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Pancreas

Efficacy of total pancreatectomy with islet autotransplantation on opioid and insulin requirement in painful chronic pancreatitis: A systematic review and meta-analysis

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ABSTRACT

Background: The rationale for total pancreatectomy in painful, treatment refractory, chronic pancreatitis is pain control. Concomitant islet cell autotransplantation can prevent the loss of islet cell function. This study aimed to systematically examine the impact of total pancreatectomy with islet cell autotransplantation on pain and quality of life.

Methods: This meta-analysis was conducted according the Meta-analyses of Observational Studies in Epidemiology guideline. The Cochrane Library, PubMed, and Embase were searched for the following terms (1990 through April 2018): total pancreatectomy and chronic pancreatitis. Studies were included when addressing total pancreatectomy with islet cell autotransplantation for chronic pancreatitis in adults. Studies that reported no data on pain, endocrine function, or quality of life were excluded. Quality was assessed using the Newcastle-Ottawa scale for evaluation of all studies.

Results: We included 15 observational studies evaluating 1,255 patients, of whom 28% had had endoscopic and 23% operative therapy. One year after total pancreatectomy with islet cell autotransplantation, the opioid-free rate had improved from between 0% and 15% to 63% (95% CI 46–77), and the insulin-free rate had decreased from between 89.5% and 100% to 30% (95% CI 20–43). An alcoholic etiology was associated with a lesser insulin-free rate after total pancreatectomy with islet cell autotransplantation. Quality of life improved statistically after total pancreatectomy with islet cell autotransplantation. Publication bias was present for both opioid and insulin outcomes.

Conclusion: In selected patients with painful, treatment refractory, chronic pancreatitis, evidence shows that total pancreatectomy with islet cell autotransplantation is effective for pain control in almost two-thirds of patients, whereas the insulin-free rate is relatively low.

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Introduction

Patients with chronic pancreatitis (CP) frequently suffer from chronic abdominal pain, which can severely affect quality of life.[1] In 50% of the patients, the pain is refractory to medical treatment and requires endoscopic and/or operative treatment.[2] A randomized controlled trial showed that operative drainage of the main pancreatic duct provides better pain relief than endoscopic drainage in patients with painful CP (75% for operative therapy vs 32% for endoscopy).[3] The exact timing of operative therapy, however, is still a matter of debate.[4] For patients with refractory CP despite having had operative treatment or whose pancreatitis is hereditary, a total pancreatectomy with islet autotransplantation (TP-IAT) can be the last resort for treatment. The timing of operation for these conditions, however, is also important because an early procedure will result in a greater yield of islets, and a late procedure potentially leads to less pain relief.

Total pancreatectomy (TP) alone leads to so-called brittle diabetes with fluctuations of blood glucose levels that are often difficult to regulate.[5] This scenario can be avoided by combining TP with islet autotransplantation (IAT). During a TP-IAT, the pancreatic islet cells are isolated and infused into the liver via the portal vein. After the procedure, the islet cells will engraft in the liver parenchyma.

In patients with painful CP refractory to other treatments, TP-IAT potentially leads to adequate pain relief and mitigates the risk or consequences of new-onset diabetes mellitus. The interest in TP-IAT is increasing rapidly worldwide despite resistance to its adoption by various specialists.

Meta-analyses have evaluated TP-IAT for CP[6,7] but did not specifically assess the effect of TP-IAT on pain and quality of life, which is remarkable, because the relief of these conditions is the primary goal of this procedure. Furthermore, numerous new studies on TP-IAT for CP have been published in the past 5 years. Therefore, the purpose of this systematic review and meta-analysis was to determine the effectiveness of TP-IAT primarily on pain and quality of life but also on endocrine function and mortality in patients with CP.

Methods

This study was conducted in accordance with the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies.[8]

Search strategy and selection criteria

For this systematic review and meta-analysis, a search was conducted in the Cochrane Library, PubMed, and Embase databases for studies published since 1990 to April 2018. We searched for studies on TP for CP (Appendix Table AI presents search details). To identify additional relevant studies, reference lists of the included studies were screened.

Three reviewers (M.A.K., L.S., and C.R.V.) independently screened all studies on title, abstract, and potentially eligible studies on full text articles. Any conflicts were resolved through discussion with a fourth reviewer (M.G.B., study investigator). Studies that reported on outcomes of TP-IAT in adult men and woman with CP were eligible for inclusion. Exclusion criteria were as follows: (1) no data reported on pain, endocrine function, or quality of life; (2) follow-up duration of less than 6 months; (3) TP combined with allogeneic islet transplantation; (4) TP-IAT performed for various indications with no separate data for patients with CP (eg, hereditary pancreatitis); (5) language other than English or German; (6) less than 5 patients included; (7) one of following study designs: review, letter, case report, book chapter, and conference abstract; and (8) full text study not retrievable or published. When multiple studies were available from a single patient cohort, the largest study was included. Studies that reported percentages or dosages of opioid and insulin use and 30-day or 1-year mortality were selected for meta-analyses.

