Table 2 Domain scores determined using the AGREE instrument for clinical practice guidelines

Domain	Total (n = 18)		The first half, March 2005–March 2007 (n = 10)		The second half, April 2007–May 2009 (n = 8)		P value[a]
	Median	IQR[b]	Median	IQR	Median	IQR	
Scope and purpose	72.2	66.7–100	66.7	55.5–100	83.3	66.7–100	0.38
Stakeholder involvement	41.7	16.7–50.0	43.1	25.0–58.3	41.7	29.2–50.0	0.93
Rigor of development	66.7	38.9–83.3	44.4	16.7–72.2	72.2	61.1–86.1	0.13
Clarity and presentation	75.0	58.3–91.7	70.8	33.3–91.7	83.3	70.8–100	0.18
Applicability	33.3	0–66.6	16.7	0–33.3	50.0	25.0–66.7	0.10
Editorial independence	0	0–50.0	0	0–0	33.3	0–50.0	0.12
Aggregated	56.3	36.5–69.8	48.6	28.6–58.7	65.9	54.8–71.4	0.11

[a] Comparison of scores between the first half of the period and the second half of the period was tested using the Wilcoxon rank-sum test

[b] Inter-quartile range

the score among its members. Item 13 indicates a requirement for an external review of the CPG. This item was not scored because review by the EC is compatible with this. Item 21 requires the CPG to present key review criteria for monitoring or audit. This item was also omitted from scoring because quality indicators for measuring adherence to CPGs have not been developed.

Results

The EC started reviewing CPGs in March 2005, and 18 of them had been reviewed by May 2009 (Table 1). Table 2 shows the standardized domain scores of these CPGs. The domains with median scores > 50 points during the entire period of review were "scope and purpose," "rigor of development," and "clarity and presentation." The median scores for "stakeholder involvement," "applicability," and "editorial independence" were <50 points. All domain scores except "stakeholder involvement" were higher during the second half of the period than during the first half of the period, although the P values were 0.10—0.93.

Figure 1 shows the distribution of crude scores for each item in all CPGs. Item numbers with median crude scores ≤ 2.0 were 5 (emphasizing patients' perspectives), 7 (pre-test before publication), 19 (discussion about potential organizational barriers), 20 (considering cost implications), 22 (editorial independence from funding body), and 23 (records of conflicts of interest). The item numbers with widely distributed crude scores were 2 (description of clinical questions), 6 (target users defined clearly), 10 (presentation of methods for formulating recommendations), and 22 (editorial independence from funding body).

Table 3 shows the inter-rater reproducibility for each item. The kappa statistics were –0.02 to 0.64, and the null hypothesis that the consistency of the results occurred by chance alone could not be rejected for items 3 (target patients described specifically), 5 (emphasizing patients' perspectives), 7 (pre-test before publication), 18 (tools for application), and 23 (records of conflicts of interest).

Discussion

The present report describes the results of continuous evaluation of CPGs assembled by the Japan Society of Clinical Oncology. Changes in standardized domain scores indicated that the methods and organization for developing CPGs have improved slightly, although the differences were not statistically significant and the number of CPGs assessed was small. The domains with median scores > 50 points were "scope and purpose" (items 1–3), "rigor of development" (items 8–14), and "clarity and presentation" (items 15–18). Domains with median scores < 50 points were "stakeholder involvement" (items 4–7), "applicability" (items 19–21), and "editorial independence" (items 22–23). Developers must consider these findings when developing new guidelines or revising those that have been already established. For individual items, low scores were observed in items 5, 7, 19, 20, 22, and 23.

Item 5 emphasizes patients' perspectives. The values of individual patients with cancer should be considered in clinical decision making. Several guidelines seemed to specifically recommend a single option without providing alternatives. Representatives of patients or paramedical staff should be involved in these processes.

Item 7 addresses the pilot use of the CPG before formal publication. When a pilot is not used to improve the quality of the CPG, early feedback about its validity, implementation, and impact on routine practice after publication should be obtained.

Item 19 addresses potential organizational barriers. Alternatives should be discussed when barriers interfere with CPG implementation.

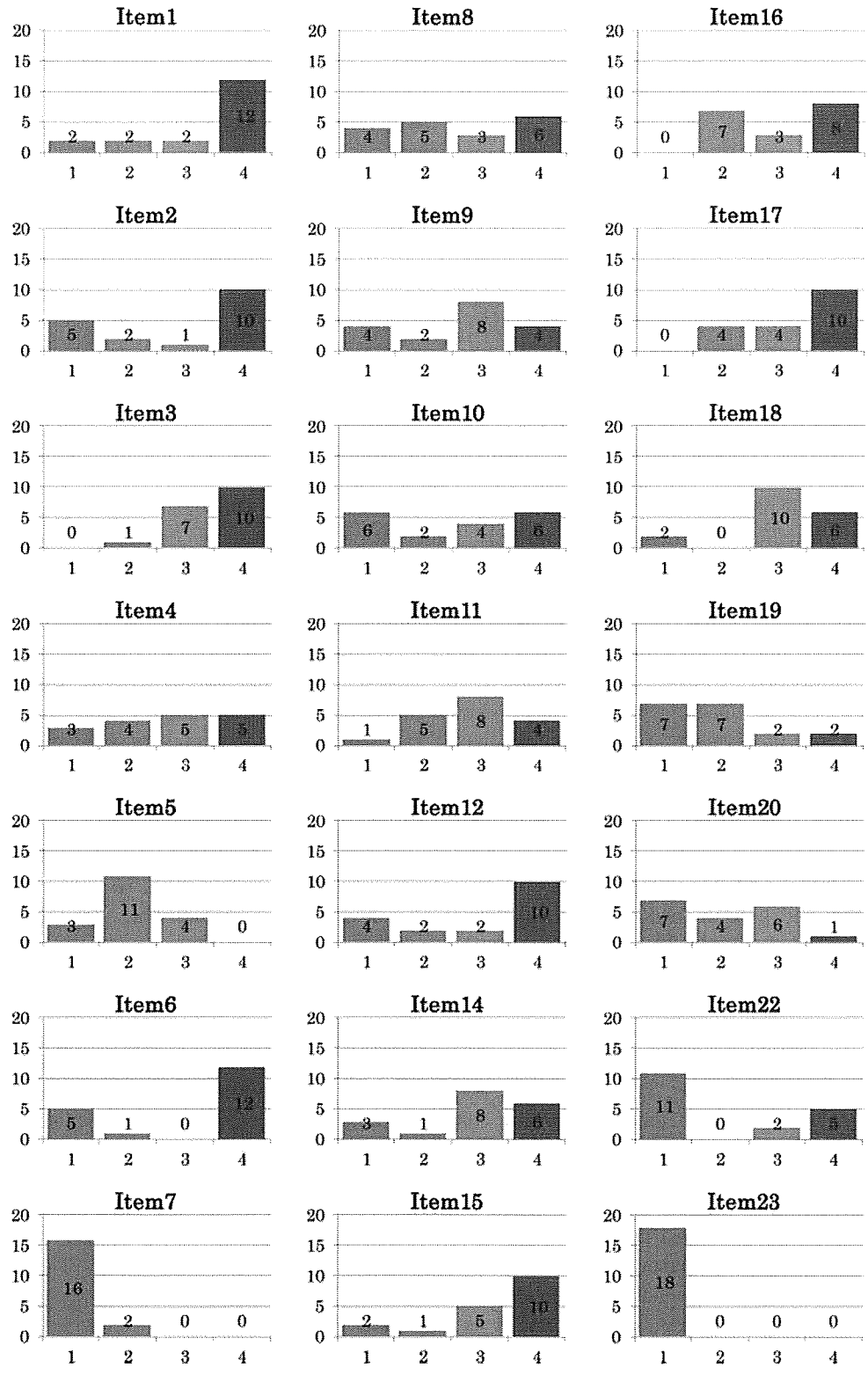

Fig. 1 Distribution of crude scores for each item. Crude scores of each item were reached by consensus after discussion in a committee meeting and are not simple means or medians of scores supplied by individual members of the Evaluation Committee

Item 20 refers to cost issues. The clinical practice of oncology must be individualized because it is based on patient status and value judgments. In general, the issue of cost is important, especially in preventive medicine and in the long-term management of prevalent chronic disorders such as hypertension or dyslipidemia. Cost is more urgent in preventive medicine than for oncologists whose patients have cancer.

Table 3 Inter-rater reproducibility of each item

Item	Kappa[a]	*P* value	Item	Kappa[a]	*P* value
1	0.23	<0.01	12	0.31	<0.01
2	0.64	<0.01	14	0.49	<0.01
3	0.00	0.49	15	0.15	<0.01
4	0.37	<0.01	16	0.20	<0.01
5	−0.02	0.61	17	0.15	<0.01
6	0.34	<0.01	18	0.05	0.18
7	0.04	0.23	19	0.19	<0.01
8	0.33	<0.01	20	0.28	<0.01
9	0.35	<0.01	22	0.14	0.01
10	0.33	<0.01	23	0.05	0.20
11	0.18	<0.01			

[a] Kappa statistics express agreement of several raters above the expected value

Item 22 requires editorial independence from funding bodies. The source of financial support should be documented. If pharmaceutical companies are the source, then the procedure for maintaining editorial independence should also be documented.

Item 23 asks about records of conflicts of interest. None of the CPGs described records for conflicts of interest, although the impact of CPGs on routine practice is substantial. Concern about conflicts of interest is increasing in Japan, where medical journals have not managed this issue as foreign journals have. The Japan Society of Clinical Oncology and the Japan Society of Medical Oncology have developed the "Clinical Oncology Research Conflict of Interest Policy (ver. 1)" [7, 8]. According to this policy, all members of the society must report their status regarding conflict of interest when they report and publish in the society, and these reports are centrally reviewed. This procedure must be followed when CPGs are developed, and records about conflicts of interest should be explicit.

The distribution of crude scores was wide for items 2, 6, 10, and 22, for which the same item scored low and high in several CPGs. Improving these points might not be difficult, although guideline-specific conditions might be involved. The involvement of experts specialized in the field of guidelines will be useful. Item 2 requires clear descriptions of clinical questions. When "Clinical Question" is first described for each CPG topic, it may help focus readers to understand the content more easily. This format of clinical question is preferable. Item 6 asks for a clear definition of the target users. It is important to define that clearly when developing and using CPGs. Item 10 addresses an explicit document that describes the methods of formulating recommendations; however, many CPGs did not provide this information. The impact of an assessment of benefits and harms after a systematic review on formulating a recommendation should be addressed. If disagreement about a recommendation arises, the methods used to reach consensus should be described.

Although the EC has reviewed a dozen CPGs, this report has some challenging issues as limitations. First, the inter-rater reproducibility of several items of the AGREE instrument was poor. Previous studies have identified good validity and reproducibility [3, 4], but we found that reproducibility was not easily achieved in our setting. Although AGREE is a good method of evaluation, the scoring remains subjective. We did not directly use the crude scores of individual members to reach the final assessment. Nevertheless, low reproducibility means that judgment by a member using the AGREE items is not a simple matter. Among low-score items, the score of items 5, 7, and 23 might be influenced by a difficult evaluation. Consensus will be achieved if the committee has criteria for scoring that maintain the original concept of the AGREE items.

