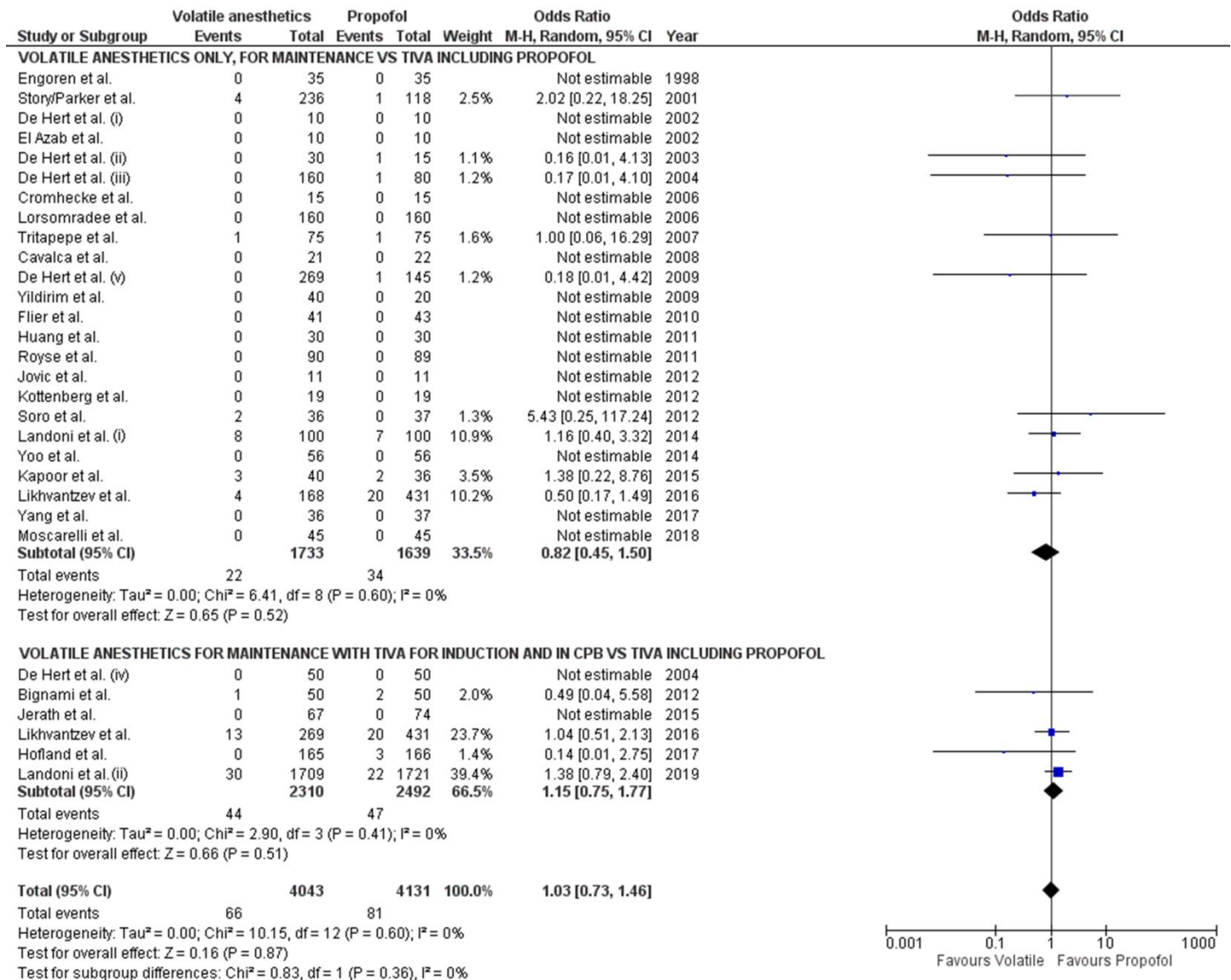**VOLATILE ANESTHETICS VERSUS PROPOFOL FOR CARDIAC SURGERY WITH CARDIOPULMONARY BYPASS: META-ANALYSIS OF RANDOMIZED TRIALS.**
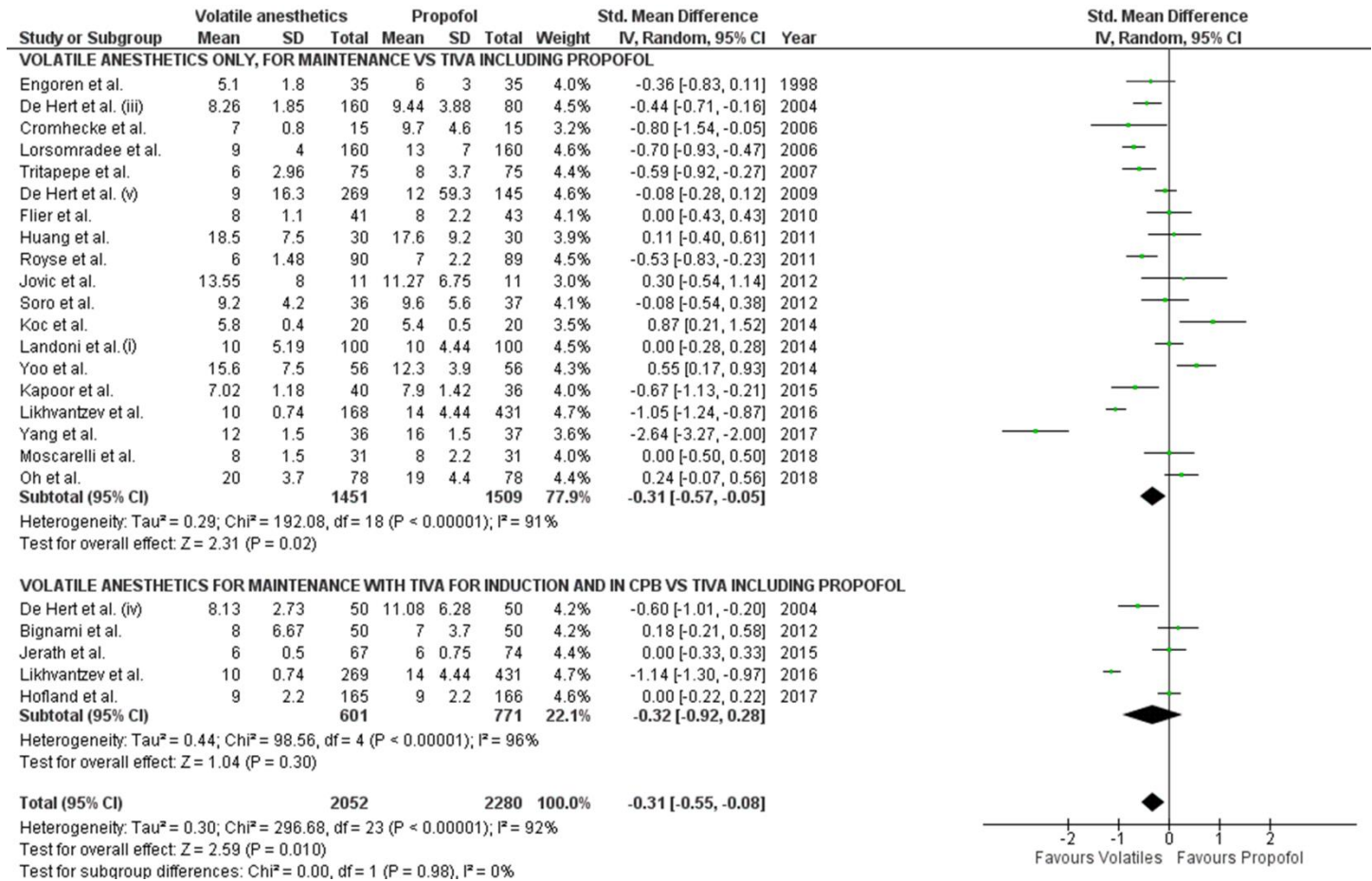
Alice Bonanni MD, Alessio Signori MD, PhD, Cristiano Alicino MD, PhD, Irene Mannucci MD, Maria Antonietta Grasso MD, Luigi Martinelli MD and Giacomo Deferrari MD, PhD.
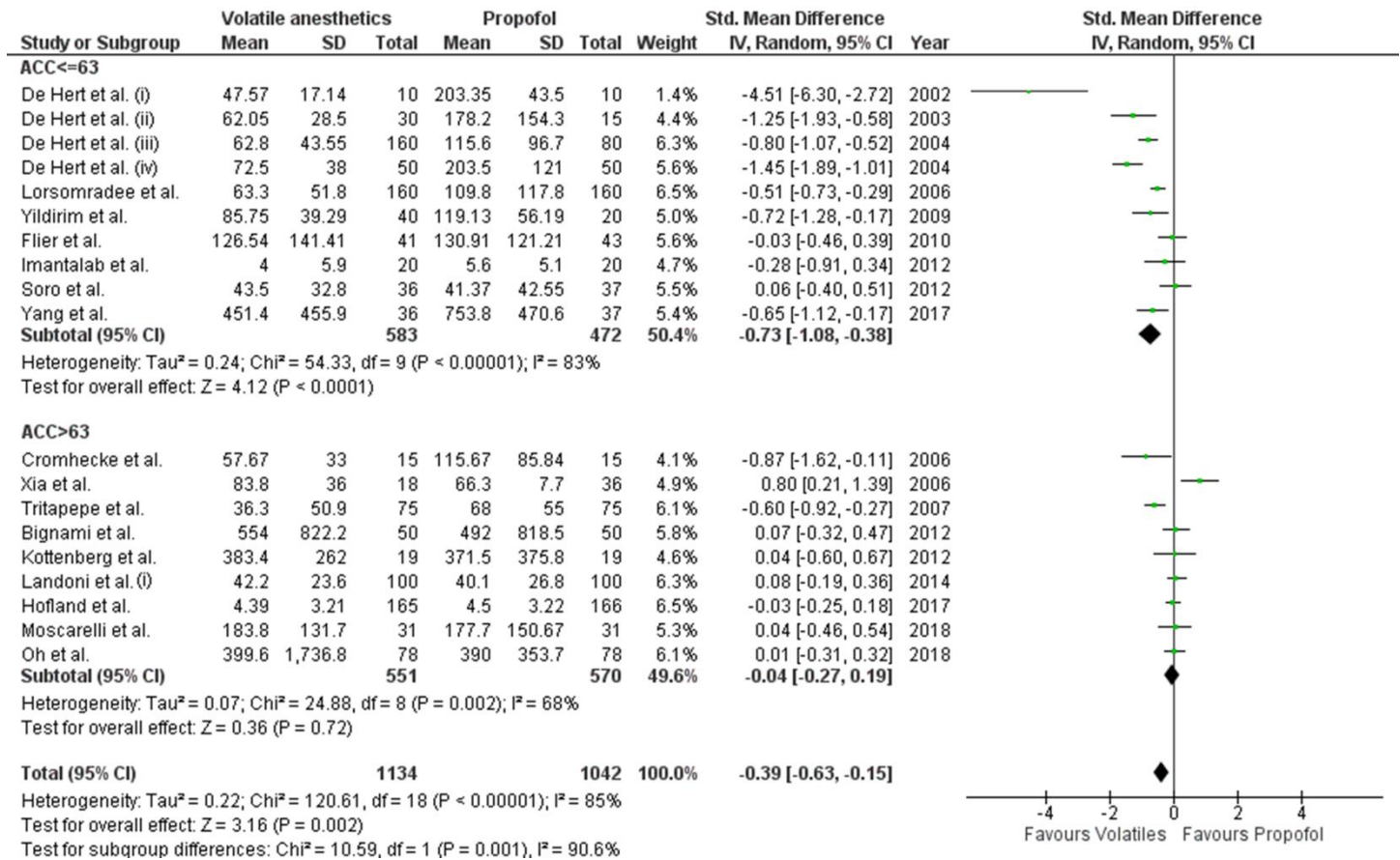
SUPPLEMENTAL DIGITAL CONTENT FILE 5