Data analysis

Three reviewers independently extracted data by using a structured record form (C.R.V., M.A.K., and L.S.). Authors were contacted for missing data regarding the duration of follow-up or when additional information was needed for outcomes included in the meta-analysis. The following data were collected about study characteristics: inclusion period, country of origin, study design, reported outcome, number of included patients, median or mean age, proportion of males, diagnosis of pancreatic disease, etiology, duration of CP, proportion of earlier endoscopic treatment for CP, proportion of an earlier operative treatment for CP, and indication for TP-IAT. The following data were collected: operative indication, type of operative procedure, duration of procedure, blood loss during procedure, ischemia time (cold and warm), transplanted islet equivalent ([IEQ] equivalent to a pancreatic islet with a diameter of 150 μm), IEQ/kg body weight, duration of hospital stay, and major complications (Clavien-Dindo grade ≥ 3). Collected pain outcomes were preoperative and follow-up opioid-free rates and opioid dosage (calculated in morphine equivalents), preoperative and follow-up visual analogue scale (VAS) pain score, pain relief, duration of follow-up, and number of patients in follow-up. Extracted outcomes related to endocrine function were duration of follow-up, number of patients in follow-up, preoperative and follow-up insulin-free rates, insulin units per day, and serum C-peptide and HbA1c levels. Collected quality of life (QoL) outcomes were type of QoL measurement, QoL score preoperatively, QoL score in follow-up, duration of follow-up, and number of patients in follow-up. Furthermore, 30-day and 1-year mortality rates were extracted.

Quality assessment

Two reviewers assessed the methodologic quality of the included articles independently, using the Newcastle-Ottawa quality assessment scale for cohort studies.[9] Because none of the included studies had a control group, it was not possible to assess the comparability. Therefore, a maximum of 6 points could be reached that represents a high-quality study. A score of 4 or 5 was considered as moderate quality, and a score less than 4 was considered as a low-quality study.

Statistical analysis

Meta-analysis

The opioid-free rates, insulin-free rates, and mortality rates were pooled in a weighted proportion meta-analysis using a random effects model. The pooled estimates were presented as proportion rates for 1-year opioid-free rate, 1-year insulin-free rate, 30-day mortality, and 1-year mortality. For opioid- and insulin-free rates at last registered follow-up, event rates per 10 person-years were presented to account for the various durations of follow-up in the studies. Preoperative and 1-year QoL scores for both the physical and the mental scale were pooled in a single means meta-analysis using a random effects model.

Metaregression

A metaregression analysis was performed to examine the association between the independent variables (eg, preoperative

