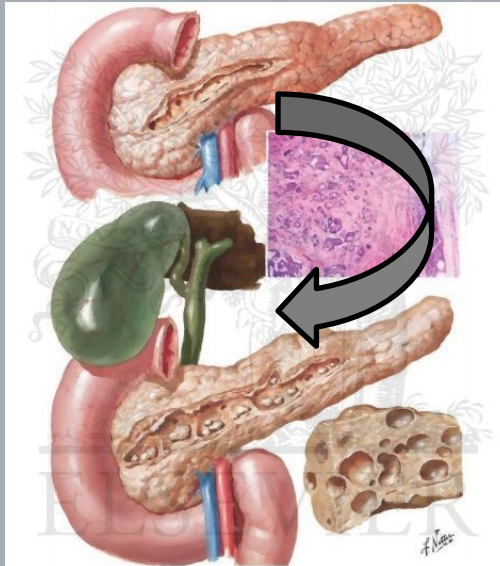


Chronische pancreatitis: pijn en andere complicaties



Marja Boermeester
m.a.boermeester@amc.nl

Chronische pancreatitis (CP)

Chronische progressieve ontstekingsziekte

Irreversibele veranderingen: calcificering/fibrosering

Obstructie en verlies van functie

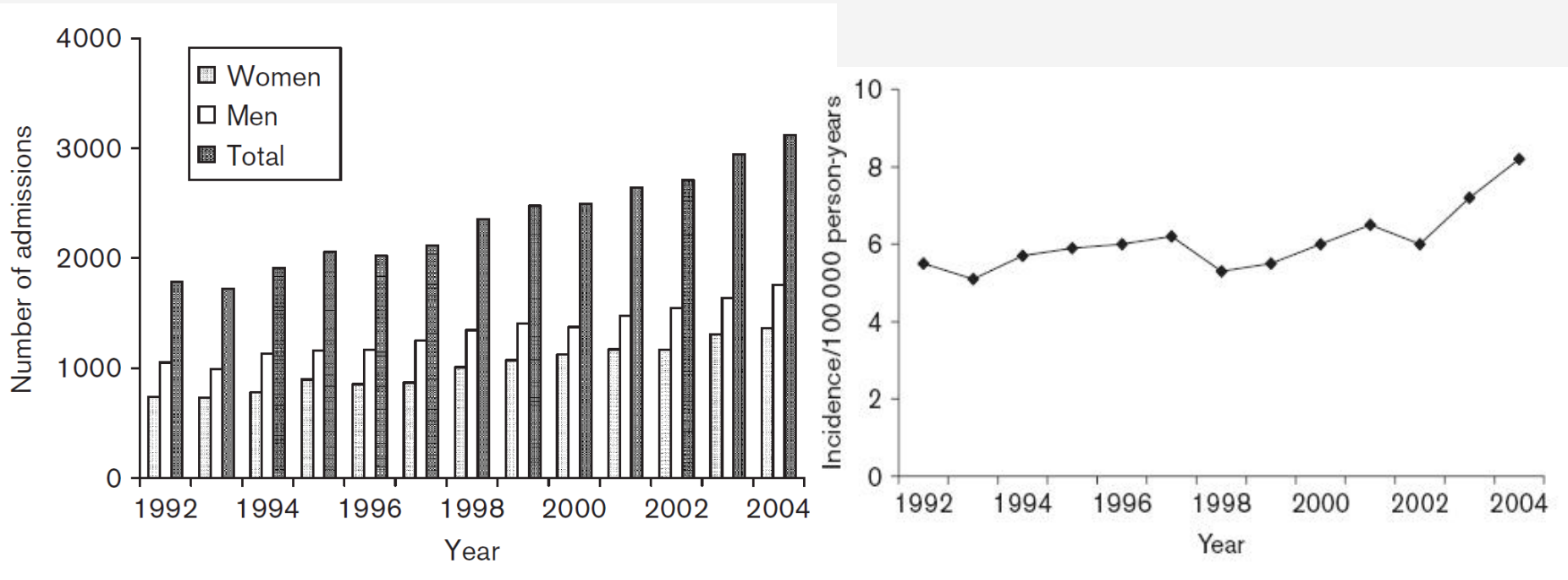
Zeer invaliderende ziekte:

Verminderde kwaliteit van leven

Beperkte (sociaal) functioneren (60%) / werkloos (37%)

Beperkte behandelingsmogelijkheden

CP – epidemiologie NL

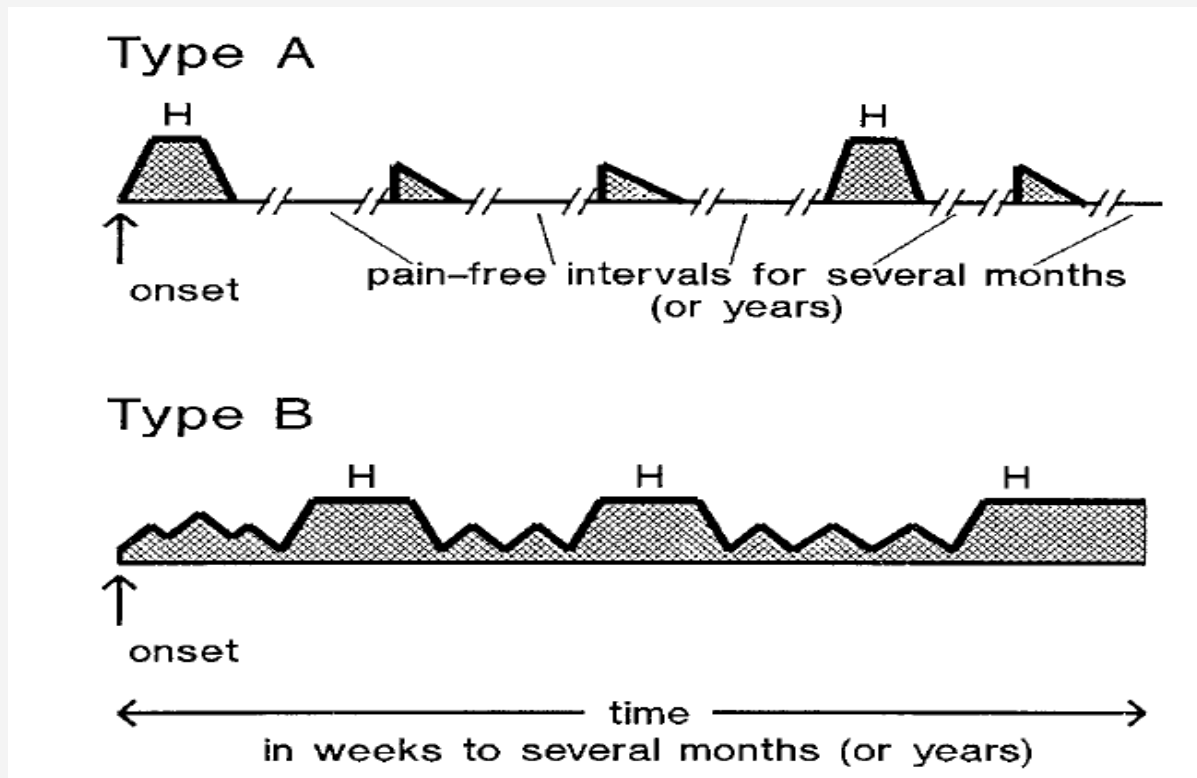


CP - etiologie

- **Alcohol:** **50%**
 - Slechts 5 a 10% van alcohol misbruikers
 - Roken!
- **Idiopatisch:** **25%**
 - Onbekende oorzaak
- **Obstructief:** **7%**
 - Anatomisch: pancreas divisum
- **Genetische factoren:** **3%**
 - Erfelijke pancreatitis
- **Zeldzame oorzaken:**
 - Autoimmuun, hyperlipidemie, hypercalcemie, Sjogren's syndroom

CP - klachten: pijn

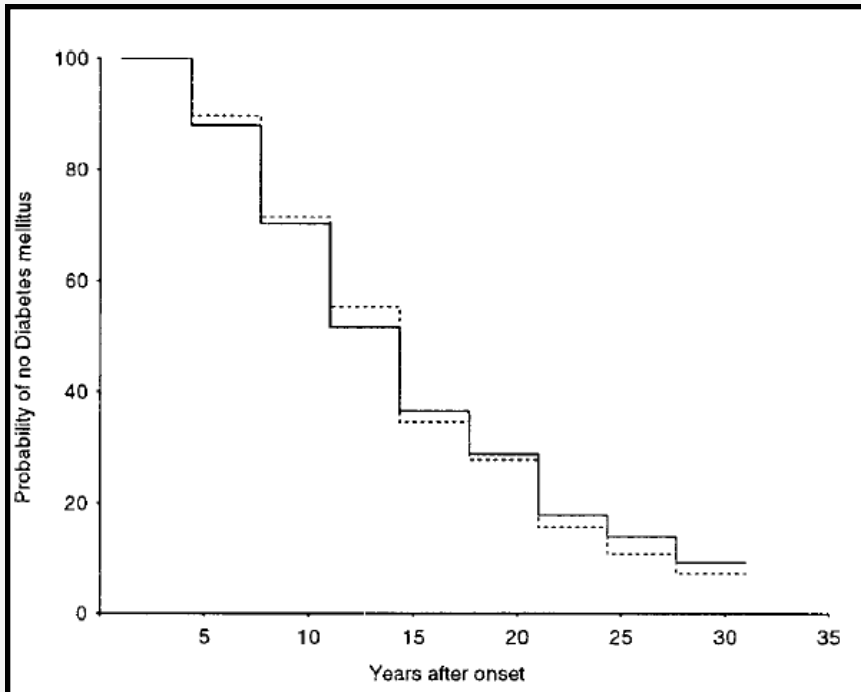
- **Belangrijkste en meest beperkende symptoom**
- **Pijnpatroon:**



CP - klachten: functieverlies

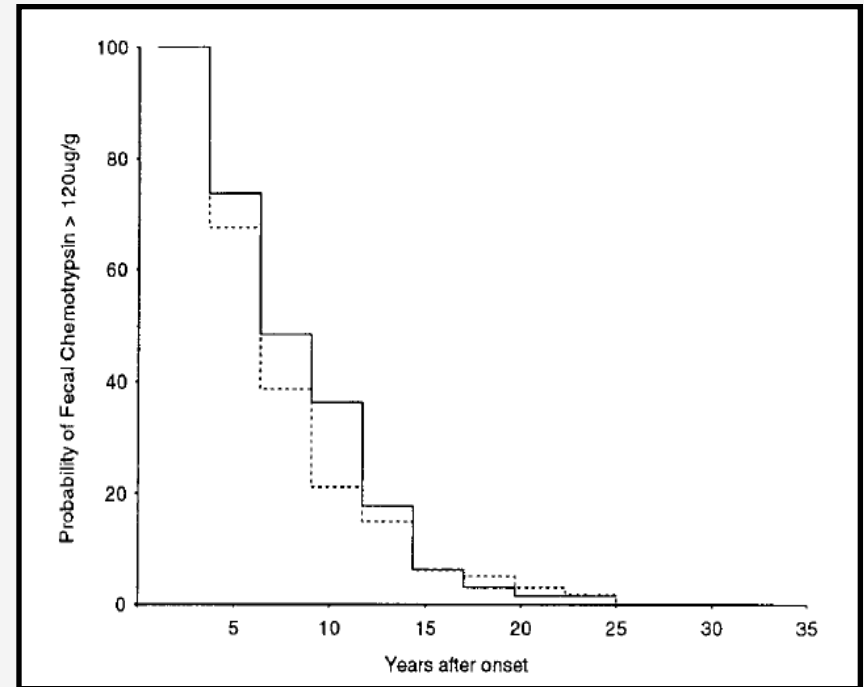
Endocriene pancreasinsufficiëntie

- 50 – 75% na 10 jaar
- diabetes mellitus



Exocriene pancreasinsufficiëntie

- 80% na 10 jaar
- gewichtsverlies/vermoeidheid/
diarree/misselijkheid



Diagnostiek - beeldvorming

- **Sensitiviteit: terecht positieve uitslag (%) bij CP patiënten**
- **Specificiteit: terecht negatieve uitslag (%) bij niet CP**

Modality	Sensitivity	Specificity	Heterogeneity (I²)
US	67% (95% CI: 53%>78%)	98% (95% CI: 89%>100%)	40%/93%
CT	75% (95% CI: 66%>83%)	91% (95% CI: 81%>96%)	50%/71%
MRI	78% (95% CI: 69%>85%)	96% (95% CI: 90%>98%)	59%/65%
EUS	82% (95% CI: 71%>90%)	91% (95% CI: 83%>95%)	82%/75%
ERCP	82% (95% CI: 76%>87%)	94% (95% CI: 87%>98%)	39%/67%

Issa.Y, Kempeneers M.A.,...,Boermeester MA.
Eur Rad 2017, Volume 27, [Issue 9](#), pp 3820-3844



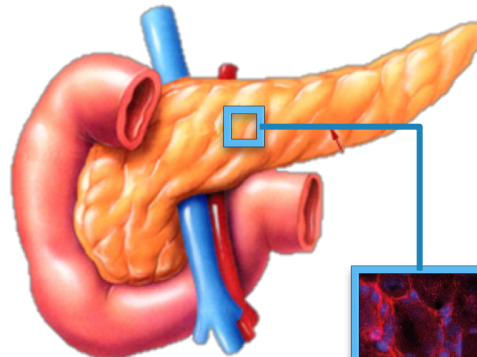
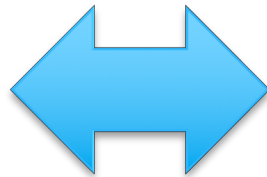
True pancreatic pain: Plumbing vs. wiring ?