Figure 11: Forest plot for the effects of volatile anesthetics alone (subgroup 1) and volatile anesthetics with TIVA including propofol for induction and in CPB (subgroup 2) versus TIVA including propofol on short-term mortality in adults undergoing cardiac surgery with cardiopulmonary bypass. M-H: Mantel-Haenszel

Study or Subgroup	Volatile anesthetics Events	Total	Propofol Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
VOLATILE ANESTHETICS ONLY, FOR MAINTENANCE VS TIVA INCLUDING PROPOFOL							
Engoren et al.	0	35	0	35		Not estimable	1998
Story/Parker et al.	4	236	1	118	2.5%	2.02 [0.22, 18.25]	2001
De Hert et al. (i)	0	10	0	10		Not estimable	2002
El Azab et al.	0	10	0	10		Not estimable	2002
De Hert et al. (ii)	0	30	1	15	1.1%	0.16 [0.01, 4.13]	2003
De Hert et al. (iii)	0	160	1	80	1.2%	0.17 [0.01, 4.10]	2004
Cromhecke et al.	0	15	0	15		Not estimable	2006
Lorsomradee et al.	0	160	0	160		Not estimable	2006
Tritapepe et al.	1	75	1	75	1.6%	1.00 [0.06, 16.29]	2007
Cavalca et al.	0	21	0	22		Not estimable	2008
De Hert et al. (v)	0	269	1	145	1.2%	0.18 [0.01, 4.42]	2009
Yildirim et al.	0	40	0	20		Not estimable	2009
Flier et al.	0	41	0	43		Not estimable	2010
Huang et al.	0	30	0	30		Not estimable	2011
Royse et al.	0	90	0	89		Not estimable	2011
Jovic et al.	0	11	0	11		Not estimable	2012
Kottenberg et al.	0	19	0	19		Not estimable	2012
Soro et al.	2	36	0	37	1.3%	5.43 [0.25, 117.24]	2012
Landoni et al. (i)	8	100	7	100	10.9%	1.16 [0.40, 3.32]	2014
Yoo et al.	0	56	0	56		Not estimable	2014
Kapoor et al.	3	40	2	36	3.5%	1.38 [0.22, 8.76]	2015
Likhvantzev et al.	4	168	20	431	10.2%	0.50 [0.17, 1.49]	2016
Yang et al.	0	36	0	37		Not estimable	2017
Moscarelli et al.	0	45	0	45		Not estimable	2018
Subtotal (95% CI)		1733		1639	33.5%	0.82 [0.45, 1.50]	
Total events	22		34				
Heterogeneity: Tau² = 0.00; Chi² = 6.41, df = 8 (P = 0.60); I² = 0%							
Test for overall effect: Z = 0.65 (P = 0.52)							
VOLATILE ANESTHETICS FOR MAINTENANCE WITH TIVA FOR INDUCTION AND IN CPB VS TIVA INCLUDING PROPOFOL							
De Hert et al. (iv)	0	50	0	50		Not estimable	2004
Bignami et al.	1	50	2	50	2.0%	0.49 [0.04, 5.58]	2012
Jerath et al.	0	67	0	74		Not estimable	2015
Likhvantzev et al.	13	269	20	431	23.7%	1.04 [0.51, 2.13]	2016
Hofland et al.	0	165	3	166	1.4%	0.14 [0.01, 2.75]	2017
Landoni et al. (ii)	30	1709	22	1721	39.4%	1.38 [0.79, 2.40]	2019
Subtotal (95% CI)		2310		2492	66.5%	1.15 [0.75, 1.77]	
Total events	44		47				
Heterogeneity: Tau² = 0.00; Chi² = 2.90, df = 3 (P = 0.41); I² = 0%							
Test for overall effect: Z = 0.66 (P = 0.51)							
Total (95% CI)		4043		4131	100.0%	1.03 [0.73, 1.46]	
Total events	66		81				
Heterogeneity: Tau² = 0.00; Chi² = 10.15, df = 12 (P = 0.60); I² = 0%							
Test for overall effect: Z = 0.16 (P = 0.87)							
Test for subgroup differences: Chi² = 0.83, df = 1 (P = 0.36), I² = 0%							