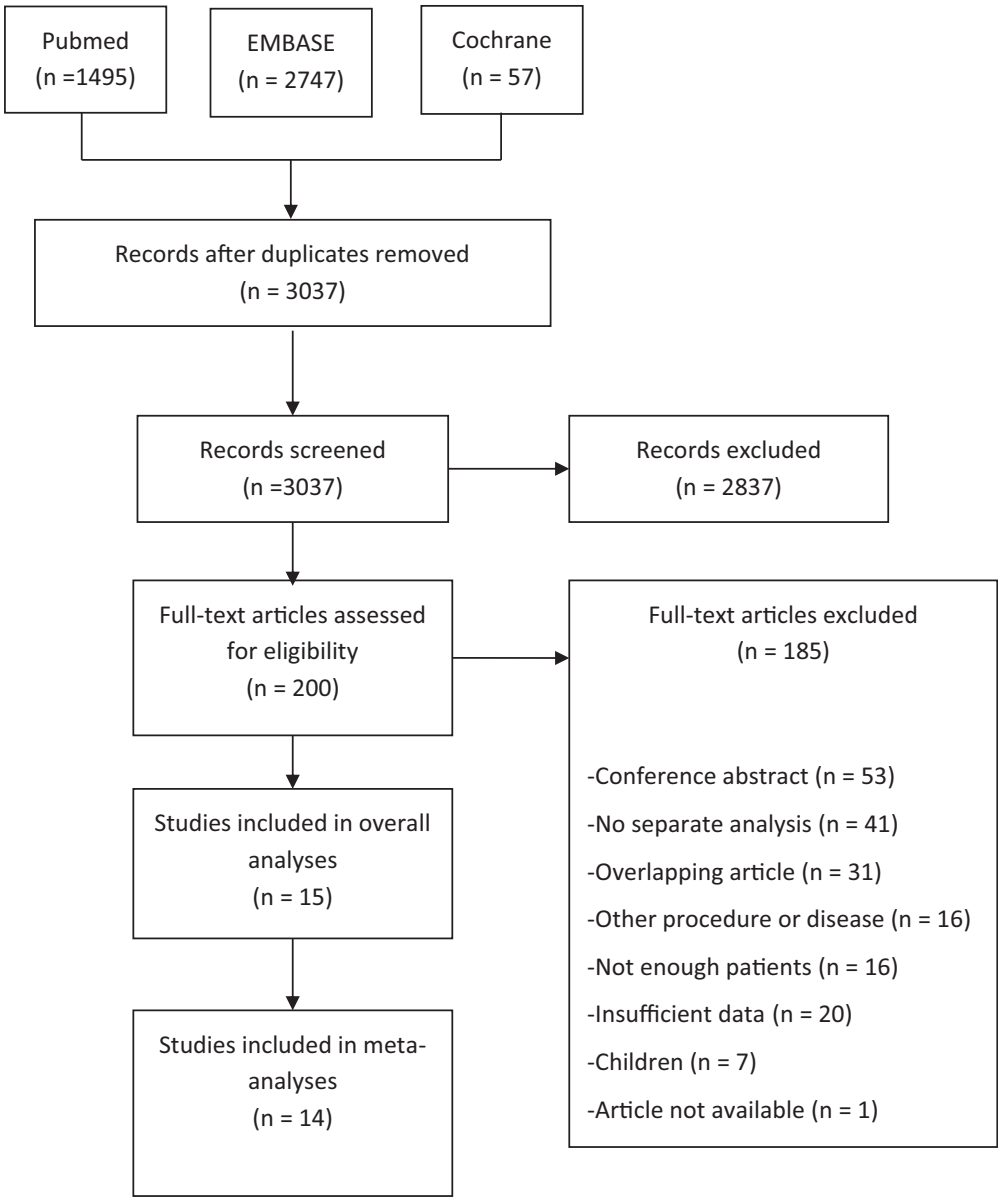

Fig 1. Flow diagram for article selection.

opioid-free rate, preoperative insulin-free rate, earlier operation for CP, alcoholic etiology, IEQ/kg) and the dependent variables (eg, opioid-free rate at last registered follow-up and insulin-free rate at last registered follow-up). For univariate regression analysis, we tested for independent variables that could be extracted from more than 5 studies. Multivariate regression analysis was not possible because of a lack of outcome data.

Publication bias was assessed by the Egger's regression test and by visual inspection of funnel plots, which plotted the effect of study effect size against their respective standard errors. All tests in this review were two-tailed, and a P value $< .05$ was considered as statistically significant. For statistical analysis, R (v 3.3.3) and Comprehensive Meta-Analysis (CMA v 3, Biostat, Englewood, NJ) were used. All summary estimates are presented with the associated (95% confidence intervals [CI]). Statistical heterogeneity was determined by using the I^2 statistic.[10]

Results

Study selection

Overall, 15 studies with 1,255 patients fulfilled the eligibility criteria (Fig 1).[11–25] One study reported only about QoL and was therefore not included in the meta-analyses.[16] Reasons for exclusions are presented in Appendix Table AII.

Study characteristics

Table I describes the study and patient characteristics. The 15 included studies were published between 2008 and 2018, with 73% (11 of 15 studies) after 2012. The pooled median age was 41 years (range in studies was 37–47 years), of which 28% were males. Follow-up ranged between 6 months and 60 months, and 1 study

