Bilaga till rapport

Åtgärder vid sten i de djupa gallgångarna
Rapport 297 (2019)

Bilaga 5 Tabeller över beskrivning av ingående studier / Appendix 5 Included studies

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Bilaga 5. Included studies

Table 1. Management of patients with common bile duct stones.

Table 1a. Laparoscopic cholecystectomy (LC) and intraoperative ERCP compared with laparoscopic cholecystectomy and choledochotomy (LCBDE)

Author Year Country	Study period	Number and gender	Median age (years)	Study design	Assessment and follow-up	Results	Harms: Complications/ Mortality	Surgery time (min)	Study quality
ElGeide 2011	2009-2010	226 patients with CBD stone	LC+ERCP 29 LCBDE 32	RCT, envelopes LC+ intraoperative ERCP n=111 LCBDE n=115	Clinical	LC and intraoperative ERCP vs LCBDE ***Stone clearance*** 104/107 vs 103/112 p=0.104 ***Length of hospital stay*** 3.1 vs 2.2 days p=0.638	LC and intraoperative ERCP vs LCBDE ***Complications*** 9.3 vs 7.1 % p=0.204 ***Retained stones*** 0 vs 3.6 %, p=0.041 ***Pancreatitis*** 3.7 vs 0.9 % p=0.025	LC and intraoperative ERCP vs LCBDE ***Surgical time*** 68 vs 57 minutes p=0.857	Young patients. Randomization by envelopes. Medium risk of bias
Hong 2006	2002-2003	234 patients with CBD-stone ultrasound/IOC		RCT, no information on how. LCBDE n=141 LC+ERCP n=93	Clinical	LC and intraoperative ERCP vs LCBDE ***Stone clearance*** 85/93 vs 126/141, p=n.s. ***Length of hospital stay***	LC and intraoperative ERCP vs LCBDE ***Complications*** 2,38 vs 5.5 % p=0.204 ***Retained stones*** 1.17 vs 2.38 %, p=n.s.		Randomization not clear Medium risk of bias

						4,66 vs 4.25 days, p=n.s.			
Barreras Gonzales 2016 Cuba	2007-2011	404 patients with suspected CBD stone 134 eligible and diagnosed with CBD stones	58 (mean) in both groups	RCT computer randomization 1.LC and intra operative ERCP (n=46) 2.ERCP and postoperative (24-48 hours) LC (n=45) 3.LCBDE (n=43)	Clinical	LC and intraoperative ERCP vs LCBDE ***Stone clearance*** 45/46 vs 42/43 RR 1.00 (95 % CI, 0.94; 1.07) ***Length of hospital stay*** 1.2 vs 2.1 days (means)	LC and intraoperative ERCP vs LCBDE ***Mortality*** None in any group ***Postoperative complications*** 0/46 vs 2/43 RR 0.00 (95 % CI, 0.00; 3.84) ***Retained stones*** 1/46 vs 1/43 RR 0.93 (95 % CI, 0.06; 14.48)	LC and intraoperative ERCP vs LCBDE 94.2 (45–300), vs 117 minutes (40–270)	Few patients in each group Medium risk of bias
Poh et al 2016 Australia	2013-2015	104 patients admitted for biliary pain and listed for emergency laparoscopic cholecystectomy, all with known CDB stones on IOC	53 (mean) in both groups	RCT Allocation concealment was carried out by means of sequentially numbered, sealed and signed opaque envelopes containing letters generated by randomization software for simple randomization in a 1:1 ratio	Phone every 3 months and patient records until November 2015 Median follow-up 15 months	LC and intraoperative ERCP vs LCBDE ***Lost to follow-up*** 9 vs 6 whereof 4 vs 2 died. ***Stone clearance*** 45/52 vs 36/52 P=0.057 ***Postoperative hospital stay*** 2 vs 3 days p=0.015	LC and intraoperative ERCP vs LCBDE ***Mortality*** 4 vs 2, none biliary associated in any group ***Postoperative complications*** 14/52 vs 20/52 p=0.30) ***Retained stones*** 8/52 vs 22/52 P=0.04	LC and intraoperative ERCP vs LCBDE 112 (102–125), vs 110 minutes (95–140)	Few patients in each group Randomization procedure with envelopes. Medium risk of bias