Endoscopy
or surgery

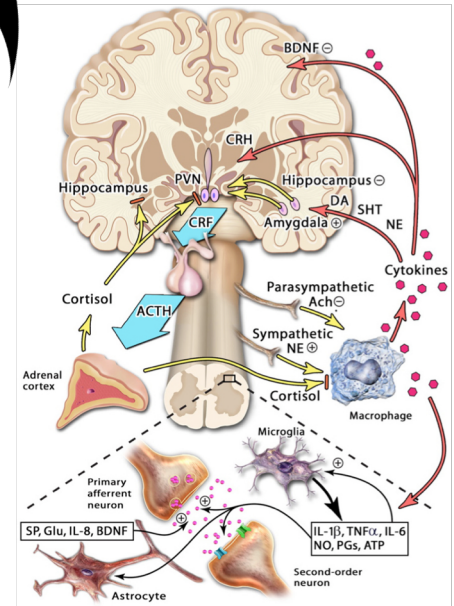
Non-invasive
treatment



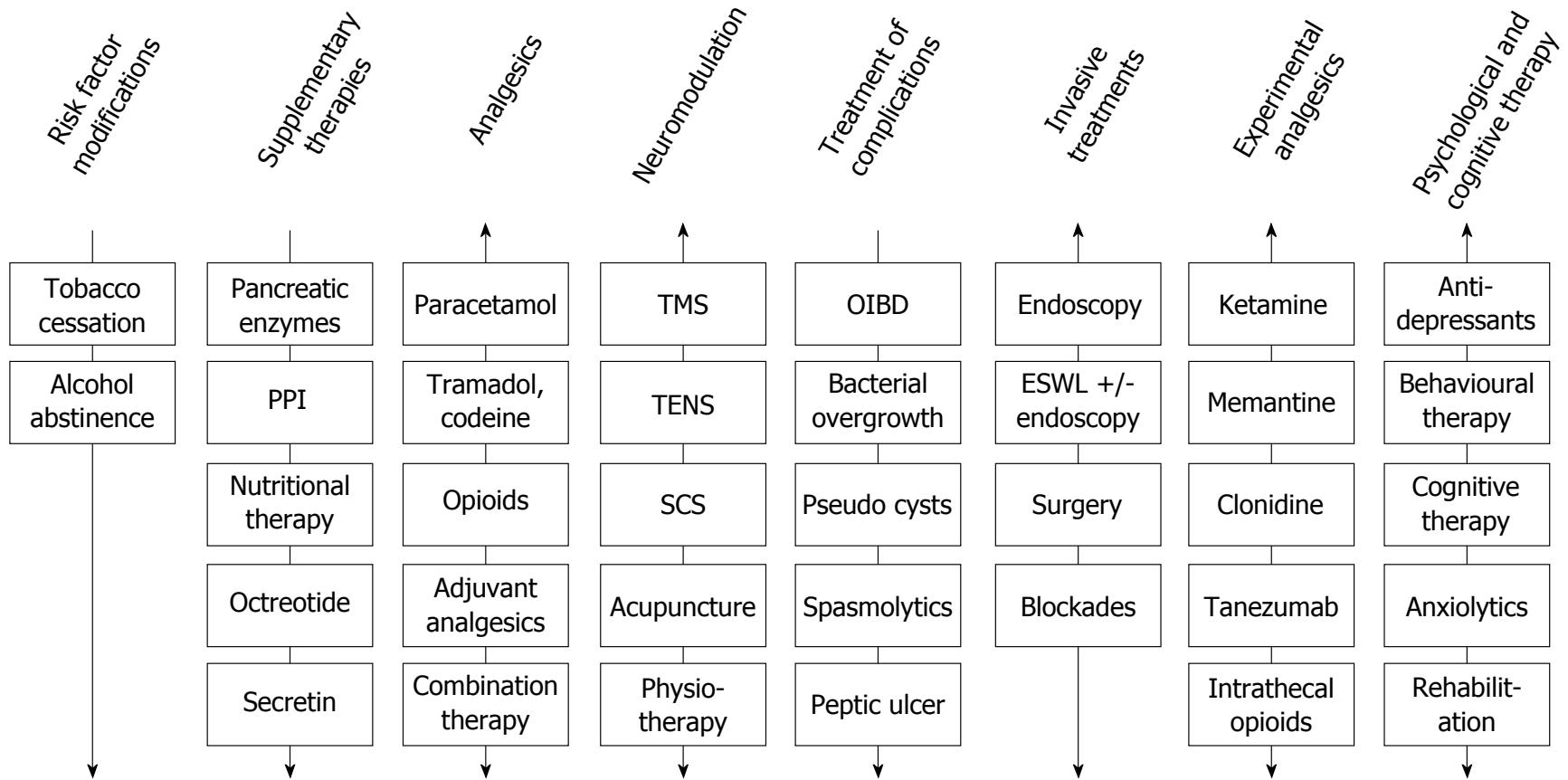
plumbing



wiring

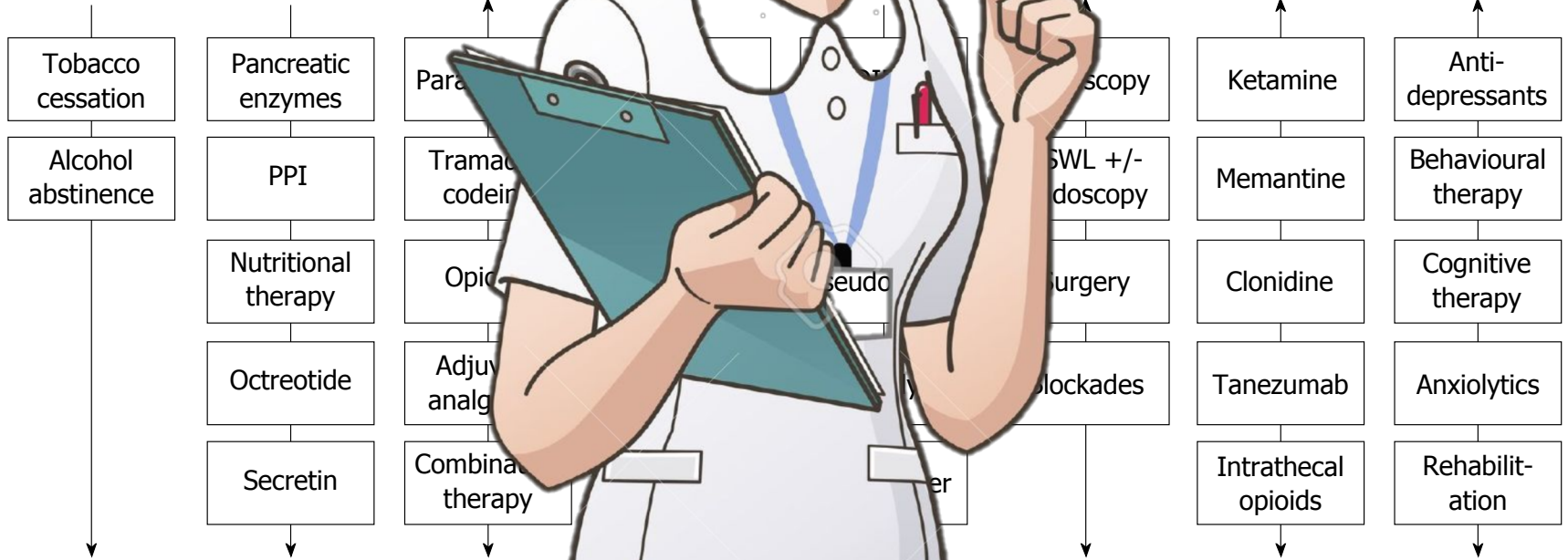


Treatment for pancreatic pain



Treatment possibilities for pancreatic pain

Risk factor modifications



The effect of intervention against alcohol

120 with acute alcohol-associated pancreatitis



repeated intervention every 6 month, n=59
30 min conversation (toxic, habits, social)

initial intervention only, n=61



n=9 with recurrent pancreatitis

2 y follow-up
P=0.02



n=20 with recurrent pancreatitis

The effect of intervention against smoking

27 smokers with chronic pancreatitis and 200 smokers with other diseases



smoking cessation program

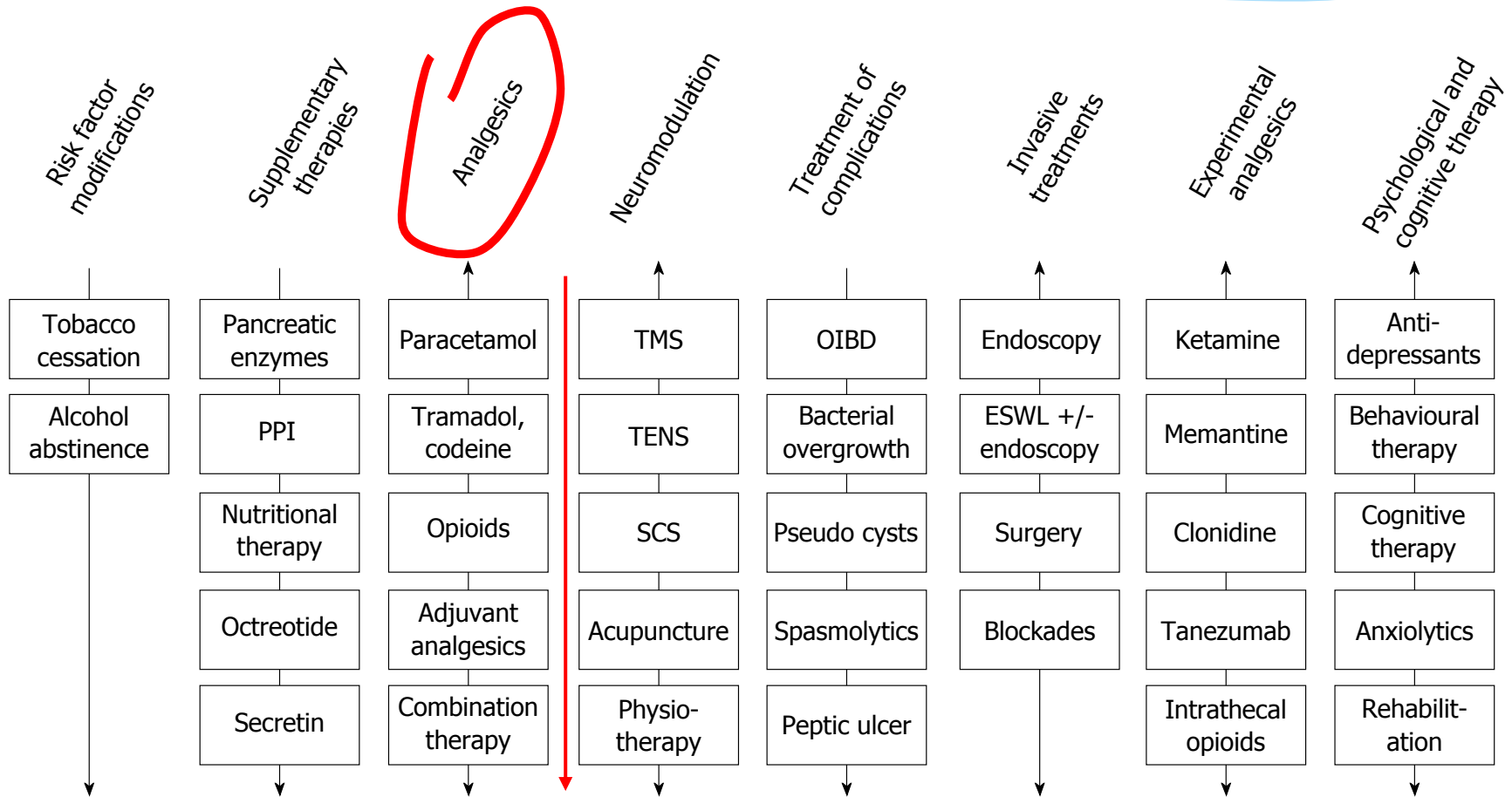
- ① Interview
- ② 2 w nicotine patches
- ③ 5 telephone counselling)