Odds Ratio M-H, Random, 95% CI
0.001 0.1 1 10 1000
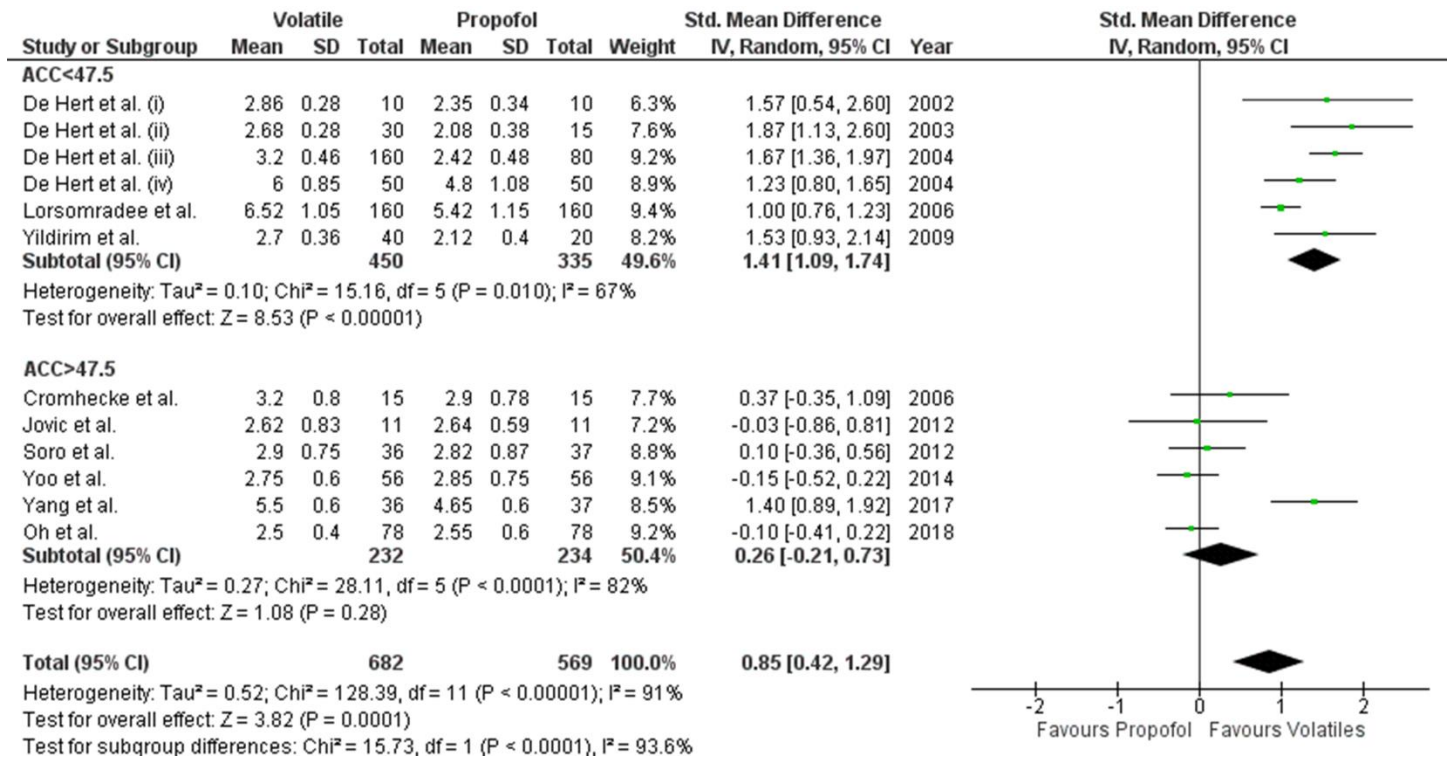Favours Volatile   Favours Propofol

Figure 12: Forest plot for the effects of volatile anesthetics alone (subgroup 1) and volatile anesthetics with TIVA including propofol for induction and in CPB (subgroup 2) versus TIVA including propofol on hospital stay (days) in adults undergoing cardiac surgery with cardiopulmonary bypass. Std. mean difference: standardized mean difference; IV: inverse variance.

Study or Subgroup	Volatile anesthetics Mean	SD	Total	Propofol Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
VOLATILE ANESTHETICS ONLY, FOR MAINTENANCE VS TIVA INCLUDING PROPOFOL									
Engoren et al.	5.1	1.8	35	6	3	35	4.0%	-0.36 [-0.83, 0.11]	1998
De Hert et al. (iii)	8.26	1.85	160	9.44	3.88	80	4.5%	-0.44 [-0.71, -0.16]	2004
Cromhecke et al.	7	0.8	15	9.7	4.6	15	3.2%	-0.80 [-1.54, -0.05]	2006
Lorsomradee et al.	9	4	160	13	7	160	4.6%	-0.70 [-0.93, -0.47]	2006
Tritapepe et al.	6	2.96	75	8	3.7	75	4.4%	-0.59 [-0.92, -0.27]	2007
De Hert et al. (v)	9	16.3	269	12	59.3	145	4.6%	-0.08 [-0.28, 0.12]	2009
Flier et al.	8	1.1	41	8	2.2	43	4.1%	0.00 [-0.43, 0.43]	2010
Huang et al.	18.5	7.5	30	17.6	9.2	30	3.9%	0.11 [-0.40, 0.61]	2011
Royse et al.	6	1.48	90	7	2.2	89	4.5%	-0.53 [-0.83, -0.23]	2011
Jovic et al.	13.55	8	11	11.27	6.75	11	3.0%	0.30 [-0.54, 1.14]	2012
Soro et al.	9.2	4.2	36	9.6	5.6	37	4.1%	-0.08 [-0.54, 0.38]	2012
Koc et al.	5.8	0.4	20	5.4	0.5	20	3.5%	0.87 [0.21, 1.52]	2014
Landoni et al. (i)	10	5.19	100	10	4.44	100	4.5%	0.00 [-0.28, 0.28]	2014
Yoo et al.	15.6	7.5	56	12.3	3.9	56	4.3%	0.55 [0.17, 0.93]	2014
Kapoor et al.	7.02	1.18	40	7.9	1.42	36	4.0%	-0.67 [-1.13, -0.21]	2015
Likhvantzev et al.	10	0.74	168	14	4.44	431	4.7%	-1.05 [-1.24, -0.87]	2016
Yang et al.	12	1.5	36	16	1.5	37	3.6%	-2.64 [-3.27, -2.00]	2017
Moscarelli et al.	8	1.5	31	8	2.2	31	4.0%	0.00 [-0.50, 0.50]	2018
Oh et al.	20	3.7	78	19	4.4	78	4.4%	0.24 [-0.07, 0.56]	2018
Subtotal (95% CI)			1451			1509	77.9%	-0.31 [-0.57, -0.05]	

Heterogeneity: Tau² = 0.29; Chi² = 192.08, df = 18 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.31 (P = 0.02)

Study or Subgroup	Volatile anesthetics Mean	SD	Total	Propofol Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
VOLATILE ANESTHETICS FOR MAINTENANCE WITH TIVA FOR INDUCTION AND IN CPB VS TIVA INCLUDING PROPOFOL									
De Hert et al. (iv)	8.13	2.73	50	11.08	6.28	50	4.2%	-0.60 [-1.01, -0.20]	2004
Bignami et al.	8	6.67	50	7	3.7	50	4.2%	0.18 [-0.21, 0.58]	2012
Jerath et al.	6	0.5	67	6	0.75	74	4.4%	0.00 [-0.33, 0.33]	2015
Likhvantzev et al.	10	0.74	269	14	4.44	431	4.7%	-1.14 [-1.30, -0.97]	2016
Hofland et al.	9	2.2	165	9	2.2	166	4.6%	0.00 [-0.22, 0.22]	2017
Subtotal (95% CI)			601			771	22.1%	-0.32 [-0.92, 0.28]	

Heterogeneity: Tau² = 0.44; Chi² = 98.56, df = 4 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.04 (P = 0.30)

| **Total (95% CI)** | | | 2052 | | | 2280 | 100.0% | -0.31 [-0.55, -0.08] | |

Heterogeneity: Tau² = 0.30; Chi² = 296.68, df = 23 (P < 0.00001); I² = 92%
Test for overall effect: Z = 2.59 (P = 0.010)
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.98), I² = 0%