				LC and intraoperative ERCP (n=52) Vs LCBDE + transcystic (n=43) or choledochotomy (n=5)) (n=52)					

CBD= common bile duct
LCBDE = Laparoscopic common bile duct exploration
ERCP= endoscopic retrograde cholangiopancreatography
LC= laparoscopic cholecystectomy
RCT = randomized controlled trial
MD = mean difference

Table 1b. Laparoscopic cholecystectomy with choledochotomy (LCBDE) compared with laparoscopic cholecystectomy with transcystic stone extraction (LTCBDE)

Author Year Country	**Study period**	**Number and gender**	**Median age (years)**	**Study design**		**Assessment and follow-up**	**Results**	**Harms: Complications/ Mortality**	**Surgery time (min)**	**Study quality**
Feng et al 2016 Systematic review	Database search Last updated May 2016	Total n= 2 782 LCBDE n= 1 222 LTCBDE n= 1 560 Gender not stated	Not stated	Systematic review meta-analysis Total: 18 controlled experimental trials (CT) whereof 4 are RCTs.			LCBDE vs LTCBDE: ***Stone clearance from the CBD*** *(12 CT)* 87.2/88,9 % OR 0.73 (95 % CI 0.50; 1.07 ***Postoperative length of stay*** *(days)* (14 CT) MD 2.52 (95 % CI 1.29; 3.75)	LCBDE vs LTCBDE ***Total morbidity*** (11 CT) 15.0/10.3 % OR 1.65 (95 % CI 0.92; 2.96) ***Biliary morbidity*** (9 CT) 6.1/1.3 % OR 4.25 (95 % CI 2.30; 7.85) ***Conversion to other procedures*** *(10 CT)* 7.5/10.9 % OR 0.62 (95 % CI 0.21; 1.79) ***Blood loss*** (2 CT) MD 1.95 ml, (95 % CI −9.56; 13.46)	LCBDE vs LTCBDE ***Total operating time*** (12 CT) MD 12.34, (95 % CI −0.10; 24.78)	Medium quality AMSTAR

CBD= common bile duct
LCBDE = Laparoscopic common bile duct exploration
LTCBDE = laparoscopic transcystic common bile duct exploration

CT = controlled trial
RCT = randomized controlled trial
MRCP = Magnetic resonance cholangiopancreatography
OR = odds ration
CI = confidence interval
MD = mean difference

Table 1c. Management of common bile duct stones in patients with gallstone pancreatitis

Author Year Country	**Study period**	**Number and gender**	**Median age (years)**	**Study design**	**Assessment and follow-up**	**Results**	**Harms: Complications/ Mortality**	**Study quality**
Burstow et al 2015 Systematic review	Database search: 1970–2014	Total n= 1 314 Early* ERCP ± ES n= 652 conservative management (CM) n= 662 * between 24 and 72 h Gender not stated	Not stated	Systematic review meta-analysis 11 RCT	n/a	Stone free rate not stated	ERCP ± ES vs CM: ***Overall complications*** <u>Any GSP</u> OR 0.43 (95 % CI 0.27; 0.68) <u>Mild GSP</u> OR 0.67 (95 % CI 0.43; 1.03) <u>Severe GSP</u> OR 0.32 (95 % CI 0.17; 0.61) ***Renal failure*** 6 RCT OR 0.84 (95 % CI 0.35; 2.05) *Cardiac failure* 5 RCT OR 0.77 (95 % CI 0.35; 1.71)	Medium quality AMSTAR

							Respiratory failure 6 RCT OR 0.75 (95 % CI 0.32; 1.75) ***Biliary sepsis*** 6 RCT OR 0.37 (95 % CI 0.07; 2.04) ***Pseudocyst*** 7 RCT OR 0.55 (95 % CI 0.29; 1.04) ***Pancreatic abscess/phlegmon*** 8 RCT OR 0.70 (95 % CI 0.34; 1.45) *Coagulation/ disseminated intravascular coagulopathy* 5 RCT OR 1.15 (95 % CI 0.40; 3.30) ***Death***	

