Prognostic Value of Myocardial Infarction following Percutaneous Coronary Intervention: Pooled-analysis

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Introduction

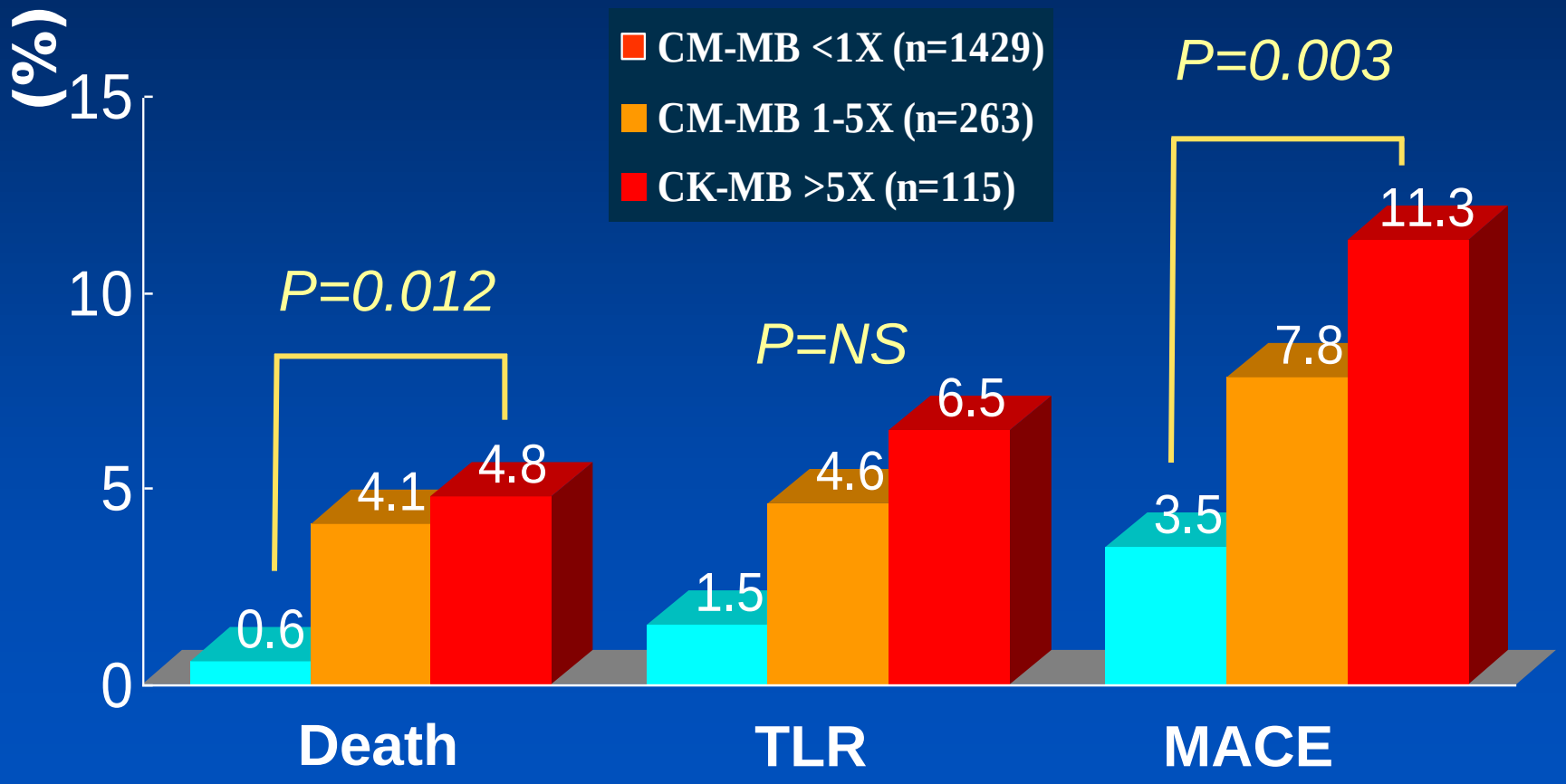
- High level of creatine kinase-myocardial band isoenzyme (CK-MB) elevation has been associated with late mortality after percutaneous coronary intervention (PCI).