Std. Mean Difference IV, Random, 95% CI

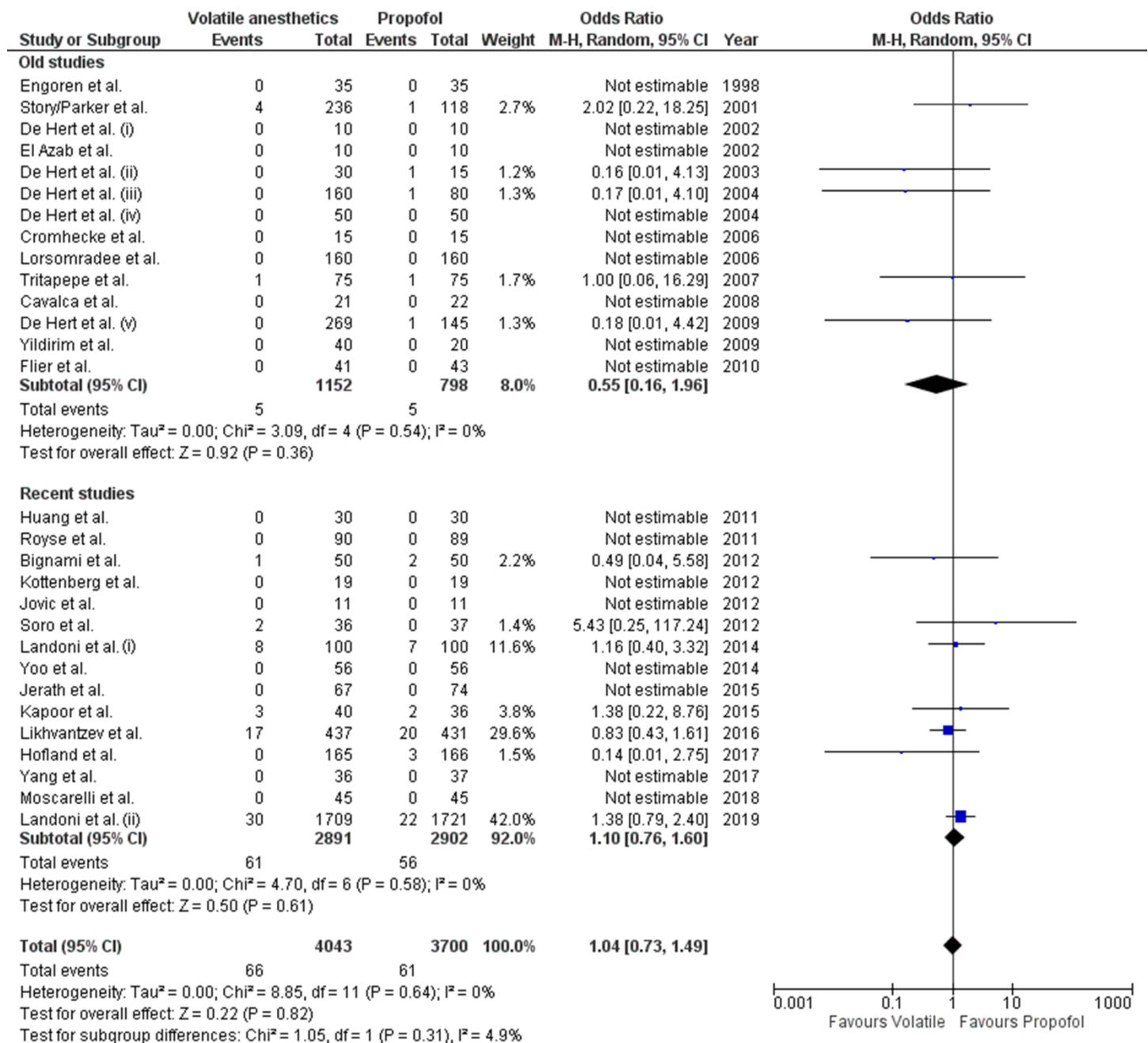-2   -1   0   1   2
Favours Volatiles   Favours Propofol

Figure 13: Forest plot for the effects of VAs versus propofol on area under the curve for cardiac troponin in adults undergoing cardiac surgery with cardiopulmonary bypass. Subgroup analysis: aortic cross clamp time ≤median (63min) versus >median . Std. mean difference: standardized mean difference; IV: inverse variance; ACC= aortic cross clamp time (min).

Study or Subgroup	Volatile anesthetics Mean	SD	Total	Propofol Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
ACC<=63									
De Hert et al. (i)	47.57	17.14	10	203.35	43.5	10	1.4%	-4.51 [-6.30, -2.72]	2002
De Hert et al. (ii)	62.05	28.5	30	178.2	154.3	15	4.4%	-1.25 [-1.93, -0.58]	2003
De Hert et al. (iii)	62.8	43.55	160	115.6	96.7	80	6.3%	-0.80 [-1.07, -0.52]	2004
De Hert et al. (iv)	72.5	38	50	203.5	121	50	5.6%	-1.45 [-1.89, -1.01]	2004
Lorsomradee et al.	63.3	51.8	160	109.8	117.8	160	6.5%	-0.51 [-0.73, -0.29]	2006
Yildirim et al.	85.75	39.29	40	119.13	56.19	20	5.0%	-0.72 [-1.28, -0.17]	2009
Flier et al.	126.54	141.41	41	130.91	121.21	43	5.6%	-0.03 [-0.46, 0.39]	2010
Imantalab et al.	4	5.9	20	5.6	5.1	20	4.7%	-0.28 [-0.91, 0.34]	2012
Soro et al.	43.5	32.8	36	41.37	42.55	37	5.5%	0.06 [-0.40, 0.51]	2012
Yang et al.	451.4	455.9	36	753.8	470.6	37	5.4%	-0.65 [-1.12, -0.17]	2017
Subtotal (95% CI)			583			472	50.4%	-0.73 [-1.08, -0.38]	

Heterogeneity: Tau² = 0.24; Chi² = 54.33, df = 9 (P < 0.00001); I² = 83%
Test for overall effect: Z = 4.12 (P < 0.0001)

ACC>63									
Cromhecke et al.	57.67	33	15	115.67	85.84	15	4.1%	-0.87 [-1.62, -0.11]	2006
Xia et al.	83.8	36	18	66.3	7.7	36	4.9%	0.80 [0.21, 1.39]	2006
Tritapepe et al.	36.3	50.9	75	68	55	75	6.1%	-0.60 [-0.92, -0.27]	2007
Bignami et al.	554	822.2	50	492	818.5	50	5.8%	0.07 [-0.32, 0.47]	2012
Kottenberg et al.	383.4	262	19	371.5	375.8	19	4.6%	0.04 [-0.60, 0.67]	2012
Landoni et al. (i)	42.2	23.6	100	40.1	26.8	100	6.3%	0.08 [-0.19, 0.36]	2014
Hofland et al.	4.39	3.21	165	4.5	3.22	166	6.5%	-0.03 [-0.25, 0.18]	2017
Moscarelli et al.	183.8	131.7	31	177.7	150.67	31	5.3%	0.04 [-0.46, 0.54]	2018
Oh et al.	399.6	1,736.8	78	390	353.7	78	6.1%	0.01 [-0.31, 0.32]	2018
Subtotal (95% CI)			551			570	49.6%	-0.04 [-0.27, 0.19]	

Heterogeneity: Tau² = 0.07; Chi² = 24.88, df = 8 (P = 0.002); I² = 68%
Test for overall effect: Z = 0.36 (P = 0.72)

| **Total (95% CI)** | | | 1134 | | | 1042 | 100.0% | -0.39 [-0.63, -0.15] | |

Heterogeneity: Tau² = 0.22; Chi² = 120.61, df = 18 (P < 0.00001); I² = 85%
Test for overall effect: Z = 3.16 (P = 0.002)
Test for subgroup differences: Chi² = 10.59, df = 1 (P = 0.001), I² = 90.6%

Favours Volatiles   Favours Propofol

Figure 14. Forest plot for the effects of VAs versus propofol on cardiac index in adults undergoing cardiac surgery with cardiopulmonary bypass. Subgroup analysis: aortic cross clamp time ≤median (47.5min) versus >median . Std. mean difference: standardized mean difference; IV: inverse variance; ACC: aortic cross clamp time (min).

Study or Subgroup	Volatile Mean	SD	Total	Propofol Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
ACC<47.5									
De Hert et al. (i)	2.86	0.28	10	2.35	0.34	10	6.3%	1.57 [0.54, 2.60]	2002
De Hert et al. (ii)	2.68	0.28	30	2.08	0.38	15	7.6%	1.87 [1.13, 2.60]	2003
De Hert et al. (iii)	3.2	0.46	160	2.42	0.48	80	9.2%	1.67 [1.36, 1.97]	2004
De Hert et al. (iv)	6	0.85	50	4.8	1.08	50	8.9%	1.23 [0.80, 1.65]	2004
Lorsomradee et al.	6.52	1.05	160	5.42	1.15	160	9.4%	1.00 [0.76, 1.23]	2006
Yildirim et al.	2.7	0.36	40	2.12	0.4	20	8.2%	1.53 [0.93, 2.14]	2009
Subtotal (95% CI)			450			335	49.6%	1.41 [1.09, 1.74]	

Heterogeneity: Tau² = 0.10; Chi² = 15.16, df = 5 (P = 0.010); I² = 67%
Test for overall effect: Z = 8.53 (P < 0.00001)