							<u>Any GSP</u> OR 0.47 (95 % CI 0.20; 1.09) <u>Mild GSP</u> : OR 0.66 (95 % CI 0.02; 28.7) <u>Severe GSP</u> OR 0.45 (95 % CI 0.19; 1.09)	
Green et al 2017 UK	2008-2010	19 510 with gallstone pancreatitis. Male 38 % Female 62 %	Early treatment (same admission or within 2 weeks) = 52 Delayed treatment = 62	NHS Hospital Episode Statistics database Register study Observational Early (n= 6 733) vs delayed or no (n= 12 777) definitive treatment Multivariable log-binomial regression (Early definitive treatment = 3 497 ERCP, 2 962 laparoscopic cholecystectomies, 274 both interventions.	Readmission events in Hospital Episode Statistics database	***Reduction in readmission*** Early treatment 39 %, RR 0.61 (95 % CI, 0.58;0.65) for new acute pancreatitis 54 %, RR 0.46 (95 % CI, 0.42;0.51)		Medium risk of bias

CBD= common bile duct
GSP = gallstone pancreatitis
RCT = randomized controlled trial
OR = odds ratio
CI = confidence interval

Table 1d. Management of common bile duct stones in patients with acute cholangitis

Author Year Country	Study period	Number and gender	Median age (years)	Study design	Assessment and follow-up	Results	Harms: Complications/ Mortality	Study quality
Khashab et al 2012 USA Johns Hopkins	1994-2010	90 acute cholangitis 47 Male 43 Female 35 with CBD stone	60 all (mean)	Retrospective observational Delayed ERCP >72hours Multivariate logistic regression	Medical records	Delayed ERCP Longer hospital stay OR19.8 (95 % CI, 2.18; 178.0) Higher hospital cost OR 11.3 (95 % CI, 1.30; 98.0)	Composite clinical outcome (in-hospital mortality, persistent organ failure, and/or ICU stay) OR, 7.8 (95 % CI, 1.1; 58).	90 patients over 16 years inclusion period, i.e., probably selected, less than half with CBD stone Wide confidence intervals Absolute values not given Those with CBD stones are not described separately Medium/high risk of bias
Lee et al 2015 USA Loma Linda	2005-2013	203 cholangitis Male 45 % Female 55 % 115 with CBD stones	59 (mean) all	Retrospective observational Delayed ERCP >48 hours after hospitalisation Multivariate analysis	Medical records		**Mortality 30-day** Early 3/98 Delayed 7/62 **Persistent organ failure** ERCP at <24, 24–48, 48–72 and >72 h from presentation were 13 %, 18 %, 23 %, and 39 % Delayed ERCP OR 3.1 (95 % CI, 1.4; 7.0)	Mix of causes of the cholangitis, approximately half had CBD stones 40 with malignant strictures Those with CBD stones are not described separately Medium risk of bias

							Every 1-day delay in ERCP was associated with a RR 17 % (95 % CI, 5; 29 %) for persistent organ failure after adjusting for significant factors	
Navaneetha n et al 2014 USA Cleveland Clinic	2001-2012	172 with cholangitis 57 % male 43 % female 67 with CBD stones	61 (mean) all	Retrospective observational Delayed ERCP >72 hours after hospitalisation Multivariate logistic regression	Medical records	Delayed ERCP Length of stay OR 1.70 (1.36-2.12)	Delayed ERCP Persistent organ failure and/or 30-d mortality. OR = 3.36, (95 % CI:1.12; 10.20)	Mix of causes of the cholangitis, 39 % had CBD stones Those with CBD stones are not described separately Medium risk of bias
Tan et al 2018 Denmark	2009-2016	4 006 ERCP 166 with acute cholangitis (Tokyo guidelines) 74 with CBD stones Malignancy as cause of cholangitis in 72 patients	71	Register Delayed >24 hours (n=118) Multiple logistic regression	Medical records		Mortality 30-days Early 4 (8 %) Delayed 23 (19 %) OR 0.23 (95 % CI, 0.05; 0.95), p=0.04	Mix of causes of the cholangitis, 45 % had CBD stones and 43 % malignancy as cause of cholangitis Those with CBD stones are not described separately Medium risk of bias
Park et al 2016 South Korea	2009-2014	331 all with acute calculous cholangitis (Tokyo guidelines	81 (mean) All 75 years or older	Retrospective observational Urgent intervention (ERCP, percutaneous	Medical records	**Hospital stay** (days) Urgent vs early All	**Mortality** n=5 whereof 3 of the 6 in whom the procedure failed.	No obvious difference in outcome in those aged 75-80 years compared with those aged 81 or older. Medium risk of bias