Table I
Characteristics of included studies

Study	Inclusion period	Country	P/R	Outcome reported	Number of patients	Age (y)	Male *n* (%)	Disease diagnosis	Etiology: Alcoholic *n* (%)	Idiopathic *n* (%)	Hereditary *n* (%)	Divisum *n* (%)	Other *n* (%)	Duration of CP (y)	Previous surgery *n* (%)	Previous endoscopic therapy *n* (%)
Argo et al[11] (2008)	2005–2007	USA	R	Insulin, mortality	21	44*	57%	severe CP	29%	38%	0%	19%	14%	N/A	24%	48%
Chinnakotla et al[12] (2015)	1977–2014	USA	R	Pain, insulin, QoL, mortality	490	N/A	25%	CP, RAP, HP	6%	49%	14%	18%	13%	7.1*	19%	57%
Dixon et al[13] (2008)	10 y	USA	R	Pain, insulin, mortality	7	40†	43%	CP	0%	0%	0%	43%	57%	N/A	100%	N/A
Fan et al[14] (2017)	2013–2015	USA	N/A	Pain, insulin, mortality	20	39*	40%	CP, RAP	10%	30%	45%	15%	0%	N/A	N/A	N/A
Garcea et al[15] (2013)	1990–2013	UK	P	Pain, insulin, mortality	60	43†	N/A	CP	32%	52%	0%	N/A	16%	5.0*	13%	N/A
Georgiev et al[16] (2015)	2009–2013	USA	P	QoL	53	47*	36%	CP	13%	54%	15%	9%	8%	N/A	N/A	N/A
Gruessner et al[17] (2014)	2009–2013	USA	R	Pain, mortality	61	42*	36%	CP	11%	73%	16%	0%	0%	N/A	13%	N/A
Mokadem et al[18] (2016)	1998–2008	USA	R	Pain, insulin, mortality	30	41*	20%	CP	13%	63%	0%	17%	7%	N/A	N/A	N/A
Morgan et al[19] (2018)	2009–2017	USA	P	Pain, insulin, Mortality, QoL	195	40*	28%	CP	6%	N/A	24%	15%	55%	8.1*	29%	N/A
Shahbazov et al[20] (2016)	2006–2014	USA	R	Pain, mortality	73	41*	32%	CP	N/A	N/A	N/A	N/A	N/A	6.2†	0%	N/A
Solomina et al[21] (2017)	N/A	USA	P	Pain, insulin, Mortality, QoL	20	41†	35%	CP	0%	0%	65%	15%	20%	8.5†	25%‡	25%‡
Takita et al[22] (2015)	2007–2014	USA	R	Insulin, mortality	76	41*	33%	CP	9%	50%	13%	15%	13%	N/A	N/A	N/A
Takita et al[23] (2010)	2006–2009	USA	R	Pain, mortality	17	40*	24%	CP	N/A	53%	N/A	N/A	47%	N/A	18%	100%
Walsh et al[24] (2012)	2007–2010	USA	P	Pain, insulin, QoL, mortality	20	43†	60%	MMCP, CCP, ICP	25%	55%	10%	10%	0%	N/A	25%	N/A
Wilson et al[25] (2014)	2000–2013	USA	R	Pain, insulin, QoL, mortality	112	37*	33%	CP, RAP	3%	75%	13%	9%	0%	N/A	38%	N/A

CP, chronic pancreatitis; *RAP*, recurrent acute pancreatitis; *HP*, hereditary pancreatitis; *MMCP*, minimal change chronic pancreatitis; *CCP*, chronic calcific pancreatitis; *ICP*, indeterminate chronic pancreatitis.
* Mean.
† Median.
‡ Previous surgery and endoscopic therapy percentage combined.

had a follow-up of 138 months.[15] Previous endoscopic therapy for CP had been performed in 28% of the patients (range 48%–100%), and previous operations for CP had been performed in 23% of the patients (range 13%–100%). Pain outcomes were reported in 12 studies, including 890 patients, of whom 124 patients were lost to follow-up.[12–15,17–21,23–25] Endocrine outcomes were reported in 11 studies, including 994 patients, of whom 140 patients were lost to follow-up.[11–15,18,19,21,22,24,25] QoL outcomes were reported in 6 studies, including 876 patients, of whom 545 were lost to follow-up.[12,16,19,21,24,25] Mortality was reported in 11 studies including 1,036 patients.[11–15,17–19,21,24,25]

Quality assessment

The overall methodologic quality, according to the Newcastle-Ottawa quality assessment scale for cohort studies, was high in four studies, moderate in nine, and low in two. Appendix Table AIII presents overall quality per study and Appendix Table AIV presents the detailed score per study.

Surgical characteristics

The main indication for operative intervention was treatment of refractory painful CP. Only 2 studies included additional indications, 1 study included the risk of pancreatic cancer in 9 patients and another study included recurrent acute pancreatitis in an unknown amount of patients.[14,25] In 3 of 15 studies (20%) the indication for operation was not reported. Appendix Table AV presents details on TP-IAT indications. The mean transplanted IEQ was 3,413 per kilogram bodyweight. The average hospital stay ranged from 9 to 20 days. Major complication rates were up to 10%. Table II presents detailed operative characteristics per study .

Pain results

Opioid-free rate

The preoperative opioid-free rate was reported in 9 of 12 studies[12–15,17,21,23–25] and ranged from 0% to 15%. A total of 6 studies were included in the meta-analyses at 1-year follow-up and 11 studies at last registered follow-up (mean 28 months), respectively. At 1-year follow-up, the opioid-free rate was 63% (95% CI 46–77); $I^2 = 89\%$ (Fig 2, *A*). The pooled event rate of being opioid free at last registered follow-up was 3.33 per 10 person-years (95% CI 1.71–6.48); $I^2 = 97\%$. Figure 2 presents the forest plots of the meta-analyses of the opioid-free rate. After TP-IAT, morphine-equivalent dosage decreased from in all 8 studies, from between 89 and 316 mg to between 10 and 88 mg.[15,18–21,23–25]

Metaregression analysis showed no statistically significant correlation between the opioid-free rate at follow-up and alcoholic versus nonalcoholic etiology, previous operative treatment, and preoperative opioid-free rate for CP (Appendix Table AXI). The funnel plot of the standard error of studies evaluating opioid-free rates shows an asymmetric pattern (Appendix Fig A12, *A*). Together with a statistically significant Egger's test ($P = .04$), this finding suggests publication bias in these studies and indicates that studies with worse results were possibly not published.