Study or Subgroup	Volatile Mean	SD	Total	Propofol Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
ACC>47.5									
Cromhecke et al.	3.2	0.8	15	2.9	0.78	15	7.7%	0.37 [-0.35, 1.09]	2006
Jovic et al.	2.62	0.83	11	2.64	0.59	11	7.2%	-0.03 [-0.86, 0.81]	2012
Soro et al.	2.9	0.75	36	2.82	0.87	37	8.8%	0.10 [-0.36, 0.56]	2012
Yoo et al.	2.75	0.6	56	2.85	0.75	56	9.1%	-0.15 [-0.52, 0.22]	2014
Yang et al.	5.5	0.6	36	4.65	0.6	37	8.5%	1.40 [0.89, 1.92]	2017
Oh et al.	2.5	0.4	78	2.55	0.6	78	9.2%	-0.10 [-0.41, 0.22]	2018
Subtotal (95% CI)			232			234	50.4%	0.26 [-0.21, 0.73]	

Heterogeneity: Tau² = 0.27; Chi² = 28.11, df = 5 (P < 0.0001); I² = 82%
Test for overall effect: Z = 1.08 (P = 0.28)

Total (95% CI)			682			569	100.0%	0.85 [0.42, 1.29]	

Heterogeneity: Tau² = 0.52; Chi² = 128.39, df = 11 (P < 0.00001); I² = 91%
Test for overall effect: Z = 3.82 (P = 0.0001)
Test for subgroup differences: Chi² = 15.73, df = 1 (P < 0.0001), I² = 93.6%

Std. Mean Difference IV, Random, 95% CI
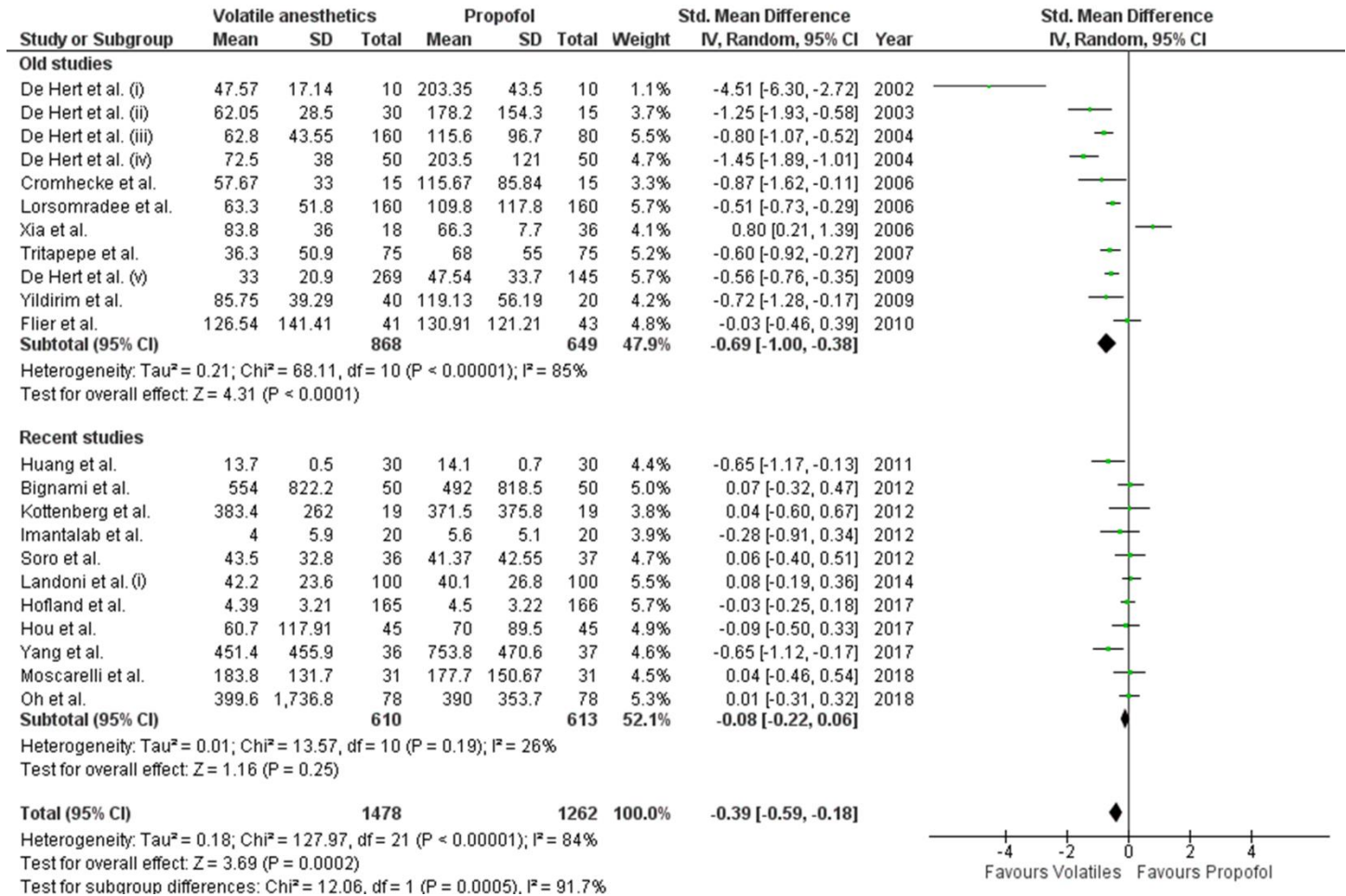-2 -1 0 1 2
Favours Propofol   Favours Volatiles

