Pancreaticogastrostomy Is Superior to Pancreaticojejunostomy for Prevention of Pancreatic Fistula After Pancreaticoduodenectomy

An Updated Meta-analysis of Randomized Controlled Trials

Benjamin Menahem, MD, Lydia Guittet, MD, PhD,† Andrea Mulliri, MD,* Arnaud Alves, MD, PhD,* and Jean Lubrano, MD**

Objective: To review prospective randomized controlled trials to determine whether pancreaticogastrostomy (PG) or pancreaticojejunostomy (PJ) is associated with lower risks of mortality and pancreatic fistula after pancreaticoduodenectomy (PD).

Background: Previous studies comparing reconstruction by PG and PJ reported conflicting results regarding the relative risks of mortality and pancreatic fistula after these procedures.

Methods: MEDLINE, the Cochrane Trials Register, and EMBASE were searched for prospective randomized controlled trials comparing PG and PJ after PD, published up to November 2013. Meta-analysis was performed using Review Manager 5.0.

Results: Seven trials were selected, including 562 patients who underwent PG and 559 who underwent PJ. The pancreatic fistula rate was significantly lower in the PG group than in the PJ group (63/562, 11.2% vs 84/559, 18.7%; odds ratio = 0.53; 95% confidence interval, 0.38–0.75; $P = 0.0003$). The overall mortality rate was 3.7% (18/489) in the PG group and 3.9% (19/487) in the PJ group ($P = 0.68$). The biliary fistula rate was significantly lower in the PG group than in the PJ group (8/400, 2.0% vs 19/392, 4.8%; odds ratio = 0.42; 95% confidence interval, 0.18–0.93; $P = 0.03$).

Conclusions: In PD, reconstruction by PG is associated with lower postoperative pancreatic and biliary fistula rates.

Keywords: meta-analysis, pancreaticoduodenectomy, pancreatic fistula, pancreaticogastrostomy, pancreaticojejunostomy

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Pancreaticoduodenectomy (PD) is the only curative treatment of malignant diseases of the periampullary region of the pancreas and is also recommended for the treatment of premalignant tumors at a high risk of degeneration. In high-volume centers, pancreatic fistula (PF) rate is nowadays about 14% [1] and the mortality rate after PD is less than 5%.[2–5] However, it is currently still unclear whether reconstruction by pancreaticogastrostomy (PG) or pancreaticojejunostomy (PJ) is associated with better outcomes after PD. PG has been advocated in the past few years, as recent randomized clinical trials reported that this procedure was associated with lower postoperative mortality and pancreatic fistula rates than PJ.[6–8] The aim of this meta-analysis of prospective randomized controlled trials comparing PG and PJ was to determine the best method of reconstruction after PD, based on the information available in December 2013. When possible, the reasons for heterogeneity among study findings were identified.

METHODS

Data Sources

We performed a systematic review of the literature published up to November 2013 by searching abstracts in MEDLINE, the Cochrane Database and Cochrane Clinical Trials Registry, and EMBASE, using the search terms [pancreaticogastrostomy OR pancreatogastrostomy] AND [pancreaticojejunostomy OR pancreatojejunostomy] AND [pancreaticoduodenectomy OR pancreatoduodenectomy] AND [random*]. The search was limited to articles published in English. Two researchers independently searched for articles and compared their results. No unpublished data, data published only in an abstract form, or not full-length articles were included in the analysis.

Inclusion and Exclusion Criteria

Only prospective randomized controlled trials were included in this study. PD procedures performed for any reason were included. The search was limited to randomized controlled trials that specifically compared PG and PJ for reconstruction after PD in humans. Rates of postoperative pancreatic fistula (POPF), biliary fistula, mortality, overall morbidity, delayed gastric emptying, and length of hospital stay were recorded. Observational studies, case reports, and prospective studies were excluded.

Outcome Definitions

The primary outcome measure of this study was the POPF rate. Most of studies used International Study Group on Pancreatic Fistula (ISPGF) definition[9] for POPF; however, some older studies used others definitions (Table 1). Regarding secondary outcomes, several definitions were used in those studies and they are resumed in Table 2.