Pain relief and VAS score

Pain relief was achieved in 90% to 100% of patients in 3 studies.[12,14,24] The VAS score was reported in 5 studies and decreased by a mean of 58 points (preoperative mean score of 79 to postoperative mean score of 21 at follow-up).[14,15,18,20,24] The mean morphine-equivalent dosage decreased from 179 before TP-IAT to 56 at last follow-up. Appendix Table AVI presents all pain results per study.

Table II
Surgical characteristics

Study	Indication	TPIAT procedure	Duration procedure (min)	Blood loss (ml)	Ischemia time (min)	Transplanted IEQ	IEQ/kg body weight	Islet preparation	Infusion site	Hospital stay (days)	Major complications (%)
Argo et al[11] (2008)	N/A	Open	432*	697*	N/A	97,692*	1,551*	Transported	Portal vein/ middle colic vein	10*	10%
Chinnakotla et al[12] (2015)	Painful CP	Open	N/A	N/A	N/A	N/A	N/A	In operating room	Portal vein	N/A	N/A
Dixon et al[13] (2008)	Painful CP	Open	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fan et al[14] (2017)	Painful RAP/CP, cancer risk	Laparoscopic	493*	628*	51* (warm)	N/A	1,325*	In operating room	Splenic or portal vein	11*	0%
Garcea et al[15] (2013)	Refractory painful CP	Open	480†	600†	N/A	N/A	N/A	Transported	Recannulated umbilical vein	20†	9%
Georgiev et al[16] (2015)	N/A	Open	N/A	N/A	N/A	N/A	N/A	Transported	Portal vein	N/A	N/A
Gruessner et al[17] (2014)	N/A	Robotic/open	N/A	N/A	N/A	221,470*	3,048*	Transported	Portal vein	12*	N/A
Mokadem et al[18] (2016)	N/A	Open	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0%
Morgan et al[19] (2018)	CP	Open	N/A	589	N/A	N/A	3,253*	N/A	Portal vein/ transhepaticpercutaneous to portal vein	9†	N/A
Shahbazov et al[20] (2016)	Refractory painful CP	Open	624*	527*	227*	N/A	N/A	N/A	N/A	N/A	0%
Solomina et al[21] (2017)	Refractory painful CP	Open	570†	N/A	N/A	228,500†	2,980†	Transported	Portal vein was cannulated	N/A	1%
Takita et al[22] (2015)	N/A	Open	N/A	N/A	N/A	N/A	N/A	Transported	Portal vein	N/A	N/A
Takita et al[23] (2010)	N/A	Open	N/A	N/A	41* (cold)	382,000*	5,279*	N/A	Portal vein via a mesenteric vein	N/A	N/A
Walsh et al[24] (2012)	Refractory painful CP	Open	N/A	N/A	N/A	299,508†	3,846†	Transported	Splenic vein stump	N/A	0%
Wilson et al[25] (2014)	Refractory painful RAP/CP	Open	544*	549*	N/A	415,518*	6,027*	N/A	Portal vein	N/A	N/A

IEQ, islet equivalent; *N/A*, not applicable.
* Mean.
† Median.

Endocrine outcomes

Insulin-free rate

The insulin-free rate was evaluated in 4 studies at 1-year follow-up and in 11 studies at the last registered follow-up (mean 31 months). After 1 year, 30% (95% CI 20–43; $I^2 = 82\%$; Fig 3, *A*) of patients were insulin free, and at last registered follow-up the pooled insulin-free event rate was 1.31 (95% CI 0.74–2.31; $I^2 = 92\%$ per 10 person-years; Fig 3, *B*). The preoperative insulin-free rate was reported in 7 of the 11 (64%) studies that reported insulin rates.[11,13,18,21,22,24,25] In these studies, preoperative insulin-free rates ranged from 90% to 100%.

Univariate metaregression analysis showed that an alcoholic etiology was negatively associated with the insulin-free rate at the last registered follow-up (Appendix Table AXI). There was evidence for publication bias because the funnel plot was asymmetric (Appendix Fig A12, *B*) and the Egger's test was statistically significant ($P = .007$).

Insulin dosage

Insulin dosage was significantly increased in all 4 studies that reported insulin dosage preoperatively and at follow-up.[15,18,24,25] Insulin dosage at the last registered follow-up ranged from 10 to 25 units per day. Appendix Table AVII presents detailed information about endocrine outcomes per study, including C-peptide and HbA1c. One study reported the insulin-free rate over time.[13] Wilson et al[25] reported a decrease in the insulin-free rate from 38% at 12 months to 27% at 60 months.

Mortality

The 30-day mortality rate was 2% (95% CI 1-4; Appendix Figure A8) in 11 studies,[11–15,17–19,21,24,25] whereas the 1-year mortality was 4% (95% CI 3-6; Appendix Figure A8) in six studies.[12–14,21,24,25] See Appendix Table A9 for mortality rates per study.