- While there is consensus that extensive cardiac enzyme elevation increase mortality significantly, there is uncertainty about the exact clinical impact of smaller CK-MB elevations.

CK-MB Elevation following DES PCI

From January 2003 to June 2005, 1807 (2550 lesions)

Mean clinical F/U: 13 ± 7 months



Jang JS, Hong MK, Park SJ et al. Int J Cardiol. 2008 Oct 13;129(3):368-72.

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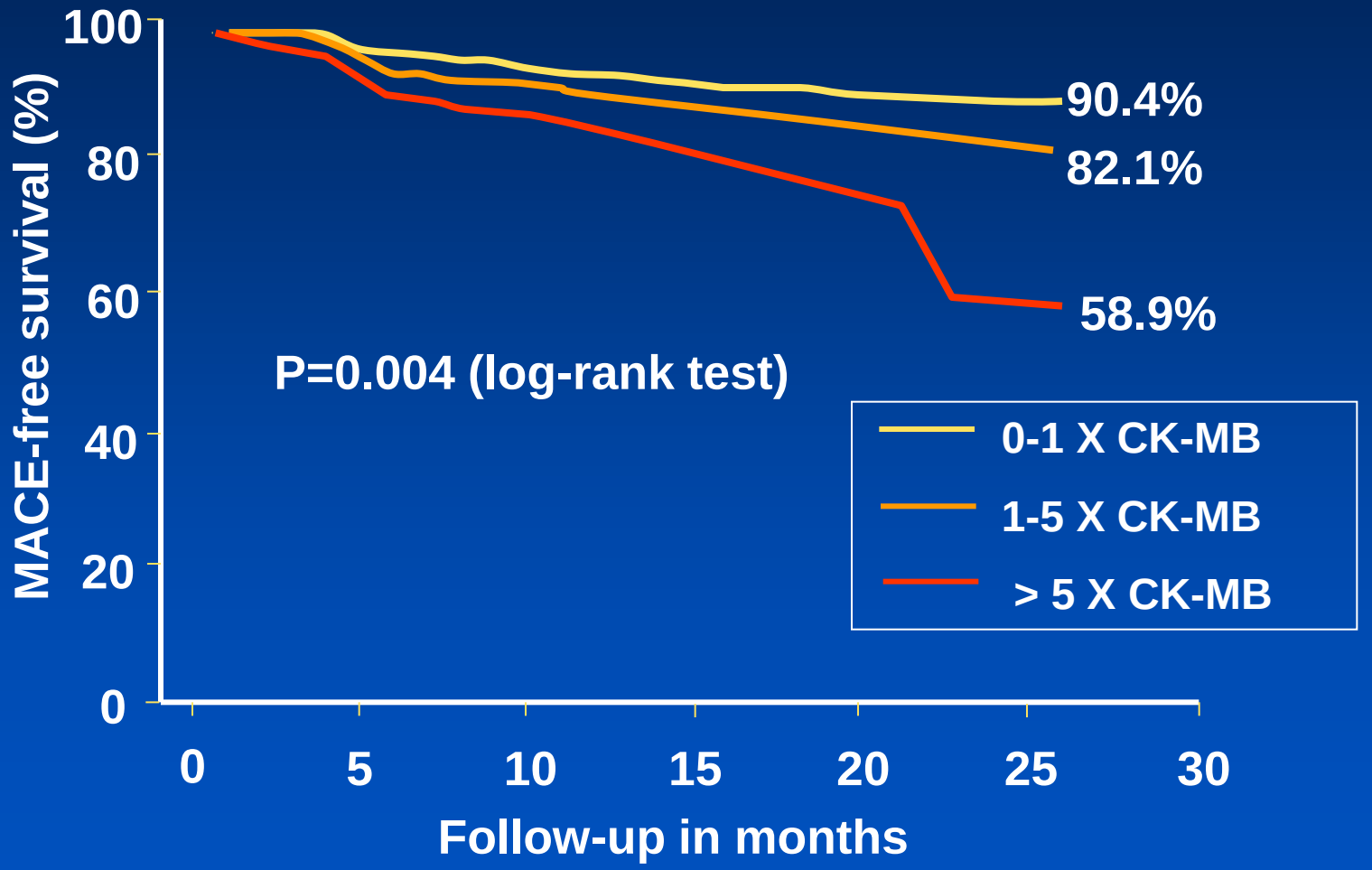