Data Review and Extraction

Two investigators independently searched the databases, read titles, abstracts, and full-length articles and selected articles to include in the analysis. The investigators also reviewed the reference lists of selected articles and previously published meta-analyses on the subject. Differences of opinion were resolved by consensus. The following information was extracted from the included studies: date, design, number of patients who underwent each type of reconstruction, sex, age, number lost to follow-up, inclusion and exclusion criteria, reconstruction techniques, overall mortality rate, definition

From the *Department of Digestive Surgery, University Hospital of Caen, Caen Cedex, France; and †Cancers and Prevention Laboratory, Research Department, University Hospital of Caen INSERM U 1086, Centre François Baclesse, Caen Cedex, France.

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Reprints: Benjamin Menahem, MD, Department of Digestive Surgery, University Hospital of Caen, Avenue de la Côte de Nacre, 14032 Caen Cedex, France. Email: menahem-b@chu-caen.fr.

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TABLE 1. Characteristics of Randomized Controlled Trials Included in the Meta-analysis

First Author	Year	No. Patients	Settings	Type of Operation	PF Definition	PG	PJ
Yeo[29]	1995	145	Single center	PPPD/PD	Drainage of >50 mL of amylase-rich fluid after POD 10 or pancreatic anastomotic disruption demonstrated radiographically	73	72
Bassi[28]	2005	151	Single center	PPPD/PD	Any clinical significant output of fluid, rich in amylase, confirmed by fistulography	69	51
Duffas[27]	2005	149	Multiple center	PPPD/PD	Chemically, 4 times normal serum values of amylase for 3 d, or clinically and radiologically, as anastomotic leaks shown by fistulography	81	68
Fernandez-Cruz[6]	2008	108	Single center	PPPD/PD	ISPGF definition[9]	53	55
Wellner[30]	2012	116	Single center	PD	ISPGF definition[9]	59	57
Figueras[8]	2013	123	Single center	PPPD/PD	ISPGF definition[9]	65	58
Topal[7]	2013	329	Multiple center	PPPD/PD	ISPGF definition[9]	162	167

POD indicates postoperative day; PPPD, pylorus-preserving pancreatoduodenectomy.

of pancreatic fistula, postoperative rates of pancreatic fistula and other complications, mean period of postoperative delayed gastric emptying, and length of hospital stay. Missing data were requested from the authors of the included studies. The quality of the studies was determined using the Jadad scale.

Statistical Analysis

All statistical analyses were performed using Review Manager 5.0 software (Cochrane Collaboration, Oxford, England). A fixed model was used if there was no evidence of heterogeneity; otherwise, a random-effects model was used. Heterogeneity was assessed by the I^2 statistic, with values of more than 50% considered to indicate significant heterogeneity. Odds ratios (ORs) were calculated for each trial from the number of evaluable patients, and 95% confidence intervals (CIs) were calculated to confirm effect size estimation and test criteria. The P value for the overall effect was calculated using the z test, with significance set at $P < 0.05$. Sensitivity analysis and estimation of publication bias were also performed.

RESULTS

Trial Characteristics

A total of 34 studies were retrieved. The process of selecting trials for inclusion is shown in Figure 1. Twenty-seven of these studies were excluded because of the type of study, study design, absence of randomization, or absence of main primary outcome. Finally, 7 randomized controlled trials published as full-length articles were included. These trials included 562 patients who underwent PG and 559 patients who underwent PJ after PD. The characteristics of these 7 studies are shown in Table 1.

Results of Meta-analysis

Pancreatic Fistula

All the included studies reported POPF rates. The pancreatic fistula rate was 11.2% (63/562) in the PG group and 18.7% (105/559) in the PJ group. Meta-analysis showed that the rate of pancreatic fistula was significantly lower in the PG group than in the PJ group (OR = 0.53; 95% CI, 0.38–0.75; $P = 0.0003$) (Fig. 2).

Biliary Fistula

Postoperative biliary fistula was defined as drainage of fluid containing bile from one of the postoperative drains. Six of the 7 studies (including 792 patients) reported postoperative biliary fistula rates. The biliary fistula rate was 2.0% (8/400) in the PG group and 4.8% (19/392) in the PJ group. Meta-analysis showed a significant difference in the biliary fistula rate between the PG and PJ groups (OR = 0.42; 95% CI, 0.18–0.93; $P = 0.03$). These results suggest that PG is associated with a lower postoperative biliary fistula rate than PJ (Fig. 3).