QoL

QoL was measured using the RAND Short Form Survey instrument with a 12-item (SF-12) in 1 study and a 36-item (SF-36) in 4 studies.[12,16,19,21,25] These questionnaires give an indicator of overall health status of patients. The Pain Disability Index and Depression Anxiety Stress Scale both were used in 1 study.[24] Overall improvement in health status was tested in 5 studies as measured with the SF-12 and the SF-36. In these studies, the pooled physical scale improved from 27 (95% CI 22–32) to 47 (95% CI 39–55), and the pooled mental scale improved from 37 (95% CI 33–42) to 55 (95% CI 42–68) ($P < .05$ in each). Appendix Table AX presents the detailed information per study.

Discussion

This systematic review and meta-analysis showed a 63% opioid-free rate, a 30% insulin-free rate, and a statistically significant improved QoL at 1-year after TP-IAT. The 30-day and 1-year mortality rates were 2% and 4% respectively. These findings suggest that TP-IAT can be a valuable treatment in selected patients with painful, treatment refractory CP. After IAT, the risk of new-onset diabetes, however, remains high at 70%. This diabetes, however, has been found to be far less severe than in patients who have been treated with total pancreatectomy alone because it is controlled with a relatively low dosage of insulin.

Previous meta-analyses on TP-IAT published in 2011 and 2015[6,7] did not address opioid-free rates but did address insulin-free rates

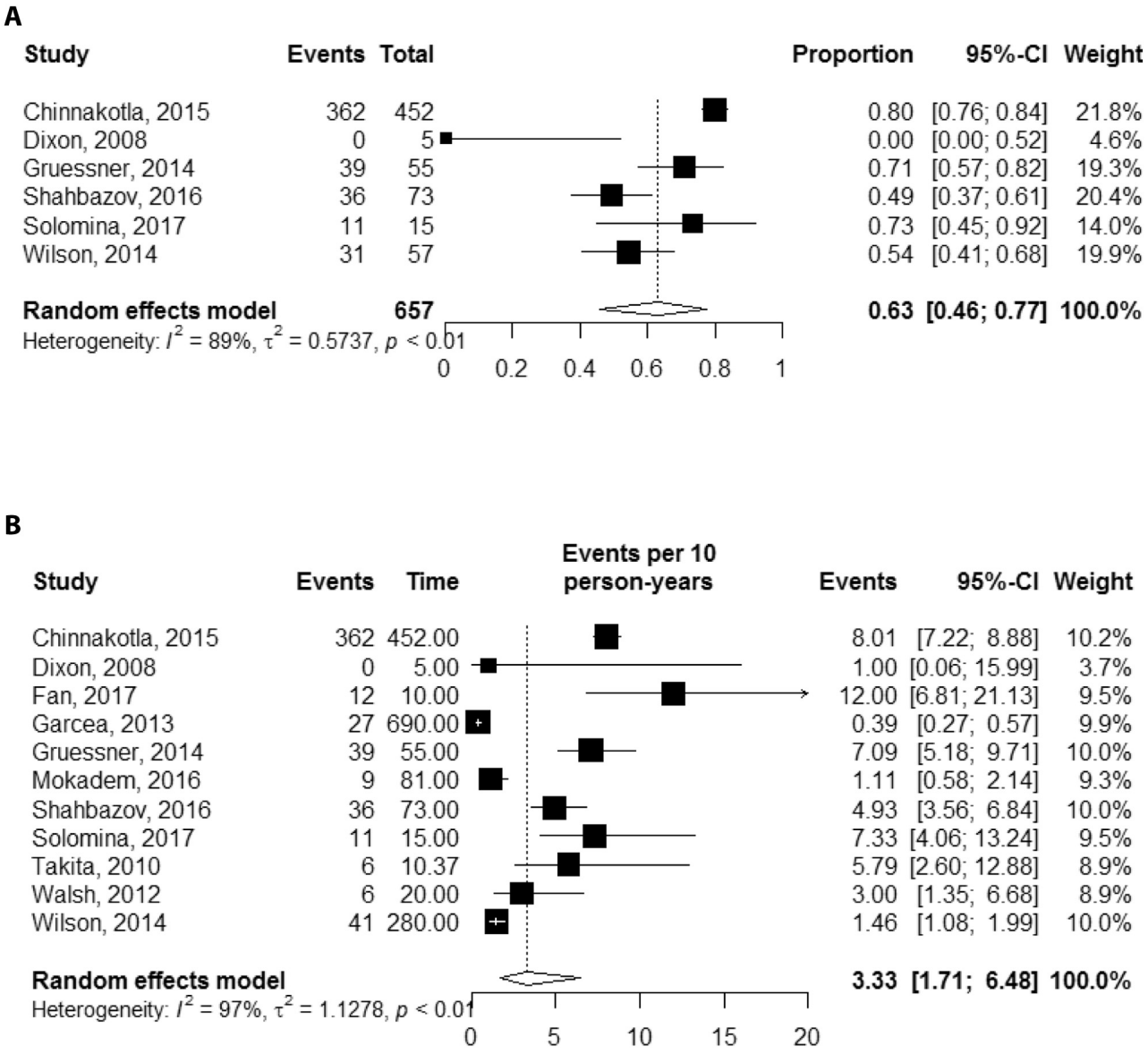

Fig 2. Forest plots of opioid-free rates. (*A*) Meta-analysis at 1-year follow-up; (*B*) meta-analysis at last follow-up, presented as event rates per 10 person-years.