Second, common scoring methods are not applicable to all CPGs, because solid evidence is not available in some fields of cancer. Although all CPGs of the society are related to cancer, each type of cancer has specific characteristics. AGREE itself does not recommend establishing a threshold to differentiate CPGs of "good" or "bad" quality.

The activity of CPG development is continuous, and CPGs of the subspecialty societies and the published material of the society (http://www.jsco-cpg.jp/) will be revised sequentially. These guidelines have also been published on the homepages of the subspecialty societies and of the Medical Information Network Distribution Service (MINDS), thus bringing the CPGs closer not only to medical professionals but also to patients. The activities of publishing and implementing CPGs within the society over the first decade seem to have begun well. Efforts to improve quality must be maintained, and users, including patients, should be able to easily understand the contents.

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Conflict of interest statement M. Toi received honoraria from GlaxoSmithKline. The other authors have no conflict of interest.

References

1. Japan Society of Clinical Oncology (2007) Clinical practice guidelines for cancer. http://www.jsco-cpg.jp/, accessed on November 10, 2009
2. AGREE collaboration (2004) http://www.agreecollaboration.org/, accessed on July 6, 2009
3. AGREE collaboration (2003) Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care 12:18–23
4. MacDermid JC, Brooks D, Solway S et al (2005) Reliability and validity of the AGREE instrument used by physical therapists in assessment of clinical practice guidelines. BMC Health Serv Res 5:18
5. Fleiss JL (1981) Statistical methods for rates and proportion, 2nd edn. Wiley, New York, pp 212–236
6. Kappa-interrater agreement (2007) STATA base reference manual, vol 2, I-P, Release 10. STATA Press, Texas, pp 83–96
7. Joint Formulation Committee (Japan Society of Clinical Oncology/ Japan Society of Medical Oncology) (2009) Clinical Oncology Research Conflict of Interest Policy (ver.1). http://jsco.umin.ac.jp/outline/COI.html
8. Joint Formulation Committee (Japan Society of Clinical Oncology/ Japan Society of Medical Oncology) (2009) Bylaws to the Clinical Oncology Research Conflict of Interest Policy (ver.1). http://jsco.umin.ac.jp/outline/saisoku4.html#saisoku4

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Meta-analysis: somatostatin or its long-acting analogue, octreotide, for prophylaxis against post-ERCP pancreatitis

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Abstract
Background Acute pancreatitis is a most serious complication following endoscopic retrograde cholangiopancreatography (ERCP). Previous meta-analyses and randomized controlled trials have shown conflicting results regarding the preventive efficacy of somatostatin or octreotide for this complication. The aim of this study was to resolve these conflicts.
Methods A standardized comprehensive literature search was performed through September 2009. Depending on heterogeneity of outcomes, either random-effects model (REM) or fixed-effects model (FEM) was applied to calculate pooled estimates of drug efficacy.
Results Seventeen studies, including 3818 participants, met the inclusion criteria. Analysis of somatostatin and octreotide trials showed that these drugs prevented post-ERCP pancreatitis (pooled risk ratio [95% confidence interval; CI], 0.63 [0.42–0.96] in REM. Pooled risk ratios [95% CI] of each subgroup were: 0.52 [0.30–0.90] for somatostatin in REM; 0.30 [0.17–0.53] for high-dose somatostatin infused over 12 h in FEM; 0.27 [0.13–0.52] for bolus somatostatin in FEM; 0.35 [0.15–0.82] for pancreatic duct (PD) injection with somatostatin in FEM; 0.33 [0.16–0.70] for biliary sphincterotomy (BS) with somatostatin in FEM; 0.53 [0.24–1.17] for intention-to-treat (ITT) analysis with somatostatin in REM; 0.42 [0.20–0.90] for high-dose octreotide in FEM; 0.61 [0.27–1.35] for PD injection with octreotide in FEM; 0.64 [0.32–1.29] for BS with octreotide in FEM; and 0.83 [0.34–2.03] for ITT analysis with octreotide in REM.
Conclusions Somatostatin and high-dose octreotide may prevent post-ERCP pancreatitis. The preventive efficacy of somatostatin is more prominent in cases of PD injection, or BS, or high-dose administration over 12 h, or bolus injection.

Keywords Somatostatin · Octreotide · Post-ERCP pancreatitis

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Introduction

Acute pancreatitis is a serious complication that can result from either diagnostic or therapeutic endoscopic retrograde cholangiopancreatography (ERCP). The causal mechanisms of post-ERCP pancreatitis are not clear but are likely to be multifactorial, including patient-related risk factors (young age, female gender, sphincter of Oddi dysfunction, prior post-ERCP pancreatitis) and procedure-related factors [pancreatic duct (PD) injection, pancreatic sphincterotomy,

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balloon dilation of the intact biliary sphincter, difficult or failed cannulation, precut sphincterotomy], as well as an interactive effect between the two [1].

Previous studies have evaluated several drugs for the prevention of post-ERCP pancreatitis, including somatostatin [2–10], octreotide [11], gabexate mesylate [12], and corticosteroids [13–16]. Although several of these have shown benefit, there have been no definitive studies showing that any of these drugs prevent post-ERCP pancreatitis. Somatostatin and its long-acting cyclic octapeptide, octreotide, have a wide spectrum of biologic activities. Most of them are inhibitory [17–20]. In addition, both agents have an effect on the contractility of the sphincter of Oddi [11]. Due to these properties, these agents have undergone much study for the prevention of post-ERCP pancreatitis. Despite this, the efficacy of somatostatin and octreotide remains controversial.

A comprehensive literature review revealed several randomized controlled trials (RCTs) investigating the preventive efficacy of somatostatin or octreotide for post-ERCP pancreatitis [3–11, 15, 21–27] employing a variety methods of administration in various populations with different risks of developing post-ERCP pancreatitis. Additionally, procedures during ERCP, such as PD injection and sphincterotomy (biliary or pancreatic) varied from study to study. The results of these different studies were not consistent.

Two previous meta-analyses found no overall preventive efficacy of somatostatin [28, 29]. Another meta-analysis suggested possible efficacy of high-dose (total dosage $\geq$0.5 mg) octreotide [30]. Stratified meta-analyses of procedure-related factors and intention-to-treat (ITT) analyses have not been reported.

Methods

Data sources and searches

We conducted a literature search using MEDLINE (January 1966 to September 2009), EMBASE (January 1974 to September 2009), and the Cochrane Central Register of Controlled Trials (January 1970 to September 2009) to identify all potential clinical trials using somatostatin or octreotide for the prevention of post-ERCP pancreatitis. We performed the literature search using the following search term: [pancreatitis AND (ERCP OR endoscopic retrograde cholangiopancreatography)] AND (somatostatin OR octreotide). Additionally, we searched review articles in the Cochrane Database of Systematic Reviews, and checked the references of these articles to ensure that we identified all relevant RCTs. The bibliographies of all relevant meta-analyses were also reviewed.

Study selection

Using the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement as a conceptual framework for this meta-analysis [31], we included only double-blinded RCTs that analyzed the efficacy of somatostatin or octreotide for the prevention of post-ERCP pancreatitis and had a primary outcome measure of acute pancreatitis following ERCP. To be as comprehensive as possible, we included all reports that met these criteria, even if they did not adequately describe the allocation sequence or concealment of allocation. Studies with hyperamylasemia as the primary outcome measure or those that were not double-blinded were excluded to avoid systematic error such as information bias. Studies involving co-administration of gabexate mesylate were not included. We restricted study eligibility to full reports in English to allow proper scrutiny of the quality of the trial.

Data extraction and quality assessment

For this study, we chose acute pancreatitis following diagnostic or therapeutic ERCP as the primary outcome measure. The definition of acute pancreatitis varied among studies, but in each case was clearly differentiated from hyperamylasemia. We independently reviewed the identified RCTs without the information on the journal, institution, or authors' names, using a standardized data abstraction form. We extracted the number of outcomes in both treatment and control groups. We also evaluated each of the studies based on the following criteria: (1) treatment details including drug, dosage, and duration; (2) details of procedures during ERCP; (3) allocation sequence; (4) concealment of allocation; and (5) ITT analysis. When the extracted data differed among our investigators, discussion was used to reach consensus.

Data synthesis and analysis

Three investigators independently extracted the number of events (pancreatitis) and total number of patients in the treatment and control groups for each study. We identified the number of events in each study arm in a standard contingency table for each study. We calculated the P value for the heterogeneity test (HT) as well as the I^2 statistic, which represents the percentage of total variation across trials that is attributable to heterogeneity rather than chance [32]. We applied a random-effects model (REM) if the I^2 was 25% or more. Otherwise, a fixed-effects model (FEM) was applied. Pooled risk ratios of FEM and REM were calculated using the Mantel–Haenszel method and DerSimonian and Laird method, respectively. Dichotomous effect measures, such as post-ERCP pancreatitis,

were expressed as a risk ratio with 95% confidence intervals (CIs) with risk ratios of less than 1.0 indicating a comparatively reduced risk of post-ERCP pancreatitis for participants in the treatment group.

We also performed stratified meta-analyses by drug type (somatostatin or octreotide), duration of administration (>12 h or not), drug dosage, and other possible risk factors such as PD injection and common therapeutic procedures such as biliary sphincterotomy (BS). Regarding the quality of the RCTs, we performed subgroup analysis only in terms of ITT analysis because sequence and concealment of allocation were not described in many studies.

We assumed that differences in the treatment regimen; differences of risk for developing acute pancreatitis, such as PD injection or BS; and differences in analytic measures, such as ITT analysis, would explain study heterogeneity. Regarding our quality analysis, we classified allocation sequences as 'adequate' for four trials that described the process as based on random number generation (computer or otherwise). We classified allocation concealment as 'adequate' for eight trials with the description of "opaque sealed envelope" or "envelope draw" [33].

We performed Egger's test to investigate funnel-plot asymmetry for small study effects including publication bias [34]. All analyses were performed using Stata Statistical Software: Release 10.0 (Stata, College Station, TX, USA).

Results

We identified 127 articles in MEDLINE, 332 in EMBASE, and 48 in the Cochrane Central Register of Controlled Trials, for a total of 507 abstracts; 399 articles remained after 108 duplicates were removed. Two investigators started with 399 articles and independently chose only papers which satisfied the prespecified inclusion criteria. Thirty-one abstracts passed the initial screening. We subsequently synthesized data from a final 17 double blinded RCTs [3–11, 15, 21–27] following the PRISMA flow diagram (Fig. 1; Table 1).

When all extracted data were pooled, 3818 subjects were considered for our analysis. 280 patients out of the 3818 were diagnosed with post-ERCP pancreatitis. In 16 of the 17 studies, acute pancreatitis was defined by clinical features including abdominal pain, nausea, or vomiting associated with elevated serum amylase more than 3 times the upper limit of normal. In one study [5], it was unclear whether nine patients diagnosed with pancreatitis had elevated serum amylase in addition to clinical symptoms. Ten of the 17 reports involved somatostatin [3–10, 21, 22] and 7 of the 17 used octreotide [11, 15, 23–27] (Table 2).

