Supplement to HaPanEU – UEG evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis

List of Abbreviations

ADA	American Diabetes Association
AGA	American Gastroenterological Association
AIP	Autoimmune pancreatitis
ALP	Alkaline phosphatase
APA	American Pancreas Association
BMD	Bone mineral density
BMI	Body mass index
BS	Biliary stricture
CBD	Common bile duct
CCK	Cholecystokinin
CEA	Carcinoembryonic antigen
CEH-EUS	Contrast-enhanced harmonic EUS
CEL	Carboxyesterlipase
CEUS	Contrast-enhanced EUS
CFA	Coefficient of fat absorption
CFTR	Cystic fibrosis transmembrane conductance regulator
CI	Confidence interval
^{13}C-MTG-BT	^{13}C mixed triglyceride breath test
CP	Chronic pancreatitis
CPA1	Carboxypeptidase A1
CT	Computed tomography
CTRC	Chymotrypsin C
DF	Duodenal filling
DPPHR	Duodenum-preserving pancreatic head resection
DXA	Dual energy X-ray absorptiometry
EMA	European Medicines Agency
ENSP	European Network for Smoking and Tobacco Prevention
EORTC	European Organization for the Research and Treatment of Cancer
EPC	European Pancreas Club
ERCP	Endoscopic retrograde cholangiopancreatography
ESGE	European Society of Gastrointestinal Endoscopy
ESPEN	European Society of Clinical Nutrition and Metabolism
ESWL	Extracorporeal shock wave lithotripsy
ERP	Endoscopic retrograde pancreatography
ET	Endoscopic therapy
EUS	Endoscopic ultrasound
FC-SEMS	Fully-covered self-expandable metallic stent
FDA	Food and Drug Administration
FFMI	Fat-free mass index
FE-1	Fecal elastase-1
FPG	Fasting plasma glucose
FIP	Fédération Internationale Pharmaceutique
GEL	granulocytic epithelial lesions
GQLI	Gastrointestinal Quality of Life Index
GRADE	Grading of Recommendations Assessment, Development & Evaluation
HaPanEU	Harmonizing Pancreatitis across Europe

IAP	International Association of Pancreatology
IDCP	Idiopathic duct centric pancreatitis
IDDM	Insulin-dependent diabetes mellitus
IM	Intramuscular
IPMN	Intraductal papillary mucinous neoplasm
IV	Intravenous
LPSP	Lymphoplasmocytic sclerosing pancreatitis
MCN	Mucinous cystic neoplasm
MCS	Mental component score
MCT	Medium chain triglyceride
MDCT	Multidetector-row computed tomography
MPD	Main pancreatic duct
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
MUST	Malnutrition universal screening tool
NAPS2	North American Pancreatitis Study 2
NCCT	Non-contrast enhanced computed tomography
NIDDM	Non-IDDM
NRS-2002	Nutritional risk screening 2002
NSAID	Non-steroidal anti-inflammatory drug
OGTT	Oral glucose tolerance test
OR	Odds ratio
PD	Pancreatoduodenectomy
PEI	Pancreatic exocrine insufficiency
PERT	Pancreatic enzyme replacement therapy
PFT	Pancreatic function test
PhEur	European Pharmocopoeia
PHPT	Primary hyperparathyroidism
PPI	Proton pump inhibitor
PRSS1 & 2	Cationic trypsinogen genes 1 & 2
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
QoL	Quality of Life
RCT	Randomized controlled trial
SEMS	Self-expandable metallic stent
SGLT-2	Sodium glucose co-transporter-2
s-MRCP	Secretin-stimulated MRCP
SNP	Single nucleotide polymorphism
SPINK1	Serine protease inhibitor Kazal type 1
SR	Systematic review
T3cDM	Type 3 diabetes mellitus
TED	Test and Evaluation Directorate
TM	Transmural
TP	Transpapillary
TPIAT	Total pancreatectomy with islet autotransplantation
UEG	United European Gastroenterology
USP	United States Pharmacopeia
VAS	Visual analog scale
WOPN	Walled-off pancreatic necrosis
WHO	World Health Organization

GRADE system

http://www.uptodate.com/home/about/tutorial/index.html (30 min tutorial)

http://www.uptodate.com/home/about/policies/grade.html

GRADE system: Step 1, grade the evidence

A= high quality evidence

B= moderate quality evidence

C= poor quality evidence

If RCTs, start by assuming high quality (grade A), but then grade down for:

- Serious methodologic limitations
- Indirectness in population, intervention, or outcome
- Inconsistent results
- Imprecision in estimates
- High likelihood of publication bias

If no RCTs, start by assuming low quality (grade C), but then grade up for:

- Large, or very large treatment effects
- All plausible biases that would diminish the effect of the intervention
- Dose-response gradient

GRADE system: Step 2, grade the recommendation

1= strong recommendation

2= weak recommendation

Table S1: Narratives detailing the evidence and grade of recommendations

Grade of Recommendation	Clarity of risk/benefit	Quality of supporting evidence	Implications
1A. Strong recommendation. High quality evidence.	Benefits clearly outweigh risk and burdens, or vice versa.	Consistent evidence from well-performed RCTs or overwhelming evidence in some other form. Further research is unlikely to change our confidence in estimating benefit and risk.	Strong recommendation, can apply to most patients in most circumstances without reservation.
1B. Strong recommendation. Moderate quality evidence.	Benefits clearly outweigh risk and burdens, or vice versa.	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence in some other form. Further research (if performed) is likely to have an impact on our confidence in estimating benefit and risk and may change the estimate.	Strong recommendation, likely to apply to most patients.
1C. Strong recommendation. Low quality evidence.	Benefits appear to outweigh risk and burdens, or vice versa.	Evidence from observational studies, unsystematic clinical experience, or from RCTs with serious flaws. Any estimate of effect is uncertain.	Relatively strong recommendation; might change when higher quality evidence becomes available.
2A. Weak recommendation. High quality evidence.	Benefits closely balanced with risks and burdens	Consistent evidence from well performed RCTs or overwhelming evidence in some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.	Weak recommendation, best action may differ depending on circumstances or patients or social values.
2B. Weak recommendation. Moderate quality evidence.	Benefits closely balanced with risks and burdens, some uncertainly in the estimates of benefits, risks and burdens	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence in some other form. Further research (if performed) is likely to have an impact on our confidence in estimating benefit and risk and may change the estimate.	Weak recommendation, alternative approaches likely to be better for some patients under some circumstances.
2C. Weak recommendation. Low quality evidence.	Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens.	Evidence from observational studies, unsystematic clinical experience, or from RCTs with serious flaws. Any estimate of effect is uncertain.	Very weak recommendation; other alternatives may be equally reasonable.

Note: the abovementioned guideline for grading evidence is specifically directed at therapeutic studies. For studies on diagnostic accuracy, the GRADE system suggests different criteria. Valid diagnostic accuracy studies – cross-sectional or cohort studies in patients with diagnostic uncertainty and direct comparison of test results with an appropriate reference standard – provide high quality evidence. However, they often are downgraded to lower quality evidence based on an assessment of limitations, particularly indirectness of outcomes, i.e. uncertainty about the link between the test accuracy and outcomes that are important to patients, inconsistency, imprecision and publication bias. For background and specific instructions on the GRADE system in evaluating diagnostic questions, see Schünemann, et al. (1).

Table S2*: Estimated overall sensitivity, specificity, and heterogeneity per imaging modality

Modality	No. of studies	No. of patients	Sensitivity (95%CI)	Specificity (95%CI)	Heterogeneity (I^2)
EUS	15	1181	82% (71%-90%)	91% (83%-95%)	82% / 75%
MRCP	14	933	78% (69%-85%)	96% (90%-98%)	59% / 65%
ERCP	11	742	82% (76%-87%)	94% (87%-98%)	39% / 67%
CT	10	700	75% (66%-83%)	91% (81%-96%)	50% / 71%
US	10	1005	67% (53%-78%)	98% (89%-100%)	40% / 93%

Random effects model. *from (2)

Table S3*: Head-to-head comparison of imaging modalities

Comparison	No. of studies	No. of patients	Modality	Sensitivity (95% CI)	Specificity (95% CI)
US vs ERCP**	6	423	**US**	57% (49%–65%)	94% (74%–99%)
			ERCP	78% (71%–85%)	98% (89%–100%)
US vs CT***	5	297	**US**	58% (49%–66%)	77% (71%–83%)
			CT	77% (68%–83%)	82% (74%–88%)
CT vs ERCP***	5	354	**CT**	75% (67%–82%)	86% (81%–90%)
			ERCP	84% (77%–89%)	90% (85%–93%)
EUS vs ERCP***	3	214	**EUS**	88% (80%–93%)	85% (76%–91%)
			ERCP	86% (78%–91%)	92% (85%–96%)
MRCP vs sMRCP***	3	226	**MRCP**	62% (49%–73%)	94% (89%–97%)
			sMRCP	68% (56%–79%)	91% (85%–94%)
EUS vs US***	2	95	**EUS**	90% (82%–98%)	100%
			US	63% (49%–76%)	91% (82%–99%)

*from (2); **Random effects model; ***Fixed effects model

Sensitivity: US vs ERCP ($p<0.001$), US vs CT ($p=0.002$), EUS vs US ($p=0.001$)