				transhepatic biliary drainage) <24 hours (n=247) Early intervention 24-48 hours (n=60)		7.0±3.7 vs 8.8±5.8, p=0.02 Mild cholangitis 6.2±4.1 vs 10.6±4.2, p=0.02 Moderate cholangitis 6.7±3.6, vs 13.5±6.6, p=0.001 Severe cholangitis 8.7±4.0 vs 11.0±1.6, p=0.03		
Zhu et al 2014 China	2009-2012	72 patients with CBD stones confirmed by MRCP and non-severe (Tokyo guidelines) acute cholangitis 36 males	Emergent 65 Elective 61	Retrospective? 37 emergent LCBDE 35 elective LCBDE No time definition of emergent and elective		***Procedure time*** 105.54 ± 6.30 versus 97.71 ± 7.77, p>0.05 ***Hospital stay*** 16.41±1.03 versus 14.54 ± 0.94, p>0.05 ***Cost*** 18,603 ± 1774.64 versus 14,951 _ 1257.09		Described as retrospective but is written as prospective !! Medium risk of bias

						Yuan, p>0.05)		
Hou et al 2017 USA	2010-2013	199 patients with cholangitis (all grades, Tokyo guidelines) In 182 successful ERCP	51 (mean) Males 83 Females 116	Prospective cohort Time cut-offs <24. <48 and <72 hours	Not specified	Length of stay (days median, range) <72 hrs 6.7 2.2-63.8) >72 hrs 10.9 (4.3-75.7)	ERCP <24 hours base line ICU admission OR >48 hrs O.3 (95 % CI 0.2; 0.6), p<0.01 >72 hrs O.4 (95 % CI 0.2; 0.8), p=0.01 Death OR >48 hrs 3.2 (95 % CI 0.6; 16.6) p=0.17 >72 hrs 3.7 (95 % CI 0.8; 0.15.9), p=0.08	Malignant obstruction in 46 (23 %) of the patients
Parikh et al 2018 USA	1998-2012	107 253 patients with choledocholithiasis and cholangitis 77 323 underwent ERCP	ERCP <24 hrs 69 24-48 hrs 70 >48 hrs 72 (means) Male/female 40/60 %	Register study, National inpatient sample	Register based	***LOS (days, estimated from figure 2)*** <24 hrs 4.9 24-48 hrs 5.4 >48 hrs 8.6 (means) p<0.001	In -hospital mortality (%) <24 hrs 1.7 24-48 hrs 1.2 >48 hrs 2.7 p<0.001	Large register study, only choledocholithiasis Analyses less well reported

CBD= common bile duct
ERCP= endoscopic retrograde cholangiopancreatography
RCT = randomized controlled trial
OR = odds ratio
CI= confidence interval

Table 2. Technique of papillotomy in endoscopic retrograde cholangiopancreatography in patients with common bile duct stones.

Table 2a. Endoscopic sphincterotomy combined with balloon dilatation compared with endoscopic sphincterotomy only

Author Year Country	**Study period**	**Number and gender**	**Median age (years)**	**Study design**	**Assessment and follow-up**	**Results**	**Harms: Complications/ Mortality**	**Surgery time (min)**	**Study quality**
De Clemente et al., 2018 Systematic review	Database search: Last update July 2017	Total: n= 835 EST + LBD n= 914 EST n=910 All stone sizes, "subgroup analysis" of stones >15 mm	Not stated	Systematic review meta-analysis Total: 11 RCT whereof 6 with stones >15 mm		EST+LBD vs EST: **Stone removal (**11 RCT) 94/91 % RD 0.03 (95 % CI 0.01; 0.06) ***Stone removal stones >15 mm, (***6 RCT) *93/91 %* RD 0.02 (95 % CI 0.02; 0.07) Use of mechanical lithotripsy (11 RCT) 11/29 % MD -0.16, (95 % CI -0.25; -0.06) Use of mechanical	EST+LBD vs EST: Postoperative pancreatitis (11 RCT) 4.4/5.4 % MD -0.01, (95 % CI -0.03; 0.01) Postoperative cholangitis (11 RCT) 0.8/0.8 % MD -0.00, (95 % CI -0.01; 0.01) Bleeding (11 RCT) 2.0/3,5 % MD -0.02 (95 % CI -0.03; 0.00)		Medium quality AMSTAR

						lithotripsy, stones >15 mm (6 RCT) 25/53 % MD -0.20, (95 % CI -0.38; -0.02)			