Delayed Gastric Emptying

There was heterogeneity in the definitions of postoperative delayed gastric emptying among studies. We tried to follow the ISGPF definition.[10] In most studies, delayed gastric emptying was defined as gastric stasis requiring nasogastric intubation for more than 7 days, more or less associated with vomiting and reinsertion of a nasogastric tube after failure of postoperative feeding. Six of the 7 studies (including 972 patients) reported postoperative delayed gastric emptying rates. The delayed gastric emptying rate was 16.2% (78/481) in the PG group 14.5% (71/491) in the PJ group. Meta-analysis showed no significant difference in the delayed gastric emptying rate between the PG and PJ groups (OR = 0.98; 95% CI, 0.53–1.82; $P = 0.95$) (Fig. 4).

Overall Morbidity

Overall morbidity included intra-abdominal and medical complications. All the studies reported postoperative morbidity rates. The overall morbidity rate was 49.1% (276/562) in the PG group and 49.3% (276/559) in the PJ group. Meta-analysis showed no significant difference in the overall morbidity rate between the PG and PJ groups (OR = 0.97; 95% CI, 0.77–1.24; $P = 0.82$) (Fig. 5).

Mortality

Six of the 7 studies (including 976 patients) reported postoperative mortality rates. The overall mortality rate was 3.7% (18/489) in the PG group and 3.9% (19/487) in the PJ group. Meta-analysis showed no significant difference in the postoperative mortality rate between the PG and PJ groups (OR = 0.87; 95% CI, 0.45–1.69; $P = 0.68$) (Fig. 6).

Length of Hospital Stay

All the studies reported the length of hospital stay. Only 4 of them reported mean and standard deviation. The mean hospital stay

TABLE 2. Characteristics of Definition of Secondary Outcomes

First Author	Biliary Fistula	Delayed Gastric Emptying	Morbidity	Mortality	Length of Hospital Stay
Yeo[29]	Not detailed in the study	Not detailed in the study	Complications occurring during the hospitalization	Not detailed in the study	Mean ± SD
Bassi[28]	Persistence of biliary drainage for > 5 d	Need for gastric tube decompression for > 10 d	Complications occurring during the hospitalization	No. hospital mortalities	Mean ± SD
Duffas[27]	Distinctive color of discharge containing bilirubin or by fistulography	Not detailed in the study	Complications occurring during hospitalization or until 30 d after discharge for patients hospitalized <1 mo	No. hospital mortalities	Median (range)
Fernandez-Cruz[6]	Not detailed in the study	Failure to resume oral liquid intake by POD 10 and/or emesis over 500 mL on or after POD 5 and/or continued gastric drainage > 500 mL and/or after POD 5	Complications occurring during the hospitalization detailed by each complications (abscess, pneumonia)	Not detailed in the study	Mean ± SD
Wellner[30]	Not detailed in the study	ISPGS definition[10]	Complications occurring during the hospitalization	No. hospital mortalities or until 90 d after surgery	Median (range)
Figueras[8]	Effluent with a bilirubin concentration 2 times greater than the blood level	ISPGS definition[10]	Clavien-Dindo classification	No. hospital mortalities or until 60 d after surgery	Median (range)
Topal[7]	Not detailed in the study	Not detailed in the study	Therapy-oriented severity grading system (panel 1)	No. hospital mortalities	Median (range)

POD indicates postoperative day.

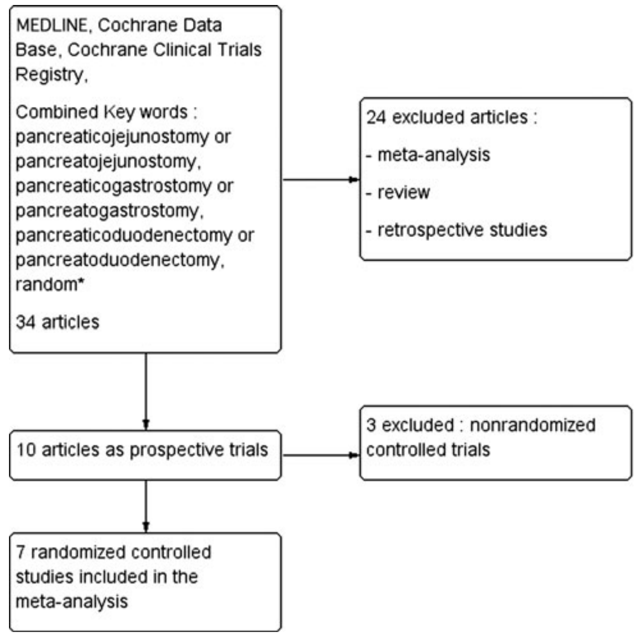

FIGURE 1. Flowchart of included and excluded studies.