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Objective

- We aimed to perform a systematic review of the literatures evaluating the impact of CK-MB elevation on long-term mortality after PCI
- To complete a meta-analysis in order to achieve greater statistical power and more robust and generalized conclusions.

Methods

- We identified relevant studies through electronic searches of MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials from January 2001 through October 2011.

- Medical subject headings and keyword searches included the terms ‘creatine kinase’, ‘stent’, ‘angioplasty’, ‘percutaneous coronary intervention’, and ‘myocardial infarction’.

Methods

- Major predetermined selection criteria were:
  - Studies reporting data on post-PCI CK-MB values in relationship to the subsequent risk of death during follow-up
  - Mean follow-up for at least 6 months

- Exclusion criteria were:
  - Lack of information on deaths according to MB isoenzyme strata
  - Reports providing information on a subgroup of another study

Endpoints

- Mortality at longest follow-up

In relationship to the strata of CK-MB elevation

- >1-fold elevation versus normal
- 1- to 5-fold elevation versus normal
- 1- to 3-fold elevation versus normal
- 3- to 5-fold elevation versus normal
- >5-fold elevation versus normal

Statistical analysis

- Random-effects models to produce across-study risk ratios (RRs) with 95% confidence intervals (CIs)
- Heterogeneity across the included studies analyzed using heterogeneity χ^2 (Cochrane Q) statistic and I^2 test
- Publication bias examined by visual inspection of constructed “funnel plot”.
- RevMan (Version 5.1.2) and MIX 2.0 professional version were used for all the analyses.

Results

- From 478 initial citations, we excluded 468 publications for various reasons. Finally, 10 studies met our inclusion criteria.

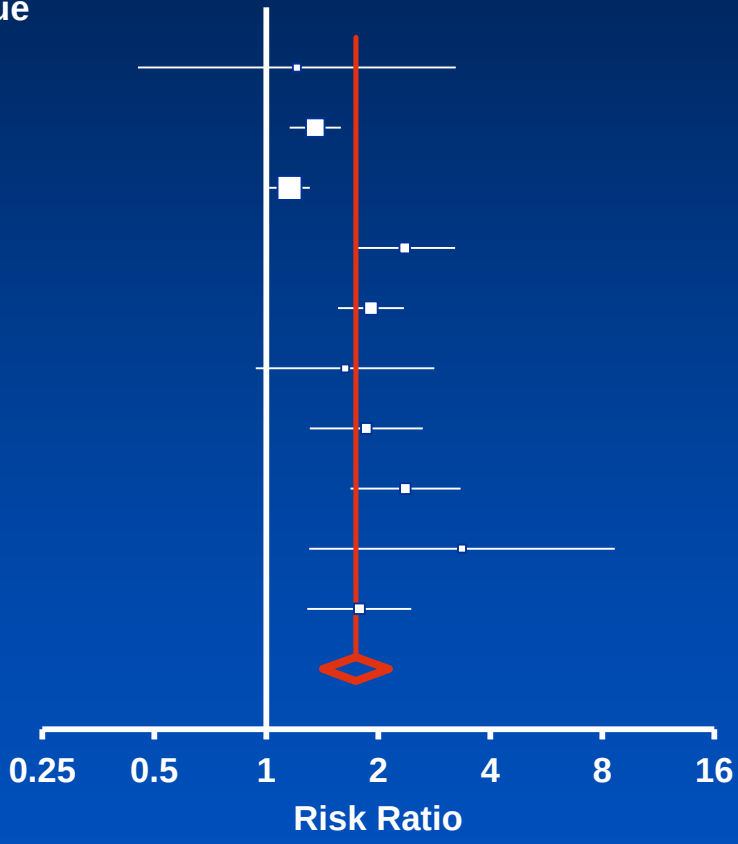
- Of the 48,022 patients in the final analysis, 12,246 patients developed CK-MB elevation after PCI and 35,776 patients did not.