6 month follow-up

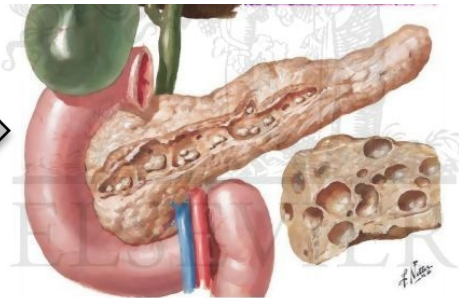
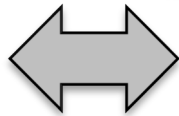
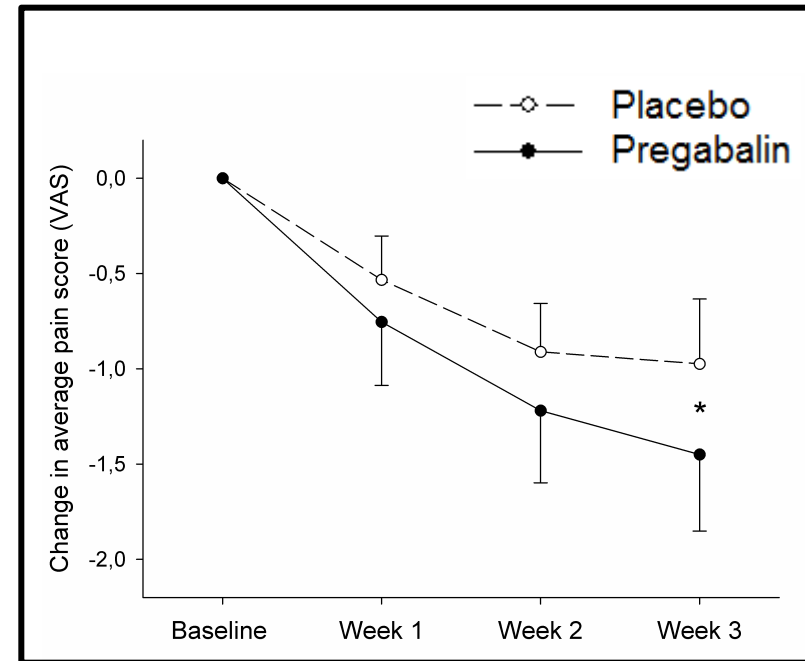
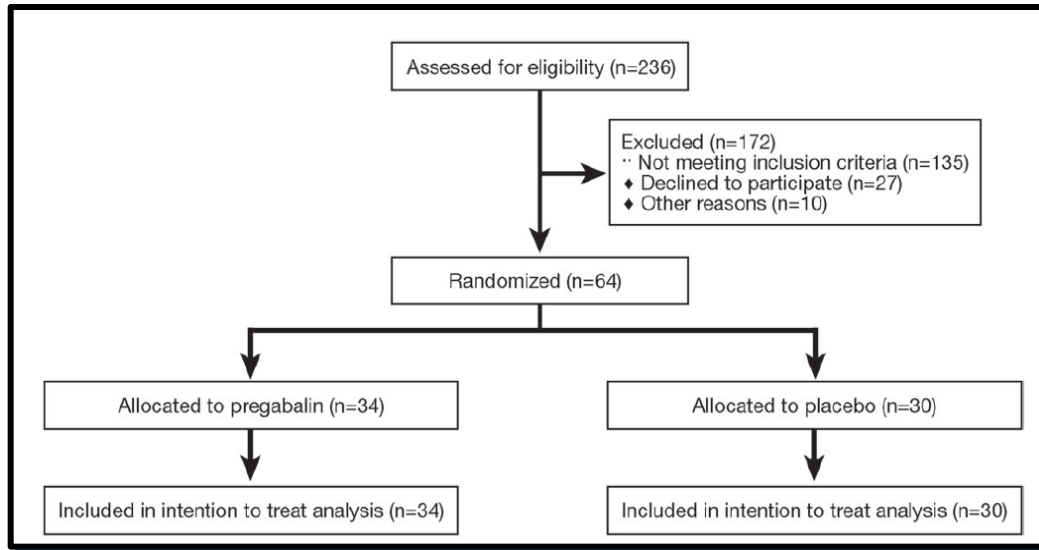
n=0 quit rate in patients
with chronic pancreatitis

n=38 (19%) quit rate
in controls

Medical treatment for pancreatic pain

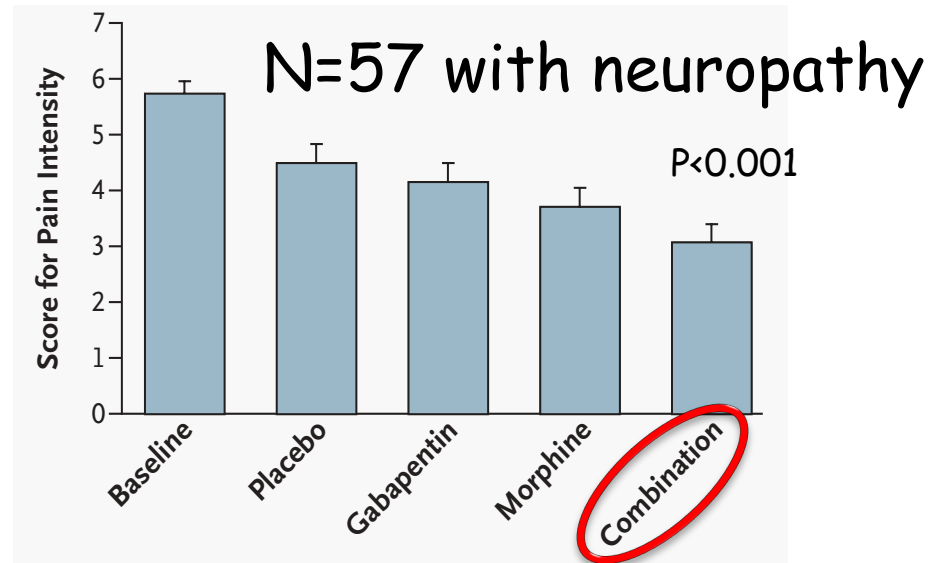


Pregabalin in chronic pancreatitis



Combination therapies

$$2 + 2 = 5$$



No GI studies exist

Gilron et al. Lancet 2009
Gilron et al. NEJM 2005
Recia et al. Med Hypotheses. 2009



Farmacologische pijnbehandeling

- **Verslaving & risico's**
 - polyfarmacie
 - multiple voorschrijvers
 - drug interacties
 - bijwerkingen
 - chirurgie minder effectief na langer opioïd gebruik
- **Beperkt effectief**
 - wordt minder ineffectief
 - CP geassocieerde hyperalgesie
 - opioïd geïnduceerde hyperalgesie

Timing surgery vs outcome

ONLINE FIRST

Clinical Outcome in Relation to Timing of Surgery in Chronic Pancreatitis

A Nomogram to Predict Pain Relief

Usama Ahmed Ali, MD; Vincent B. Nieuwenhuijs, MD, PhD; Casper H. van Eijck, MD, PhD;
Hein G. Gooszen, MD, PhD; Ronald M. van Dam, MD, PhD; Olivier R. Busch, MD, PhD;
Marcel G.W. Dijkgraaf, MD, PhD; Femke A. Mauritz, MD; Sjoerd Jens, MD; Jay Mast, MD;
Harry van Goor, MD, PhD; Marja A. Boermeester, MD, PhD; for the Dutch Pancreatitis Study Group

Ahmed Ali U,..., Boermeester MA Arch Surg 2012

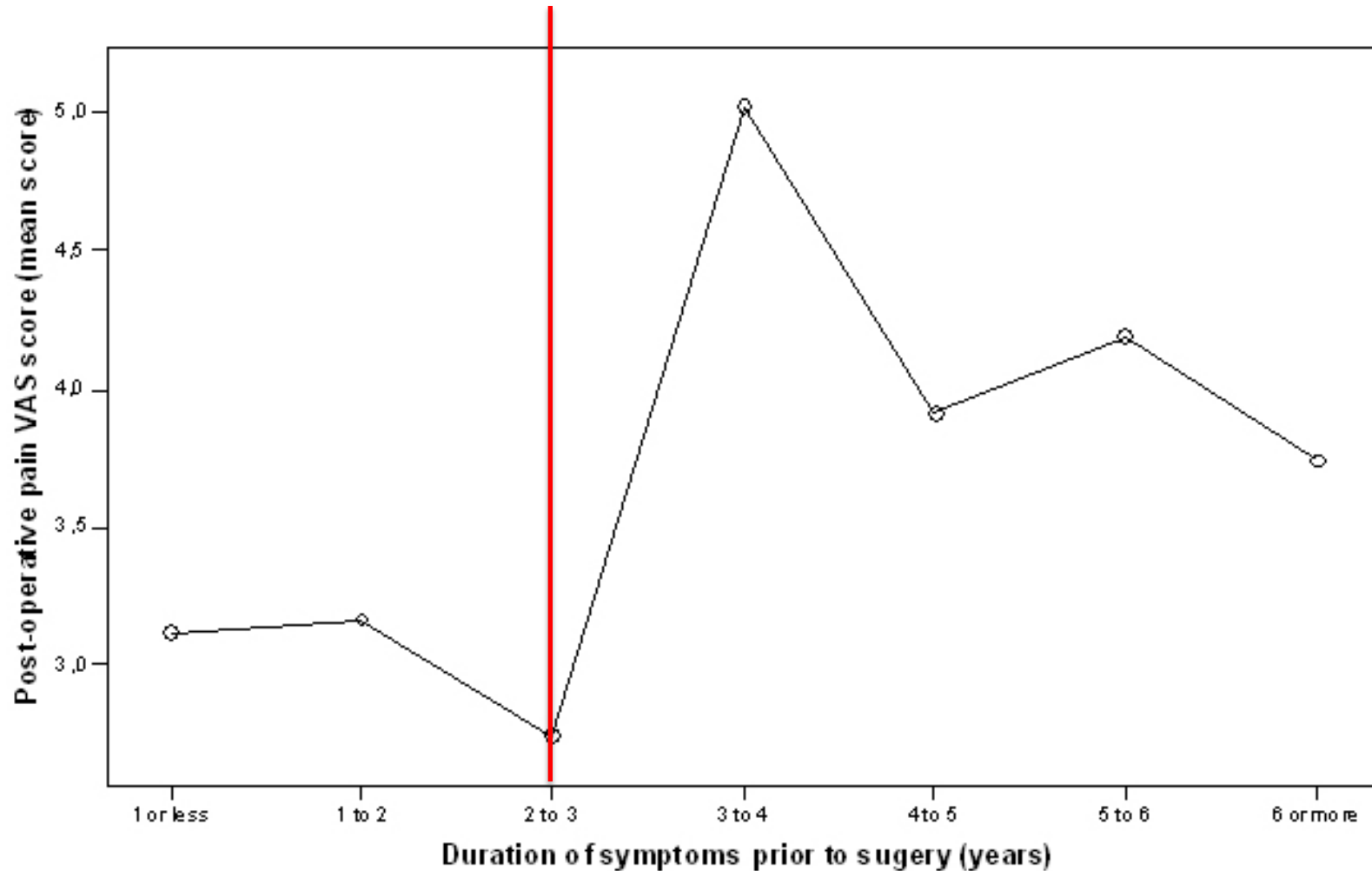
Dutch DEPAN cohort – 5 centers. N = 266

Postoperative pain relief

Factors in multivariate regression	OR (95% CI)	p-value
Reported duration of pain \leq 3 years	1.81 (1.02 - 3.37)	0.032
No preoperative opioid use	2.14 (1.23 - 3.96)	0.006
Number of endoscopic treatments \leq 5 procedures	2.46 (1.10 - 6.27)	0.039