CBD= common bile duct;
EST=endoscopic sphincterotomy
EPLBD = endoscopic sphincterotomy with large balloon dilation;
RCT = randomized controlled trial
OR = odds ration
MD = mean difference
CI = confidence interval

Table 2b. Endoscopic sphincterotomy compared with endoscopic balloon dilatation

Author Year Country	Study period	Number and gender	Median age (years)	Study design	Assessment and follow-up	Results	Harms: Complications/Mortality	Study quality
Doi et al 2013 Japan	1991-2011	1 195 patients 1 086 included Male 55 % sphincterotomy 59 % balloon dilatation	Sphincterotomy 71 Balloon dilatation 69	Retrospective cohort Observational Propensity score on 246 pairs. Endoscopic sphincterotomy vs balloon dilatation	Clinical records Median follow-up 90 months	Endoscopic sphincterotomy / balloon dilatation ***Stone size (mm)*** 9 (6-13)/8 (6-12) ***Complete CBD stone removal*** Not addressed ***Mechanical lithotripsy*** 96/246 (20 %) / 42/246 (17 %) p=0.149 ***Recurrence of CBD stone*** 37/246 (15 %) / 21/246 (8.5 %) HR 0.58 (95 % CI, 0.34; 0.99)	Endoscopic sphincterotomy / balloon dilatation ***Mortality*** Not addressed ***Cholangitis*** 6/246 (2.4 %) / 1/246 (0.4 %) HR 0.19 (95 % CI, 0.02; 1.64)	Medium risk of bias
Minakari et al 2016 Iran	2008-2011	160 patients with verified CBD stones 81 males 79 females	56 (mean)	RCT Endoscopic sphincterotomy (n=80) vs balloon dilatation (n=80)	Mode and time not given	Endoscopic sphincterotomy / balloon dilatation ***Stone size mm*** 10-20 mm	Endoscopic sphincterotomy / balloon dilatation ***Mortality*** None ***Pancreatitis***	No information on randomization procedure No information on follow-up Medium/high risk of bias

						Complete CBD stone removal 77/80 (96 %) / 78/80 (97.5 %) p=0.5 use of mechanical lithotripsy unclear	7/80 (9 %) / 9/80 (11 %) p= 0.4)	
Omar et al 2017 Egypt	2014-2016	296 patients with CBD stones 158 randomized	Endoscopic sphincterotomy 45 Balloon dilatation 48 (means)	RCT Endoscopic sphincterotomy n=63 (male/female 25/38) 61 balloon dilatation n=61 (male/female 26/35)	Cholangiogram at procedure, at least 24 hours observation for complications	Endoscopic sphincterotomy / balloon dilatation Mean stone size (mm) 13.1 ± 2.6 / 13.9 ± 2.4 Complete CBD removal 59/63 (94 %) / 59/61 (97 %) /p=0.53 Mechanical lithotripsy 11/63 (18 %) / 6/61 (10 %) p=0.04	Endoscopic sphincterotomy / balloon dilatation Mortality None Pancreatitis 4/63 (6.3 %) / 3/61 (4.9 %) p=0.38 Cholangitis 1/63 (1.9 %) / 2/61 (3.3 %) p=0.69	Almost half of eligible patients not randomized, 10 % loss to follow-up when randomized, unknown reason. Medium/high risk of bias Relatively small study
Seo et al 2014 South Korea	2006-2012	132 patients <40 years With known gallbladder stones and CBD stones	Endoscopic sphincterotomy 32 Balloon dilatation 33 (means)	RCT Endoscopic sphincterotomy (n=70) vs balloon dilatation (n=62)	Clinical follow-up Mean follow-up time 35 months	Endoscopic sphincterotomy / balloon dilatation ***Stone size mm*** 6-12, Mean 7.6 ± 3.12/7.2 ± 2.08	Endoscopic sphincterotomy / balloon dilatation ***Mortality*** None ***Pancreatitis***	Limited age group Medium risk for bias