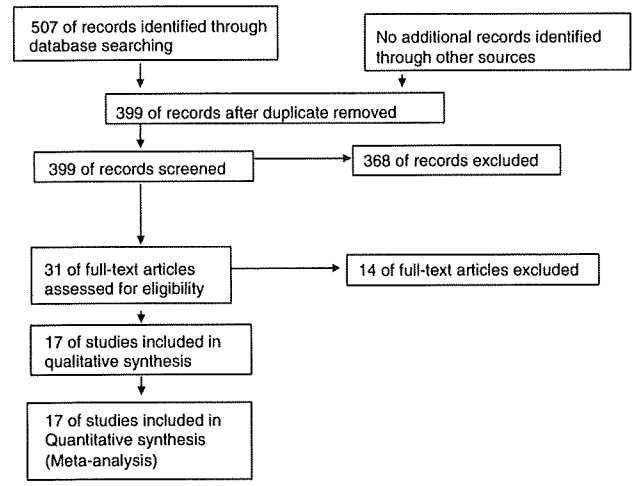


Fig. 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (*PRISMA*) flow diagram. Starting with 507 records identified in the database, 17 studies were finally selected for meta-analysis

In the study by Arvanitidis et al. [9], participants were randomized into three arms (somatostatin 3000 μg/12 h, bolus somatostatin 4 μg/kg, or placebo). We used the sample size numbers of the two respective intervention arms for subgroup analysis in terms of the dose of somatostatin and the duration of administration.

Any discrepancy in the identified literature was resolved by discussion. Discrepancies in the identified literature included the following: we excluded a paper by Bordas et al. [2] published in 1988 because all subjects in this study were included in the literature by the same author [6] published in 1998. Similarly, two reports by Duvnjak et al. [25, 35] were regarded as being based on one RCT, as both the recruitment period and the participants' basic characteristics were identical. We extracted the data from the first report and disregarded the second paper, as the primary outcome of only the former was acute pancreatitis. We excluded one paper [36] because no pancreatitis developed in either study arm, and another [37] because the measured outcome was not objectively pancreatitis.

The risk ratios of post-ERCP pancreatitis among all 17 studies ranged from 0.17 to 3.08. The overall risk ratio [95% CI] calculated using REM (HT $P < 0.001$, $I^2 = 62\%$) was 0.63 [0.42–0.96] (Fig. 2). Because the 95% CI did not include 1.0, the pooled risk ratio of all studies together with either somatostatin or octreotide was found to be statistically significant.

In the subgroup of subjects in whom somatostatin was administered, the risk ratio ranged from 0.17 to 1.76. The pooled risk ratio [95% CI] using REM (HT $P = 0.001$, $I^2 = 67\%$) was 0.52 [0.30-0.90] (Fig. 3). Somatostatin significantly reduced the risk of post-ERCP pancreatitis. Pooled risk ratios [95% CI] in terms of diagnostic and therapeutic procedures with somatostatin use were as

Table 1 Baseline characteristics of patients and somatostatin or octreotide regimen in double-blind randomized controlled trials

Publication year	References	Patients (*n*)	Mean age years (SD)		Treatment regimen	Starting time of therapy	Duration of therapy	Total dose (μg)	Rate of PD injection (%)	Rate of BS (%)
			Treatment group	Control group						
Trials of somatostatin in the order of publication year										
1988	Saari et al. [3]	47	48	50	250 μg i.v. followed by 250 μg/h) vs. NS	During procedure	3 h	1000	100	0
1991	Guelrud et al. [4]	16	NR	NR	250 μg/h i.v. vs. NS	1 h prior to dilation	12 h	3000	100	100
1992	Persson et al. [5]	54	62 (14)	61 (16)	300 μg/h i.v. for 3 h reduced to 140 μg/h for 1 h	30 min before ERCP	4 h	1040	61	NR
1998	Bordas et al. [6]	160	61 (15)	58 (18)	4 μg/kg i.v. vs. NS	On identification of papilla	Single bolus	240	100	34
1999	Poon et al. [8]	220	63 (15)	63 (16)	250 μg/h i.v. vs. NS	30 min before ERCP	12 h	3000	43	51
2002	Andriulli et al. [7]	382	59 (18)	58 (17)	300 μg/h i.v. vs. NS	30 min before ERCP	2.5 h	750	88	NR
2003	Poon et al. [21]	270	69	67	250 μg i.v. vs. NS	Immediately after diagnostic ERCP but before therapeutic ERCP	Single bolus	250	29	100
2004	Andriulli et al. [10]	746	66 (15)	66 (16)	750 μg/6.5 h i.v. vs. NS	30 min before ERCP	6.5 h	750	NR	NR
2004	Arvanitidis et al. [9]	356	65 (13), 63 (13)	61 (12)	4 μg/kg i.v. or 3000 μg/12 h i.v. vs. NS	1 h before ERCP	Single bolus or 12 h	240 vs 3000	40	89
2008	Lee et al. [22]	391	63 (14)	62 (14)	250 μg/h i.v. vs NS	30 min before ERCP	12 h	3000	40	54
Trials of octreotide in the order of publication year										
1992	Sternlieb et al. [23]	84	59	59	100 μg i.v. followed by 100 μg s.c. vs. NS	At the beginning of ERCP and 45 min later	Bolus and s.c.	200	NR	56
1992	Binmoeller et al. [11]	245	58	61	100 μg i.v. followed by 100 μg s.c. vs. NS	5 min before and immediately after ERCP	Bolus and s.c.	200	81	16
1994	Arcidiacono et al. [24]	151	61	63	100 μg s.c. X3 vs. NS	120 min, 30 min before and 4 h after ERCP	3 times	300	100	100
1999	Duvnjak et al. [25]	209	56	54	500 μg s.c. vs. NS	1 h before ERCP	Single s.c.	500	100	100
2000	Hardt et al. [26]	59	60	58	200 μg s.c. X5	10 p.m. (day −1), 6 a.m., 2 p.m., 10 p.m. (day 0), 6 a.m. (day 1)	5 times s.c.	1000	NR	100
2002	Manolakopoulos et al. [15]	227	62	64	100 μg s.c. vs. NS	30 min before ERCP	Single s.c.	100	71	35
2006	Thomopoulos et al. [27]	201	70 (14)	70 (15)	500 μg s.c. X6 vs. NS	8 a.m., 4 p.m., 12 p.m. (day −1), 8 a.m., 4 p.m. (day 0)	5 times s.c.	3000	59	81

SD Standard deviation, *PD* pancreatic duct, *S* somatostatin, *NR* not reported, *i.v.* intravenously, *s.c.* subcutaneously, *NS* normal saline, *BS* biliary sphincterotomy, *ERCP* endoscopic retrograde cholangiopancreatography

Table 2 Methodological quality characteristics of included articles

Publication year	References	Allocation sequence[a]	Concealment of allocation[b]	Intention-to-treat[c]	% (patients analyzed/randomization)
Trials of somatostatin in the order of publication year					
1988	Saari et al. [3]	NR	NR	No	84 (47/56)
1991	Guelrud et al. [4]	Adequate	NR	Yes	100
1992	Persson et al. [5]	NR	NR	No	90 (54/60)
1998	Bordas et al. [6]	NR	Adequate	No	83 (160/192)
1999	Poon et al. [8]	Adequate	Adequate	Yes	96 (220/230)
2002	Andriulli et al. [7]	Adequate	NR	Yes	91 (382/420)
2003	Poon et al. [21]	Adequate	Adequate	Yes	100
2004	Andriulli et al. [10]	Adequate	NR	Yes	100
2004	Arvanitidis et al. [9]	NR	Adequate	Yes	96 (356/372)
2008	Lee et al. [22]	NR	Adequate	No	98 (391/400)
Trials of octreotide in the order of publication year					
1992	Sternlieb et al. [23]	NR	NR	Yes	100
1992	Binmoeller et al. [11]	NR	NR	Yes	100
1994	Arcidiacono et al. [24]	NR	Adequate	No	66 (151/229)
1999	Duvnjak et al. [25]	NR	NR	Yes	100
2000	Hardt et al. [26]	NR	NR	No	63 (59/94)
2002	Manolakopoulos et al. [15]	NR	Adequate	Yes	NR
2006	Thomopoulos et al. [27]	NR	Adequate	Yes	99 (201/202)

NR Not reported

[a] Description of allocation sequence was considered adequate if the study used computer-generated random number or number system by chance

[b] Concealment of allocation was considered adequate if the study used opaque sealed envelopes or envelope draw

[c] The analysis including all participants who underwent ERCP was considered as intention-to-treat analysis even if there were some dropout cases caused by failure of duodenal intubation, or drug allergy, or inability to undergo ERCP

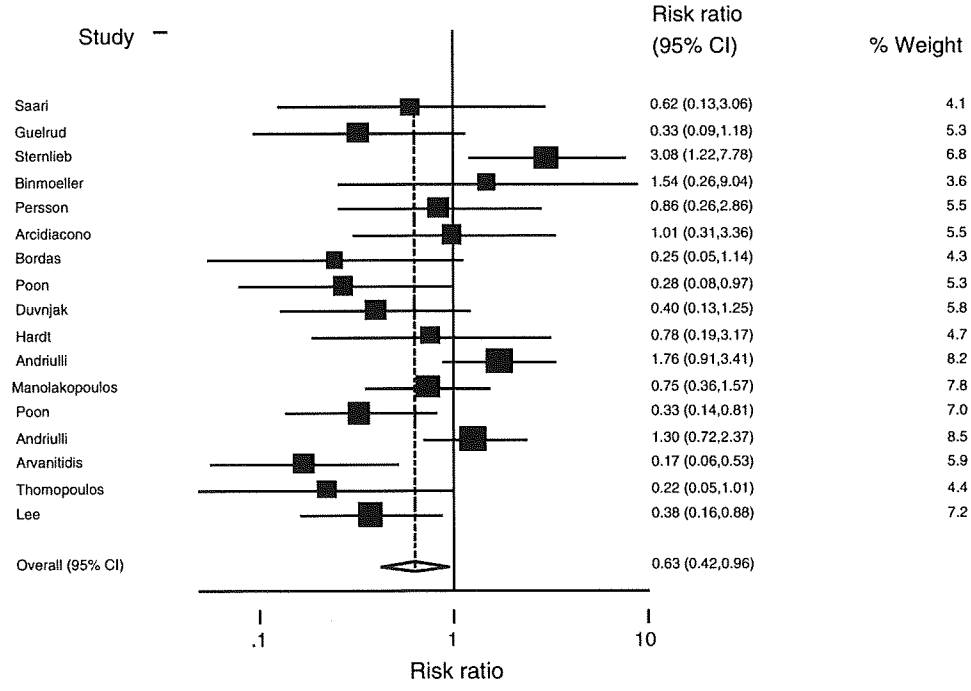
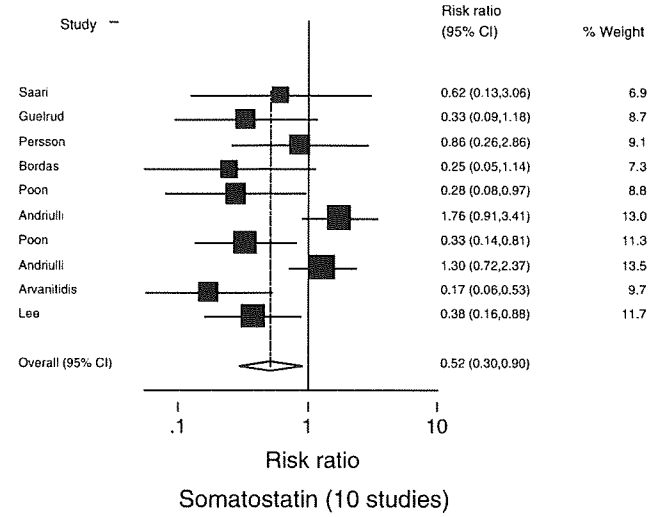