Specificity: US vs ERCP ($p=0.003$), EUS vs US ($p=0.04$)

Table S4: Characteristics of studies and results of Roux-en-Y pancreaticojejunostomy

Author (ref)	Year	Study design	No. of patients	WJ only WJ+Frey Frey only	Perioperative Mortality (%)	Mean Follow-up (months)	Pain relief (complete or partial)
Delcore et al. (3)	1994	retro	28	WJ	0%	42	86%
Adams et al.	1994	retro	85	WJ	0%	76	68%
Hakaim et al. (22)	1994	retro	23	WJ	0%	62	60%
Frey et al. (6)	1994	retro	50	Frey	0%	37	87%
Sielezneff et al. (23)	2000	retro	57	WJ	0%	65	84%
Sakorafas et al. (24)	2000	retro	120	WJ	0%	96	81%
Paye et al. (25)	2001	retro	37	WJ+Frey	2.7%	52	70%
Boerma et al. (26)	2002	retro	50	WJ	0%	27	88%
Nealon et al. (17)	2003	retro	103	WJ	0%	73	87%
Falconi et al. (27)	2006	prosp	40	Frey	0%	60	90%
Pessaux et al. (28)	2006	retro	34	Frey	0%	15	88%
Terrace et al. (9)	2007	retro	50	WJ+Frey	4%	36	71%
Cahen et al. (4)	2007	RCT	20	AWJ	0%	24	75%
Sakata et al. (15)	2009	retro	57	Frey	0%	61	77%
Roch et al. (29)	2012	prosp	44	Frey	0%	76	68%
Van der Gaag et al. (30)	2012	prosp	146	AWJ	0.7%	63	87%
Cooper et al. (31)	2013	prosp	35	Frey	3%	22	79%
Pothula Rajendra et al. (14)	2014	prosp	25	Frey	0%	12	92%

Retro = retrospective; prosp = prospective; RCT = randomized controlled trial; WJ = wirsungojejunostomy; Frey = Frey's procedure

Table S5: Surgical procedures in Groove pancreatitis

Author (ref)	*Type of study*	*Year*	*Surgery (No of cases)*	*Type of surgery*	*Pain Resolution/ Relief*	*Body weight gain*	*Pain recurrence*	*Grade of recommendation*
Casetti (4)	Observational cohort study	2009	58	PD	58/58 (100%)	Increased post-op median BMI	11/58 (24%)	1C
Vullierme (5)	Retrospective	2000	20	PD	nr	nr	nr	2C
Rebours (6)	Observational cohort study	2007	29	PD Double bypass	27/29 (93%)	nr	2/29 (7%)	1C
Jouannaud (7)	Observational cohort study	2006	14	PD Double bypass Drainage Gastroenterostomy	14/14 (100%)	nr	nr	1C
Egorov (8)	Observational cohort study	2014	52	PD DPHR PPDR Drainage	36/52 (69%)	100%	nr	1C

nr: not reported; PD: pancreaticoduodenectomy; DPHR: duodenum-preserving pancreatic head resection; PPDR: pancreas-preserving duodenal resection; BMI: body mass index.

Table S6: Studies in PERT with gastric acid suppression

Ref. Author (year)	Intervention	Study design	No. of patients (total)	Main outcome, follow-up time	Main results	Grade
Bruno 1994 (9)	Comparative effects of adjuvant cimetidine and omeprazole during PERT.	Double-blind, randomized, crossover	10	Fecal fat excretion, PERT+cimetidine vs. PERT+omeprazole	Both therapies significantly lowered fat excretion compared to single PERT; omeprazole showed a trend towards a greater decrease, but not significant	Moderate
Carroccio 1992 (10)	Use of famotidine in severe EPI with persistent maldigestion on PERT, a long-term study in CF.	Prospective, double-blind, crossover	10	Famotidine vs. Placebo, 2x6-month periods	Significant reduction in fecal wet weight, improvement of CFA and steatocrit test.	Moderate
Dominguez-Munoz, 2006 (11)	Optimizing the therapy of EPI by the association of a PPI with enteric-coated pancreatic extracts	Prospective monocenter cohort study, unblinded	21	13C-MTG-BT at diagnosis, Creon (3x40000) after 3 months and + 40 mg esomeprazole after 2 extra weeks.	Significant increase in 13C-exhalation with Creon, no further increase with added PPI for total group, but no effect in patients who normalized fat digestion with Creon only (n=12); further improvement in others (n=9).	Moderate
Durie, 1980 (12)	Effect of cimetidine and sodium bicarbonate on PRT in CF.	Monocenter, randomized crossover study	15	Pancrelipase vs. pancrelipase + sodium bicarbonate vs. pancrelipase + cimetidine vs. pancrelipase + sodium bicarbonate + cimetidine.	Significant reduction of fat and nitrogen excretion with additional drugs compared to pancrelipase alone and no significant differences between additional therapies; different intakes.	Moderate
Lankisch, 1986 (13)	Therapy of pancreatogenic steatorrhea: does acid protection of pancreatic enzymes offer any advantage?	Randomized controlled cross-over study	8	Pankreon vs. pankreon + cimetidine vs. creon	Significantly higher effect with pankreon+cimetidine and with creon than with conventional enzyme therapy alone.	Moderate
Regan, 1977 (14)	Comparative effects of antacids, cimetidine and enteric coating on the therapeutic response to oral enzymes in severe pancreatic insufficiency	Case-control study (with and without treatment)	6	Steatorrhea; duodenal enzyme outputs (intubation technique)	Steatorrhea abolished in 4 patients, reduced in all; significantly higher postprandial recoveries and concentrations of trypsin and lipase with pancreatin + cimetidine; EC-preparation and EC-preparation + antacids are not more effective than pancreatin alone.	Moderate
Sander-Struckmeier 2013 (15)	Retrospective analysis to investigate the effect of concomitant use of gastric acid suppressing drugs on the efficacy and safety of pancrelipase/ pancreatin (CREON) in patients with EPI.	Systematic review (retrospective analysis) of Abbott data base	337 patients with acid suppression, 619 without	CFA	CFA similar in patients with and without concomitant use of PPIs/H2RAs	Moderate