was 15.6 days in the PG group and 17.3 days in the PJ group. Meta-analysis showed that the mean hospital stay was significantly shorter in the PG group than in the PJ group (mean difference = 1.62; 95% CI, 0.61–2.63; $P = 0.02$) (Fig. 7).

Sensitivity Analysis and Publication Bias

Sensitivity analysis and estimation of publication bias were performed with the aim of determining the significance of results. For delayed gastric emptying, overall complications, and length of hospital stay, the combined OR was calculated using both a fixed-effects model and a random-effects model and the results were compared. Because statistically significant data are published more frequently than nonsignificant data, our results may be influenced by publication bias.

DISCUSSION

The results of this meta-analysis show that PG is superior to PJ for reconstruction after PD. The results indicate that PG is associated with significantly lower postoperative pancreatic and biliary fistula rates and a shorter length of hospital stay than PJ. However, these 2 procedures were not significantly different in terms of delayed gastric emptying, overall morbidity, or mortality.

Pancreatic anastomosis after PD is an important aspect of pancreatic surgery. POPF formation is the most important cause of morbidity and mortality after PD. Despite recent improvements, this complication still occurs in 30% of cases.[11] Other complications after PD such as biliary fistula formation and delayed gastric emptying are also concerning. Previous studies reported contradictory results regarding the impact of PG versus PJ on the postoperative fistula rate. Previous retrospectives studies,[11–14] prospective studies,[1,15,16] randomized controlled trials, and 5 meta-analyses[17–21] have reported on the technical aspects influencing the pancreatic fistula rate. Pharmacological treatment has also been used to help reduce the pancreatic fistula rate.[22–24]

Numerous PJ anastomotic techniques have been described, using end-to-end or side-to-end anastomoses, with or without invagination of the pancreas into the digestive tract in a single layer or

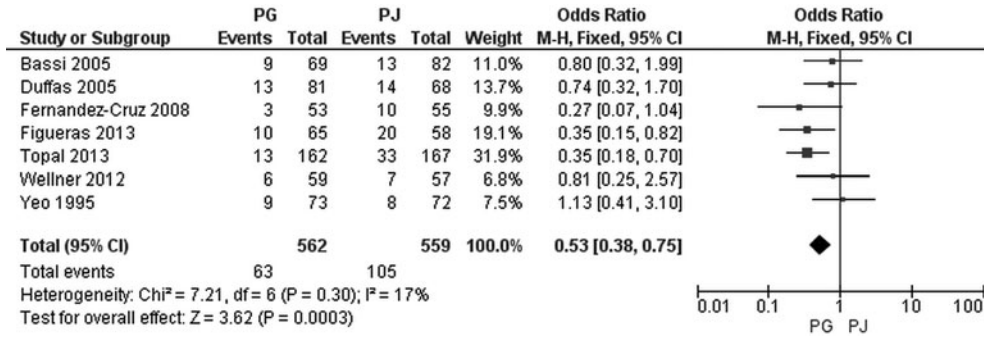

FIGURE 2. Forrest plot of postoperative pancreatic fistula between PG and PJ.

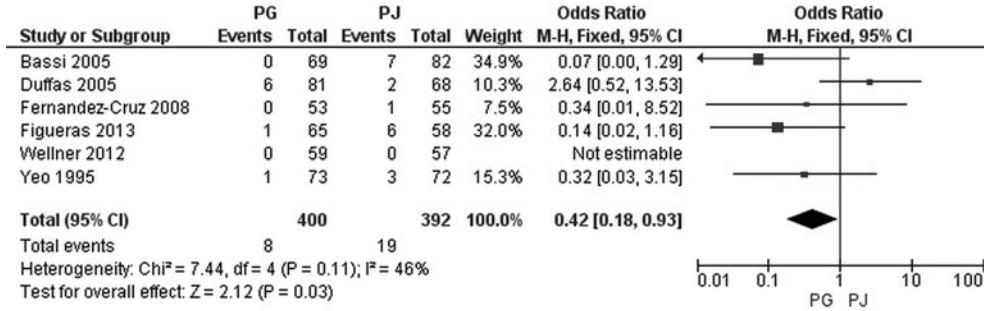

FIGURE 3. Forrest plot of postoperative biliary fistula between PG and PJ.