Fig. 2 Forest plot (somatostatin and octreotide). The pooled risk ratio of 17 studies was calculated by random-effects model. The pooled risk ratio including both somatostatin and octreotide was significant. Egger's test ($P = 0.023$) suggested small study effects including publication bias. *CI* Confidence interval



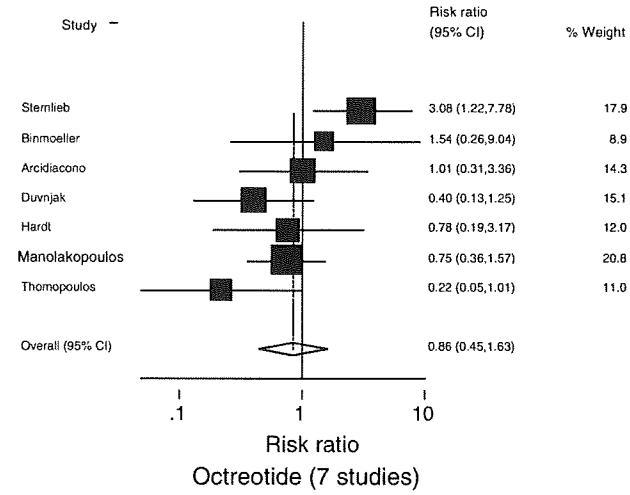
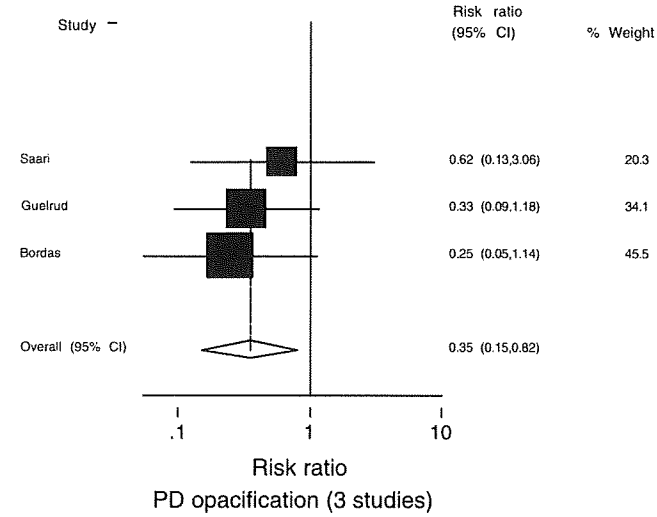


Fig. 3 Forest plot of subgroups by drug; ten studies of somatostatin and seven studies of octreotide. The pooled risk ratio of somatostatin was significant by random-effects model. In contrast, the pooled risk ratio of octreotide was not significant by random-effects model. Egger's test ($P = 0.01$) suggested small study effects including publication bias in the meta-analysis of somatostatin, while Egger's test ($P = 0.86$) was not significant in the meta-analysis of octreotide



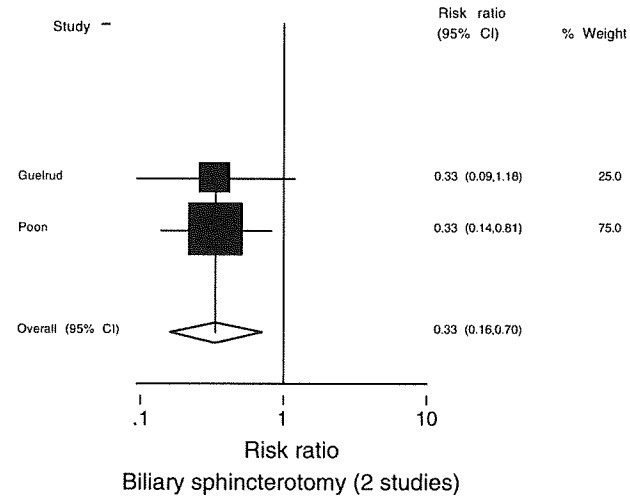


Fig. 4 Forest plot of subgroups by procedure with somatostatin use. The pooled risk ratios of three studies for pancreatic duct (*PD*) injection and two studies for biliary sphincterotomy were significant by fixed-effects model. Egger's test ($P = 0.76$) of the former meta-analysis was not significant

follows: 0.35 [0.15–0.82] for PD injection using FEM (HT $P = 0.711$, $I^2 = 0\%$) and 0.33 [0.16–0.70] for BS using FEM (HT $P = 1$, $I^2 = 0\%$) (Fig. 4). The preventive efficacy of somatostatin was prominent in some particular cases: using FEM, the pooled risk ratios [95% CI] were 0.30 [0.17–0.53] for high-dose somatostatin (3 mg administered over 12 h) (HT $P = 0.84$, $I^2 = 0\%$), and 0.27 [0.13–0.52] for bolus injection (HT $P = 0.75$, $I^2 = 0\%$) (Fig. 5).

The pooled risk ratio [95% CI] of six ITT studies with somatostatin use was 0.53 [0.24–1.17] using REM (HT $P < 0.001$, $I^2 = 78\%$) (Fig. 8). The pooled risk ratios [95% CI] of additional subgroup analysis restricted by ITT-based studies were 0.25 [0.11–0.54] for high-dose somatostatin using FEM (HT $P = 0.796$, $I^2 = 0\%$) and 0.27 [0.13–0.58] for bolus somatostatin using FEM (HT $P = 0.45$, $I^2 = 0\%$). The pooled risk ratio [95% CI] for ITT BS studies was exactly the same as that with somatostatin BS studies, 0.33 [0.16–0.70], because there were no non-ITT BS studies. The result of one ITT study [4] for PD injection was not significant.

In the subgroup of patients receiving octreotide, the risk ratio ranged from 0.22 to 3.08. The pooled risk ratio [95% CI] was 0.86 [0.45–1.63] using REM (HT $P = 0.049$,

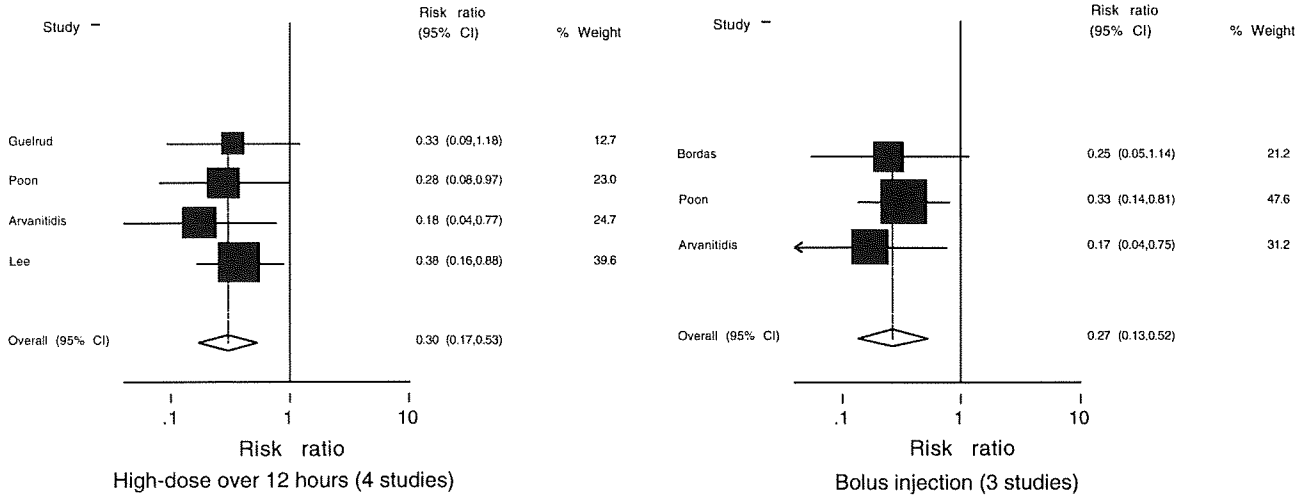


Fig. 5 Forest plot of subgroups by somatostatin use. The pooled risk ratios of high-dose somatostatin given over 12 h and by bolus injection were statistically significant by fixed-effects model. Egger's tests ($P = 0.13$ for high-dose somatostatin, $P = 0.28$ for bolus) were not significant

$I^2 = 53\%$) (Fig. 3). However, high-dose octreotide appeared to be effective, with a pooled risk ratio [95% CI] of 0.42 [0.2–0.9] using FEM (HT $P = 0.49$, $I^2 = 0\%$) (Fig. 6). Pooled risk ratios [95% CI] in terms of diagnostic and therapeutic procedures using octreotide were 0.61 [0.27–1.35] for PD injection using FEM (HT $P = 0.27$, $I^2 = 17\%$) and 0.64 [0.32–1.29] for BS using FEM (HT $P = 0.53$, $I^2 = 0$) (Fig. 7).

The pooled risk ratio [95% CI] of five octreotide studies with ITT analysis was 0.83 [0.34–2.03] using REM (HT $P = 0.013$, $I^2 = 68\%$) (Fig. 8). However, additional subgroup analysis of two studies [25, 27] using high-dose octreotide on an ITT basis was 0.32 [0.13–0.78] using FEM (HT $P = 0.54$, $I^2 = 0\%$).

Egger's test was significant in some meta-analyses: $P = 0.023$ for 17 studies of somatostatin or octreotide, $P = 0.01$ for ten studies of somatostatin, and $P = 0.024$ for six studies of somatostatin on an ITT basis. Adverse events related to somatostatin or octreotide were reported in one study [27], in which one patient in the octreotide group developed an allergic reaction and was excluded from the analysis.

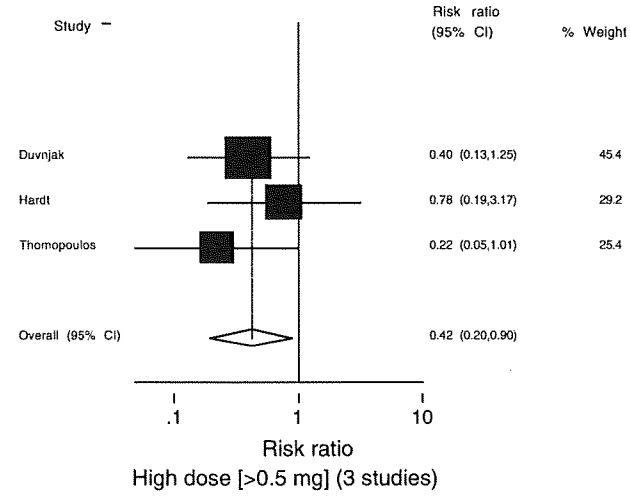


Fig. 6 Forest plot of subgroups by high-dose octreotide use. High-dose octreotide showed preventive efficacy for post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis by a fixed-effects model. Egger's test ($P = 0.97$) was not significant

Discussion

Our study is the most updated and comprehensive meta-analysis of RCTs involving post-ERCP pancreatitis described in the English-language literature. Our study suggests that somatostatin is effective and its preventive efficacy becomes even more prominent when it is either administered in high doses infused over 12 h, bolused, or used in patients undergoing PD injection or BS. Our study also showed that high-dose octreotide (more than 0.5 mg) may be effective for preventing post-ERCP pancreatitis.