Characteristics of Included studies

Study	Year	No.	Age	Male (%)	Intervention	F/U (mo)	CK-MB Measurements
Kini et al.	1999	1,675	64	68	Stent (29%), Rotational atherectomy (25%), both (32%), PTCA (10%), other (4%)	13±3	At baseline, 6–8 and 16–24 h
Stone et al.	2001	7,147	64	70	Stent (37%), atheroablation (37%), both (17%), PTCA (9%)	24	At baseline, 8–12 and 16–24 h; if abnormal, also every 8–12 h until normalized
Ellis et al.	2002	8,409	65	72	Atherectomy (14.6%, stent (66.3%)	48	At 6-8 h, next morning and with ischemic symptoms
Akkerhuis	2002	8,838	60	69	PTCA (81%), stent (8%), DCA (6%), other (5%)	6	Peak value within 48 h
Brenner et al.	2002	3,573	64	71	NA	34	At 8 h, next morning and with suspected ischemia
Kini et al. (2)	2004	2,873	66	70	Various, stent (88%)	12±6	At baseline, at 6 to 8 and 12 to 24 h, and thereafter if still increasing
Cavallini et al.	2005	3,494	64	78	Various, stent (78%)	24	At baseline, at 8–12 and 18–24 h
Jang et al.	2008	1,807	63	68	DES PCI	13±7	At baseline,at 6 h; If elevated, every 6 h until normalized
Andron et al.	2008	3,864	62	71	DES (44.4%), BMS (55.6%)	6-42	At baseline, at 18–24 h
Lindsey et al.	2011	6,347	65	69	DES (88.1%), BMS	12	At baseline, every 8 hs for a