Table S7: Selected retrospective studies assessing long-term results of ESWL combined with endotherapy

First author, Year (Ref.)	No.	*Pain relief	Pain relapse	Surgery	Follow up (months)
Delhaye, 2004 (16)	56	85%	NR	22%	172
Tadenuma, 2005 (17)	70	70%	37 %	1.4%	77
Clarke, 2012 (18)	55	51%	NR	31%	58
Seven, 2012	120	85%	29%	12%	52
Tandan, 2013 (19)	272	96%	40 %	9%	>60

NR, not reported

*Partial or complete pain relief at the end of follow-up

Table S8: Pancreatic stenting for strictures of the main pancreatic duct

	Selected retrospective studies (follow-up ≥24 months) assessing results of single plastic stenting for symptomatic dominant MPD stricture related to chronic pancreatitis			
Author, year (Ref)	**No. of patients**	**Type of stent**	**Pain improvement after stent removal**	**Follow-up (months)**
Binmoeller, 1995 (20)	93	Single (5–7–10 Fr)	65%	58
Smits, 1995 (21)	49	Single (10 Fr)	82%	34
Vitale, 2004 (22)	89	Single (5–7–10 Fr)	68%	43
Eleftheriadis, 2005 (23)	100	Single (8.5–10 Fr)	62%	69
Weber, 2007 (24)	17	Single (7–8.5–10–11.5 Fr)	83%	24
	Prospective study assessing results of multiple plastic stenting for symptomatic refractory dominant MPD stricture related to chronic pancreatitis			
Costamagna, 2006 (25)	19	Multiple (10–11,5 Fr)	84%	38
	Prospective studies assessing results of FC-SEMS for symptomatic refractory dominant MPD stricture related to chronic pancreatitis			
Park, 2008 (26)	13	FC-SEMS (Niti D-type)	NR	5
Sauer, 2008 (27)	6	FC-SEMS (Viabil)	67%	NR
Moon, 2010 (28)	32	FC-SEMS (Niti-S, bumpy type)	84%	5
Giacino, 2012 (29)	10	FC-SEMS (1 biliary WST, 9 biliary WFX)	90%	19.8

NR: Not reported

Table S9: Mid-term results of endoscopic treatment in pediatric patients with CP

Author, year (Ref)	No. of patients	Complete pain relief	Partial pain relief	Surgery	Follow-up (months)
Agarwal, 2014 (30)	126	63.6%	21.6%	2%	13
Li, 2010 (31)	42	57%	14%	12%	61
Oracz, 2014 (32)	72	NR**	NR**	14%	54

NR, not reported
*All patients had pancreatic stenting
** The number of pancreatitis episodes per year decreased significantly decreased, from 1.75 to 0.23, after pancreatic stent placement