In 2000, Andriulli et al. [38] conducted a meta-analysis reviewing the preventive efficacy of somatostatin, octreotide, and gabexate mesylate on post-ERCP pancreatitis. That analysis concluded that pancreatic injury after ERCP could be prevented with the administration of either somatostatin or gabexate mesylate, with an odds ratio of 0.38 (95% CI [0.14–0.42]) and 0.27 (95% CI [0.13–0.57]), respectively. In contrast, the odds ratio for octreotide was 1.43 (95% CI [0.87–2.49]). In comparing Andriulli's meta-analysis with ours, they included five studies on somatostatin [2, 39–42], which we ultimately excluded. We

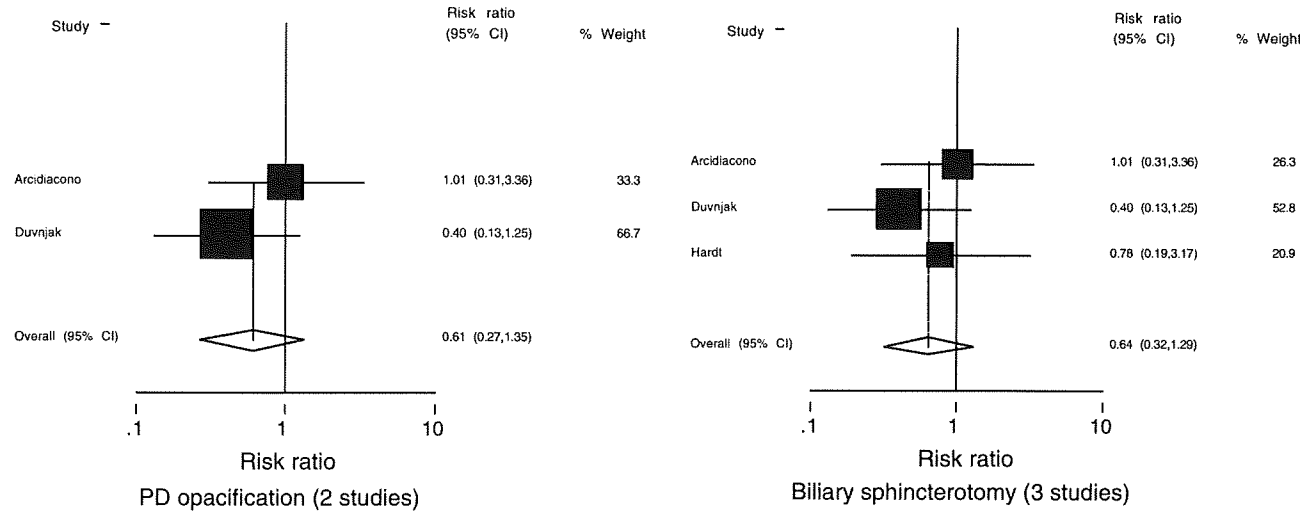


Fig. 7 Forest plot of subgroups by procedure with octreotide use. Subgroup analysis by procedure did not show preventive effectiveness of octreotide by fixed-effects model. Egger's test ($P = 0.65$) for PD injection was not significant

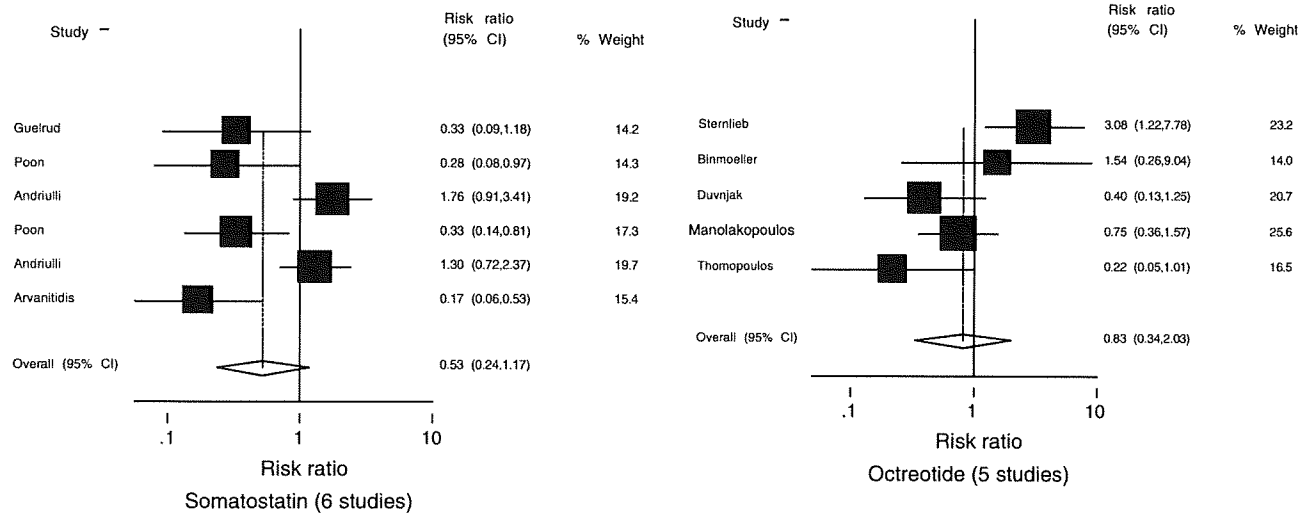


Fig. 8 Subgroup analysis of intention-to-treat studies by drugs. The pooled risk ratios of somatostatin and octreotide became less significant if restricted by intention-to-treat-based studies, using random-effects model. Egger's test ($P = 0.024$) was significant for somatostatin, while it was not significant ($P = 0.90$) for octreotide

excluded two [39, 41] because they were non-English language, one [40] for no description of double-blindedness, and one [2] which included subjects duplicated in another study. In addition, we included five studies [7, 9, 10, 21, 22] published after 2000, which were not available to them. Regarding studies of octreotide, Andriulli et al. [38] included five trials [43–47] that we excluded. We excluded two [43, 45] for non-English language and three [44, 46, 47] for no information on double-blindedness. We included an additional four studies [15, 25–27] published after 1999.

Andriulli et al. [28] updated their meta-analysis in 2007 to include nine high-quality trials on somatostatin and reported that there was no significant preventive effectiveness of somatostatin for post-ERCP pancreatitis. Significant efficacy was obtained only in the subgroup of patients who received somatostatin as a bolus injection. Their meta-analysis included the abstract by Benvenuti et al. [48], which we excluded because it was not a full article, precluding thorough evaluation. They excluded one report for an unknown reason [4] that we included in our meta-analysis. These differences in inclusion and exclusion of studies, in addition to one recently published RCT [22], resulted in a significantly different pooled risk ratio for somatostatin between our respective studies.

In 2007, Rudin et al. [29] also performed a meta-analysis of five somatostatin studies, stratifying somatostatin administration into three groups: an infusion for 12 h or

more, an infusion for less than 12 h, and bolus infusion. They reported significant efficacy of somatostatin with an infusion for 12 h or more as well as for bolus infusion, with risk differences [95% CI] of 7.7% [3.4–12] and 8.2% [4.4–12], respectively [29]. They did not include three studies [3–5] that we included. Additionally, they double-counted the control group of one study [9] when calculating the overall risk ratio of somatostatin. Despite these differences, our results also suggested significant efficacy of bolus infusion of somatostatin and high-dose somatostatin, defined as more than 3000 μg infused over 12 h.

In 2009, Zhang et al. [30] conducted a meta-analysis including six studies [25, 27, 46, 49–51] about the preventive efficacy of octreotide for post-ERCP pancreatitis and suggested possible significant efficacy of high-dose octreotide over 0.5 mg. Their meta-analysis included three non-double-blinded RCTs [46, 50, 51] and one abstract [49], all of which we excluded from our meta-analysis. They excluded one study [26] in which 1000 μg of octreotide was given in five divided doses. Our stratified meta-analysis, involving three double-blinded RCTs, also showed significant efficacy of high-dose octreotide.

By using ITT analysis, results of RCTs can be analyzed more conservatively, thereby avoiding bias induced by loss to follow-up. Eleven RCTs were identified that used ITT analysis, six studies [4, 8–10, 21, 22] involving somatostatin and five [11, 15, 23, 25, 27] using octreotide. Although the pooled estimate of the somatostatin studies became less significant if restricted to ITT analysis, the pooled estimates of high-dose somatostatin, bolus somatostatin, and somatostatin for BS, as well as the pooled estimates for high-dose octreotide, suggested significant preventive efficacy of both drugs.

Sofuni et al. [52] reported the effectiveness of pancreatic stent (polyethylene 5F diameter, 3-cm long, unflanged on the pancreatic ductal side, with 2 flanges on the duodenal side) placement for the prevention of post-ERCP pancreatitis. They showed a significant reduction of post-ERCP pancreatitis with the administration of gabexate mesylate (100 mg dissolved in 500 ml solution for 12 h) in both stent and control groups. We may also speculate on the additive preventive effectiveness of combining a pancreatic stent and drugs such as somatostatin or octreotide.

Our study has some limitations. First, we disregarded non-English-language literature, though these studies were few. This might be one of the reasons for publication bias in some meta-analyses, as suggested by Egger's test. We also included studies that did not describe the allocation sequence or concealment of allocation. Finally, in the subgroup analyses, the pooled estimates may have become significant by chance, and further studies with these subgroups are warranted [53].

In conclusion, somatostatin may have significant preventive efficacy against post-ERCP pancreatitis, especially when used in appropriate diagnostic or therapeutic procedures or with high-dose administration as a 12-h infusion or a bolus. High-dose octreotide may also prevent post-ERCP pancreatitis. The efficacy of both drugs in these contexts is expected to be confirmed by large high-quality RCTs in future.

Acknowledgments The authors thank Jose M. Bordas, MD, for his comments on his two reports and Yoshinori Noguchi, MD, for his comments. The authors also thank Kayo Ichikawa for secretarial assistance, and Fujiko Kawai and Harumi Oikawa for excellent library support.