Figure 15: Forest plot for the effects of volatile anesthetics versus propofol on 30 days mortality in adults undergoing cardiac surgery with cardiopulmonary bypass. Subgroup analysis: old studies versus recent studies; M-H: Mantel-Haenszel
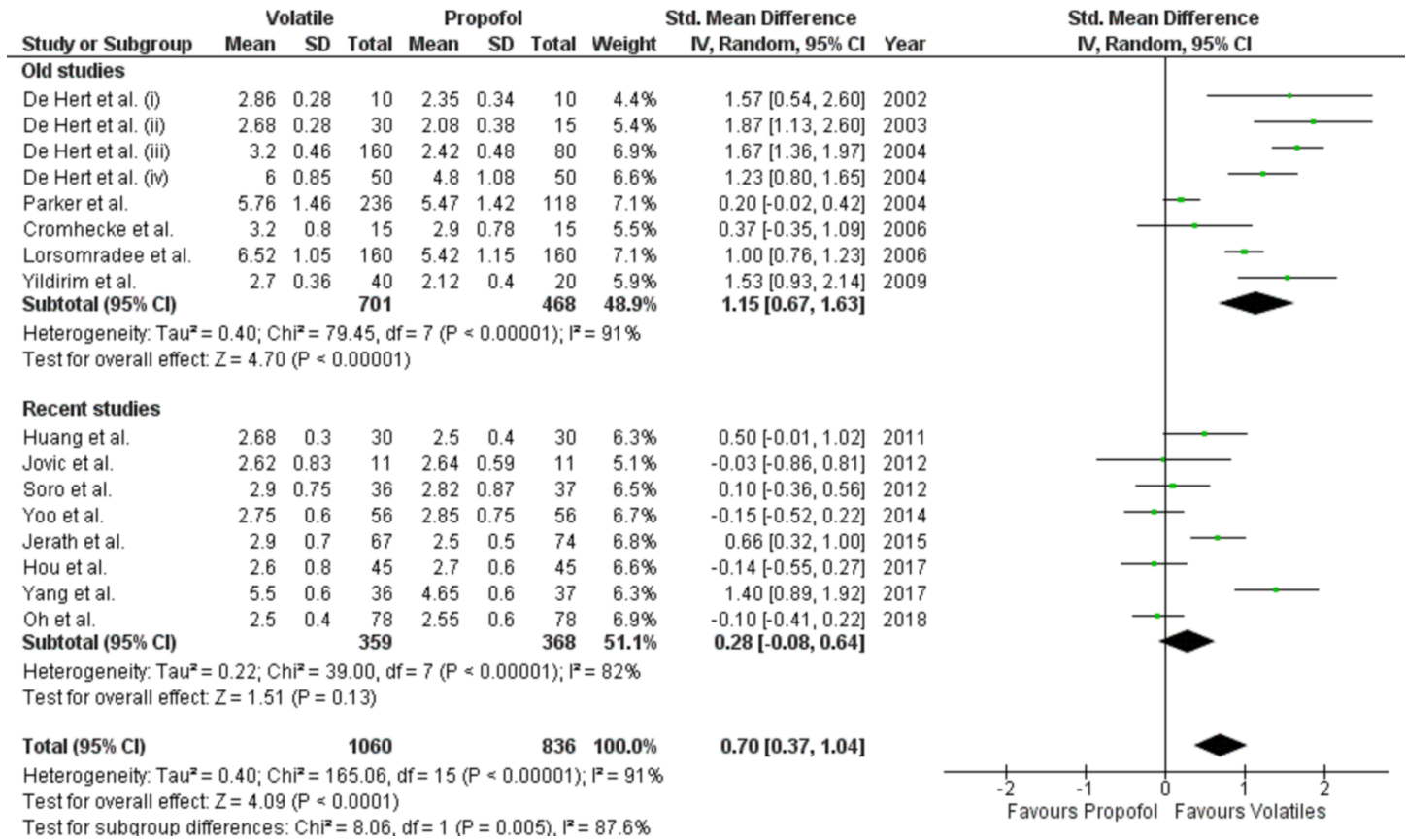
Study or Subgroup	Volatile anesthetics Events	Total	Propofol Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year	Odds Ratio M-H, Random, 95% CI
Old studies								
Engoren et al.	0	35	0	35		Not estimable	1998	
Story/Parker et al.	4	236	1	118	2.7%	2.02 [0.22, 18.25]	2001	
De Hert et al. (i)	0	10	0	10		Not estimable	2002	
El Azab et al.	0	10	0	10		Not estimable	2002	
De Hert et al. (ii)	0	30	1	15	1.2%	0.16 [0.01, 4.13]	2003	
De Hert et al. (iii)	0	160	1	80	1.3%	0.17 [0.01, 4.10]	2004	
De Hert et al. (iv)	0	50	0	50		Not estimable	2004	
Cromhecke et al.	0	15	0	15		Not estimable	2006	
Lorsomradee et al.	0	160	0	160		Not estimable	2006	
Tritapepe et al.	1	75	1	75	1.7%	1.00 [0.06, 16.29]	2007	
Cavalca et al.	0	21	0	22		Not estimable	2008	
De Hert et al. (v)	0	269	1	145	1.3%	0.18 [0.01, 4.42]	2009	
Yildirim et al.	0	40	0	20		Not estimable	2009	
Flier et al.	0	41	0	43		Not estimable	2010	
Subtotal (95% CI)		**1152**		**798**	**8.0%**	**0.55 [0.16, 1.96]**		
Total events	5		5					
Heterogeneity: Tau² = 0.00; Chi² = 3.09, df = 4 (P = 0.54); I² = 0%								
Test for overall effect: Z = 0.92 (P = 0.36)								
Recent studies								
Huang et al.	0	30	0	30		Not estimable	2011	
Royse et al.	0	90	0	89		Not estimable	2011	
Bignami et al.	1	50	2	50	2.2%	0.49 [0.04, 5.58]	2012	
Kottenberg et al.	0	19	0	19		Not estimable	2012	
Jovic et al.	0	11	0	11		Not estimable	2012	
Soro et al.	2	36	0	37	1.4%	5.43 [0.25, 117.24]	2012	
Landoni et al. (i)	8	100	7	100	11.6%	1.16 [0.40, 3.32]	2014	
Yoo et al.	0	56	0	56		Not estimable	2014	
Jerath et al.	0	67	0	74		Not estimable	2015	
Kapoor et al.	3	40	2	36	3.8%	1.38 [0.22, 8.76]	2015	
Likhvantzev et al.	17	437	20	431	29.6%	0.83 [0.43, 1.61]	2016	
Hofland et al.	0	165	3	166	1.5%	0.14 [0.01, 2.75]	2017	
Yang et al.	0	36	0	37		Not estimable	2017	
Moscarelli et al.	0	45	0	45		Not estimable	2018	
Landoni et al. (ii)	30	1709	22	1721	42.0%	1.38 [0.79, 2.40]	2019	
Subtotal (95% CI)		**2891**		**2902**	**92.0%**	**1.10 [0.76, 1.60]**		
Total events	61		56					
Heterogeneity: Tau² = 0.00; Chi² = 4.70, df = 6 (P = 0.58); I² = 0%								
Test for overall effect: Z = 0.50 (P = 0.61)								
Total (95% CI)		**4043**		**3700**	**100.0%**	**1.04 [0.73, 1.49]**		
Total events	66		61					
Heterogeneity: Tau² = 0.00; Chi² = 8.85, df = 11 (P = 0.64); I² = 0%								
Test for overall effect: Z = 0.22 (P = 0.82)								
Test for subgroup differences: Chi² = 1.05, df = 1 (P = 0.31), I² = 4.9%								

0.001   0.1   1   10   1000
Favours Volatile   Favours Propofol

Figure 16: Forest plot for the effects of volatile anesthetics versus propofol on area under the curve for cardiac troponin in adults undergoing cardiac surgery with cardiopulmonary bypass.
Subgroup analysis: old studies versus recent studies. Std. mean difference: standardized mean difference; IV: inverse variance.
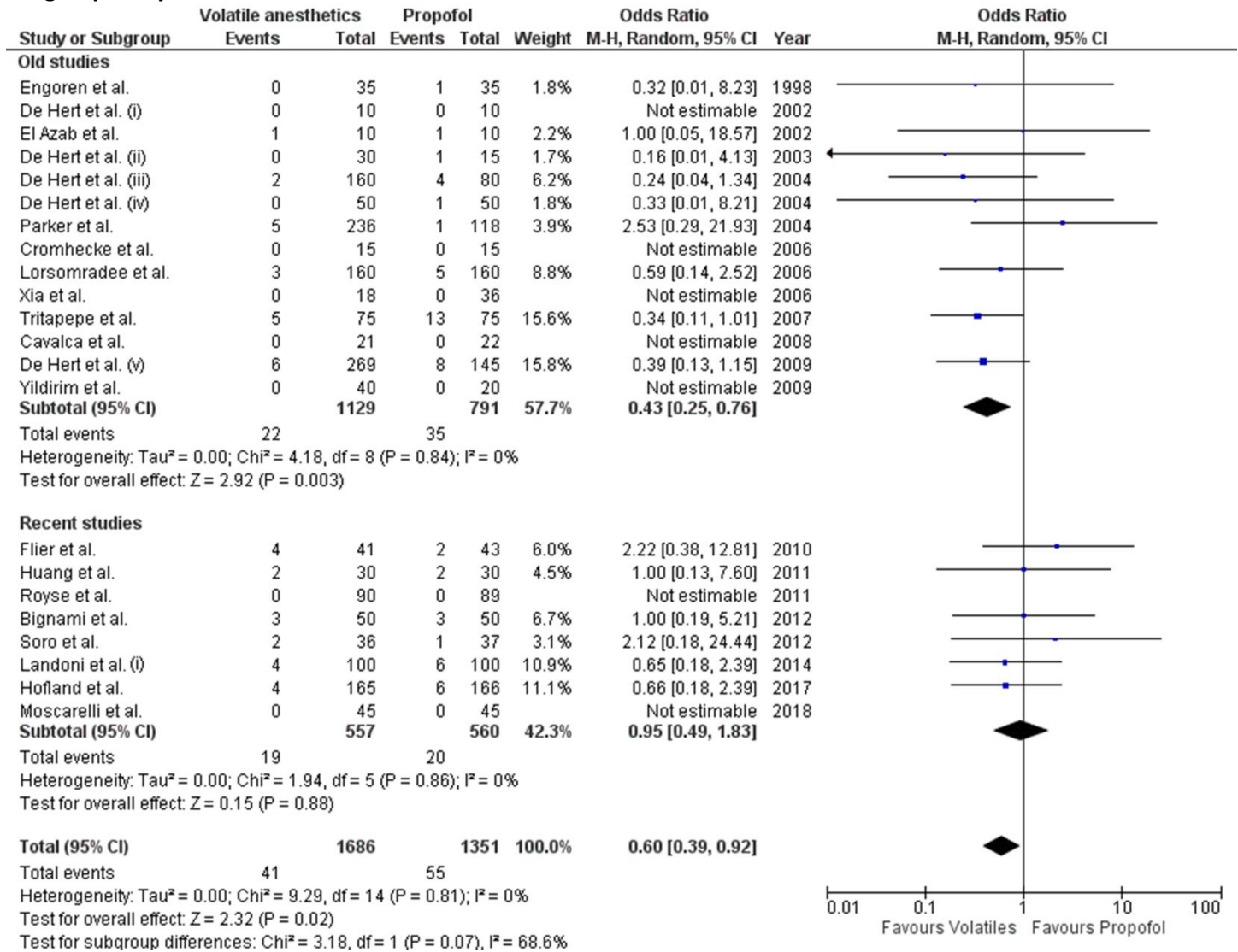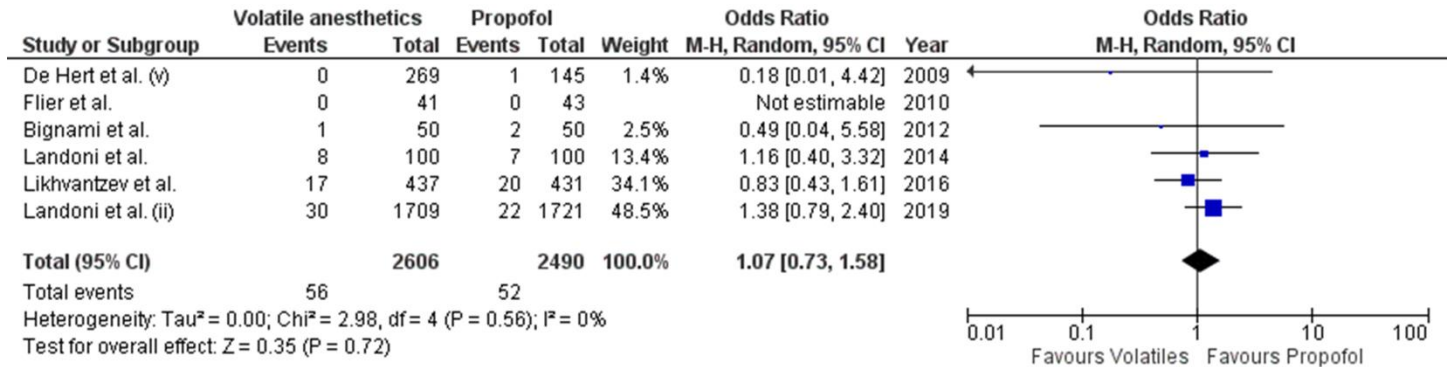
Study or Subgroup	Volatile anesthetics Mean	SD	Total	Propofol Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Old studies									
De Hert et al. (i)	47.57	17.14	10	203.35	43.5	10	1.1%	-4.51 [-6.30, -2.72]	2002
De Hert et al. (ii)	62.05	28.5	30	178.2	154.3	15	3.7%	-1.25 [-1.93, -0.58]	2003
De Hert et al. (iii)	62.8	43.55	160	115.6	96.7	80	5.5%	-0.80 [-1.07, -0.52]	2004
De Hert et al. (iv)	72.5	38	50	203.5	121	50	4.7%	-1.45 [-1.89, -1.01]	2004
Cromhecke et al.	57.67	33	15	115.67	85.84	15	3.3%	-0.87 [-1.62, -0.11]	2006
Lorsomradee et al.	63.3	51.8	160	109.8	117.8	160	5.7%	-0.51 [-0.73, -0.29]	2006
Xia et al.	83.8	36	18	66.3	7.7	36	4.1%	0.80 [0.21, 1.39]	2006
Tritapepe et al.	36.3	50.9	75	68	55	75	5.2%	-0.60 [-0.92, -0.27]	2007
De Hert et al. (v)	33	20.9	269	47.54	33.7	145	5.7%	-0.56 [-0.76, -0.35]	2009
Yildirim et al.	85.75	39.29	40	119.13	56.19	20	4.2%	-0.72 [-1.28, -0.17]	2009
Flier et al.	126.54	141.41	41	130.91	121.21	43	4.8%	-0.03 [-0.46, 0.39]	2010
Subtotal (95% CI)			868			649	47.9%	-0.69 [-1.00, -0.38]	