Table S10: Studies on pain in chronic pancreatitis

Author (Ref)	Year	Design	Timing groups	No. of patients	Follow-up	End-points	Quality assessment
Ahmed Ali (1)	2012	Cross-sectional survey	- ≤3 vs. 3 years - Preoperative use of opioids - <5 endoscopic interventions vs more	266	Median 62 months	- Pain relief (VAS<4) - Pancreatic function - Quality of life	+ Large N + Adequate follow-up duration + Patient's questionnaire - Partly retrospective cohort - Excluded patients with no follow-up
Yang2Yang (2)	2015	Retrospective cohort	- ≤26.5 vs. > 26.5 months	66	All 3 years	- Pain free status - Opioid use - Pancreatic insufficiency	- Small N + Adequate follow-up duration - Only chart review (no questionnaires) - Retrospective design - Excluded patients with no follow-up
Riediger (3)	2007	Cross-sectional survey	- ≤3 vs. > 3 years	224	Median 56 months	- Pain (Y/N, >weekly)	+ Large N + Adequate follow-up duration + Patient's questionnaire + Prospective cohort - Excluded patients with no follow-up - Not focused on timing issue
Nealon (4)	1993	RCT	- Surgical drainage vs. conservative	37	Median 124 months	- Pain relief (partial, complete) - Pancreatic function	- Unclear randomization technique + Follow-up complete - No sample size (pilot study) - No interventions in the control arm
(5)	2014	IPD MA (of Dite 2003 & Cahen 2007)	- Early vs. late surgery (not clearly defined)	406	Unclear	- Pain relief (partial or complete)	+ Meta-analysis of raw data + Large N + Prospective data - Unclear cut-off point - Unclear definition of end-point

Outcomes:

Study	No.	Factor	Summary statistic	Results
Pain relief				
Ahmed Ali 2012 (1)	259	≤3 vs. >3 years	OR (multivariate)	**1.81 (1.02-3.37), P=0.03**
	No preoperative opioid use	OR (multivariate)	**2.14 (1.23-3.96), P=0.006**	
	Endoscopic treatment (<5)	OR (multivariate)	**2.46 (1.10-6.27), P=0.04**	
Yang 2015 (2)	66	≤26.5 vs. >26.5 months	% Pain free	**58% vs. 23%, P<0.001**
	≤26.5 vs. >26.5 months	% Postoperative opioid use	**36% vs. 57%, P=0.05**	
Riediger 2007 (3)	224	≤3 vs. >3 years	% Pain (any frequency)	37% vs. 43%, P=0.41
	≤3 vs. >3 years	% Weekly or daily pain	13% vs. 15%, P=0.66	
Nealon 1993 (4)	37	Surgery vs. no surgery (conservative)	% Pain relief (any)	**16 (94%) vs. 2 (13%), P<0.001**
		% Complete pain relief	**14 (82%) vs. 0 (0%), P<0.001**	
		% Partial pain relief	2 (12%) vs. 2 (13%), NS	
Yang 2014 (5)	406	Early vs. late surgery	RR (IPD MA)	**1.67 (1.09–2.56), P=0.02**
Exocrine pancreatic function				
Yang 2015 (2)	66	≤26.5 vs. >26.5 months	% exocrine pancreatic function	42% vs. 60%, P=0.22
Riediger 2007	224	≤3 vs. >3 years	% exocrine	**54% vs. 75%, P=0.001**

(3)			pancreatic function	
Riediger 2007 (3)	224	≤3 vs. >3 years	OR (multivariate)	**2.47 (1.38-4.41), P=0.002**
Nealon 1993 (4)	29	Surgery vs. no surgery (conservative)	% new onset exocrine insufficiency	**1 (7%) vs. 11 (79%), P<0.001**
Endocrine pancreatic function				
Ahmed Ali 2012 (1)	258	≤3 vs. >3 years	OR	**0.57 (0.33-0.96), P=.04**
Yang 2015 (2)	66	≤26.5 vs. >26.5 months	% endocrine pancreatic function	48% vs. 49%, P=0.99
Riediger 2007 (3)	224	≤3 vs. >3 years	% endocrine pancreatic function	49% vs. 58%, P=0.15
Nealon 1993 (4)	25	Surgery vs. no surgery (conservative)	% new onset endocrine insufficiency	**2 (15%) vs. 10 (83%), P=0.001**
Quality of life				
Ahmed Ali 2012 (1)		Preoperative opioid use	WMD, SF-36, physical composed score	**−4.81 (−7.36 to −2.28), P<0.001**
	Preoperative opioid use		WMD, SF-36, mental composed score	**−5.34 (−8.01 to −2.70), P<0.001**