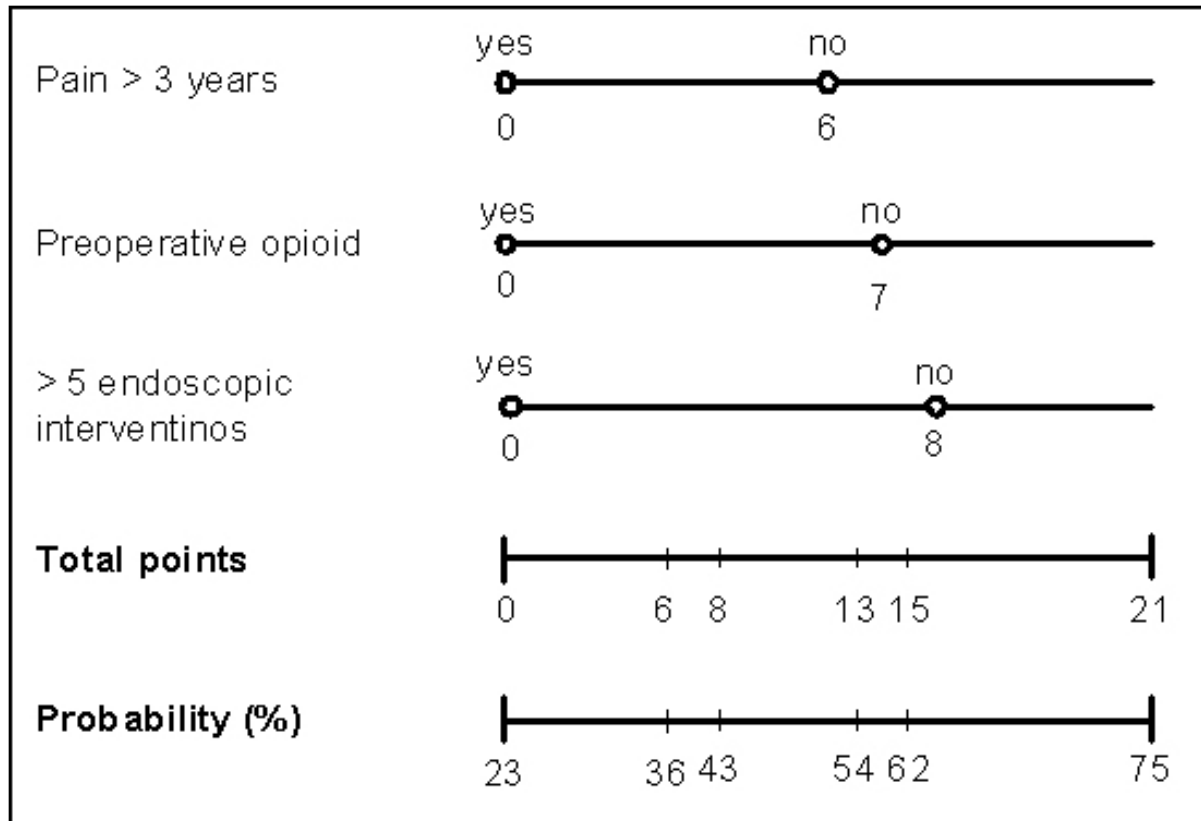
Ahmed Ali U,,, Boermeester MA Arch Surg 2012

Cut-off → duration of pain preoperative ~ post-operative pain symptoms (VAS 0-10)



Nomogram for pain relief

- Probability of pain relief varies between 23% and 75% based on timing of surgery



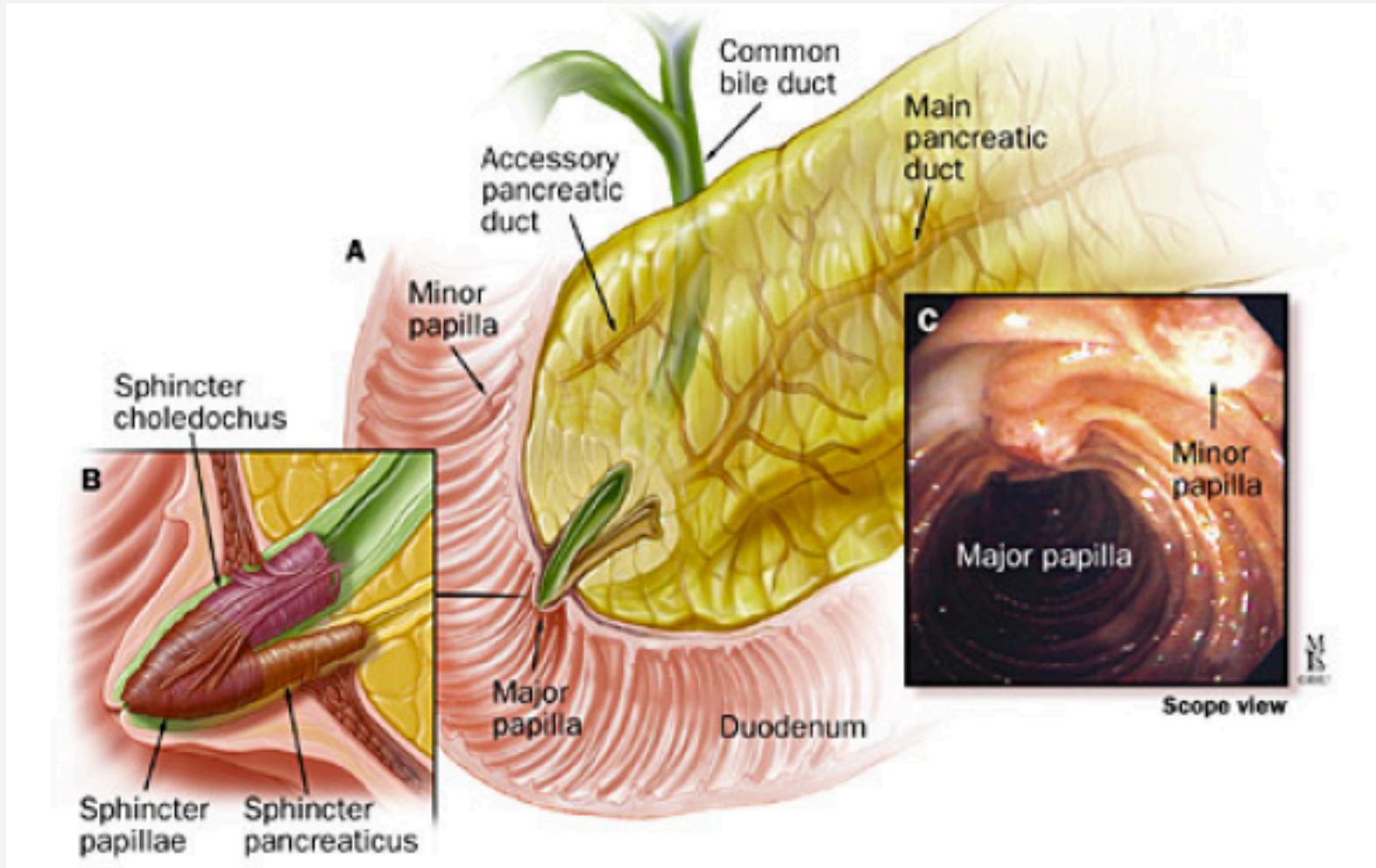
Surgical pain pathophysiology

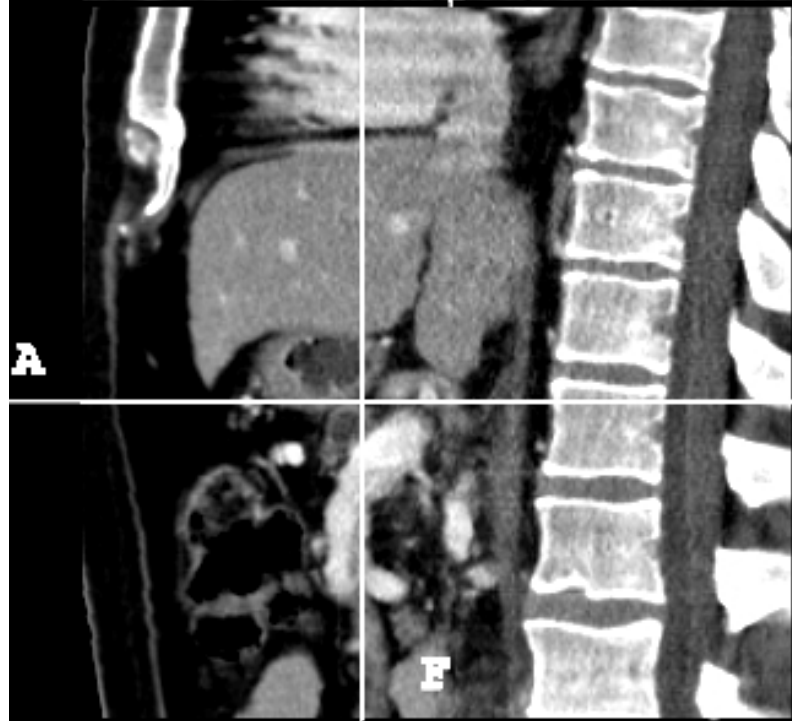
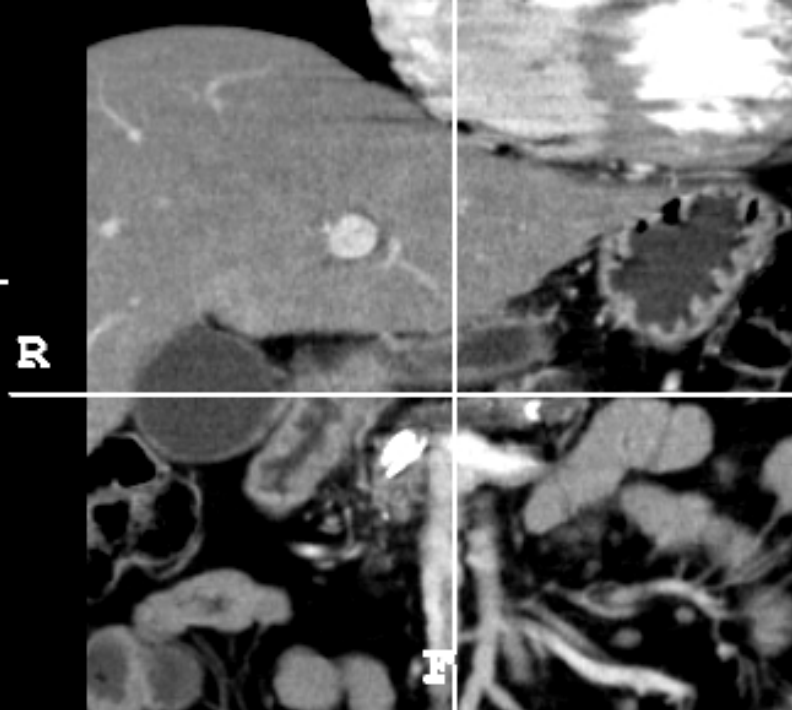
Pain in CP is caused by:

- Duct obstruction
BIG ducts (plumbing, ductal hypertension)



Surgical pain pathophysiology





Surgical pain pathophysiology

Pain in CP is caused by:

- Duct obstruction
BIG ducts (plumbing, ductal hypertension)



- Inflammatory 'pacemaker' in the head
BIG heads (wiring, perineural)



Surgical pain pathophysiology pacemaker theory

Univariate analysis of disease factors.

	Poor pain control (<i>n</i> =15)	Good pain control (<i>n</i> =62)	<i>p</i> -Value
Pancreatic head size, cm (mean±SD)	4.39±0.75	5.81±1.08	<i>p</i> =0.001
Pancreatic duct diameter, mm	4.47±1.30	8.42±2.72	<i>p</i> =0.001
Volume percentage of head mass cored	48%	65%	<i>p</i> =0.001
Pseudocyst, number (%)	5(6.5%)	12(15.5%)	NS
Associated procedures, number (%)	3 (4%)	4 (5%)	NS

Amudhan A et al. *HPB (Oxford)*. 2008 Dec 1; 10(6): 477–482.

Surgical pain pathophysiology

Pain in CP is caused by:

- Duct obstruction
BIG ducts (plumbing, ductal hypertension)