References

1. Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. Gastrointest Endosc. 2004;59:845–64.
2. Bordas JM, Toledo V, Mondelo F, Rodes J. Prevention of pancreatic reactions by bolus somatostatin administration in patients undergoing endoscopic retrograde cholangio-pancreatography and endoscopic sphincterotomy. Horm Res. 1988;29:106–8.
3. Saari A, Kivilaakso E, Schroder T. The influence of somatostatin on pancreatic irritation after pancreatography. An experimental and clinical study. Surg Res Comm. 1988;2:271–8.
4. Guelrud M, Mendoza S, Viera L, Gelrud D. Somatostatin prevents acute pancreatitis after pancreatic duct sphincter hydrostatic balloon dilation in patients with idiopathic recurrent pancreatitis. Gastrointest Endosc. 1991;37:44–7.
5. Persson B, Slezak P, Efendic S, Haggmark A. Can somatostatin prevent injection pancreatitis after ERCP? Hepatogastroenterology. 1992;39:259–61.
6. Bordas JM, Toledo-Pimentel V, Llach J, Elena M, Mondelo F, Gines A, et al. Effects of bolus somatostatin in preventing pancreatitis after endoscopic pancreatography: results of a randomized study. Gastrointest Endosc. 1998;47:230–4.
7. Andriulli A, Clemente R, Solmi L, Terruzzi V, Suriani R, Sigillito A, et al. Gabexate or somatostatin administration before ERCP in patients at high risk for post-ERCP pancreatitis: a multicenter, placebo-controlled, randomized clinical trial. Gastrointest Endosc. 2002;56:488–95.
8. Poon RT, Yeung C, Lo CM, Yuen WK, Liu CL, Fan ST. Prophylactic effect of somatostatin on post-ERCP pancreatitis: a randomized controlled trial. Gastrointest Endosc. 1999;49:593–8.
9. Arvanitidis D, Anagnostopoulos GK, Giannopoulos D, Pantes A, Agaritsi R, Margantinis G, et al. Can somatostatin prevent post-ERCP pancreatitis? Results of a randomized controlled trial. J Gastroenterol Hepatol. 2004;19:278–82.
10. Andriulli A, Solmi L, Loperfido S, Leo P, Festa V, Belmonte A, et al. Prophylaxis of ERCP-related pancreatitis: a randomized, controlled trial of somatostatin and gabexate mesylate. Clin Gastroenterol Hepatol. 2004;2:713–8.
11. Binmoeller KF, Dumas R, Harris AG, Delmont JP. Effect of somatostatin analog octreotide on human sphincter of Oddi. Dig Dis Sci. 1992;37:773–7.
12. Cavallini G, Tittobello A, Frulloni L, Masci E, Mariana A, Di Francesco V. Gabexate for the prevention of pancreatic damage related to endoscopic retrograde cholangiopancreatography. Gabexate in digestive endoscopy—Italian Group. N Engl J Med. 1996;335:919–23.

13. Weiner GR, Geenen JE, Hogan WJ, Catalano MF. Use of corticosteroids in the prevention of post-ERCP pancreatitis. Gastrointest Endosc. 1995;42:579–83.
14. Dumot JA, Conwell DL, O'Connor JB, Ferguson DR, Vargo JJ, Barnes DS, et al. Pretreatment with methylprednisolone to prevent ERCP-induced pancreatitis: a randomized, multicenter, placebo-controlled clinical trial. Am J Gastroenterol. 1998;93:61–5.
15. Manolakopoulos S, Avgerinos A, Vlachogiannakos J, Armonis A, Viazis N, Papadimitriou N, et al. Octreotide versus hydrocortisone versus placebo in the prevention of post-ERCP pancreatitis: a multicenter randomized controlled trial. Gastrointest Endosc. 2002;55:470–5.
16. Sherman S, Blaut U, Watkins JL, Barnett J, Freeman M, Geenen J, et al. Does prophylactic administration of corticosteroid reduce the risk and severity of post-ERCP pancreatitis: a randomized, prospective, multicenter study. Gastrointest Endosc. 2003;58:23–9.
17. Raptis S, Schlegel W, Lehmann E, Dollinger HC, Zoupas C. Effects of somatostatin on the exocrine pancreas and the release of duodenal hormones. Metabolism. 1978;27:1321–8.
18. Dollinger HC, Raptis S, Pfeiffer EF. Effects of somatostatin on exocrine and endocrine pancreatic function stimulated by intestinal hormones in man. Horm Metab Res. 1976;8:74–8.
19. Schlegel W, Raptis S, Harvey RF, Oliver JM, Pfeiffer EF. Inhibition of cholecystokinin-pancreozymin release by somatostatin. Lancet. 1977;2:166–8.
20. Baxter JN, Jenkins SA, Day DW, Roberts NB, Cowell DC, Mackie CR, et al. Effects of somatostatin and a long-acting somatostatin analogue on the prevention and treatment of experimentally induced acute pancreatitis in the rat. Br J Surg. 1985;72:382–5.
21. Poon RT, Yeung C, Liu CL, Lam CM, Yuen WK, Lo CM, et al. Intravenous bolus somatostatin after diagnostic cholangiopancreatography reduces the incidence of pancreatitis associated with therapeutic endoscopic retrograde cholangiopancreatography procedures: a randomised controlled trial. Gut. 2003;52:1768–73.
22. Lee KT, Lee DH, Yoo BM. The prophylactic effect of somatostatin on post-therapeutic endoscopic retrograde cholangiopancreatography pancreatitis: a randomized, multicenter controlled trial. Pancreas. 2008;37:445–8.
23. Sternlieb JM, Aronchick CA, Retig JN, Dabezies M, Saunders F, Goosenberg E, et al. A multicenter, randomized, controlled trial to evaluate the effect of prophylactic octreotide on ERCP-induced pancreatitis. Am J Gastroenterol. 1992;87:1561–6.
24. Arcidiacono R, Gambitta P, Rossi A, Grosso C, Bini M, Zanasi G. The use of a long-acting somatostatin analogue (octreotide) for prophylaxis of acute pancreatitis after endoscopic sphincterotomy. Endoscopy. 1994;26:715–8.
25. Duvnjak M, Supanc V, Simicevic VN, Hrabar D, Troskot B, Smircic-Duvnjak L, et al. Use of octreotide-acetate in preventing pancreatitis-like changes following therapeutic endoscopic retrograde cholangiopancreatography. Acta Med Croatica. 1999;53:115–8.
26. Hardt PD, Kress O, Fadgyas T, Doppl W, Schnell-Kretschmer H, Wusten O, et al. Octreotide in the prevention of pancreatic damage induced by endoscopic sphincterotomy. Eur J Med Res. 2000;5:165–70.
27. Thomopoulos KC, Pagoni NA, Vagenas KA, Margaritis VG, Theocharis GI, Nikolopoulou VN. Twenty-four hour prophylaxis with increased dosage of octreotide reduces the incidence of post-ERCP pancreatitis. Gastrointest Endosc. 2006;64:726–31.
28. Andriulli A, Leandro G, Federici T, Ippolito A, Forlano R, Iacobellis A, et al. Prophylactic administration of somatostatin or gabexate does not prevent pancreatitis after ERCP: an updated meta-analysis. Gastrointest Endosc. 2007;65:624–32.
29. Rudin D, Kiss A, Wetz RV, Sottile VM. Somatostatin and gabexate for post-endoscopic retrograde cholangiopancreatography pancreatitis prevention: meta-analysis of randomized placebo-controlled trials. J Gastroenterol Hepatol. 2007;22:977–83.
30. Zhang Y, Chen QB, Gao ZY, Xie WF. Meta-analysis: octreotide prevents post-ERCP pancreatitis, but only at sufficient doses. Aliment Pharmacol Ther. 2009;29:1155–64.
31. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151:264–9, W64.
32. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.
33. Juni P, Altman DG, Egger M. Meta-analysis in Stata. In: Egger M, Smith G, Altman D, editors. Systematic Reviews in Health Care British medical journal. 2003. p. 90.
34. Sterne J, Bradburn M, Egger M. Meta-analysis in Stata. In: Egger M, Smith G, Altman D, editors. Systematic Reviews in Health Care British medical journal. 2003. p. 200.
35. Duvnjak M, Supanc V, Šimičević V, Hrabar D, Troskot B, Smirčić-Duvnjak L, et al. A randomized, double-blind trial of the efficacy of octreotide acetate administration in the prevention of abdominal pain. Acta Clin Croat. 2001;40:9–13.
36. Tulassay Z, Papp J. The effect of long-acting somatostatin analogue on enzyme changes after endoscopic pancreatography. Gastrointest Endosc. 1991;37:48–50.
37. Cicero GF, Laugier R, Sahel J, Manganaro M, Sarles H. Effects of somatostatin on clinical, biochemical and morphological changes following ERCP. Ital J Gastroenterol. 1985;17:265–8.
38. Andriulli A, Leandro G, Niro G, Mangia A, Festa V, Gambassi G, et al. Pharmacologic treatment can prevent pancreatic injury after ERCP: a meta-analysis. Gastrointest Endosc. 2000;51:1–7.
39. Börsch G, Bergbauer M, Nebel W, Sabin G. Effect of somatostatin on amylase level and pancreatitis rate following ERCP. Med Welt. 1984;35:109–12.
40. Testoni PA. Endoscopic papillo-sphincterotomy: prevention of pancreatic reaction by somatostatin. Ital J Gastroenterol. 1988;20:70–3.
41. Flati G, Porowska B, Negro P, Flati D, Chiarinelli ML, Carboni M. Effect of somatostatin on the sequelae of endoscopic retrograde cholangiopancreatography. Rev Esp Enferm Apar Dig. 1988;74:17–9.
42. Deschner K, Kalloo A, Collen M, Cattau EL, Maher KA, et al. Somatostatin: an evaluation of its utility as adjunctive medication for ERCP. Gastrointest Endosc. 1989;35:A149.
43. Russo A, Virgilio C, Aprile G, Magnano A, Cosentino S. Influenza dell'octreotide sulla reazione pancraticaa indotta da colangiopancreatografia retrograda (Effect of octreotide on pancreatic reactions following ERCP). Giorn Ital End Dig. 1992;15:139–45.
44. Testoni PA, Lella F, Bagnolo F, Buizza M, Colombo E. Controlled trial of different dosages of octreotide in the prevention of hyperamylasemia induced by endoscopic papillosphincterotomy. Ital J Gastroenterol. 1994;26:431–6.
45. Baldazzi G, Conti C, Spotti EG, Arisi GP, Scevola M, Gobetti F, et al. Prevention of post-ERCP acute pancreatitis with octreotide. G Chir. 1994;15:359–62.
46. Testoni PA, Lella F, Bagnolo F, Caporuscio S, Cattani L, Colombo E, et al. Long-term prophylactic administration of octreotide reduces the rise in serum amylase after endoscopic procedures on Vater's papilla. Pancreas. 1996;13:61–5.
47. Arvanitidis D, Hatzipanayiotis J, Koutsounopoulos G, Frangou E. The effect of octreotide on the prevention of acute pancreatitis and hyperamylasemia after diagnostic and therapeutic ERCP. Hepatogastroenterology. 1998;45:248–52.

48. Benvenuti S, Zancanell L, Piazzi L, Comberlato M, Chilovi F, Germana B, et al. Prevention of post-ERCP pancreatitis with somatostatin versus gabexate mesilate: a randomized placebo-controlled multicenter study. Dig Liver Dis. 2006;38:S15.
49. Badra G, Galal AS, Rowaisha I, Waked I, Moustafa MS, Saleh SM. Allopurinol vs octreotide in the prevention of post-ERCP pancreatitis in patients with biliary obstruction. A randomized controlled trial. Hepatology 2000;32:163A.
50. Testoni PA, Bagnolo F, Andriulli A, Bernasconi G, Crotta S, Lella F, et al. Octreotide 24-h prophylaxis in patients at high risk for post-ERCP pancreatitis: results of a multicenter, randomized, controlled trial. Aliment Pharmacol Ther. 2001;15:965–72.
51. Li ZS, Pan X, Zhang WJ, Gong B, Zhi FC, Guo XG, et al. Effect of octreotide administration in the prophylaxis of post-ERCP pancreatitis and hyperamylasemia: a multicenter, placebo-controlled, randomized clinical trial. Am J Gastroenterol. 2007;102:46–51.
52. Sofuni A, Maguchi H, Itoi T, Katanuma A, Hisai H, Niido T, et al. Prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis by an endoscopic pancreatic spontaneous dislodgement stent. Clin Gastroenterol Hepatol. 2007;5:1339–46.
53. Sutton A, Abrams K, Jones D, Sheldon T, Song F. Exploring between study heterogeneity. Methods for meta-analysis in medical research. New York: Wiley; 2000. p. 88.

