

Supplemental Table 1: Summary of included studies (N=17)

Author, year, location	Total N enrolled in study	N completed follow-up	Male	Type of surgery, anesthesia	Mean age \pm SD or median (IQ)	Follow-up	Cognitive measurement	Definition/ incidence of POCD	Exposure	Adjustment variables	Exposure association with POCD (original reporting)	STROBE score
Di Carlo et al. 2001 ¹⁹ Italy	123	110	71	CPB. General anesthesia.	64 \pm 9 years	6 months	Randt Memory Test; Token Test; naming test; test of abstract thinking; MMSE.	Consensus rating of patients as 'unchanged/ improved', 'mildly or moderately deteriorated' or 'severely deteriorated' by 2 neuro-psychologists. POCD defined as 'severely deteriorated' (n=10/110; 9.1%) versus 'unchanged/ improved' (n=78/110; 70.9%) for purpose of present analysis.	1. High cholesterol (serum levels \geq 6.20 mmol/l [240 mg/dl]) 2. High triglycerides (serum levels \geq 194 mmol/l [170 mg/dl])	None	1. 3/10 (30.0%) of patients in 'severely deteriorated' group had high cholesterol. 28/78 (35.9%) of patients in 'unchanged/improved' group had high cholesterol. 2. 3/10 (30.0%) of patients in 'severely deteriorated' group had high triglycerides. 20/78 (25.6%) of patients in 'unchanged/improved' group had high triglycerides.	19/22
Suksompong et al. 2002 ³⁰ Thailand	110	110	76	CABG. General anesthesia.	62 \pm 8 years	3 to 5 days	Thai Mental State Exam.	POCD defined as decline of \geq 1SD on cognitive test. POCD in n=20/110 (18.2%) of patients.	"Hypercholesterolemia" (undefined)	Age, sex, total of 16 clinical factors	RR= 4.73 (95% CI= 1.56, 14.40)	14/22
Mathew et al. 2005 ¹⁴ USA	440	418	68	CABG with CPB. General anesthesia.	61 \pm 10 years	6 weeks	4 factors of cognitive domains derived from 5 neuropsychological tests with 10 outcome measures.	1. POCD defined as decline of \geq 1SD on \geq 1 cognitive domains. POCD in n=152/418 (36.4%) of patients. 2. POCD assessed continuously as change score of cognitive index.	1. Statin treatment before surgery. 147/418 (35.2%) of patients on statins ^b Simvastatin (29.3%) Pravastatin (26.4%) Atorvastatin	None (except analysis 2.2: baseline cognitive function, age, education, age x	1.1 51/147 (34.7% ^d) of patients on pre-op statins had POCD. 101/271 (37.2%) of patients not on pre-op	16/22

							'Composite cognitive index' as sum of 4 factor scores. Change score calculated by subtracting baseline from follow-up cognitive index.		(22.9%) Lovastatin (13.6%) Fluvastatin (7.1%) Cerivastatin (0.7%) 2. Statin treatment at discharge 3. LDL <90 mg/dl	education interaction, diabetes)	<p>statins had POCD.</p> <p>1.2 Cognitive change score similar in both groups (p=0.97)</p> <p>2.1 42/100 (42.0%) of patients on statins at discharge had POCD.</p> <p>118/318 (37.2%) of patients not on statins at discharge had POCD.</p> <p>2.2 Discharge statin use associated with lower improvement in cognitive score (beta - 0.265; SE 0.103; p=0.011)</p> <p>3.1 62.5% of patients on statins at discharge and low LDL had POCD.</p> <p>26.2% of patients not on statins at discharge and low LDL had POCD.</p> <p>(p=0.09)</p>	
Mocco et al. 2006 ²⁴	186	153	68	CEA.	70 ± 8 years	30 days	5 neuropsychol	POCD defined as total deficit score ≥2SD mean	1.Hypercholesterol emia defined as	None	1. 7/14 (50.0%)	15/22