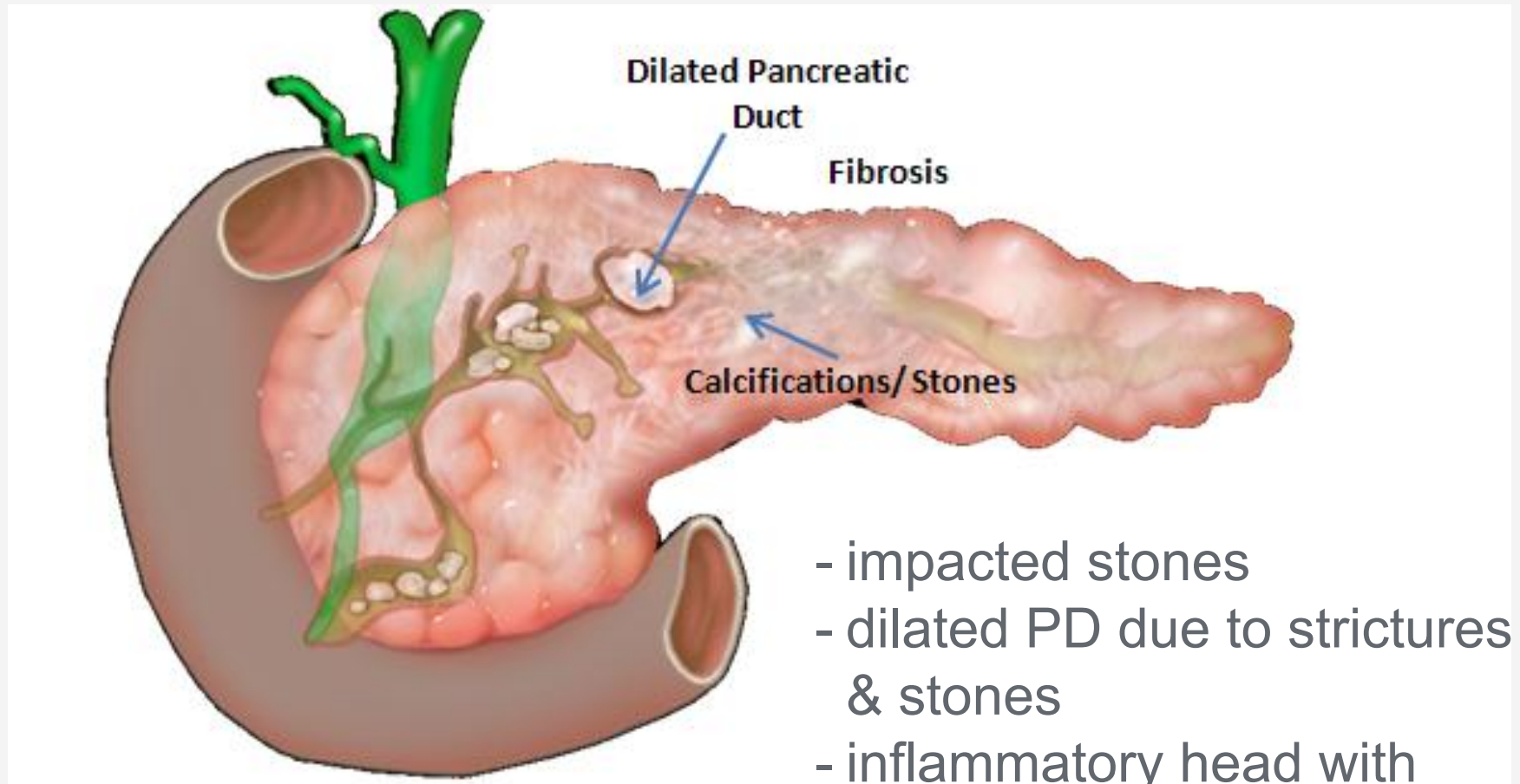


- Inflammatory 'pacemaker' in the head
BIG heads (wiring, perineural)



- **Both**

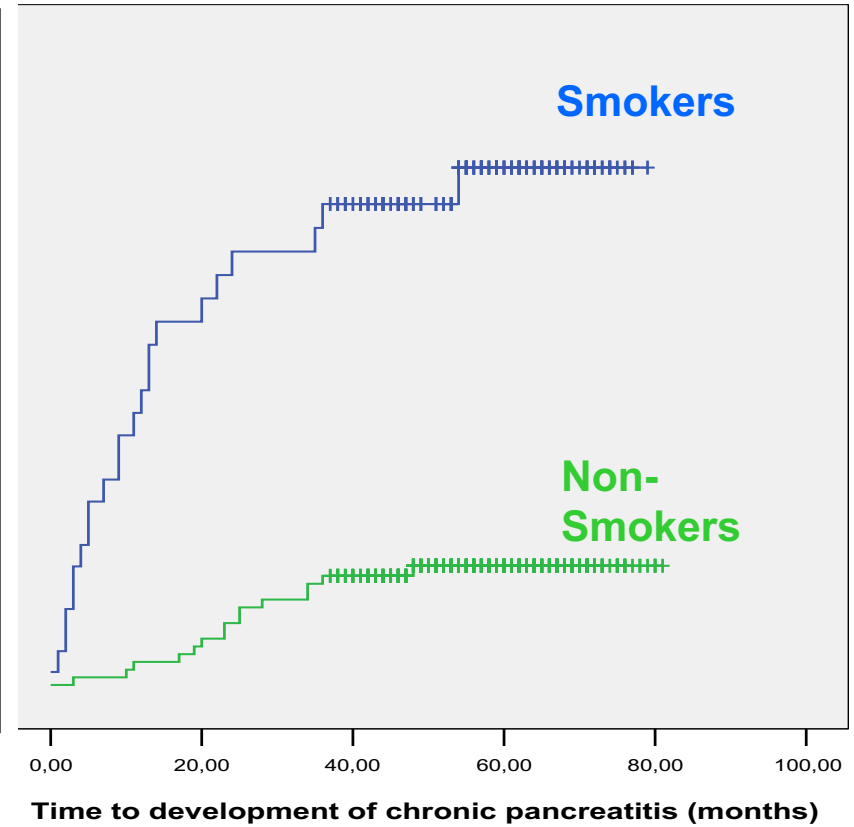
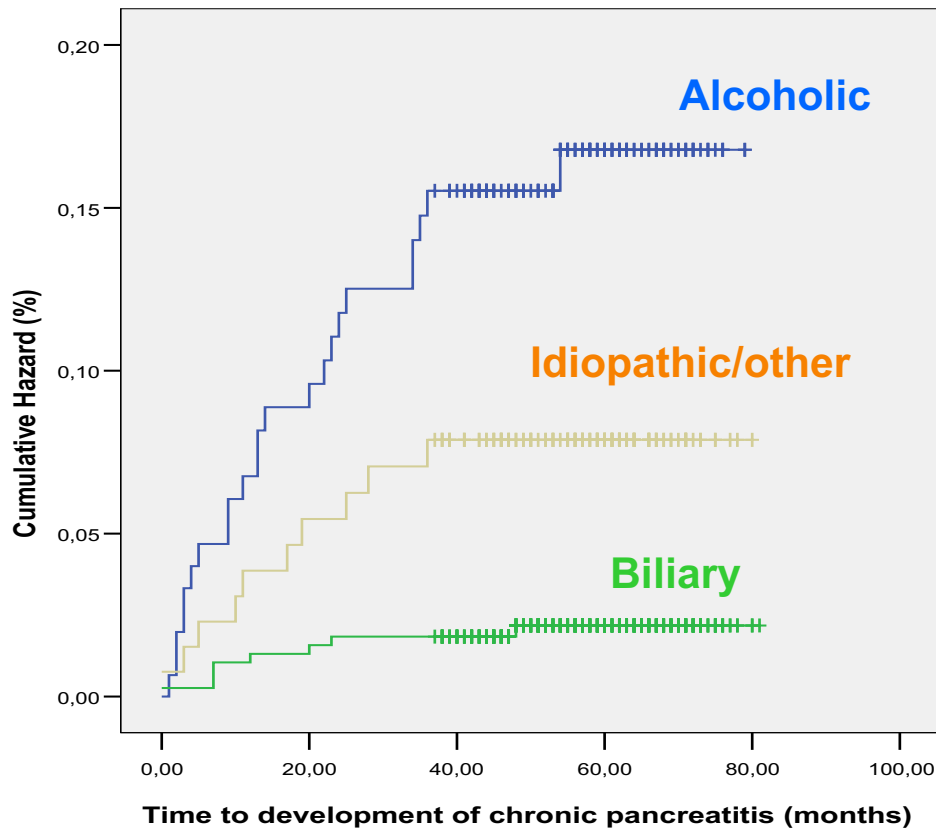
Surgical pain pathophysiology



Risico factor behandelning

Risico factor behandeling - van acute pancreatitis naar CP -

Alcohol, roken



Ahmed Ali U,..., Boermeester MA. Clin Gastroenterol Hepatol. 2016

Risiko factor behandeling - ? VOOR chirurgie voor CP ?

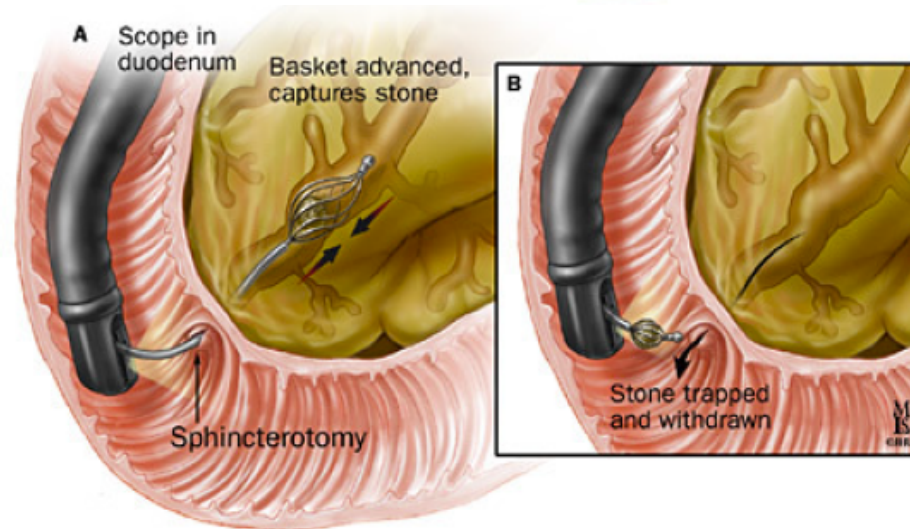
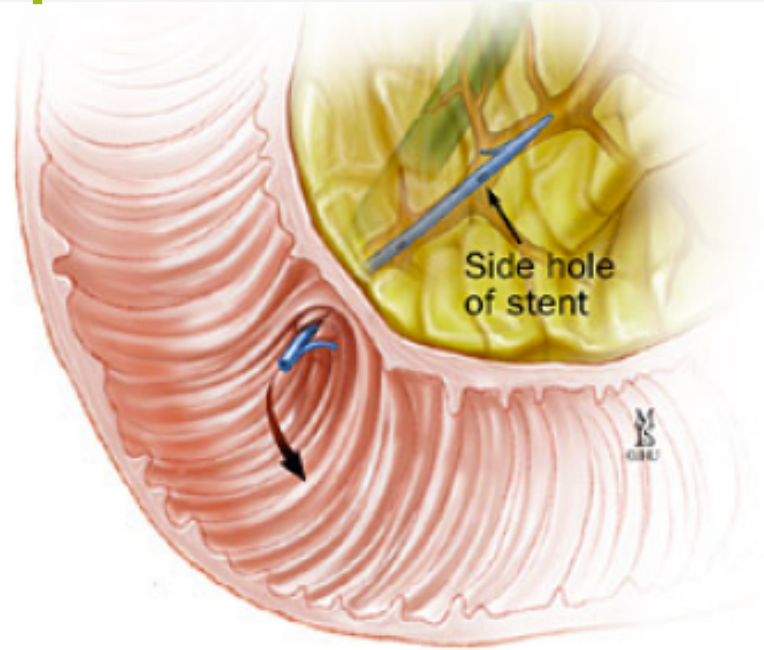
Alcohol, roken

- Er is geen goed bewijs dat stoppen met **alcohol** op zich de pijn vermindert
- Het is een illusie dat patiënten stoppen met drinken als ze veel pijn hebben
- Eis wel alcohol stop voordat tot operatie over te gaan

- **Roken** is geassocieerd met het drinken
- Het is een illusie dat patiënten stoppen met roken als het ze eenmaal gelukt is om te stoppen met drinken

Endoscopic pain treatment

PD stenting



Endoscopic pain treatment - series

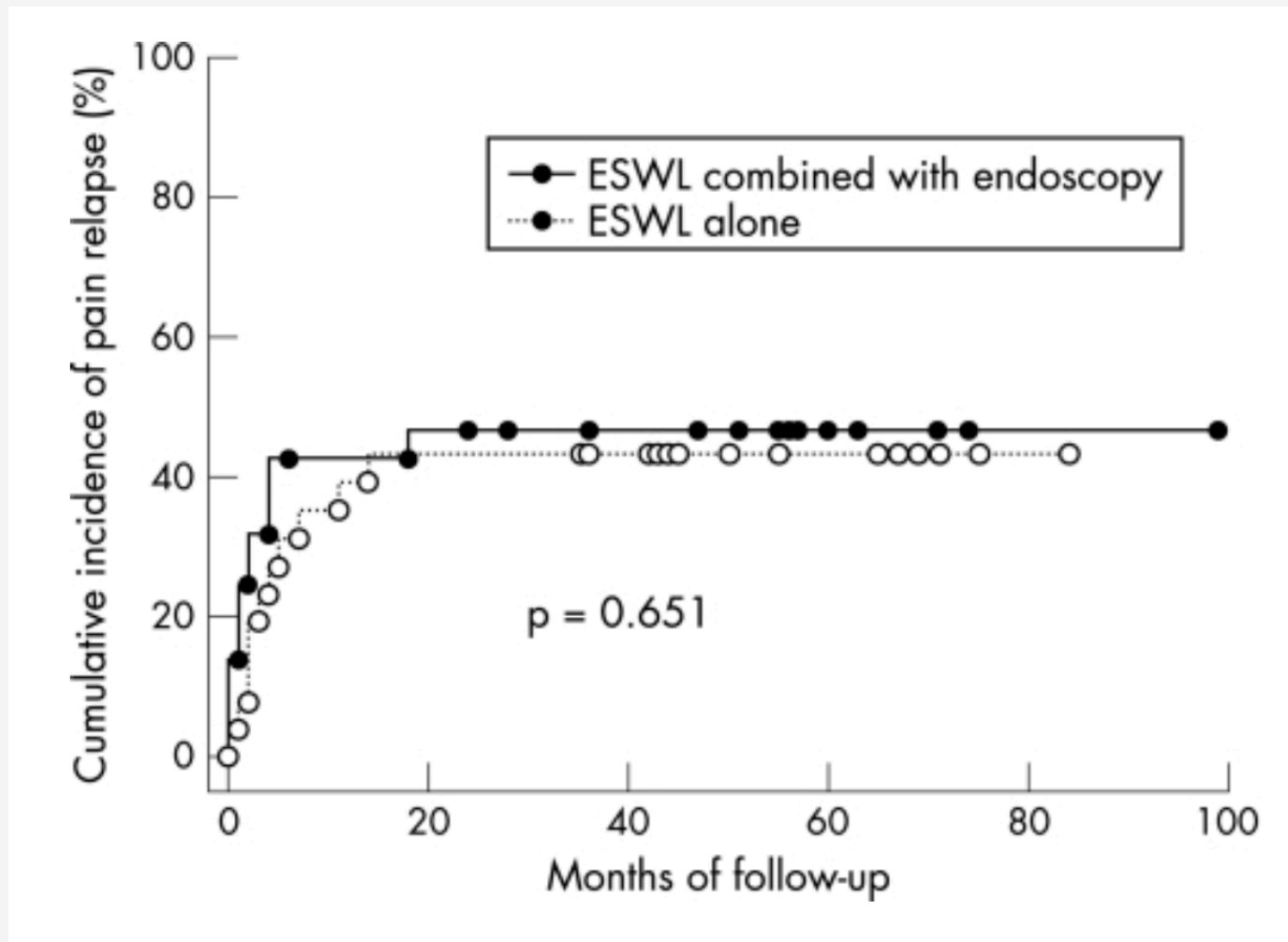
Table 1. Results of endoscopy and ESWL for pancreatic stones in series of >20 patients