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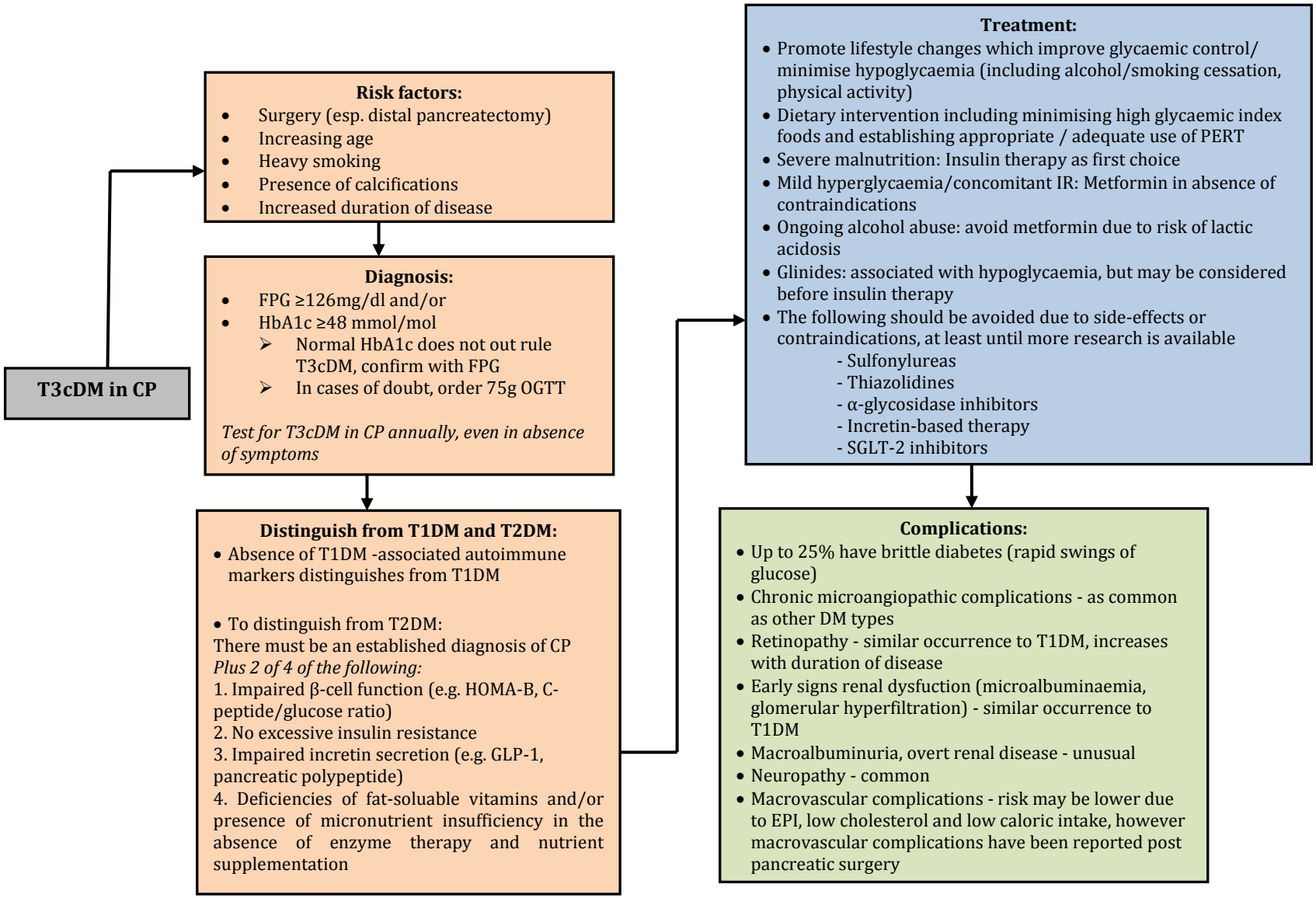
Figure S1: Type 3c Diabetes mellitus



FPG: fasting plasma glucose, T3cDM: type 3c diabetes mellitus, CP: chronic pancreatitis, OGTT: oral glucose tolerance test, PERT: pancreatic enzyme replacement therapy, IR: insulin resistance, T1DM: type 1 diabetes mellitus, T2DM: type 2 diabetes mellitus, EPI: exocrine pancreatic insufficiency

Appendix

Ad 4.1 Surgery

In-depth comparison of studies comparing surgery and endoscopic therapy in chronic pancreatitis