USA				General anesthesia.			<p>logical tests.</p> <p>For each test, calculation of RCI^a.</p> <p>RCI used to derive deficit score according to point system.</p> <p>Deficit scores summed to derive 'total deficit score'.</p> <p>Control group n=67.</p>	<p>change in total deficit score of control group.</p> <p>POCD in n=14/153 (9.2%).</p>	<p>cholesterol >200 mg/dl or use of anti-cholesterol medication</p> <p>81/153 (52.9%) have hypercholesterolemia.</p> <p>2. Statin treatment</p> <p>80/153 (52.3%) on statins.</p>		<p>of patients in POCD group had hypercholesterolemia.</p> <p>74/139 (53.2%) of patients in no POCD group had hypercholesterolemia.</p> <p>2. 7/14 (50.0%) of patients in no POCD group were on statins.</p> <p>73/139 (52.5%) of patients in no POCD group were on statins.</p>	
Ramlawi et al. 2006 ¹⁶ USA	43	40	88	Primary CABG, aortic/mitral valvular surgery, or combination of the 2 using CPB.	67 ± 11 years	4 days	8 neuropsychological tests of 5 cognitive domains (including 1 test of pre-morbid IQ).	<p>POCD defined as decline of ≥1SD on ≥2 cognitive tests.</p> <p>POCD in 16/40 (40.0%).</p>	"Hypercholesterolemia" (undefined)	None	<p>9/16 (56.3%) patients with POCD had hypercholesterolemia.</p> <p>11/24 (45.8%) patients with no POCD had hypercholesterolemia.</p>	19/22
Baba et al. 2007 ²⁶ Japan	218	218	70	On-pump or off-pump CABG. General anesthesia.	71 ± 6 years	1 week	4 neuropsychological tests; Hasegawa dementia scale.	<p>POCD defined as decline of ≥20% on ≥3/4 cognitive tests.</p> <p>POCD in 39/218 (17.9%).</p>	"Hyperlipidemia" defined as total cholesterol ≥240 mg/dl or triglyceride ≥150 mg/dl	None	<p>21/39 (53.8%) of patients with POCD had hyperlipidemia.</p> <p>93/179 (52.0%) patients with no POCD had hyperlipidemia.</p> <p>p=0.830</p>	16/22
Saito et al. 2007 ²⁹	55	55	94 ^d	CEA.	67 ± 8 years	1 month	5 neuropsychological tests	<p>POCD defined as decline of ≥1SD on ≥1 cognitive tests.</p>	"Hyperlipidemia" (undefined)		1/6 (16.7%) of patients in POCD group	13/22

Japan							(including 1 test of pre-morbid IQ).	POCD in 6/55 (10.9%).			hyperlipidemia . 8/49 (16.3%) of patients in no POCD group had hyperlipidemia .	
Wilson et al. 2008 ²⁵ USA	22 ^c	21 ^c	76	CEA. General anesthesia.	69 ± 8 years	1 day	5 neuropsychological tests. For each test, calculation of RCI ^a . RCI used to derive 'total deficit score' according to point system (score range 0-6 for each test). Deficit scores summed to derive 'total deficit score'. Control group n=20.	POCD defined as total deficit score ≥2SD mean change in total deficit score of control group. POCD in n=6/21 (28.6%).	1. "Hypercholesterolemia" defined as blood cholesterol >200 mmHg (assumed typographical error meaning "mg/dl") or use of anti-cholesterol medication Hypercholesterolemia in 99/183 (54.1%) of patients. 2. Statin treatment 97/183 (53.0%) of patients on statins.	None	1. 16/33 (48.5%) of patients in POCD group have hypercholesterolemia. 83/153 (54.2%) of patients in no POCD group have hypercholesterolemia. (based on report on N=186) 2. 13/33 (39.4%) of patients in POCD group on statins. 84/153 (54.9%) of patients in no POCD group on statins.	16/22
Gaudet et al. 2009 ¹⁸ USA	24	24	75	Carotid artery stenting.	70 ± 4 years	1 day	6 neuropsychological tests with 10 outcome variables. For each test, calculation of RCI ^a . RCI used to derive deficit	'Moderate to severe cognitive dysfunction' used as POCD in present analysis. "Moderate to severe cognitive dysfunction" defined as ADS ≥1.5 SD larger than control mean ADS and/or RCI ≤-1.5 on ≥2 cognitive tests. 'Moderate to severe cognitive dysfunction' in	1. "Dyslipidemia" (undefined) Dyslipidemia in 21/24 (87.5%) of patients. 2. Oral statin treatment 22/24 (91.7%) of patients on statins.	None	1. No analysis of dyslipidemia and POCD 2. 7/10 (70.0%) of patients in POCD group on statins. 14/14 (100.0%) of	16/22