First author	Year	Patients n	Mean follow-up months	Complete or partial pain relief %	Overall morbidity %	Late mortality %	Need for surgery %	Exocrine/endo-crine function improved %	ESWL %	Fragmen-tation %	Com-plete clearance %
Delhaye [35]	1992	123	14	85	23	1.7	8	55/10	99	99	59
Sauerbruch [43]	1992	24	24	83	NR	NR	8	NR	100	87.5	42
Schneider [44]	1994	50	20	62	14	4	12	NR	100	86	60
Johanns [40]	1996	35	23	83	23	NR	14	NR	100	100	46
Ohara [42]	1996	32	44	86	25	NR	3	61/17	100	100	75
Dumonceau [46]	1996	70	24	50	13	NR	6	0/0	59	100	50
Costamagna [39]	1997	35	27	72	23	3	3	NR	100	100	74
Adamek [37]	1999	80	40	76	17.5	6	10	47/0	54	54	NR
Brand [32]	2000	48	7	82	10.5	0	4	77/15	100	60	44
Kozarek [41]	2002	40	29	80	20	10	20	NR	100	100	NR
Farnbacher [30]	2002	114	29	48	NR	7.8	13	NR	82	82	39
Rosch [25]	2002	1,018	59	69	13	12.2	24	51/8	26	NR	NR
Inui [31]	2005	555	44	91	6.3	3.2	4	38/24	92	92	73
Tadenuma [38]	2005	117	77	70	8.5	11.5	1.4	NR	100	97	56
Ong [149]	2006	250	NR	NR	6.8	NR	NR	NR	66	NR	60
Tandan [34]	2010	1,006	6	84	15	NR	3.8	NR	100	93	76
Seven [45]	2012	120	52	85	NR	17.6	16	NR	100	NR	NR

NR = Not reported.

Issa Y,..., Boermeester MA. Digestive Surgery, 2013;30: 35-50

Endoscopic pain treatment - RCT



Dumonceau et al. Gut 2007

BUT...

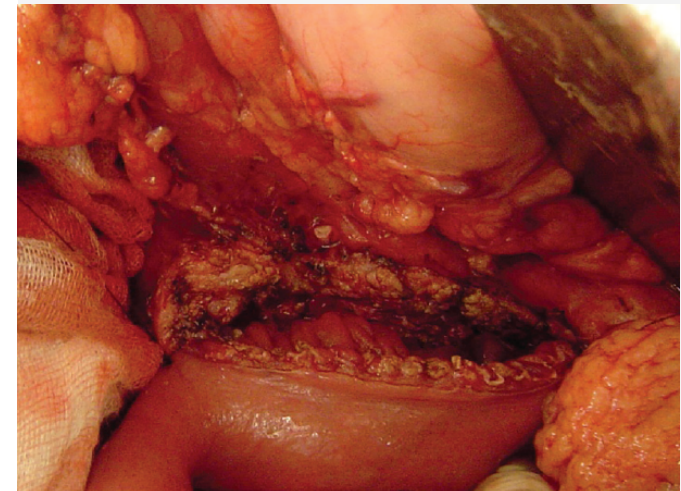
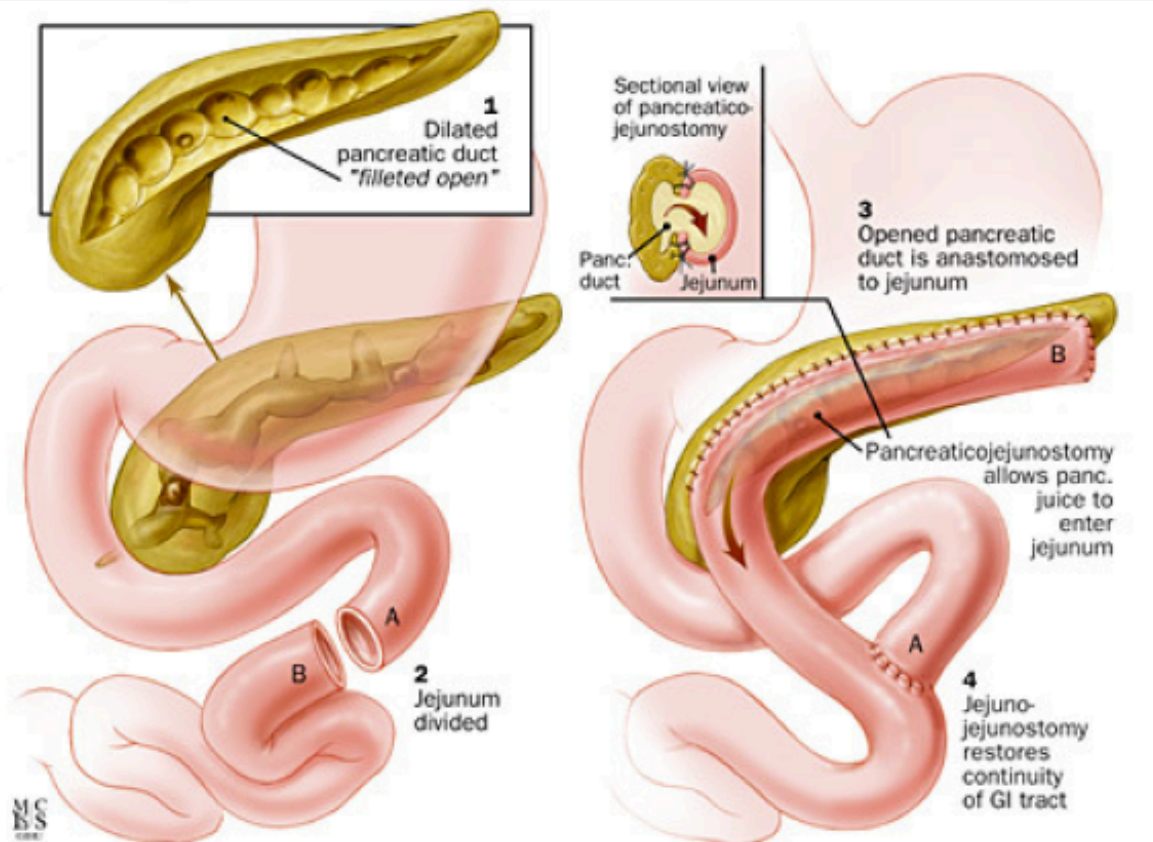
persistent pain after surgery if

TABLE 5. Multinomial Logistic Regression for Factors Associated With Persistent Pain*

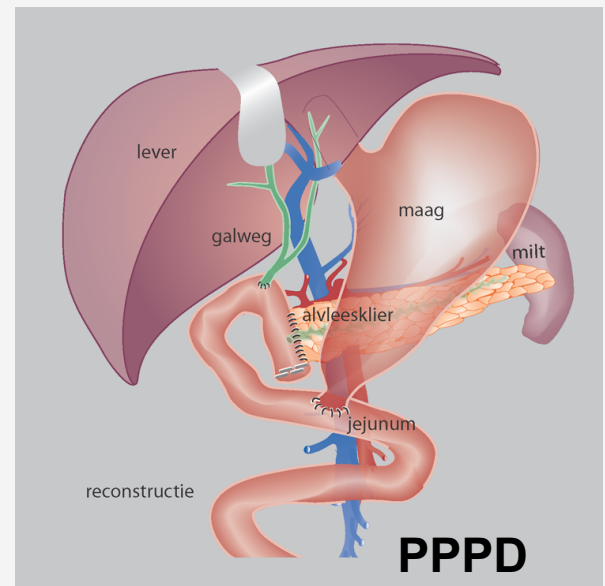
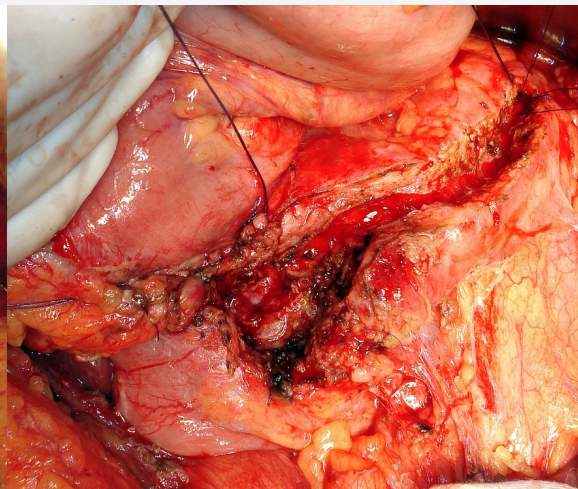
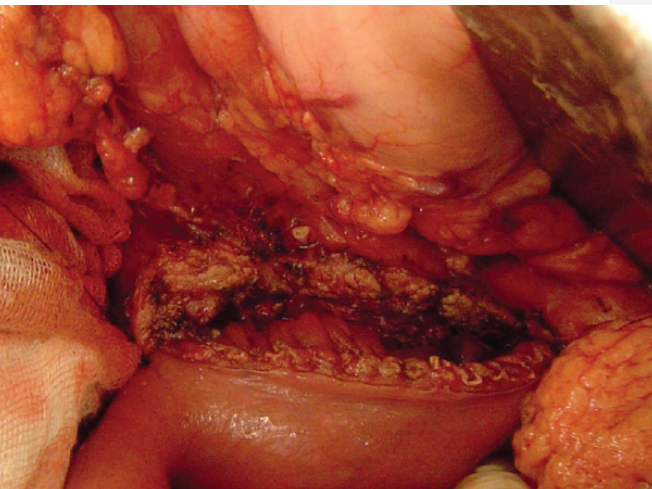
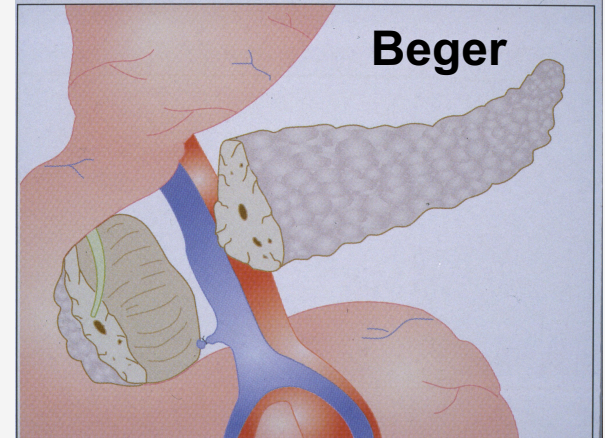
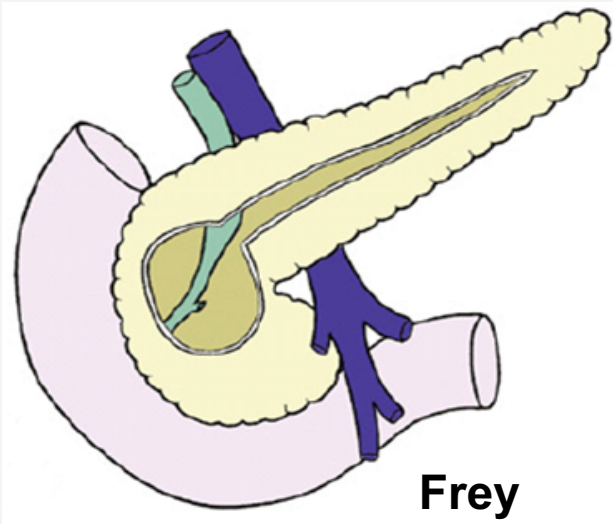
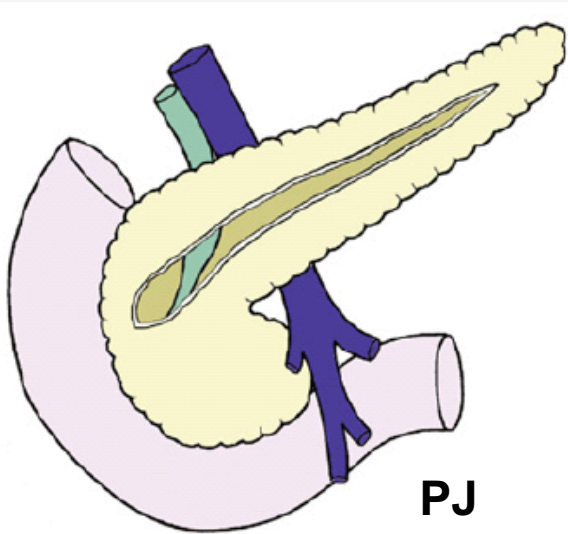
Variables*	Intermediate Pain, OR [95% CI]	Severe Pain, OR [95% CI]
Age at follow-up†	1.01 [0.97–1.05]	0.95 [0.92–1.01]
Female sex	1.24 [0.51–3.01]	1.79 [0.64–4.98]
Reported duration of pain preoperatively†	1.04 [0.98–1.10]	0.94 [0.84–1.06]
Preoperative daily opioid use	1.35 [0.55–3.28]	3.04 [1.09–8.49]**
Prior therapeutic endoscopic procedures (n)‡		
2–4	0.91 [0.33–2.53]	2.19 [0.59–8.14]
≥5	1.41 [0.47–4.24]	3.89 [1.01–14.9]**