						Complete CBD removal 70/70 (100 %) / 61/62 (98 %) p=0.47 ***Mechanical lithotripsy*** 6/70 (9 %) / 5/62 (8 %) p>0.999 ***Recurrence of CBD stone*** 4/70 (6 %) / 1/62 (1.6 %) p=0.37	5/70 (7 %) / 5/62 (8 %) p>0.999)	
Lu et al 2014 China	2008-2011	863 patients with CBD stones 468 males	Endoscopic sphincterotomy 62 Balloon dilatation 65 (means)	Observational cohort Retrospective Endoscopic sphincterotomy (=636) vs balloon dilatation (n=227) Multivariate analysis of long-term risk factors 663 possible to evaluate for long-term events	Clinical records Phone interviews Median 54 (37-78) months	Endoscopic sphincterotomy / balloon dilatation ***Stone size (mm + range)*** 10 (2-40)/10 (3-45) ***Complete CBD stone removal*** 577/636 (91 %) / 215/227 (95 %) p=0.06 ***Mechanical lithotripsy*** 33/636 (5 %) / 26/227 (11 %) p=0.0013 ***Recurrence of CBD stone*** 59/494 (11 %) / 12/170 (7 %)	Endoscopic sphincterotomy / balloon dilatation ***Mortality*** None ***Pancreatitis*** 16/636 (2.5 %) / 16/277 (7 %) p=0.0019 ***Cholangitis*** OR balloon dilatation 0.288 (95 % CI, 0.0118; 0.699) OR gallbladder stones 2.212 (95 % CI, 1.197; 4.086) ***Cholecystitis*** OR balloon dilatation 0.292	Medium risk for bias

						p=0.07 OR balloon dilatation 0.448 (95 % CI, 0.288; 0.879) OR mechanical lithotripsy 3.916 (95 % CI, 1.734; 8.846)	(95 % CI, 0.093; 0.918) OR gallbladder stones 7.615 (95 % CI, 2.193; 26.442)	

CBD= common bile duct
EST=endoscopic sphincterotomy
EPLBD = endoscopic sphincterotomy with large balloon dilation
RCT = randomized controlled trial
OR = odds ratio
HR = hazard rate
CI = confidence interval

Table 3. Active or conservative management of small common bile duct stones

Author Year Country	Study period	Number and gender	Median age (years)	Study design	Assessment and follow-up	Results	Harms: Complications/Mortality	Study quality
Ammori et al 2000 UK	1990-1997	922 consecutive patients treated with LC 70 had filling defects at IOC 26 < 5 mm 44 >- 5 mm	Observation 58 ERCP 54	Prospective observational Cohort Patients assigned to observation or ERCP according to surgeon's preference. 26 with filling defect <5 mm. 8 ERCP, 14 on observation, 4 excluded due to previous sphincterotomy	Clinical follow-up 6 weeks, 6 and 18 months Abdominal ultrasound in the observation group	4/14 of the observation patients developed symptoms and were treated with ERCP 1 stone free, 2 with stone, 1 failed. Planned ERCP (n=8) 4 stone free, 3 with stone, 1 failed ERCP/ observation Median 5/1.5 days in hospital p=0.011 Postop outpatient visits Median 3/5.5 p=0.011 Cost 2669£/1508£	No complications	Medium/high risk for bias few probably selected patients unprecise follow-up <5 mm 12 proceeded to ERCP, 2 failed, 5 with stone 5 stone free

Collins et al 2004 Ireland	1990-2001	999 patients operated with LC for gallbladder stone (single surgeon), 810 females, 189 males IOC succeeded in 962 46 had filling defect on IOC	49 (mean)	Cohort, prospective	Cholangiogram catheter left in place and cholangiogram was repeated at 48 hours and 6 weeks postop	12 patients free of filling defect at 48 hours, i.e. possible artefact, Another 12 free at 6 weeks . 22 had a persistent filling defect at 6 weeks and were treated with ERCP all with CBD stones Spontaneous passage not correlated to size of the stone or the diameter of the common bile duct	"There were no intraoperative complications attributable to the cholangiography. No patient reported any catheter related problems either before or after its removal. In particular, there was no case of cholangitis while the catheter was in situ and no bile leaks occurred on its removal"	Low risk of bias.
El Nakeeb et al 2016 Egypt	2012-2014	605 patients with CBD stone. 100 with CBD diameter <10 mm and stone less or equal 5 mm All stones verified with MRCP	Conservative 42 Preoperative ERCP 45	RCT, conservative (antibiotics + antispasmodics) + LC+IOC vs ERCP + LC+IOC 50/50 patients Procedures in both arms done within 3 days from dx of stone	Ultrasound LC and IOC	Observation group spontaneously passed stone in 38/50 patients ERCP-group 22 stone passed spontaneously 26 cleared by ERCP 2 cleared by transcystic extraction Cost 799$ in observation group and 1265$ in ERCP-group	2 patients with pancreatitis in the observation group and 8 in ERCP-group	Low/medium risk of bias.
Frossard et al 2000 Switzerland/France	1994-1996	211 patients referred for possible CBD stone 155 had a stone on	Not stated	Prospective observational cohort	ERCP	12 (21 %) patients free of stones at ERCP within 1 month after ultrasonography.	Complications not addressed	Medium risk of bias.