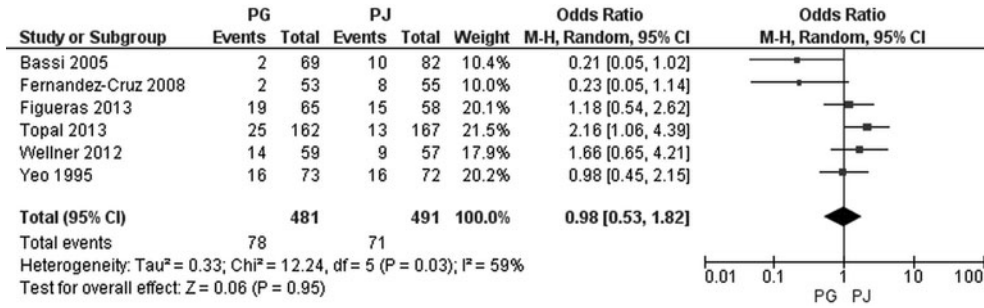

FIGURE 4. Forrest plot of delayed gastric emptying between PG and PJ.

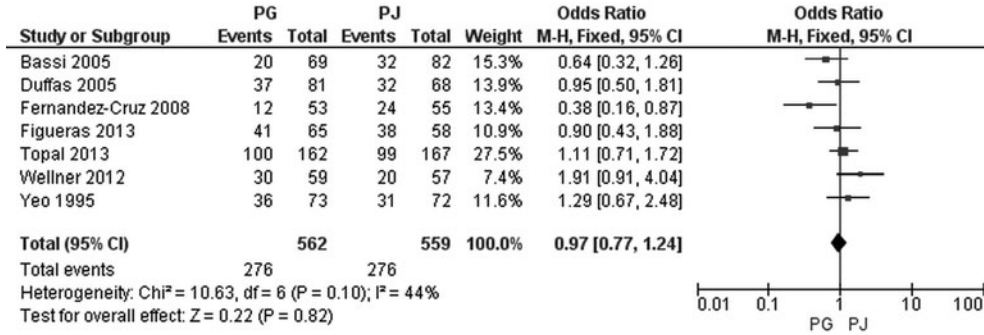

FIGURE 5. Forrest plot of overall morbidity between PG and P.

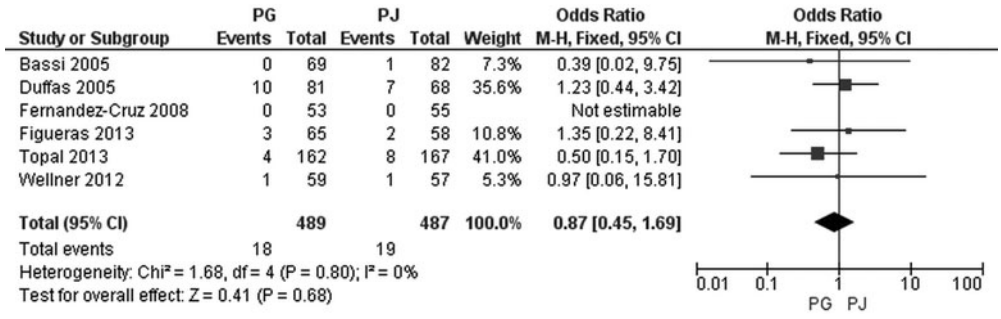

FIGURE 6. Forrest plot of overall mortality between PG and PJ.