N=223

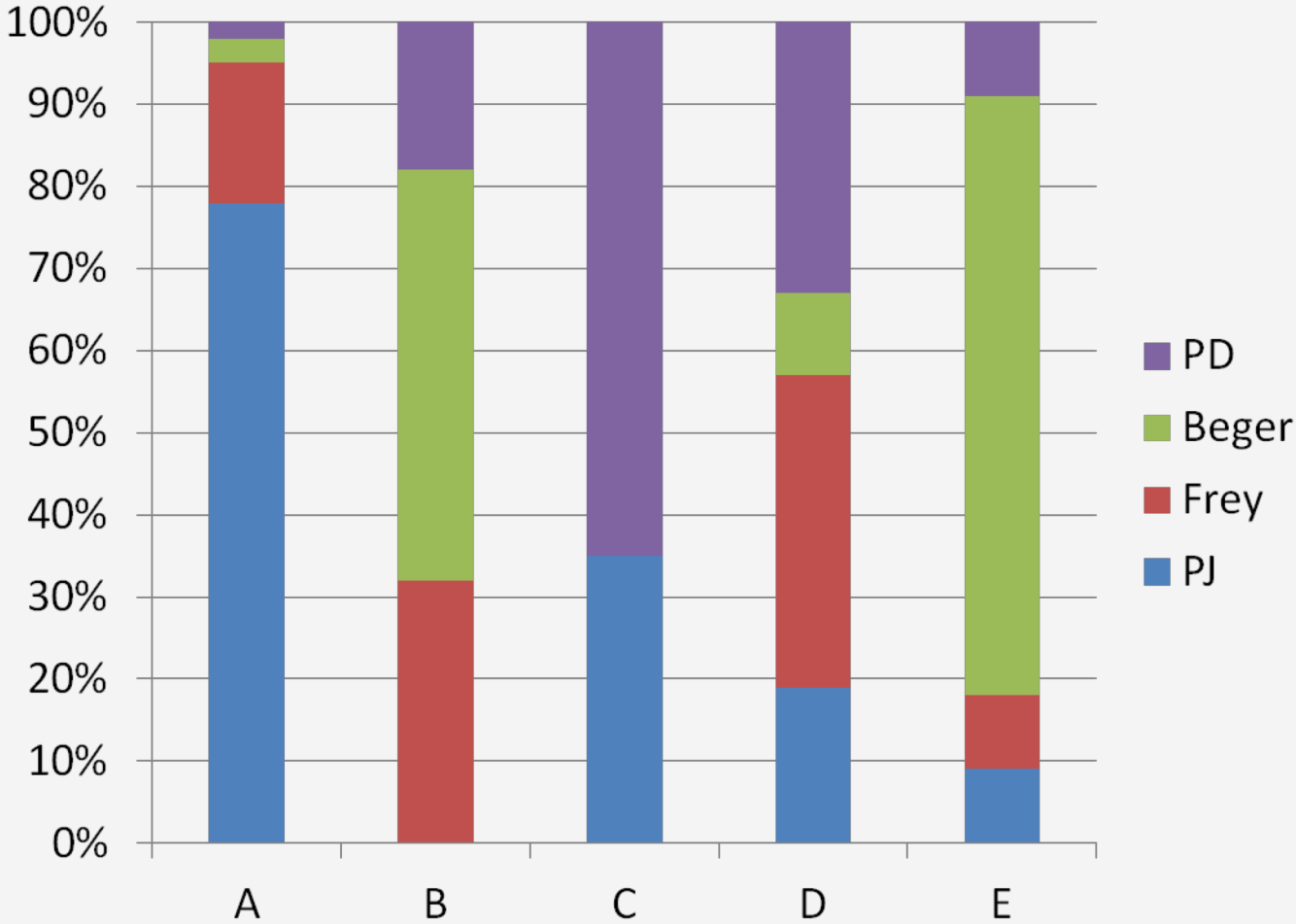
Surgical pain treatment



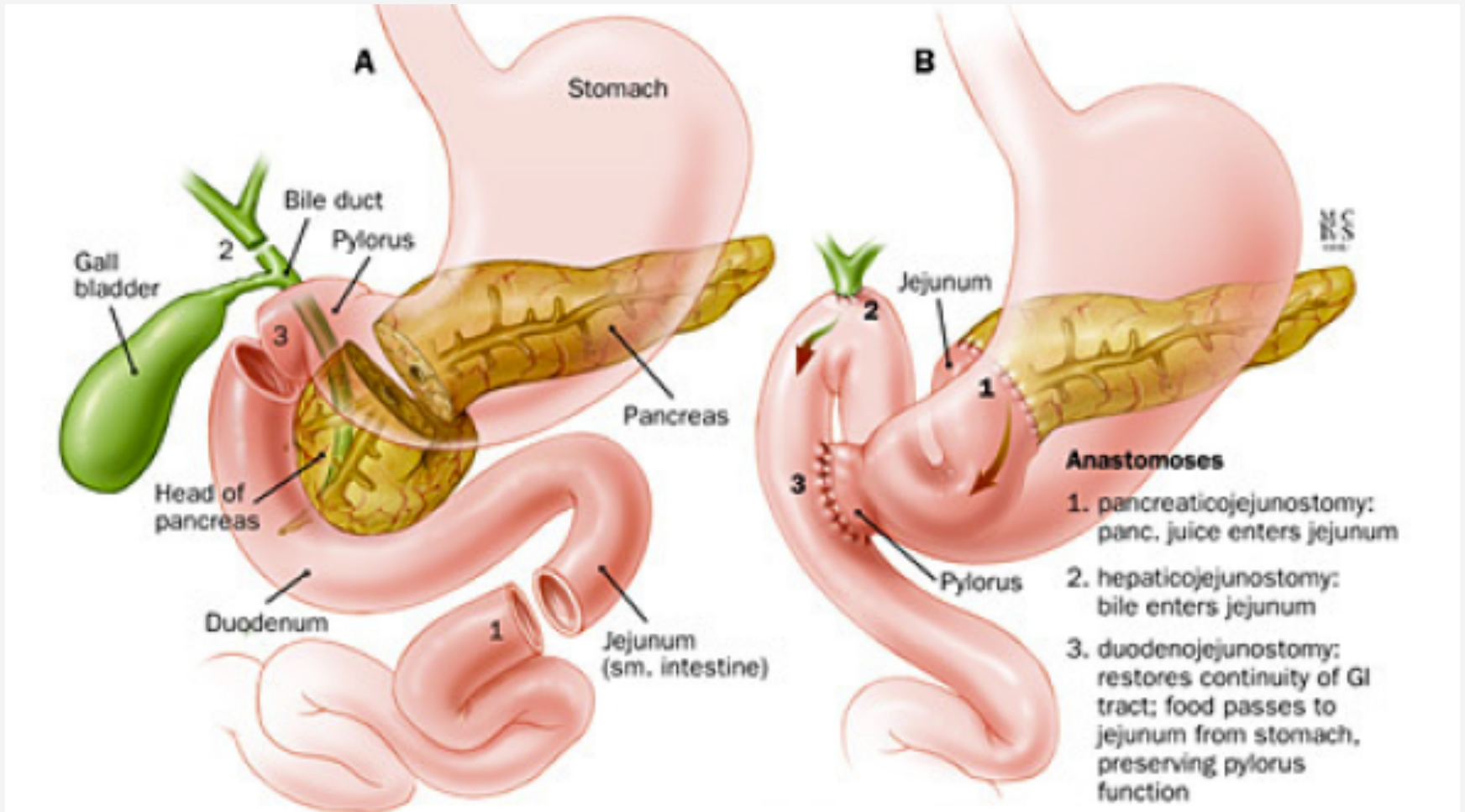
Practice variation drainage only vs. resection



Practice variance of surgery for CP in The Netherlands



? Major resection not drainage only ? – PPPD (PP Whipple)

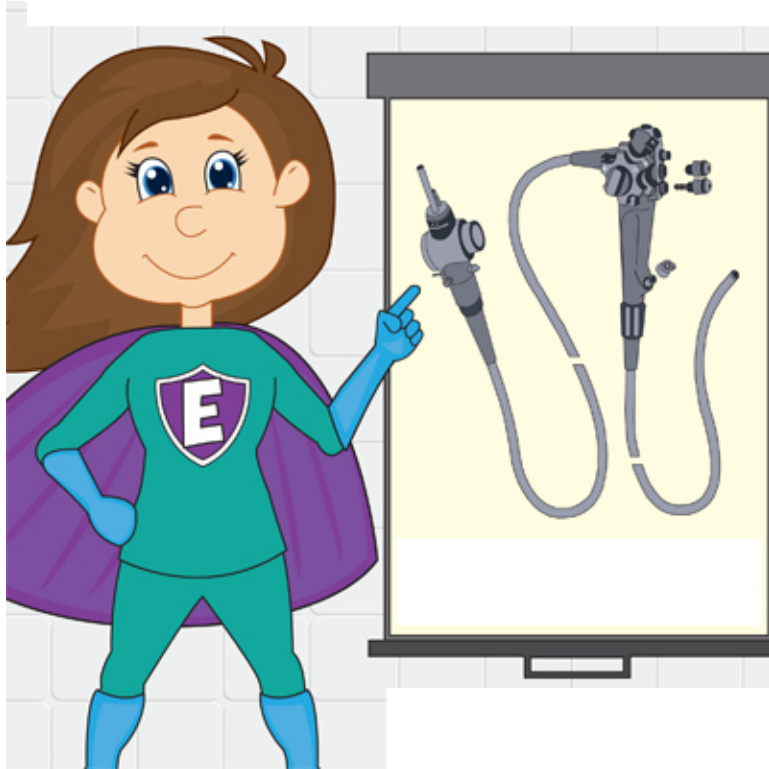


? Why major resection when drainage only suffices ?

TABLE 3: Randomized controlled studies on the surgical treatment of painful CP.

Authors	Publication	Number of patients	Results
Izbicki et al.	Ann. Surg. 1995 [33]	42	Frey equal to Beger
Izbicki et al.	Chirurg 1997 [37]	74	Frey equal to Beger
Strate et al.	Ann. Surg. 2005 [34]	74	Frey equal to Beger
Klempa et al.	Chirurg 1995 [27]	43	Beger better than Whipple
Büchler et al.	Am. J. Surg. 1995 [13]	40	Beger better than Whipple
Köninger et al.	Surgery 2008 [35]	65	Berne/Farkas better than Beger
Izbicki et al.	Ann. Surg. 1998 [30]	61	Frey better than Whipple
Farkas et al.	Langenbecks Arch Surg. 2006 [29]	40	Frey better than Whipple
Bachmann et al.	Ann. Surg. 2013 [31]	64	Frey better than Whipple

Hartmann D, Friess H. Gastroenterol Res Pract. 2015



VS.