Gender Differences in Clinical Confidence: A Nationwide Survey of Resident Physicians in Japan

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Abstract

Purpose
The number of women physicians is increasing in Japan. The authors investigated gender differences in self-perceptions of clinical confidence.

Method
This cross-sectional study was conducted in March 2007 by using a stratified random sample of 1,124 second-year resident physicians. Residents' confidence levels were assessed, using four-point Likert scales (e.g., 1 for "not at all" to 4 for "very much"), in four competency sets: physical exams, procedural skills, interpretations of clinical tests, and physician–patient relationships and social service application. Gender effect was investigated for clinical confidence levels by general linear models adjusting for age, types of hospitals, number of clinical experiences, satisfaction with residency conditions, future career, and perspectives on life and work.

Results
The overall mean confidence scores in the four sets ranged between 2.9 and 3.1. Compared with men, women were younger ($P = .001$), more likely to be oriented more to life than to work ($P < .001$), less interested in doctor of medical science degrees ($P = .001$), and less likely to be satisfied with residency conditions ($P = .020$). A significantly greater proportion of women chose "family" (70% versus 54% for men) as "the most important thing in life." Compared with men, women were less confident in the majority of competency areas even after adjusting for the number of clinical experiences.

Conclusions
This nationwide resident survey demonstrated gender differences in clinical confidence levels. Future studies require careful monitoring of self-confidence and its impact on physicians' professional development.

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Editor's note: A commentary on this article appears on pages 575–577.

Today in Japan, women constitute approximately 30% of all medical students (except at Tokyo Women's Medical College, which has only women students) and nearly half of the young physicians in some specialties such as obstetrics, gynecology, and pediatrics. In spite of the increasing number of women in medicine, one study reported a marked decline in workforce participation, especially among women physicians in their late 20s and 30s.[1] Not limited to Japan, low participation rates among women physicians have also been reported in Western countries.[2] Women are more likely to work fewer hours and to be in part-time practice.[2–4] Thus, it is anticipated that the increase in number of women physicians may lead to a decrease in the full-time workforce.

Because women physicians may also have the social roles of housewives and mothers, they may devote more of their time to family responsibilities rather than to work. However, their low participation rates may not simply be accounted for by family constraints. On the contrary, Heiliger and Hingstman[5] reported that home domain characteristics did not predict a part-time preference in women physicians. McMurray et al[6] reported that the presence of children was associated with less work-related stress for women under the age of 45, and Frank et al[7] reported that physicians with children were more interested in again working as physicians. These studies suggest that multiple roles may bring benefits that mitigate work strain.

Nevertheless, many reports agree that women physicians work fewer hours than do their male colleagues.[2–4] Several studies reported that women physicians were more likely to receive fewer rewards for their work, both in academic advancement and monetary compensation.[3,4,8–12] Such gender inequity favoring men may undermine women's self-esteem and result in difficulty in developing their potential competencies. For example, McMurray et al[6] reported that women physicians were more likely to have a lower level of work control in hospital practice than men, and this was significantly associated with burnout in women. Frank et al[7] also reported that women with work stress, lack of work control, and experience of harassment had a lower likelihood of being satisfied with their careers and of wishing to become physicians again even if given the choice.

The purposes of our study were (1) to determine whether a difference exists between men and women in levels of confidence about clinical competency among second-year residents in Japan and (2) to investigate the effect of gender on confidence levels after adjusting for basic resident characteristics, satisfaction,

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future career, and perspectives on life and work. The workplace in Japanese medicine is a male-dominated society, and there are still very few women professors in university settings or hospital director positions. Studying gender differences in self-perceptions of clinical confidence may reflect the impact of a male-oriented society on career development among women physicians. The results of our study may have important implications for potential involvement and retention of women physicians in the workforce.

Method

Japanese postgraduate medical education

In Japan, according to the Japanese Medical Practitioners Law, medical residents are not allowed to perform medical procedures independently until they have completed a six-year undergraduate program at a medical school and passed the National Board Examination to obtain a doctor's license. Therefore, the new Japanese postgraduate medical education (PGME) was designed to provide various clinical opportunities that allow residents to obtain primary care skills and knowledge.[13] In this regard, the Japanese PGME may be equivalent to the clinical rotation program for third- and fourth-year medical students in the United States.

Study participants

During fiscal years 2005 through 2007, the Ministry of Health, Labor, and Welfare (the Ministry) organized a scientific study committee to evaluate the new, two-year, variable rotation PGME program. In each of the three years, the committee conducted surveys of residents and hospitals; scientific papers based on the surveys in 2006 and 2005 have already been published.[14,15]

The data from our study were obtained from the second-year survey conducted in March 2007. We sent the questionnaire to the 813 teaching hospitals accredited by the Ministry that year, asking the program directors to recruit one out of five of the 7,495 second-year residents (i.e., every fifth resident from the top of the roster in sequence). When fewer than five residents were listed on a roster, the first resident on the roster was asked to answer the questionnaire. As a result, 1,880 residents became our target sample. Because the academic calendar in Japan starts on April 1 and ends on March 31 of the following year, our study participants were about to complete the two-year PGME program. The Ministry gave ethical approval for the study, and all participants provided informed consent.

Questionnaire

The questionnaire consisted of 16 sections with a total of 23 questions. Sections included basic characteristics, hospital information, rotation schedule, on-call information, number of patients experienced, satisfaction, consultation, course after PGME, specialties, intention to obtain DMSc and specialist qualification, areas of interest, whether one is work- or life-oriented, the most important thing in life, clinical confidence, and clinical experience (including basic skills and knowledge, and medical documents). Of these, the variables we investigated in this study were basic characteristics including age, gender, and types of hospitals (i.e., university or community hospital); clinical experience; clinical competency; residents' satisfaction with residency conditions ("satisfied"/"not satisfied"/"do not know"); attributes related to satisfaction; future career, including areas of interest and an intention to obtain a DMSc and specialist qualification; and perspective on life and work (i.e., "work- or life-oriented" and "the most important thing in life").

Residents were queried regarding the number of cases they had encountered for 82 conditions, including the most common disorders and symptoms such as headache, infection, edema, difficulty breathing, hypertension, cardiopulmonary arrest, abdominal pain, liver and kidney disease, genital organ disease, trauma, burn, and suicide. Each item had four choices (1 = none, 2 = 1–5 cases, 3 = 6–10 cases, 4 = 11 or more cases), and the average of the 82 items was defined as the "clinical experience."

The clinical competency confidence scale included 99 items and measured residents' confidence levels based on a four-point Likert scale (i.e., 1 = "not confident at all/cannot perform at all," 2 = "not very confident/cannot perform independently," 3 = "somewhat confident/may be able to perform independently," and 4 = "very confident/able to perform independently").

Residents were asked to rate satisfaction with residency conditions (options provided). Attributes included educational opportunities (i.e., excellence in teaching, clinical opportunities, teaching resources, and consultation system) and working conditions (i.e., workplace atmosphere, distasteful work, salary, cooperation among departments, and coordination with paramedical staff). Questions regarding areas of interested allowed the following options: "clinical practice," "education," "research," "administration," "others," and "do not know." Residents were asked whether they were work- or life-oriented using the question, "Which are you oriented to, work or life?" with the five-point Likert scale (1 = "very much work-oriented" to 5 = "very much life-oriented"). Options for the most important thing in life included "professional commitment," "academic records," "income," "skill improvement," and "family."

Data analyses

Responses to the clinical experience items were further divided into two groups according to their respective medians and treated as binary variables. The clinical competency confidence scale was developed into a questionnaire to reflect the theoretical concepts of the new PGME. The new PGME[13] had three guiding principles: (1) to improve basic skills and knowledge of primary care and build core clinical competency in evaluating a patient as a whole, (2) to improve salary, and (3) to cultivate physicianship. Consequently, irrelevant items were excluded. The excluded items were those related to orthopedic surgery and radiology, because these subjects were not core requirements, and those related to pediatrics, psychiatry, and obstetrics–gynecology, because items in these areas are skewed on a specific domain of content. We grouped the remaining items into four skill categories: physical exams (8 items), procedural skills (8 items), interpretation of clinical tests (11 items), and physician–patient relationships and social service application (7 items).

Each score, as well as overall scores, in the four clinical skill sets were assessed for gender by a *t* test. The internal

Table 1

Characteristics of 1,120 Second-Year Residents, Comparing Men and Women, Residency Survey in Japan, 2007*

Characteristic	Men (n = 778) n (%)	Women (n = 342) n (%)	P value
Basic characteristics			
Age, mean (SD)	28 (0.1)	27 (0.2)	.001
Type of hospitals			.03
University hospitals	276 (36)	146 (42)	
Community hospitals	500 (64)	198 (58)	
Clinical experience			.64
Higher group	558 (72)	252 (73)	
Lower group	218 (28)	92 (27)	
Satisfaction			
Overall satisfaction with residency conditions			.02
Satisfied	465 (61)	177 (53)	
Not satisfied	194 (25)	96 (28)	
Do not know	105 (14)	64 (19)	
Attributes—overall satisfaction (multiple answers)			
Educational opportunities			
Excellence in teaching	405 (52)	187 (54)	.50
Clinical opportunities	353 (45)	151 (44)	.62
Teaching resources	165 (21)	65 (19)	.37
Consultation system	144 (19)	53 (15)	.20
Working conditions			
Atmosphere at workplace	377 (49)	194 (56)	.02
Scut work	215 (28)	100 (29)	.64
Salary	218 (28)	70 (20)	<.01
Cooperation among departments	190 (24)	66 (19)	.05
Coordination with paramedical staff	243 (31)	98 (28)	.34
Future career			
Area interested (multiple answer)			
Clinical practice	732 (94)	331 (96)	.18
Education/research/administration	166 (21)	45 (13)	.001
Others/do not know	30 (4)	13 (4)	.94
Intention to obtain specialist qualification			.18
Yes	719 (93)	326 (95)	
No	20 (3)	3 (1)	
Do not know	34 (4)	15 (4)	
Intention to obtain doctor of medical science			
Yes	306 (40)	96 (28)	.000
No	215 (28)	127 (37)	
Do not know	250 (32)	119 (35)	
Perspectives on life and work			
Work- or life-oriented			<.0001
Life-oriented	120 (16)	109 (32)	
Work-oriented	231 (30)	45 (13)	
Between	415 (54)	190 (55)	
The most important thing in a life			<.0001
Family	361 (54)	211 (70)	
Academic records/income/skill improvement	129 (20)	36 (12)	
Professional commitment	173 (26)	54 (18)	

* Missing data: sex (4), satisfaction (19), specialist qualification (3), doctor of medical science (7), work- or life-oriented (10), the most important thing (156).

consistency reliability of the confidence questionnaire was calculated using item-total correlation and Cronbach alpha. The content validity of the questionnaire was assessed by 10 PGME experts. These experts were asked whether each item (1) reflected the theoretical concepts of PGME, (2) evaluated basic skills and knowledge in primary care, and (3) was clearly understandable. The expert group consisted of a professor at a national university, a professor at a private university, two deans of teaching hospitals, two PGME program directors at teaching hospitals, two medical officers from the Ministry's Office for Clinical Training Medical Professions, and two primary care physicians. Residents' basic characteristics, satisfaction, future career, and perspectives on life and work were assessed between men and women by chi-square tests for categorical variables and *t* tests for continuous variables. The details of each variable are shown in Table 1. Finally, to investigate the effect of gender on resident confidence levels, we used general linear regression models, adjusting for age, types of hospitals, clinical experience, and satisfaction with residency conditions. We computed beta coefficients that reflected an increase or decrease in a unit of clinical confidence levels in the four skill areas.