and mortality after TP-IAT. Dong et al[6] reported an insulin-free event rate at last follow-up (range 1–96 months) of 4.6 per 100 person-years and a 30-day mortality rate of 5%. Wu et al[7] reported an insulin-free event rate at the last follow-up of 3.7 per 100 person-years and a 30-day mortality rate of 2.1%. Although these mortality rates are comparable with our results, the insulin-free event rate is more than twice as great as in our study. This finding can be explained possibly by the fact that our meta-analyses only included 2 overlapping articles with Dong et al[6] and six with Wu et al.[7] The present review excluded several studies, because they performed TP-IAT for indications other than CP. It is known that CP leads to the destruction of pancreatic parenchyma, thus hampering the harvest of islets. One systematic review without meta-analysis included 5 studies, all of which reported on insulin use and 2 on opioid use.[26] As in the current study, the insulin-free rate ranged widely from 10% to 64%.

Studies that included pediatric patients who underwent TP-IAT were excluded in our systematic review to avoid heterogeneity. Compared with the adult patients, the effect of TP-IAT in pediatric patients is much better with opioid-free rates sustained between 80% and 90% and insulin independence in 41% of the patients with good QoL.[27,28]

This review has several limitations. First, most of the included studies are retrospective, observational studies, which may have led to underreporting on complications. Second, we noted high heterogeneity in 4 of our meta-analyses (82%–97%). The metaregression analysis also included only a small number of studies. Because of inconsistent reporting, it was not possible to extract specific data about the indication for operation and the timing of the operative intervention. Together with the wide range in duration of follow-up in the meta-analysis at the last registered follow-up, this consideration contributes possibly to the high heterogeneity. Third, preoperative opioid and insulin use was not reported in all studies. Therefore, no correction for preoperative opioid and insulin use could be performed; however, the metaregression analysis showed no correlation between preoperative use