							score according to point system. 'Average deficit score' (ADS) as sum of deficit scores divided by number of completed tests. Control group n=23.	10/24 (41.7%) of patients. 'Severe cognitive dysfunction' defined as ADS ≥ 2 SD larger than control mean ADS and/or RCI ≤ -2 on ≥ 2 cognitive tests, but associations with dyslipidemia or statins unreported.			patients in no POCD group on statins.	
Evered et al. 2011 ¹⁷ Australia	644	443	63	Coronary angiography, CABG, total hip replacement surgery. Local, spinal or general anesthesia.	68 \pm 8 years	7 days	8 neuropsychological tests. For each test, calculation of RCI ⁸ . To obtain composite RCI, RCI summed across tests and divided by SD of RCI sum of controls. Control group n=34.	POCD defined as RCI < 1.96 on ≥ 2 tests and/or composite RCI < -1.96 . POCD in n=150/443 (33.9%).	1. "Hypercholesterolemia" (undefined) Hypercholesterolemia in 400/644 (62.1%) of patients. 2. Statin treatment 345/644 (53.6%) of patients on statins.	Age, BMI, diabetes, beta blockers, statins, PAD, MI, type of surgery, hypercholesterolemia/statins respectively	1. RR = 0.72 (95% CI = 0.40, 1.32; p=0.29) 2. RR = 1.37 (95% CI = 0.78, 2.39; p=0.27)	16/22
Heyer et al. 2013a ²¹ USA	115	115	Unreported	Patients with type 2 diabetes undergoing CEA. General anesthesia.	30% >75 years	1 day	12 neuropsychological tests of 4 cognitive domains. RCI ⁸ calculated for each test. Control group n=156.	POCD defined as RCI ≥ 2 on ≥ 2 cognitive domains or RCI ≥ 1.5 on all 4 cognitive domains. POCD in n=25/115 (21.7%).	1. LDL 2. HDL 3. Total cholesterol 4. Triglycerides 5. Statin treatment 70/115 (60.8%) on statins	1. to 4.: None. 5. Symptomatic status, APOE ϵ 4 carrier, monocyte count, c-reactive protein concentration, ICAM-1 concentration, MMP-9 activity	1. RR = 1.00 (95% CI = 0.99, 1.01; p=0.79) 2. RR = 1.03 (95% CI = 1.00, 1.07; p=0.59) 3. RR = 1.00 (95% CI = 0.99, 1.01; p=0.72) 4. RR = 1.00 (95% CI = 0.99, 1.01; p=0.78)	13/22

											5. $RR = 0.64$ (95% $CI = 0.13, 3.24$; $p = 0.20$) More people in patient group than controls on statins	
Heyer et al. 2013b ²² USA	324	324	66	CEA. Anesthesia unreported.	29% >75 years	1 day	12 neuropsychol ogical tests of 4 cognitive domains. RCI ^a calculated for each test. Control group n unreported.	POCD defined as RCI ≥ 2 on ≥ 2 cognitive domains or RCI ≥ 1.5 on all 4 cognitive domains. POCD in $n = 47/324$ (14.5%).	1. Statin treatment 200/324 (61.7%) on statins. Simvastatin (33.0%) Pravastatin (4.5%) Atorvastatin (47.0%) Lovastatin (8.5%) Fluvastatin (1.0%) Rosuvastatin (6.0%) 2. Simvastatin versus atorvastatin 3. Maximum dose versus sub- maximum dose	None	1. 22/200 (11.0%) of patients on statins had POCD. 25/124 (20.2%) of patients not on statins had POCD. 2. 2/66 (3.0%) of patients on simvastatin had POCD. 15/94 (16.0%) of patients on atorvastatin had POCD ($p = 0.005$). Groups differed on HDL (simvastatin $58.7 \pm$ 17.6 mg/dl vs. atorvastatin $41.7 \pm$ 14.0 mg/dl ; $p < 0.001$) and LDL (simvastatin $78.6 \pm$ 36.3 mg/dl vs. atorvastatin $108.6 \pm$ 67.0 mg/dl ; $p = 0.001$).	17/22