		endoscopic ultrasonography 92 agreed to partake in the study 45 males and 47 females				10 out of the 12 patients had stones <8 mm. < 8 mm. 10/45 free of stones after 1 month Diameter of passed stones were significantly smaller (p<0.01) than of those retained		
Möller et al 2014 Sweden	2005-2009	38 864 cholecystectomies 3 969 CBD stone 3 828 included in analysis 1 248 males, 2 580 females.	Males 57.8 Females 50.3	Retrospective register study Cohort 594 patients with no intraoperative measures 3 234 with any intraoperative measure	Postoperative pancreatitis, cholangitis, or obstruction of bile duct/jaundice recorded in the register		All stone sizes 25.3 % unfavourable outcomes in the group with no intraoperative measures and 12.7 % in the group where any measures were taken Risk multiple logistic regression OR 0.44 (95 % CI, 0.35; 0.55) Stones <4 mm 15.9 % unfavourable outcomes in the group with no intraoperative measures and 8.9 % if any measures were taken Risk multiple logistic OR 0.52 (95 % CI, 0.34; 0.79) Stones 4-8 mm 36.9 % unfavourable outcomes in the group with no	Low risk of bias.

							intraoperative measures and 12.5 % if any measures were taken Risk multiple logistic OR 0.24 (95 % CI, 0.17; 0.32)	
Gao et al 2013 China	2009-2013	197 patients with CBD stone verified with CT or MRCP	Anisodamine 58 Placebo 59	RCT Anisodamine versus placebo (iv infusion of saline with similar volume and dosage pattern) 100 patients anisodamine 97 placebo (in the analysis) 47 males, 55 females	CT or MRCP	Placebo Stone free within 1 month Stone <5mm 15/44 (31.8 %) Stone 5-10 mm 7/53 (15.1 %) Stone size OR 3.1 (95 % CI, 1.9; 5.0)		No conclusion regarding the placebo group Low risk of bias in the placebo group

CBD= common bile duct
ERCP= endoscopic retrograde cholangiopancreatography
LC= laparoscopic cholecystectomy
RCT = randomized controlled trial
MRCP = Magnetic resonance cholangiopancreatography
OR = odds ratio
CI = confidence interval

Table 4. Cholecystectomy or not in elderly and frail patients with common bile duct stones