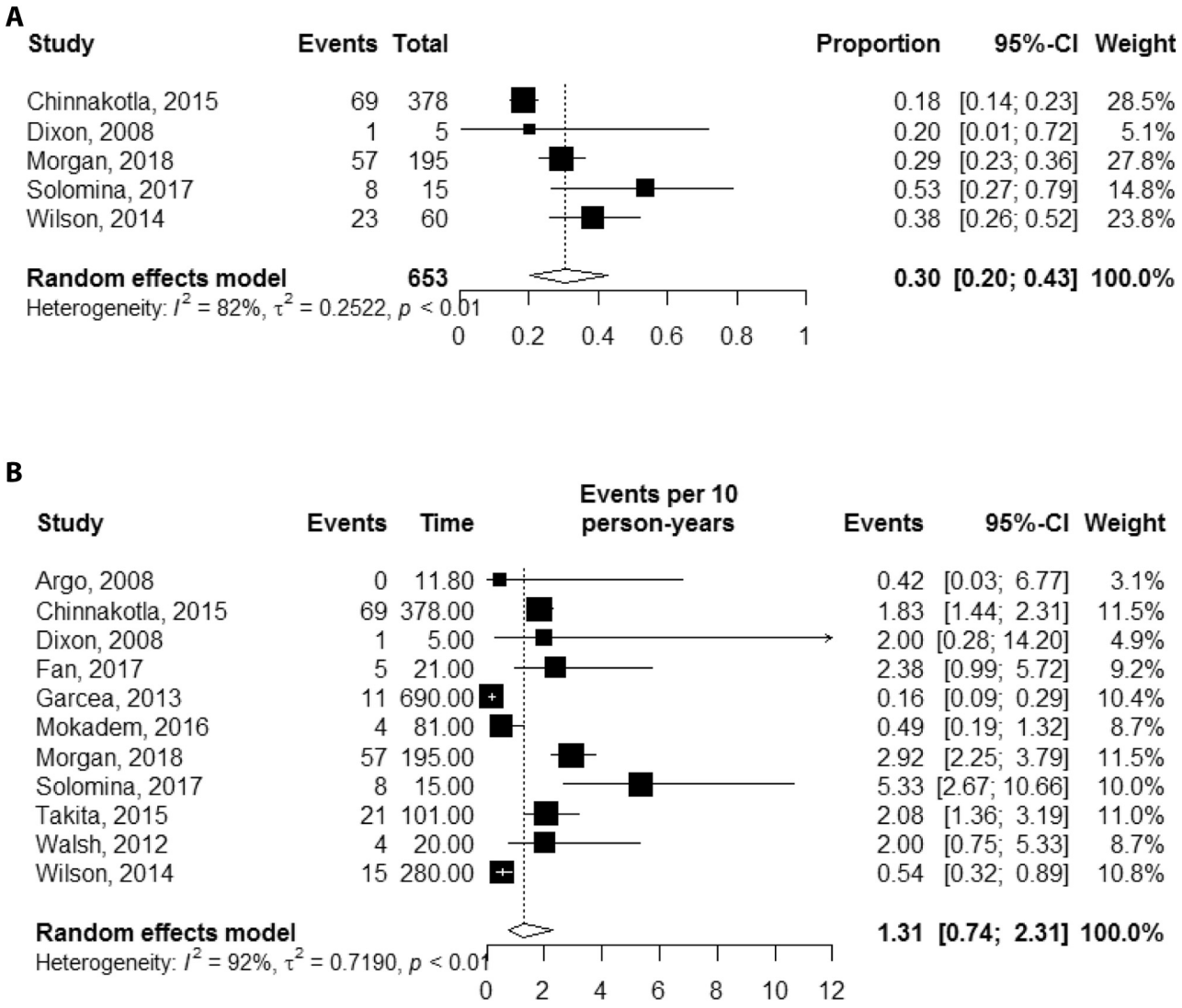

Fig 3. Forest plots of insulin-free rates. (*A*) Meta-analysis at 1-year follow-up; (*B*) meta-analysis at last follow-up, presented as event rates per 10 person-years.

of opioids or insulin and postoperative use of opioids or insulin. Fourth, visual inspection of the funnel plots and the statistically significant Egger's test revealed there is a risk for publication bias, favoring a better outcome, which possibly led to overestimated results.

One obvious area of concern is the exact indication for TP-IAT. In most of the studies included in this review, the indication for TP-IAT was painful CP refractory to narcotics and endoscopic treatment. Some 13% to 100% of patients were even refractory to operative treatment (eg, lateral pancreatojejunostomy). In none of the studies, however, was the specific indication and correlation with postoperative outcome given. Therefore, the effect of TP-IAT in specific indications still remains unclear. In most of the included studies, it is not well described what type of CP is treated with this procedure (eg, dilated duct disease versus small duct disease). This consideration is especially concerning because most of the studies did not describe the opioid-free rate before TP-IAT. In a large series of 223 CP patients with tailored operative procedures (ie, excluding TP) with a median follow up of a 5-year, opioid-free rate was 66% and increased to 83%. The insulin-free rate decreased from 87% to 63%.[29]

Another point of heterogeneity is the varying timing of intervention between studies. In some studies, TP-IAT was performed as a last-resort option when other therapies, including operative therapy, had failed. This consideration definitely has influenced the results because an early operation is more likely to result in a high islet yield. In most patients, however, TP-IAT was performed as the primary operative therapy after only medical and endoscopic therapy had failed. For patients with TPI-AT as a last-resort option, the outcomes of our meta-analyses are potentially too beneficial.

Subanalyses between primary operative therapy and completion TP-IAT was not possible because most studies used aggregated data. Future research should focus on the indications and timing of the intervention of TP-IAT. Moreover, this procedure has to be compared with other operative treatments such as pancreatic head resection or a drainage procedure (eg, lateral pancreatojejunostomy, duodenum-preserving pancreatic head resection).

The insulin-free rate after TP-IAT was relatively low in our analysis and most likely related to CP. An alcoholic etiology of CP was associated with a lesser insulin-free rate after TP-IAT. In the included studies, the diabetes mellitus seems to be mostly

controlled with a relative low dosage of insulin. Potentially, patients who are insulin dependent after TP-IAT have a stable diabetes mellitus without episodes of hypoglycemia; however, in the included studies, information about the severity of diabetes mellitus or the frequency of treatment needed for diabetes mellitus is lacking. Therefore, further research into insulin-free rates and complications of the diabetes at long-term follow-up is needed to investigate long-term complications of this specific type of diabetes mellitus, type 3.[30,31]

In conclusion, although TP-IAT seems safe, its exact indication and optimal timing in patients with painful CP remains unclear. The current body of evidence is suboptimal because essential baseline characteristics (ie, opioid use and insulin use) were missing in 40% of studies. Also, technical details from previous treatments are lacking. It appears that TP-IAT in CP may, at the most, achieve opioid-free rates of 63%, and most patients develop insulin-dependent diabetes. Future research should therefore focus on the selective indication and timing of TP-IAT in CP.

Conflict of interest

The authors have indicated that they have no conflict of interest regarding the content of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2019.03.014.

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