											3. 2/74 (2.4%) of patients on maximum dose had POCD. 20/126 (15.9%) of patients on sub-maximum dose had POCD (p=0.002).	
Heyer et al. 2014 ²³ USA	411	306	66 ^b	CEA. General anesthesia.	29% >75 years ^b	1 month	9 neuropsychological tests of 4 cognitive domains. RCI ^a calculated for each test. Control n=156.	POCD defined as RCI ≥ 2 on ≥ 2 cognitive domains or RCI ≥ 1.5 on all 4 cognitive domains. POCD in n=41/306 (13.4%).	Statin treatment 272/411 (66.2%) on statins ^b .	None	RR = 0.85 (95% CI = 0.43, 1.72)	19/22
Plaschke et al. 2013 ²⁸ Germany	139	117	76%	CABG. Anesthesia unreported.	69 \pm 8	3 months	6 neuropsychological tests with 12 outcome variables used to calculate RCI ^a . RCI summed across tests and divided by SD of RCI sum of controls to obtain composite RCI Control group n=34.	POCD defined as RCI ≥ 1.96 on ≥ 2 tests and/or combined RCI ≥ 1.96 . POCD in n=30/117 (25.6%).	"Hypercholesterolemia" (undefined)	None	28/30 (93.3%) of patients in POCD group had hypercholesterolemia. 84/87 (96.6%) of patients in no POCD group had hypercholesterolemia.	19/22
Joudi et al. 2014 ²⁷ Iran	171	171	Unreported.	CABG. General anesthesia.	64 \pm 10 years	1 day	MMSE.	Unclear definition of POCD. POCD in 129/171 (75.4%).	"Hyperlipidemia" (undefined) Hyperlipidemia in 73/171 ^a (42.7%) of patients.	None	52/129 (40.6%) of patients in POCD group had hyperlipidemia.	13/22

											21/42 (49.6%) of patients in no POCD group had hyperlipidemia.	
Shoair et al. (2015) ^{e 15} USA	69	69	33%	Orthopedic or neurosurgery (noncardiac). Regional and/or general anesthesia	71 ± 5	3 months	5 neuro-psychological tests Calculation of RCI ^a RCI summed across tests and divided by SD of RCI sum of controls to obtain composite RCI. Control group n=54.	POCD defined RCI <1.96 on ≥2 tests and/or combined RCI <1.96. POCD in n=11/69 (15.9%)	Hypercholesterolemia defined by combination of self-report and verification on basis of medical records. Hypercholesterolemia in n=12/69 (20.3%) of patients.	None	2/12 (16.7%) with POCD have hypercholesterolemia. 9/57 (15.8%) without POCD have hypercholesterolemia.	19/22
Knipp et al. 2017 ³¹ Germany	36	31	64 ^d	Isolated cardiac valve surgery. Anesthesia unreported.	65 ± 9 years (range 32-82 years)	3 to 4 years (mean 3.7 years)	11 neuropsychological tests of 7 domains. Follow-up scores z-standardized according to baseline scores.	POCD defined as decline of ≥1SD on ≥3 cognitive tests. POCD in n=5/31 (16.1%) of patients.	"Hyperlipidemia" (undefined)	None	RR=0.77 (95% CI=0.15, 3.86)	17/22

All data refer to analysis sample that completed follow-up, unless otherwise indicated. CABG, coronary artery bypass grafting; CEA, carotid endarterectomy; CPB, cardiopulmonary bypass; ICAM-1, intercellular adhesion molecule-1; IQ, interquartile range; MMP-9, matrix metalloproteinase-9; MMSE, Mini Mental State Examination; RCI, reliable change index; RR, relative risk; SD, standard deviation; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

^aformula to obtain Reliable Change Index (RCI; often referred to as 'z-score' in original publication): $RCI = (\text{change score of patient} - \text{change score of control or patient group}) / \text{SD of change score of control or patient group}$.