Risk of Death
>1-fold elevation versus normal

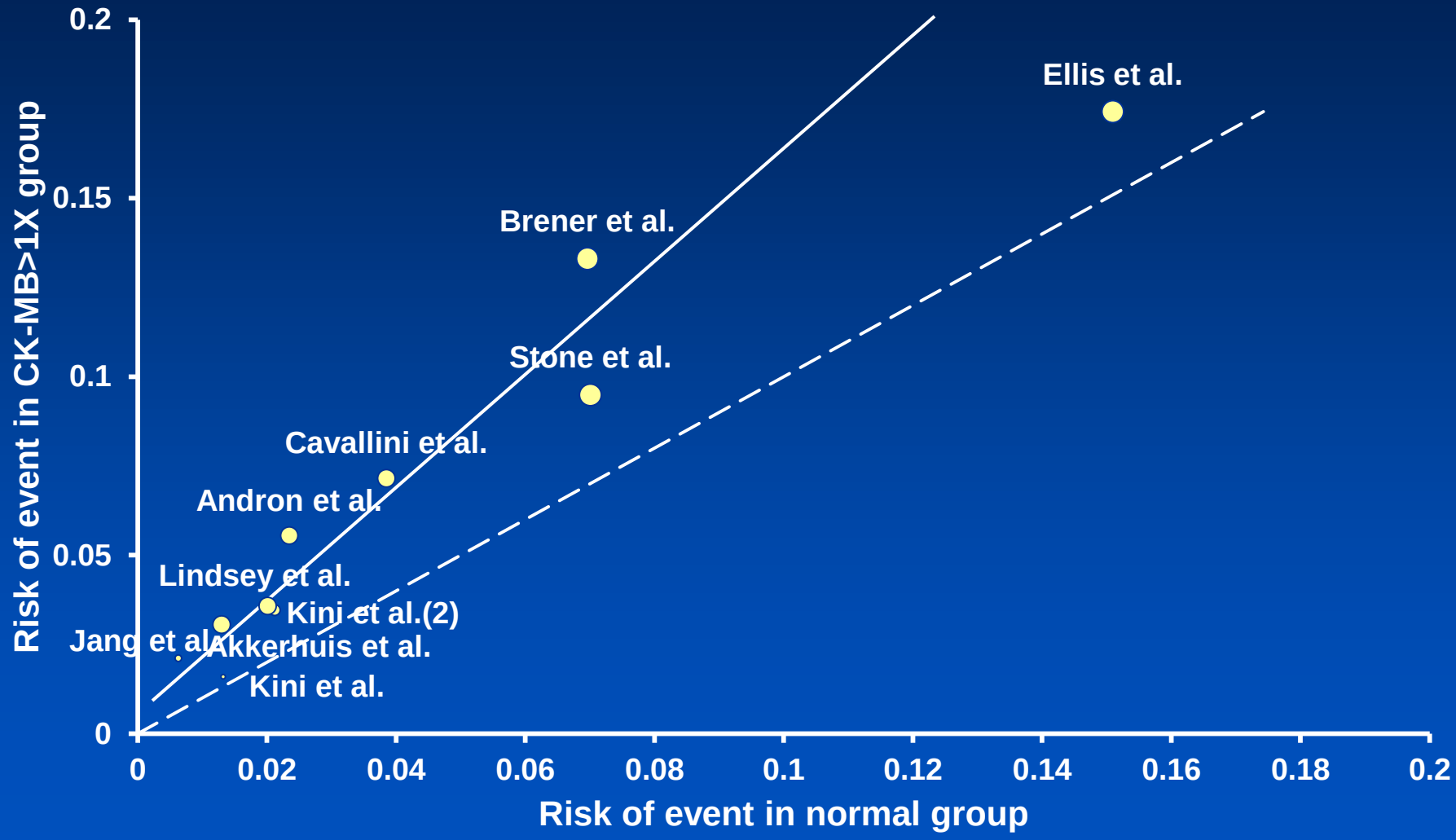
	Year	Weight %	Measure (CI)	P value
Kini et al.	1999	3.35%	1.21 (0.45; 3.23)	0.71
Stone et al.	2001	14.11%	1.35 (1.16; 1.59)	0
Ellis et al.	2002	14.57%	1.15 (1.02; 1.31)	0.02
Akkerhuis et al.	2002	11.31%	2.35 (1.72; 3.22)	0
Brener et al.	2002	13.36%	1.91 (1.56; 2.34)	0
Kini et al.(2)	2004	7.22%	1.63 (0.94; 2.83)	0.08
Cavallini et al.	2005	10.61%	1.86 (1.31; 2.63)	0
Andron et al.	2008	10.77%	2.37 (1.68; 3.33)	0
Jang et al.	2008	3.56%	3.36 (1.31; 8.65)	0.01
Lindsey et al.	2011	11.14%	1.78 (1.29; 2.46)	0
Synthesis		100%	1.74 (1.42; 2.13)	0



Heterogeneity: Tau^2=0.07, Chi^2=44.22, df=9 (p<0.001); I^2=80%
Test for overall effect: Z=5.34 (p<0.001)