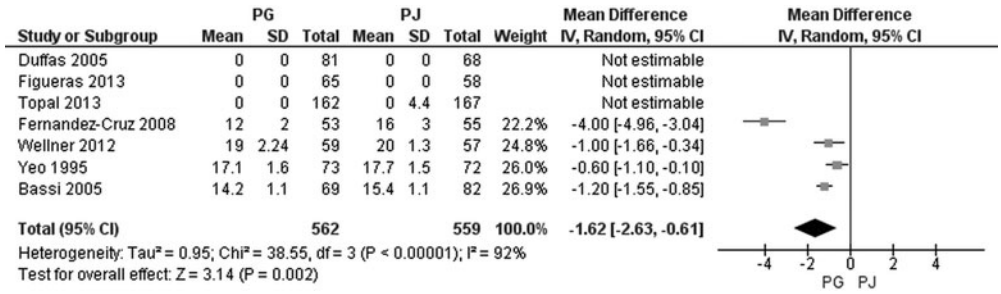

FIGURE 7. Forrest plot of length of hospital stay between PG and PJ.

double layers. In PG, the remnant pancreas is anastomosed to the posterior wall of the stomach, with or without invagination of the pancreas. This procedure is easy to perform because the posterior wall of the stomach can be mobilized toward the pancreas. Several explanations regarding the protective role of PG have been described in the literature.[25] Some authors have suggested that pancreatic secretions may be less corrosive to the stomach after PG than to the digestive tract after PJ, because the acidity of gastric secretions inactivates the pancreatic enzymes.[19] In PJ, the pancreatic enzymes are activated by alkaline biliary and enteric secretion. Furthermore, gastric and pancreatic secretion is easily diverted with a nasogastric tube after PG, and PG reconstruction may divert potential pancreatic fistulas away from major blood vessels. In PJ, complex fistulas may form with leakage of biliary and pancreatic secretion.

Previous meta-analyses have also investigated pancreatic fistula rates after PD. Only Shen et al[19] found no significant difference in the pancreatic fistula rate between PG and PJ. They included only 4 randomized controlled trials in their analysis, which may have been an insufficient number of patients to reach definitive conclusions. Ma et al[17] found that PG was associated with a lower pancreatic fistula rate than PJ. However, their data had significant heterogeneity because they included both randomized controlled trials and prospective trials in their analysis. He et al[20] and Wente et al[18] included both randomized controlled trials and observational studies in their analyses and did not find superiority of either PG or PJ. More recently, the meta-analysis by Yang et al[21] could not determine the best method of reconstruction among PG, PJ, intraduct ligation of the pancreatic duct, duct-to-mucosa PJ, and binding PJ.

Other factors also influence the pancreatic fistula rate after PD. For example, a fatty pancreas and a pancreatic duct size of less than 3 mm are associated with an increased risk of POPF.[1] Other patient factors also affect the risk of pancreatic fluid leakage, including age, preoperative jaundice, body mass index, and cardiovascular comorbidities.[26]

Our meta-analysis has some limitations. First, the types of intervention and the indications for surgery are heterogeneous among published studies. For example, Duffas et al,[27] Bassi et al,[28] Yeo et al,[29] and Topal et al[7] reported outcomes after PD and Fernandez-Cruz et al,[6] Topal et al,[7] and Wellner et al[30] reported outcomes after pylorus-preserving PD. These different interventions may lead to different complications. Second, the definition of pancreatic fistula varied among studies, and the ISGPF definition was used in only 4 of the 7 studies included in our analysis.[7,8,29,30] Finally, it would have been useful to consider the reason for performing PD in the analysis, but this was not possible because of the limited information available.

In the study by Yeo et al,[29] one patient who died was excluded from the study because his death was judged to be caused by pulmonary embolism and multiorgan failure. We excluded this study from the meta-analysis of postoperative mortality but included it in the other groups to determine whether this would alter the conclusions and found that it did not.

PG seems to be associated with a shorter length of hospital stay than PJ. This information should be interpreted with care because the definition of length of hospital stay varied among studies (eg, only postoperative days were reported in the study by Yeo et al[29]). There was also a higher rate of rehospitalization in the PG group than in the PJ group in the study by Figueras et al,[8] but this difference was not statistically significant.

CONCLUSIONS

This meta-analysis shows that PG is superior to PJ for reconstruction after PD. PG is associated with significantly lower pancreatic and biliary fistula rates and a shorter length of hospital stay than PJ. Further studies that use the widely accepted ISGPF definition of POPF will help confirm our results.

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