Characteristics of included studies

Cahen 2007

Methods	*Study design*: RCT *Setting of study*: single center, AMC Amsterdam, the Netherlands. *Follow-up period*: 24 months, with a second long-term publication after minimal follow-up of 5 years. Loss to follow-up (2 years follow-up): 1 patient in the surgical group. Loss to follow-up (5 years follow-up): 3 patient in the endoscopy group, and 5 patients in the surgery group. *Type of analysis*: intention-to-treat analysis. *Sample size calculations*: yes, a sample size of 50 patients was calculated.
Participants	*Number of participants*: 39 (19 in the endoscopy group, 20 in the surgical group). *Gender*: endoscopy group: 11 males, 8 females; surgery group: 15 males, 5 females. *Age [mean (SD)]*: endoscopy group: 52 years (9); surgery group: 46 years (12). *BMI [mean (SD)]*: endoscopy group: 21 kg (4.1); surgery group: 21 kg (3.7) *Type of pain*: *endoscopy group*: 7 patients with intermittent pain (type A), 12 patients with continuous pain (type B). *surgery group*: 9 patients with intermittent pain (type A), 11 patients with continuous pain (type B). *Inclusion criteria*: Established CP Obstruction of pancreatic duct (>5 mm) No pancreatic head enlargement Severe recurrent pancreatic pain intractable to non-narcotic analgesics *Exclusion criteria*: Age <18 or >80 years Enlargement of pancreatic head >4 cm Contra-indications to surgery or endoscopic interventions Previous pancreatic surgery

	Suspected pancreatic malignancy, or life expectancy <2 years Pregnancy Duration of symptoms: endoscopy group: 16 months (SD 14); surgery group 21 months (SD 19) Ongoing alcohol abuse at randomization: endoscopy group: 0 patients; surgical group: 5 patients. Ongoing smoking at randomization: endoscopy group: 15 patients; surgical group: 17 patients.
Interventions	Endoscopic drainage versus surgical drainage: *Endoscopic drainage*: endoscopic drainage of the pancreatic duct by ERCP with (repeated) dilatation and stent placement if required. Patients with large stones in the pancreatic duct (>7 mm) underwent ESWL before drainage. *Surgical drainage*: surgical drainage of the pancreatic duct by means of a longitudinal pancreaticojejunostomy as intended treatment. In 1 patient, a Whipple procedure was performed because of peripancreatic inflammation. In another patient, stone extraction required a Frey procedure. *Endoscopic experience*: study interventions were performed by experienced endoscopists (performed >1000 ERCPs). *Surgical experience*: surgical procedures were performed by experienced pancreatic surgeons (no specific criteria stated).
Outcomes	*Primary outcome (prespecified in method section)*: Pain score (Izbicki questionnaire) *Secondary outcomes (prespecified in method section)*: Pain relief (defined by Izbicki score) Physical and mental health (SF-36 questionnaires) Post-interventional complications Length of hospital stay Number of performed procedures Change in pancreatic function Mortality *Other outcomes (results reported, but not specified in method section)*: Conversion to surgery Technical success of intervention Hospital re-admittance Time points of outcomes: 6 weeks and 3, 6, 12, 18 and 24 months. Long-term follow-up: minimum of 5 years (mean follow-up was 85 months in the endoscopy and 92 months in the surgery group).
Notes	Study was terminated prematurely by the safety committee on the basis of a significant difference in outcome favoring the surgical group with P<0.001 regarding the primary outcome (pain on the Izbicki pain score). Author provided us with additional methodological information and data.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Automated assignment system.
Allocation concealment (selection bias)	Low risk	Specifically stated.
Blinding (performance bias and detection bias)	High risk	
Incomplete outcome data (attrition bias)	Low risk	Proportion of loss to follow-up did not exceed 20%.
Selective reporting (reporting bias)	Low risk	All relevant and pre-specified outcomes reported.
Other bias	Low risk	Study terminated prematurely, but authors performed adequate adjustment for treatment effect and P value for early termination.

Dite 2003

Methods	*Study design*: pseudo-RCT (alternating allocation) *Setting of study*: single center, University Hospital Brno, Czech Republic *Follow-up period*: 5 years *Loss to follow-up*: patients not compliant to follow-up were excluded *Type of analysis*: per protocol analysis *Sample size calculation*: yes, a sample size of 140 patients was calculated.
Participants	*Number of randomized participants*: 72 (36 in the endoscopy group, 36 in the surgical group). The population of the RCT is part of a larger prospective cohort reported in the same publication. The total sample of the cohort is 140. *Gender*: not specified for the randomized group (only for the complete cohort, with 119 males and 21 females). *Age*: not specified for the randomized group (only for the complete cohort with a mean age of 41.7 years ranging between 26–53). *BMI*: not specified *Type of pain (continuous vs recurrent flair ups)*: not specified. *Inclusion criteria*: Established CP Obstruction of pancreatic duct (dilated pancreatic duct) Painful CP (pain score >3 on the Melzack's pain score). Failure of conservative management in the previous 3 years. Duration of clinical CP >5 years Consensus of surgeon and gastroenterologist regarding suitability of patient for both endoscopy and surgery. *Exclusion criteria*:

	Age <18 or >70 years Previous interventional therapy for CP (surgery, endoscopy or nerve block). Suspected pancreatic malignancy. Non-compliance to follow-up examinations. Pregnancy. Duration of symptoms: >5 years (inclusion criteria). Ongoing alcohol abuse and/or smoking at randomization: not reported.
Interventions	*Endoscopic drainage versus surgical intervention (drainage and resection):* *Endoscopic drainage*: endoscopic drainage of the pancreatic duct by ERCP with pancreatic sphincterotomy, stone extraction, dilation of strictures and stenting, as appropriate. ESWL was not applied as part of the endoscopic intervention. *Surgical intervention*: choice of operation was dependent on the morphology of the pancreas on pre-operative imaging. Pancreaticojejunostomy was performed in patients with absence of focal pancreatic enlargement. In patients in whom disease was limited predominantly to the pancreatic head, either duodenum-preserving pancreatic head resection or pancreatoduodenectomy (Whipple resection) were performed. CP predominantly affecting the pancreatic tail was treated by left pancreatic resection. *Endoscopic experience*: study interventions were performed by 2 experienced endoscopists (performed >200 drainage procedures). *Surgical experience*: surgical procedures were performed by 1 abdominal surgeon (performed 90 pancreatic operations before the start of the study).
Outcomes	*Primary outcome (prespecified in method section)*: Pain relief (defined by Melzack score) Necessity for further interventions *Secondary outcomes (prespecified in method section):* Change in body weight Presence of diabetes *Other outcomes (results reported, but not specified in method section)*: Complications Mortality Time points of outcomes: 6 months and 1, 3 and 5 years.
Notes	The population of the RCT is part of a larger prospective cohort reported in the same publication. Author provided us with additional information regarding methodology of the study, but not with additional data regarding missing baseline characteristics and outcomes.

Risk of bias table

Bias	Authors'	Support for judgement

	judgement	
Random sequence generation (selection bias)	High risk	Allocation by alternation.
Allocation concealment (selection bias)	High risk	
Blinding (performance bias and detection bias)	High risk	
Incomplete outcome data (attrition bias)	High risk	Patients not compliant to follow-up were excluded.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported.
Other bias	Unclear risk	The study did not present a baseline table with relevant patient characteristics and potential confounders (e.g. smoking, alcohol use, pre-operative pain, etc). Study allowed for inclusion of patients with enlarged pancreatic head. These patients potentially benefit more from surgery than endoscopy, since surgery allows for resection of the inflamed mass while endoscopy does not.

Nealon 1993

Methods	*Study design*: RCT *Setting of study*: single center, The University of Texas Medical Branch, Galveston, Texas. *Follow-up period*: median 124 months *Loss to follow-up*: no *Type of analysis*: intention-to-treat analysis. *Sample size calculations*: no (pilot study)
Participants	*Number of participants*: 32 patients (17 in the surgical group, 15 in the conservative group) *Gender*: not specified *Age [mean]*: 41.7 years in the surgical group, 44.6 in the conservative group *Inclusion criteria*: Established CP Dilation of pancreatic duct Mild, non-debilitating pain Mild to moderate grade of CP: using a self developed grading system (1 point

	for morphology on ERCP, 2 points for exocrine function, 2 points for endocrine function). Patients were categorized as mild/moderate (3 points or less) or severe CP (>3 points). *Exclusion criteria*: not specified *Duration of symptoms*: not specified *Ongoing alcohol abuse at randomization*: not specified for patients within the RCT. *Ongoing smoking at randomization*: not specified
Interventions	*Surgical drainage versus conservative treatment* *Surgical drainage*: surgical drainage of the pancreatic duct by means of a longitudinal pancreaticojejunostomy, with choledochoenterostomy and pseudocyst drainage when deemed necessary. In patients with duodenal obstruction, a gastrojejunostomy was performed as well. *Conservative treatment*: not specified. *Surgical experience*: not specified
Outcomes	*Primary and secondary outcomes (prespecified in method section): not specified as such.* *Outcomes (specified in method section)*: Presence of abdominal pain Grade of CP (using the self-developed grading system described above). *Other outcomes (results reported, but not specified in method section):* Exocrine and endocrine pancreatic function Time points of outcomes: standardized follow-up each 14 to 16 months
Notes	The population of the RCT is part of a larger prospective cohort reported in the same publication. The author only published the results of the first 17 patients. Other data were provided by the author for the purpose of this review.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Last digit of the MRI number was used (odd versus even digits). It is unclear if the numbers generated by such a mechanism are truly random.
Allocation concealment (selection bias)	High risk	
Blinding (performance bias and detection bias)	High risk	
Incomplete outcome data (attrition bias)	Low risk	Proportion of losses to follow-up did not exceed 20%.

Selective reporting (reporting bias)	Low risk	All specified data were reported.
Other bias	Unclear risk	The study did not present a baseline table with relevant patient characteristics and potential confounders.