Heterogeneity: Tau² = 0.21; Chi² = 68.11, df = 10 (P < 0.00001); I² = 85%
Test for overall effect: Z = 4.31 (P < 0.0001)

Recent studies									
Huang et al.	13.7	0.5	30	14.1	0.7	30	4.4%	-0.65 [-1.17, -0.13]	2011
Bignami et al.	554	822.2	50	492	818.5	50	5.0%	0.07 [-0.32, 0.47]	2012
Kottenberg et al.	383.4	262	19	371.5	375.8	19	3.8%	0.04 [-0.60, 0.67]	2012
Imantalab et al.	4	5.9	20	5.6	5.1	20	3.9%	-0.28 [-0.91, 0.34]	2012
Soro et al.	43.5	32.8	36	41.37	42.55	37	4.7%	0.06 [-0.40, 0.51]	2012
Landoni et al. (i)	42.2	23.6	100	40.1	26.8	100	5.5%	0.08 [-0.19, 0.36]	2014
Hofland et al.	4.39	3.21	165	4.5	3.22	166	5.7%	-0.03 [-0.25, 0.18]	2017
Hou et al.	60.7	117.91	45	70	89.5	45	4.9%	-0.09 [-0.50, 0.33]	2017
Yang et al.	451.4	455.9	36	753.8	470.6	37	4.6%	-0.65 [-1.12, -0.17]	2017
Moscarelli et al.	183.8	131.7	31	177.7	150.67	31	4.5%	0.04 [-0.46, 0.54]	2018
Oh et al.	399.6	1,736.8	78	390	353.7	78	5.3%	0.01 [-0.31, 0.32]	2018
Subtotal (95% CI)			610			613	52.1%	-0.08 [-0.22, 0.06]	

Heterogeneity: Tau² = 0.01; Chi² = 13.57, df = 10 (P = 0.19); I² = 26%
Test for overall effect: Z = 1.16 (P = 0.25)

Total (95% CI)			1478			1262	100.0%	-0.39 [-0.59, -0.18]	

Heterogeneity: Tau² = 0.18; Chi² = 127.97, df = 21 (P < 0.00001); I² = 84%
Test for overall effect: Z = 3.69 (P = 0.0002)
Test for subgroup differences: Chi² = 12.06, df = 1 (P = 0.0005), I² = 91.7%

Std. Mean Difference IV, Random, 95% CI
-4 -2 0 2 4
Favours Volatiles Favours Propofol

Figure 17: Forest plot for the effects of volatile anesthetics versus propofol on post bypass cardiac index/output in adults undergoing cardiac surgery with cardiopulmonary bypass.
Subgroup analysis: old studies versus recent studies. Std. mean difference: standardized mean difference; IV: inverse variance.

Study or Subgroup	Volatile Mean	SD	Total	Propofol Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Old studies									
De Hert et al. (i)	2.86	0.28	10	2.35	0.34	10	4.4%	1.57 [0.54, 2.60]	2002
De Hert et al. (ii)	2.68	0.28	30	2.08	0.38	15	5.4%	1.87 [1.13, 2.60]	2003
De Hert et al. (iii)	3.2	0.46	160	2.42	0.48	80	6.9%	1.67 [1.36, 1.97]	2004
De Hert et al. (iv)	6	0.85	50	4.8	1.08	50	6.6%	1.23 [0.80, 1.65]	2004
Parker et al.	5.76	1.46	236	5.47	1.42	118	7.1%	0.20 [-0.02, 0.42]	2004
Cromhecke et al.	3.2	0.8	15	2.9	0.78	15	5.5%	0.37 [-0.35, 1.09]	2006
Lorsomradee et al.	6.52	1.05	160	5.42	1.15	160	7.1%	1.00 [0.76, 1.23]	2006
Yildirim et al.	2.7	0.36	40	2.12	0.4	20	5.9%	1.53 [0.93, 2.14]	2009
Subtotal (95% CI)			**701**			**468**	**48.9%**	**1.15 [0.67, 1.63]**	
Heterogeneity: Tau² = 0.40; Chi² = 79.45, df = 7 (P < 0.00001); I² = 91%									
Test for overall effect: Z = 4.70 (P < 0.00001)									
Recent studies									
Huang et al.	2.68	0.3	30	2.5	0.4	30	6.3%	0.50 [-0.01, 1.02]	2011
Jovic et al.	2.62	0.83	11	2.64	0.59	11	5.1%	-0.03 [-0.86, 0.81]	2012
Soro et al.	2.9	0.75	36	2.82	0.87	37	6.5%	0.10 [-0.36, 0.56]	2012
Yoo et al.	2.75	0.6	56	2.85	0.75	56	6.7%	-0.15 [-0.52, 0.22]	2014
Jerath et al.	2.9	0.7	67	2.5	0.5	74	6.8%	0.66 [0.32, 1.00]	2015
Hou et al.	2.6	0.8	45	2.7	0.6	45	6.6%	-0.14 [-0.55, 0.27]	2017
Yang et al.	5.5	0.6	36	4.65	0.6	37	6.3%	1.40 [0.89, 1.92]	2017
Oh et al.	2.5	0.4	78	2.55	0.6	78	6.9%	-0.10 [-0.41, 0.22]	2018
Subtotal (95% CI)			**359**			**368**	**51.1%**	**0.28 [-0.08, 0.64]**	
Heterogeneity: Tau² = 0.22; Chi² = 39.00, df = 7 (P < 0.00001); I² = 82%									
Test for overall effect: Z = 1.51 (P = 0.13)									
Total (95% CI)			**1060**			**836**	**100.0%**	**0.70 [0.37, 1.04]**	
Heterogeneity: Tau² = 0.40; Chi² = 165.06, df = 15 (P < 0.00001); I² = 91%									
Test for overall effect: Z = 4.09 (P < 0.0001)									
Test for subgroup differences: Chi² = 8.06, df = 1 (P = 0.005), I² = 87.6%									