^bbased on total sample enrolled into study (data on analysis sample completing follow-up unreported).

^ctotal N uncertain on basis of article

^ddiscrepancy from original N or % reported in article for unclear reasons

^eunpublished data

Supplemental Table 2: Subgroup analysis of hypercholesterolemia and risk of POCD according to study characteristics (total N=12)

	Characteristic		Study N	References	Pooled estimates and heterogeneity in sub-group analysis
Surgery type	CABG (on/off-pump) and/or cardiopulmonary bypass	Cardiac surgery	7	Baba (2007) Di Carlo (2001) Joudi (2014) Plaschke (2013) Suksompong (2002) Ramlawi (2006)	RR=0.95 (95% CI=0.81, 1.12; p=0.57) Chi ² (6) = 9.70; p=0.14; I ² =38%
	CABG and/or valve surgery			Knipp (2017)	
	Isolated cardiac valve surgery				
	Carotid endarterectomy or carotid artery stenting	Non-cardiac surgery	4	Mocco (2006) Saito (2007) Wilson (2008) Shoair (2015)	RR=0.88 (95% CI=0.54, 1.41; p=0.59) Chi ² (3) = 0.12; p=0.99; I ² =0%
	Orthopedic or neurosurgery				
	Various cardiac and non-cardiac	Mixed	1	Evered (2011)	RR=0.72 (95% CI=0.40, 1.32; p=0.29)
Follow-up	≤1 month		8	Baba (2007) Evered (2011) Joudi (2014) Mocco (2006) Ramlawi (2006) Saito (2007) Suksompong (2002) Wilson (2008)	RR=0.94 (95% CI=0.81, 1.09; p=0.42) Chi ² (7) = 10.01; p=0.19; I ² =30%
	>1 month		4	Di Carlo (2001) Knipp (2017) Plaschke (2013) Shoair (2015)	RR=0.77 (95% CI=0.40, 1.49; p=0.44) Chi ² (3) = 0.33; p=0.95; I ² =0%
Sample size completing follow-up	N≤100		5	Knipp (2017) Ramlawi (2006) Saito (2007) Wilson (2008) Shoair (2015)	RR=0.97 (95% CI=0.63, 1.50; p=0.91) Chi ² (4) = 0.87; p=0.93; I ² =0%
	N>100		7	Baba (2007) Di Carlo (2001) Evered (2011) Joudi (2014) Mocco (2006) Plaschke (2013) Suksompong (2002)	RR=0.92 (95% CI=0.79, 1.08; p=0.33) Chi ² (6) = 9.74; p=0.14; I ² =38%
Mean age*	≤65 years		3	Di Carlo (2001) Knipp (2017) Suksompong (2002)	RR=1.75 (95% CI=0.83, 3.69; p=0.14) Chi ² (2) = 5.56; p=0.06; I ² =64%
	>65 years		8	Baba (2007) Evered (2011) Mocco (2006) Plaschke (2013) Ramlawi (2006) Saito (2007)	RR=0.91 (95% CI=0.69, 1.20; p=0.50) Chi ² (7) = 2.21; p=0.95; I ² =0%