Author Year Country	Study period	Number and gender	Median age (years)	Study design	Assessment and follow-up	Results	Harms: Complications/ Mortality	Study quality"
Archibald et al 2007 Canada	1993-2000	124 had a prophylactic cholecystectomy at ERCP 186 deferred cholecystectomy (DC), 106 females and 80 males	DC 66 (mean)	Retrospective observational cohorts No attempt to correct for differences	Medical records Follow-up up to 3 years (mean 24 months)	DC 46 (25 %) cholecystectomy eventually whereof 29 (63 %) had cholecystolithiasis at the ERCP. In the group with continued deferred treatment 49 % had cholecystolithiasis	Mortality 5 deaths (not directly related to the gall stone disease) in the DC group 9 patients (30 %) of those with pancreatitis as indication for the primary ERCP had recurrent pancreatitis	The two groups had large differences and no measures to correct for this were taken. Medium/ High risk for bias
Boerma et al 2002 The Netherlands		120 patients ERCP for CBD-stone and with proven cholecystolithiasis	Wait and see (WS) 63 Laparoscopic cholecystectomy (LC) 60	RCT WS (n=64) vs LC (n=56) 12 patients lost to follow-up 55 WS patients and 49 LC patients in the analysis	Follow-up over phone at 6 weeks, 3, 6, 12 and 24 months. Quality of life assessed with MOS-24-scale	Biliary events in 27 (47 %) WS patients and 1 in LC patients RR 22.4 (95 % CI, 3.2; 159.1) Cholecystectomy in 22 (37 %) and ERCP in 6 WS patients, Quality of life no difference 3 months after treatment	WS 5 wound infections, 1 intraabdominal abscess and 1 pneumonia .LC 1 perioperative uncontrollable haemorrhage. 3 intraabdominal abscesses, 2 wound infections, and 1 wound haematoma).	Low/medium risk of bias.
Cui et al 2013 South Korea	2000-2004	461 CBD stone removal with ERCP 232 included in the study	Surgery 64 Gallbladder in situ 72 (mean)	Retrospective observational cohort 68 patients had a cholecystectomy in conjunction with the ERCP In 164 patients, the gallbladder	"Chart reviews and personal interviews at our outpatient clinic or by phone calls" Follow-up	Recurrence of CBD stone, patients 10/68 (15 %) in cholecystectomy group 31/164 (19 %) in gallbladder in situ group whereof 7/44 (16 %) in those with known		Medium/high risk of bias,

				was left in situ, where of 44 had cholecystolithiasis	in cholecystectomy group 73 months in gallbladder in situ group 66 months	cholecystolithiasis and 24/120 (20 %) in those without known cholecystolithiasis. 9/44 (14 %) in those with known cholecystolithiases developed a cholecystitis while 3 (2.5 %) in those without known cholecystolithiasis so 9/164 (5 %) of the patients in the gallbladder in situ group eventually had a cholecystectomy		
Heo et al 2015 South Korea	2008-2011	554 patients referred for ERCP 90 with proven gallbladder stones, CBD stones and cholangitis 25 males in each randomized group	64 (mean) in both groups	RCT 45 immediate cholecystectomy (26 were actually operated) and 2 were withdrawn. 45 gallbladder left in situ 4 lost to follow-up	Clinical follow-up every 3 months	**Recurrent biliary events** Intention to treat no difference Treatment received 4 in cholecystectomy group 13 in gallbladder in situ group RR 1.22 (95 % CI, 1.00; 1.49)	5 died from non-biliary disease Complications (bleeding, abdominal abscess, bile leak) 2 in cholecystectomy group	Analysis in the primary paper according treatment received. Analysis according intention to treat in supplementary table 1. Medium/high risk of bias
Yasui et al 2012 Japan	1974-2008	327 patients with CBD stones and ERCP 250 < 80 years (Y) 134 males 116 females	Y 64 O 85 (means)	Retrospective cohort No attempt to adjust for differences between Y and O	Follow-up Y 114 months O 76 months (means).	**Biliary complications** 10 year cumulative incidence Cholecystectomy/gallbladder in situ Y 7.5/22 %, p=0.0037 O 8.3/7.4 %, p=0.92	Mortality No data	No absolute numbers on complications in the groups with and without the gallbladder in situ. Only relative numbers from the Kaplan- Myer analysis. Medium/high risk for bias

		77 80 or older (O) 46 males 31 females						
Zargar et al 2014 India	2010-2012	162 patients 70 years or older with CBD stones cleared with ERCP and known gallbladder stones.	Conservative 77 Cholecystectomy 78 (means)	RCT random numbers from randomization table Conservative n=82 Cholecystectomy n =80	Follow-up at 3 months and every 6 months thereafter. 18 months in both groups (mean9	**Biliary events** **n patients** Conservative 22 Cholecystectomy 4 RR 5.4 (1.9; 14.9) **n biliary events** Conservative 27 Cholecystectomy 4 RR 6.6 (2.4; 17.9)	**Death** **Conservative** 10 Cholecystectomy 12. Only 1 death (in the conservative group) as considered biliary related (cholangitis)	Medium/high risk for bias

CBD= common bile duct
ERCP= endoscopic retrograde cholangiopancreatography
LC= laparoscopic cholecystectomy
RCT = randomized controlled trial
RR=relative risk
CI = confidence interval
MRCP = Magnetic resonance cholangiopancreatography