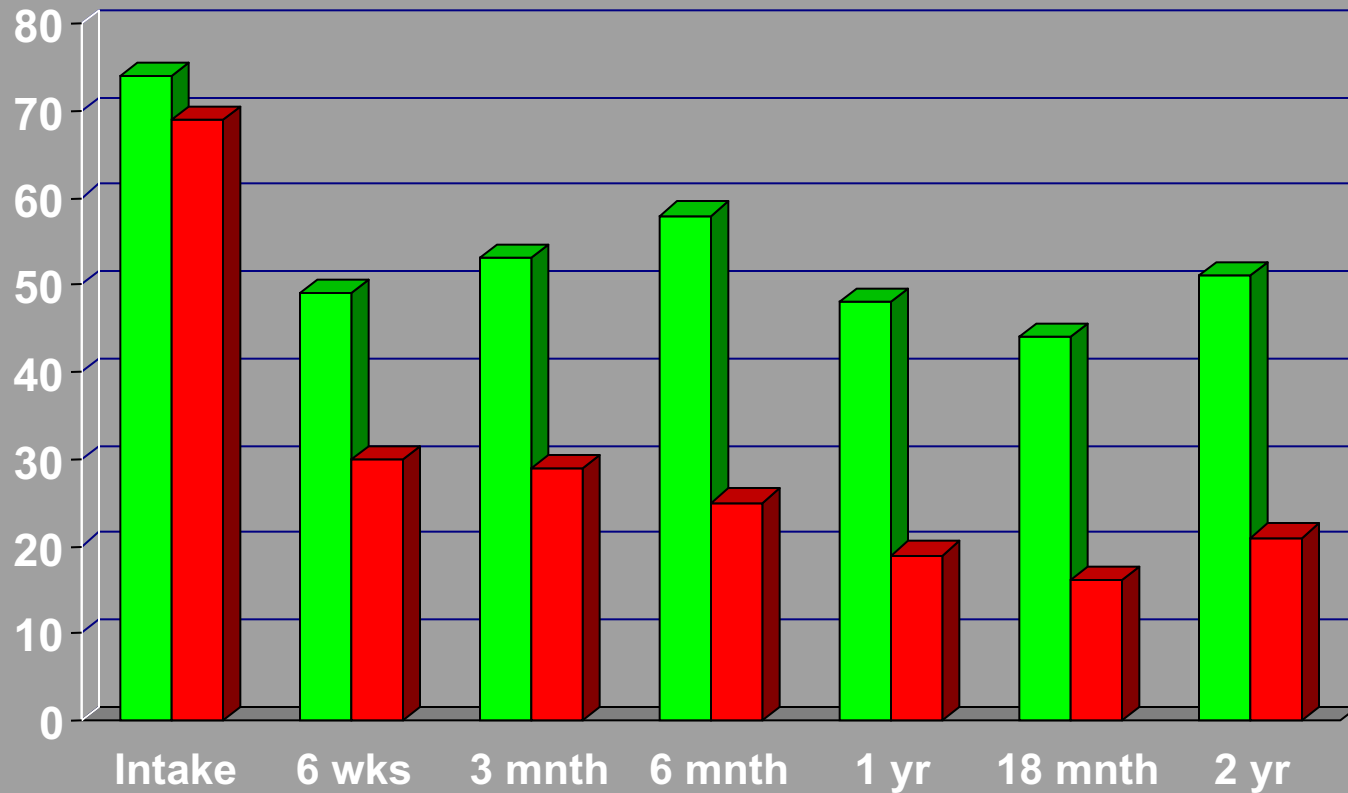
Endoscopy vs. Surgery



ESWL + Endoscopic drainage	Partington- Rochelle	Complications and pancreatic function	Pain relief Follow-up 1
N=19 (18/19 ESWL)	N=20	No differences	2 years: 32% vs. 75%

Cahen DL et al – NEJM 2007

Endoscopic drainage vs surgery: Izbicki pain score



■ Endoscopy (mean Izbicki score 51)

■ Surgery (mean Izbicki score 25; $p < 0.001$)

Morbidity / mortality



	morbidity	mortality
surgery (AMC cohort)	22 %	0.9 %
surgery (CEPAN)	35%	0 %
endoscopy (CEPAN)	53 %	5.3 %

CEPAN: Cahen et al – NEJM 2007

AMC cohort: Van der Gaag et al – Ann Surg 2012

Endoscopy vs. Surgery (2)

ESWL + Endoscopic drainage	Partington-Rochelle	Complications and pancreatic function	Pain relief Follow-up 1	Pain relief Follow-up 2
N=19 (18/19 ESWL)	N=20	No differences	2 years: 32% vs. 75%	5 years: 38% vs. 80%

- Long term follow-up in the endoscopy group:
47% needed surgery after endoscopy

Cahen DL et al – NEJM 2007

Cahen DL et al – Gastroenterology 2011

Endoscopic or surgical intervention for painful obstructive chronic pancreatitis

Cochrane review 2012

Usama Ahmed Ali¹, Johanna M Pahlplatz¹, Wiliam H Nealon², Harry van Goor³, Hein G Gooszen⁴, Marja A Boermeester⁵

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Endoscopy compared to surgery for painful obstructive chronic pancreatitis

Patient or population: patients with painful obstructive chronic pancreatitis

Settings:

Intervention: surgery

Comparison: endoscopy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Endoscopy	Surgery			
Pain relief Follow-up: 2-3 years	509 per 1000	825 per 1000 (621 to 1000)	RR 1.62 (1.22 to 2.15)	111 (2 studies)	⊕⊕⊕○ moderate ¹
Major complications	See comment	See comment	Not estimable	179 (2 studies)	⊕⊕○○ low ^{2,3}

Dite 2003 and Cahen 2007

Multidisciplinary guideline 2017

UNITED EUROPEAN
GASTROENTEROLOGY

ueg journal

Review Article

United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU)

United European Gastroenterology Journal

2017, Vol. 5(2) 153–199

© Author(s) 2017

Reprints and permissions:

sagepub.co.uk/journalsPermissions.nav

DOI: 10.1177/2050640616684695

journals.sagepub.com/home/ueg



J Matthias Löhr¹, Enrique Dominguez-Munoz², Jonas Rosendahl³,
Marc Besselink⁴, Julia Mayerle²⁵, Markus M Lerch⁵, Stephan Haas¹,
Fatih Akisik⁶, Nikolaos Kartalis⁷, Julio Iglesias-Garcia², Jutta Keller⁹,
Marja Boermeester⁴, Jens Werner¹⁰, Jean-Marc Dumonceau¹¹,
Paul Fockens^{4,8}, Asbjorn Drewes¹², Gürlap Ceyhan¹³, Björn Lindkvist¹⁴,
Joost Drenth¹⁵, Nils Ewald¹⁶, Philip Hardt¹⁶, Enrique de Madaria¹⁷,
Heiko Witt¹⁸, Alexander Schneider¹⁹, Riccardo Manfredi²⁰,
Frøkjær J Brøndum²¹, Sasa Rudolf²², Thomas Bollen²³ and Marco Bruno²⁴;
HaPanEU/UEG Working Group

Search: “pancreatitis”



GET IT ON

Google Play



Download on the
App Store

Treatment for CP

Surgery in CP (WP 5)

Q4-1.1: In patients with symptoms of CP, should endoscopy or surgery be performed?

Statement 4-1.1. Surgery is superior to endoscopy in terms of mid-term and long-term pain relief in patients with painful CP. (**GRADE 2B, agreement**)

Q4-1.2: What is the optimal timing for surgical therapy in CP?

Statement 4-1.2a. To achieve optimal long-term pain relief in patients suffering from CP, early surgery is favoured over surgery at a more advanced stage of the disease.²⁵¹ **(GRADE 2B, weak agreement)**

Statement 4-1.2b. The risk of developing PEI is lower after early surgery for CP than after surgery performed at an advanced disease stage. Pancreatic resection techniques have a higher risk of PEI than drainage techniques. **(GRADE 2C, weak agreement)**



Early Surgery versus Optimal Current Step-up Practice
for Chronic Pancreeatitis

ESCAPE trial
randomised multicenter trial

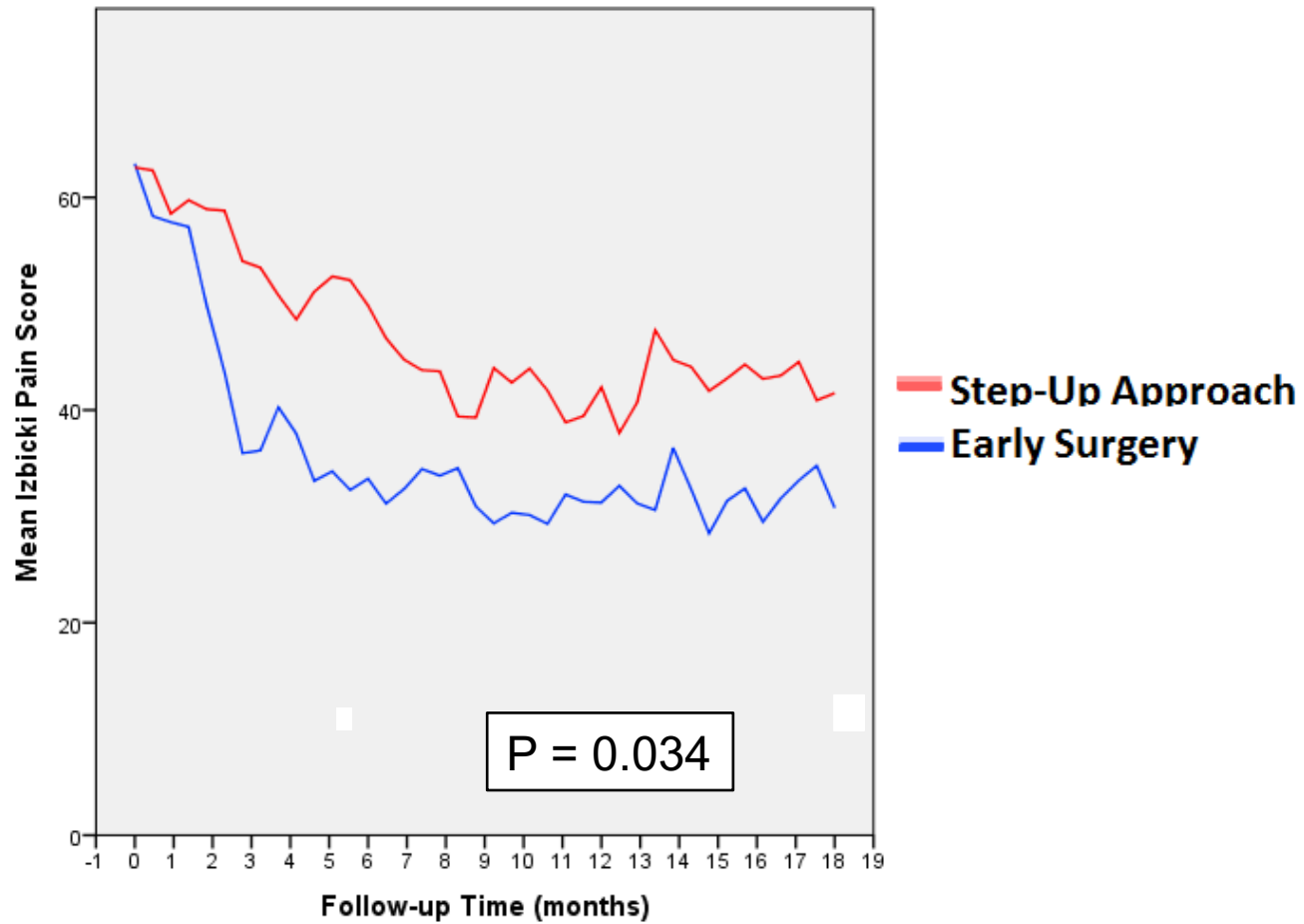
Protocol RCT: Ahmed Ali U,..., Boermeester MA. BMC Gastroenterol. 2013

ESCAPE trial: PICO



- *Patients:* 88 patients with chronic pancreatitis (PD > 5 mm), opioids < 2 months
- *Intervention:* Surgery: pancreatojejunostomy or Frey
- *Comparison:* Surgical step-up approach: 1) opioids, 2) endoscopy, 3) surgery)
- *Outcome:* Izbicki pain questionnaire, every 2 weeks during follow-up of 18 months

20 Dutch hospitals, 2011-2014



Take home messages

Elke patiënt met pijnlijke chronische pancreatitis moet worden besproken tijdens **een MDO met een gastroenteroloog en chirurg, beiden ervaren in CP interventies**

‘Tailor your approach’

- leeftijd, co-morbiditeit, wens van de patiënt
- steen grootte, steen locatie, aantal stenen, stenen in/buiten de PD
- stricturen PD
- grootte pancreaskop
- eerdere interventies

Besluit vooraf de maximale tijd voor effect endoscopie, ideaal max 6-8 weken