Std. Mean Difference
IV, Random, 95% CI
-2   -1   0   1   2
Favours Propofol   Favours Volatiles

Figure 18: Forest plot for the effects of volatile anesthetics versus propofol on the incidence of myocardial infarction in adults undergoing cardiac surgery with cardiopulmonary bypass.
Subgroup analysis: old studies versus recent studies. M-H: Mantel-Haenszel

Study or Subgroup	Volatile anesthetics Events	Total	Propofol Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Old studies							
Engoren et al.	0	35	1	35	1.8%	0.32 [0.01, 8.23]	1998
De Hert et al. (i)	0	10	0	10		Not estimable	2002
El Azab et al.	1	10	1	10	2.2%	1.00 [0.05, 18.57]	2002
De Hert et al. (ii)	0	30	1	15	1.7%	0.16 [0.01, 4.13]	2003
De Hert et al. (iii)	2	160	4	80	6.2%	0.24 [0.04, 1.34]	2004
De Hert et al. (iv)	0	50	1	50	1.8%	0.33 [0.01, 8.21]	2004
Parker et al.	5	236	1	118	3.9%	2.53 [0.29, 21.93]	2004
Cromhecke et al.	0	15	0	15		Not estimable	2006
Lorsomradee et al.	3	160	5	160	8.8%	0.59 [0.14, 2.52]	2006
Xia et al.	0	18	0	36		Not estimable	2006
Tritapepe et al.	5	75	13	75	15.6%	0.34 [0.11, 1.01]	2007
Cavalca et al.	0	21	0	22		Not estimable	2008
De Hert et al. (v)	6	269	8	145	15.8%	0.39 [0.13, 1.15]	2009
Yildirim et al.	0	40	0	20		Not estimable	2009
Subtotal (95% CI)		**1129**		**791**	**57.7%**	**0.43 [0.25, 0.76]**	
Total events	22		35				

Heterogeneity: Tau² = 0.00; Chi² = 4.18, df = 8 (P = 0.84); I² = 0%
Test for overall effect: Z = 2.92 (P = 0.003)

Study or Subgroup	Volatile anesthetics Events	Total	Propofol Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Recent studies							
Flier et al.	4	41	2	43	6.0%	2.22 [0.38, 12.81]	2010
Huang et al.	2	30	2	30	4.5%	1.00 [0.13, 7.60]	2011
Royse et al.	0	90	0	89		Not estimable	2011
Bignami et al.	3	50	3	50	6.7%	1.00 [0.19, 5.21]	2012
Soro et al.	2	36	1	37	3.1%	2.12 [0.18, 24.44]	2012
Landoni et al. (i)	4	100	6	100	10.9%	0.65 [0.18, 2.39]	2014
Hofland et al.	4	165	6	166	11.1%	0.66 [0.18, 2.39]	2017
Moscarelli et al.	0	45	0	45		Not estimable	2018
Subtotal (95% CI)		**557**		**560**	**42.3%**	**0.95 [0.49, 1.83]**	
Total events	19		20				

Heterogeneity: Tau² = 0.00; Chi² = 1.94, df = 5 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)

Total (95% CI)		**1686**		**1351**	**100.0%**	**0.60 [0.39, 0.92]**	
Total events	41		55				

Heterogeneity: Tau² = 0.00; Chi² = 9.29, df = 14 (P = 0.81); I² = 0%
Test for overall effect: Z = 2.32 (P = 0.02)
Test for subgroup differences: Chi² = 3.18, df = 1 (P = 0.07), I² = 68.6%

Odds Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours Volatiles   Favours Propofol

Figure 19: Forest plot for the effect of volatile anesthetics versus propofol on short-term mortality in the studies that evaluated 1 yr mortality in adults undergoing cardiac surgery with CPB (see Figure 2B); M-H: Mantel-Haenszel

Study or Subgroup	Volatile anesthetics Events	Total	Propofol Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year	Odds Ratio M-H, Random, 95% CI
De Hert et al. (v)	0	269	1	145	1.4%	0.18 [0.01, 4.42]	2009	
Flier et al.	0	41	0	43		Not estimable	2010	
Bignami et al.	1	50	2	50	2.5%	0.49 [0.04, 5.58]	2012	
Landoni et al.	8	100	7	100	13.4%	1.16 [0.40, 3.32]	2014	
Likhvantzev et al.	17	437	20	431	34.1%	0.83 [0.43, 1.61]	2016	
Landoni et al. (ii)	30	1709	22	1721	48.5%	1.38 [0.79, 2.40]	2019	
Total (95% CI)		**2606**		**2490**	**100.0%**	**1.07 [0.73, 1.58]**		
Total events	56		52					

Heterogeneity: Tau² = 0.00; Chi² = 2.98, df = 4 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.72)

Favours Volatiles   Favours Propofol

Table 3. Univariate and multivariate analysis to identify major factors influencing the effect of VAs on MI incidence in adults undergoing cardiac surgery with cardiopulmonary bypass

Univariate analysis

Characteristic	OR (95% CI)	P	I^2 heterogeneity
Surgery type	1.35 (0.39-4.64)	0.61	0%
Recent vs Old papers	2.20 (0.90-5.79)	0.07	0%
Aortic cross clamp time (>66.5 vs ≤66.5 min)	0.83 (0.26-2.62)	0.72	0%

Multiple analysis

Characteristic	OR (95% CI)	P	I^2 heterogeneity
Surgery type	0.64 (0.06-7.10)	0.67	0%
Recent vs Old papers	3.09 (0.59-16.4)	0.15	0%
Aortic cross clamp time (>66.5 vs ≤66.5 min)	1.06 (0.19-5.94)	0.94	0%

Table 4. Univariate and multivariate analysis to identify major factors influencing the effect of VAs on cTn release in adults undergoing cardiac surgery with cardiopulmonary bypass

Univariate analysis

Characteristic	Coeff (95% CI)	P	R^2	I^2 heterogeneity
Surgery type	0.38 (0.01-0.76)	0.03	2.9%	79.4%
Recent vs Old papers	0.61 (1.10-1.13)	0.00005	30.6%	91.7%
Aortic cross clamp time (>63 vs ≤63 min)	0.69 (0.04-1.33)	0.039	39.3%	78.6%

Multiple analysis

Characteristic	Coeff (95% CI)	P	R^2 overall	I^2 heterogeneity
Surgery type	-0.30 (-1.15 to 0.55)	0.47	44.4%	77.6%
Recent vs Old papers	0.55 (-0.21 to 1.32)	0.14		
Aortic cross clamp time (>63 vs ≤63 min)	0.60 (-0.14 to 1.33)	0.11		

Table 5. Univariate and multivariate analysis to identify major factors influencing the effect of VAs on cardiac index in adults undergoing cardiac surgery with cardiopulmonary bypass

Univariate analysis

Characteristic	Coeff (95% CI)	P	R^2	I^2 heterogeneity
Surgery type	-0.78 (-1.47 to -0.07)	0.01	25.6%	83.8%
Recent vs Old papers	-0.87 (-1.50 to -0.23)	0.005	37.3%	87.6%
Aortic cross clamp time (>47 vs ≤47.5min)	-1.18 (-1.82 to -0.54)	0.002	66%	76.9%

Multiple analysis

Characteristic	Coeff (95% CI)	P	R^2 overall	I^2 heterogeneity
Surgery type	0.18 (-1.19 to 1.55)	0.77		
Recent vs old papers	-0.09 (-1.61 to 1.42)	0.89	56.3%	81.3%
Aortic cross clamp time (>47 vs ≤47.5min)	-1.25 (-3.26 to 0.77)	0.19		