in pancreatic secretions following drug administration, which subsequently leads to an increased efficacy in preventing POPF or improving post-operative morbidity or mortality. Hence, all SA were treated as equivalent in the present analysis. The results demonstrate that the administration of SA does not offer benefit in all of the outcome measures assessed. We evaluated the possibility of publication bias and demonstrated that studies with positive findings were more likely to be published. Additionally, certain RCTs were sponsored by industry stakeholders [16, 18, 20] and other trials did not clearly state the sources of funding [17, 19, 21].

All meta-analyses are limited by the quality of the included studies, which is a measure of the appropriateness of the study conduct and the validity of the results. In recent years, the implementation of the CONSORT checklist [40] for publications has ensured a degree of consistency and transparency [41]. The primary and secondary end points of the included studies, although investigating SA, differed between studies, which reduces the power when pooling data. Such differences in the study conduct and quality also account for some of the clinical and statistical heterogeneity in the quantitative synthesis. In this analysis most studies were of low to medium risk of bias. However, to account for the possibility of heterogeneity we adopted the random-effects meta-analysis in our quantitative analysis.

Recently, the International Study Group in Pancreatic Surgery (ISGPS) have updated the grading system and have redefined the previous Grade A POPF to a 'biochemical leak' and introduced stricter criteria to classify Grades B and C POPF [42]. To date, there are no studies using this updated ISGPS definition. However, this new classification will ensure a more uniform definition in future trials and reduce further the degree of clinical and statistical heterogeneity.

Conclusion

The currently available data suggest that the prophylactic administration of SA following PD did not reduce the incidence of POPF. Furthermore, SA did not show any significant benefit in preventing delayed gastric emptying, infected abdominal collection and mortality following PD. The routine use of SA following PD cannot be recommended based on the current evidence available.

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Authors' contribution AA conceived and designed the study, extracted and analysed the data, drafted the write-up and approved the final manuscript; ZA and FB extracted and analysed the data, drafted

the write-up and approved the final manuscript; SS performed the analyses, drafted the write-up and approved the final manuscript; NL designed the study, drafted the manuscript and approved the final manuscript; DG conceived and designed the study, analysed the data, drafted the write-up and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Appendix: Detailed search strategy

Database: Ovid MEDLINE(R) <1946 to May Week 1 2017>

Search strategy

1	Randomized Controlled Trials as Topic/(113072)
2	randomized controlled trial/(461944)
3	Random Allocation/(92524)
4	Double Blind Method/(146986)
5	Single Blind Method/(24505)
6	clinical trial/(520955)
7	clinical trial, phase i.pt. (18692)
8	clinical trial, phase ii.pt. (30051)
9	clinical trial, phase iii.pt. (13709)
10	clinical trial, phase iv.pt. (1465)
11	controlled clinical trial.pt. (94024)
12	randomized controlled trial.pt. (461944)
13	multicenter study.pt. (226952)
14	clinical trial.pt. (520955)
15	exp Clinical Trials as topic/(312693)
16	or/1–15 (1227275)
17	(clinical adj trial$).tw. (257855)
18	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (144052)
19	PLACEBOS/(34925)
20	placebo$.tw. (178301)
21	randomly allocated.tw. (20018)
22	(allocated adj2 random$).tw. (22793)
23	or/17–22 (483928)
24	16 or 23 (1379829)
25	case report.tw. (216632)
26	letter/(929319)
27	historical article/(347336)
28	or/25–27 (1479758)
29	24 not 28 (1347097)
30	exp Pancreatic Fistula/or pancreas fistula.mp. (2648)

Appendix continued

31	pancreas leak.mp. (2)
32	pancreas.mp. or *Pancreas/(121867)
33	anastomotic leak.mp. or *Anastomotic Leak/or *Anastomosis, Surgical/(8829)
34	32 and 33 (223)
35	exp Pancreatic Fistula/or pancreas fistula.mp. (2648)
36	30 or 31 or 34 or 35 (2841)
37	exp Pancreatectomy/or exp Pancreaticoduodenectomy/or pancreas surgery.mp. (17109)
38	exp Pancreatectomy/or pancreaticoduodenectomy.mp. or exp Pancreaticoduodenectomy/(17748)
39	pancreaticojejunostomy.mp. or exp Pancreaticojejunostomy/(1428)
40	exp Pancreaticoduodenectomy/or whipples procedure.mp. (6490)
41	exp Pancreatectomy/or pancreas resection.mp. (11572)
42	distal pancreatectomy.mp. (2359)
43	subtotal pancreatectomy.mp. (352)
44	partial pancreatectomy.mp. (517)
45	37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 (19502)
46	36 and 45 (1363)
47	somatostatin.mp. or exp Somatostatin/(30589)
48	exp Octreotide/or exp Somatostatin/or somatostatin analogue.mp. (24335)
49	exp Octreotide/or exp Somatostatin/or somatostatin analogues.mp. (24535)
50	exp Octreotide/or octreotide.mp. (7164)
51	pasireotide.mp. (355)
52	lanreotide.mp. (880)
53	angiopeptin.mp. (102)
54	vapreotide.mp. (197)
55	47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 (33483)
56	46 and 55 (103)

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