We conducted analyses using SAS version 8.12 for Windows (SAS Institute, Cary, North Carolina). All tests were two sided, with a significance level of 0.05 using the Wald chi-square test.

Results

A total of 1,124 residents agreed to participate in this study (a response rate of 60%). Nevertheless, we were unable to determine the sex of four of the residents, and therefore the number of the study participants for analyses was 1,120.

Scores for confidence levels in the four skill sets between men and women

The scores of the responding 1,120 residents are reported in Table 2. The internal consistency values of the four skill sets for measures of clinical competency were adequate: $\alpha = 0.83$ in physical exams, $\alpha = 0.86$ in procedural skills, $\alpha = 0.88$ in interpretation of clinical tests, and $\alpha = 0.87$ in physician–patient relationships and social service application. The item-total correlations were all positive and ranged from 0.41 to

Table 2

Scores of 1,120 Second-Year Residents' Confidence Levels in Four Skill Groups of Clinical Competency, Residency Survey in Japan, 2007*

	Mean		
	Men	Women	Mean difference (95% CI)
Physical exam skills (α = 0.83)†			
Overall	3.11	3.00	0.11 (0.06 to 0.17)
History taking	3.32	3.31	0.01 (−0.06 to 0.07)
Vital sign	3.59	3.58	0.02 (−0.05 to 0.09)
Thyroid	2.80	2.76	0.03 (−0.06 to 0.11)
Heart auscultation	3.01	2.88	0.13 (0.05 to 0.21)
Lung auscultation	3.19	3.06	0.13 (0.06 to 0.20)
Heart apex beat palpation	3.16	3.10	0.07 (−0.02 to 0.15)
Resistance on abdomen	3.30	3.16	0.16 (0.09 to 0.24)
Digital prostate exam	2.55	2.18	0.38 (0.27 to 0.48)
Procedural skills (α = 0.86)†			
Overall	3.40	3.27	0.12 (0.06 to 0.18)
Technique for drawing venous blood	3.64	3.66	−0.02 (−0.09 to 0.04)
Technique for drawing arterial blood	3.65	3.64	0.01 (−0.06 to 0.08)
Lumbar puncture technique	3.22	2.97	0.26 (0.16 to 0.36)
Urinary catheterization	3.50	3.53	−0.03 (−0.11 to 0.04)
Chest compressions	3.54	3.47	0.06 (−0.01 to 0.14)
Intubation	3.39	3.23	0.16 (0.08 to 0.24)
Lung ventilation	3.05	2.76	0.29 (0.20 to 0.39)
Electric defibrillator	3.20	2.92	0.28 (0.19 to 0.37)
Interpretation of clinical tests (α = 0.88)†			
Overall	3.06	2.94	0.11 (0.05 to 0.17)
Urinalysis	2.36	2.33	0.02 (−0.10 to 0.15)
Stool test for occult blood	3.05	2.98	0.06 (−0.04 to 0.16)
Arterial blood gas	3.33	3.21	0.12 (0.05 to 0.19)
Complete blood count	3.39	3.31	0.09 (0.02 to 0.16)
A battery of blood chemistry tests	3.37	3.27	0.10 (0.03 to 0.17)
Coag panel	3.27	3.14	0.13 (0.05 to 0.20)
Immunology tests	2.98	2.88	0.10 (0.01 to 0.19)
Endocrine tests	2.71	2.61	0.11 (0.02 to 0.20)
Cerebral fluid tests	2.91	2.69	0.22 (0.13 to 0.31)
ECG	3.13	2.92	0.21 (0.13 to 0.29)
Spirometry	3.13	3.01	0.13 (0.05 to 0.21)
Physician–patient relationship and social service application (α = 0.87)†			
Overall	2.92	2.86	0.06 (−0.01 to 0.12)
Patients' interpretative models	3.30	3.27	0.03 (−0.04 to 0.09)
Nonverbal communication	3.24	3.20	0.04 (−0.04 to 0.11)
Psychosocial care of patients	2.93	2.90	0.03 (−0.06 to 0.11)
Medical fees and social welfare service	2.63	2.54	0.08 (−0.02 to 0.18)
Collaboration with social workers	2.75	2.69	0.06 (−0.04 to 0.15)
Health education	2.92	2.85	0.07 (−0.01 to 0.15)
Social service application	2.64	2.54	0.11 (0.01 to 0.20)

* Confidence levels were based on a four-point Likert scale (1 = "not confident at all/cannot perform at all"; 2 = "not very confident/cannot perform independently"; 3 = "somewhat confident/may be able–perform independently"; and 4 = "very confident/able–perform independently").

† Cronbach alpha coefficients.

0.70 for physical exams, 0.55 to 0.73 for procedural skills, 0.40 to 0.73 for interpretations of clinical tests, and 0.48 to 0.70 for physician–patient relationships and social service application. Because the deletion of any item would not result in an increase in Cronbach alpha of more than 0.01, we decided to retain all items in each group of competency skills. The content validity of the questionnaire was confirmed by the independent decision of all 10 PGME experts. Each expert felt that every question for each item reflected the theoretical concepts of PGME, evaluated basic skills and knowledge in primary care, and was clearly understandable.

The overall mean confidence scores in the four skill sets ranged between 2.9 and 3.1. When stratified by gender, the scores were generally higher in men than in women in physical exam skills, procedural skills, and interpretation of clinical tests. In contrast, the gap of scores between men and women narrowed in physician–patient relationships and social service application.

Basic characteristics, satisfaction, future career, and perspectives on life and work between men and women

Basic characteristics of the responding residents, comparing men and women, are shown in Table 1. The mean age of the residents was 28 years, and the majority of the participants were male (n = 776, 69%) and chose community hospitals (n = 706, 63%). The mean level of clinical experience was 3.15 on an ordinal scale where 3 indicated "6–10 cases" and 4 indicated "11 or more cases."

Women were found to be younger than men (P = .001) and more likely to choose university hospitals for their residency (P = .029). Men were more likely than women to be satisfied with residency conditions (P = .020), and their attribution for their satisfaction was significantly different in the areas of workplace atmosphere, salary, and cooperation between departments. Both men and women chose clinical practice as area of interest, but men were found to be more interested than women in education/research/administration (P = .001). Similarly, more men than women reported that they intended to obtain a DMSc degree (P = .001). On the other

hand, with regard to perspectives on life and work, nearly half of both men and women reported that they value both their personal lives and work; among the others, 30% of men (n = 231) versus only 13% of women (n = 45) reported that they were more work-oriented ($P <$ .001). A markedly greater proportion of women than men chose "family" (70% versus 54%) as "the most important thing in life," followed by "professional commitment" (18% versus 26% for women and men, respectively, $P <$ .0001).

General linear model results of the gender effects on residents' confidence levels

Table 3 presents general linear model results of the gender effects on residents' confidence levels. After adjusting for age, clinical experience, types of hospitals, satisfaction with residency conditions, future career, and perspectives on life and work, women were found to be less confident compared with men about all skill sets except for physician–patient relationship and social service application (all $P < .05$). Although identification as "life- or work-oriented" was not a significant contributor to confidence levels, designation of "the most important thing in life" was marginally significant (data not shown); compared with residents who reported "academic records," "income," or "skill improvement" as most important, residents reporting "family" were found to be less confident about their interpretation of clinical tests ($P = .086$). No significant interaction of confidence levels with gender and other factors was found.

Discussion

Our results demonstrate that women were less likely than men to be confident about the majority of clinical skill sets except for physician–patient relationships and social service application, even after adjusting for number of clinical opportunities experienced. Gender differences were also identified in the basic characteristics of residents' satisfaction with residency conditions, future career, and perspectives on life and work. We discuss our results in light of their strengths and limitations while referring to the previous literature.

Previous studies both at clinical practice settings[16,17] and at research settings[18] reported that women tend to underestimate their abilities, although they perform better than men.[16–18] Such lower self-perceptions of competency among women may be accounted for by psychological vulnerability in women. Two studies reported that such vulnerability starts during medical school. Moffat et al[19] reported that female students had greater stress about workload and personal competence, and Dahlin and Runeson[20] reported that women worried about their future workload, citing issues like long working hours and responsibility in their careers. Gude et al[21] suggested that the role of the doctor is traditionally more male than female in its characteristics of being active, dominating, and responsible as opposed to passive, submissive, and dependent, and women may therefore have a lower level of role identification than do men. Alternatively, such vulnerability may result from gender inequity in the workplace. For example, McMurray et al[6] reported that women had less work control than men, which significantly contributed to burnout among women physicians. A few studies investigating gender inequity reported that women receive less institutional support for research,[9] fewer mentoring opportunities,[22] and fewer academic resources[23] than men. In this regard, our study showed that women seemed to be less satisfied with residency conditions than were men. However, no gender difference was found in educational opportunities. Women seemed to be more satisfied than men with the "workplace atmosphere," and this relationship contradicted the idea that gender climate favors male physicians. These findings may be explained by the characteristics of our study subjects; they were second-year residents who were not yet eligible to do research and who were in a rotation period too short for them to yet perceive the gender climate in the workplace that might create specific obstacles to professional development.

Lower levels of clinical confidence among women residents were observed in the majority of clinical skill sets; however, the gap between men and women narrowed in the area of the physician–patient relationship (i.e., understanding of patients' interpretative models, nonverbal communication performance, psychosocial care of patients, and health education in compliance with the levels of patient knowledge and interests). Although the scores for confidence in physician–patient relationship seemed lower among men than those of other skill groups, such narrowed differences between men and women may be explained by the findings of previous studies that women physicians are good at listening and counseling, that is, at skills that build trusting relationships between physicians and patients.[24–26] Women physicians facilitate patient participation in the medical exchange more effectively than do men and are more likely to engage their patients in discussions of their social and psychological contexts and to deal more often with feelings and emotions. This is consistent with the results of previous studies, most of which were conducted in Western countries, verifying the clinical advantage of women physicians in this domain.

Table 3

General Linear Model Results of Gender Effect on Confidence Levels of 1,120 Second-Year Residents in Four Skill Sets of Clinical Competency, Residency Survey in Japan, 2007

The four clinical skill sets	Women versus men					
	Univariate			Multivariate*		
	β	SE	P	β	SE	P
Physical exam skills	−.114	.028	<.0001	−.093	.030	<.01
Procedural skills	−.123	.030	<.0001	−.084	.032	<.01
Interpretation of clinical tests	−.113	.030	.000	−.083	.033	.01
Physician–patient relationship and social service application	−.059	.033	.07	−.012	.036	.73

* Adjusting for age, clinical experience, types of hospitals, satisfaction with residency conditions, future career, and perspectives on life and work.