			Wilson (2008) Shoair (2015)	
Sex*	≤75% male	6	Baba (2007) Di Carlo (2001) Evered (2011) Knipp (2017) Mocco (2006) Shoair (2015)	RR= 0.88 (95% CI= 0.62, 1.25; p=0.48) Chi ² (5) = 0.96; p=0.97; I ² =0%
	>75% male	5	Plaschke (2013) Ramlawi (2006) Saito (2007) Suksompong (2002) Wilson (2008)	RR= 1.14 (95% CI= 0.76, 1.71; p=0.52) Chi ² (4) = 8.53; p=0.07; I ² =53%
Definition of “hypercholesterolemia”	Undefined (“hypercholesterolemia”/“hyperlipidemia”)	7	Evered (2011) Joudi (2014) Knipp (2017) Plaschke (2013) Ramlawi (2006) Saito (2007) Suksompong (2002)	RR= 0.93 (95% CI= 0.79, 1.09; p=0.38) Chi ² (6) = 10.20; p=0.12; I ² =41%
	Combination of self-report and medical history	1	Shoair (2015)	RR= 1.06 (95% CI= 0.26, 4.28; p=0.94)
	Total cholesterol ≥240 mg/dl	1	Di Carlo (2001)	RR= 0.79 (95% CI= 0.22, 2.83; p=0.72)
	Total cholesterol ≥240 mg/dl and/or triglycerides ≥150 mg/dl	1	Baba (2007)	RR= 1.06 (95% CI= 0.60, 1.88; p=0.83)
	Total cholesterol ≥200 mg/dl and/or medication	2	Mocco (2006) Wilson (2008)	RR= 0.84 (95% CI= 0.50, 1.43; p=0.53)
Definition of “hypercholesterolemia” (2 categories)	Undefined/self-report/medical history	8	Evered (2011) Joudi (2014) Knipp (2017) Plaschke (2013) Ramlawi (2006) Saito (2007) Shoair (2015) Suksompong (2002)	RR= 0.93 (95% CI= 0.79, 1.09; p=0.39) Chi ² (7) = 10.23; p=0.18; I ² =32%
	Lab measurements and/or medication	4	Di Carlo (2001) Baba (2007) Mocco (2006) Wilson (2008)	RR= 0.93 (95% CI= 0.64, 1.34; p=0.68) Chi ² (3) = 0.42; p=0.94; I ² =0%

*data missing for N=1 study

Supplemental Table 3: Subgroup analysis of statin use and risk of POCD according to study characteristics (total N=8)

	Characteristic		Study N	References	Pooled estimates and heterogeneity in sub-group analysis
Surgery type	CABG (on/off-pump) and/or cardiopulmonary bypass	Cardiac surgery	1	Mathew (2005)	RR=0.93 (95% CI=0.71, 1.22; p=0.60)
	Carotid endarterectomy or carotid artery stenting	Non-cardiac surgery	6	Gaudet (2009) Heyer (2013a) Heyer (2013b) Heyer (2014) Mocco (2006) Wilson (2008)	RR=0.60 (95% CI=0.44, 0.80; p=0.0005) Chi ² (5) = 3.30; p=0.65; I ² =0%
Follow-up	Various cardiac and non-cardiac	Mixed	1	Evered (2011)	RR=1.37 (95% CI=0.78, 2.39; p=0.27)
	≤1 month		7	Evered (2011) Gaudet (2009) Heyer (2013a) Heyer (2013b) Heyer (2014) Mocco (2006) Wilson (2008)	RR=0.71 (95% CI=0.55, 0.92; p=0.01) Chi ² (6) = 10.01; p=0.12; I ² =40%
	>1 month		1	Mathew (2005)	RR=0.93 (95% CI=0.71, 1.22; p=0.60)
Sample size completing follow-up	N≤100		2	Gaudet (2009) Wilson (2008)	RR=0.49 (95% CI=0.31, 0.78; p=0.003) Chi ² (1) = 0.79; p=0.37; I ² =0%
	N>100		6	Evered (2011) Heyer (2013a) Heyer (2013b) Heyer (2014) Mathew (2005) Mocco (2006)	RR=0.89 (95% CI=0.73, 1.09; p=0.27) Chi ² (5) = 5.88; p=0.32; I ² =15%
Mean age*	≤65 years		1	Mathew (2005)	RR=0.93 (95% CI=0.71, 1.22; p=0.60)
	>65 years		4	Evered (2011) Gaudet (2009) Mocco (2006) Wilson (2008)	RR=0.77 (95% CI=0.55, 1.07; p=0.12) Chi ² (3) = 8.58; p=0.04; I ² =65%
Sex**	≤75% male		6	Evered (2011) Gaudet (2009) Heyer (2013b) Heyer (2014) Mathew (2005) Mocco (2006)	RR=0.84 (95% CI=0.69, 1.02; p=0.08) Chi ² (5) = 10.88; p=0.05; I ² =54%
	>75% male		1	Wilson (2008)	RR=0.60 (95% CI=0.32, 1.13; p=0.11)

*data missing for N=3 studies

**data missing for N=1 study