Risk of Death

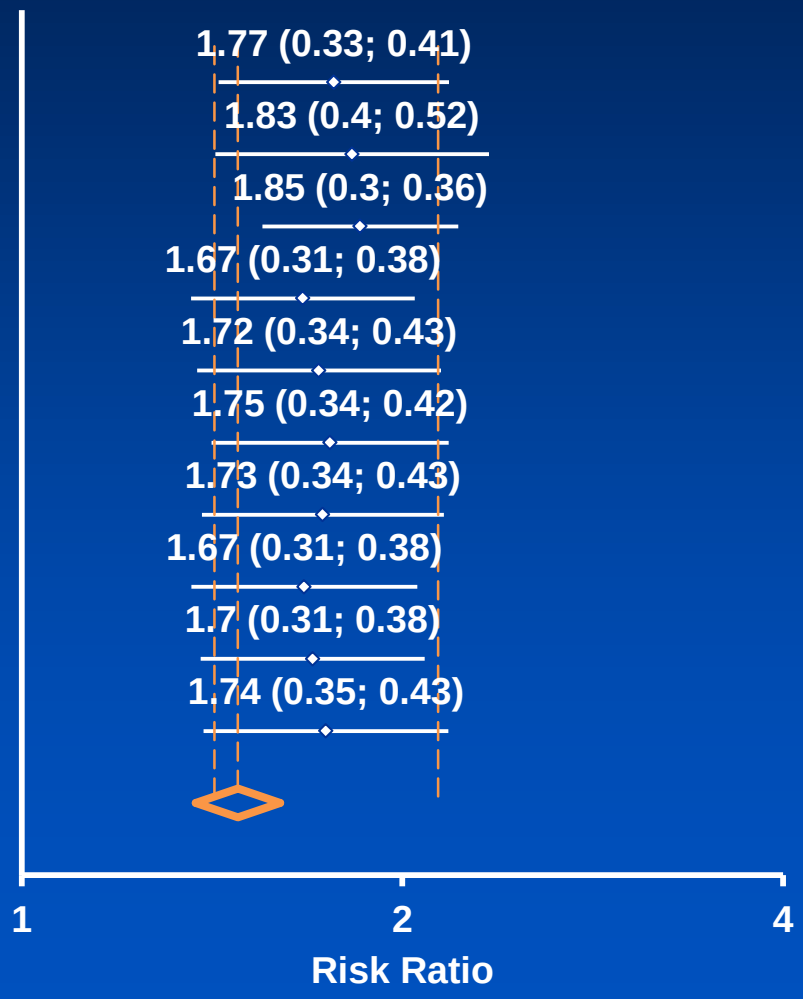
L'Abbe plot for CK-MB >1-fold elevation vs. normal



Exclusion Sensitivity Analysis

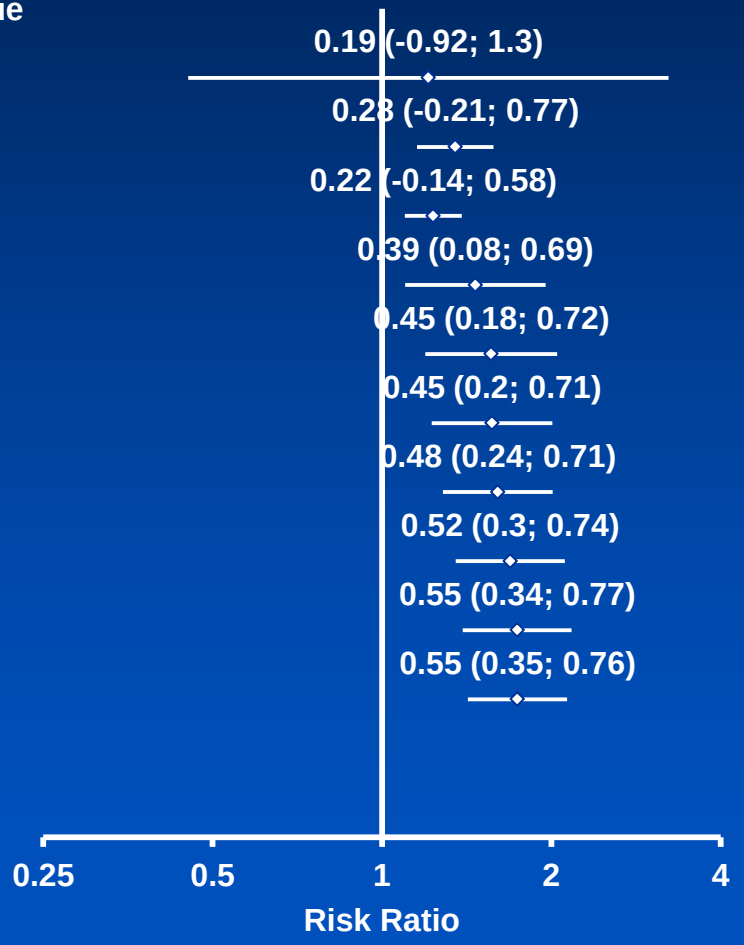
CK-MB >1-fold elevation on Mortality

	Year	Post-exclusion N
Kini et al.	1999	46347
Stone et al.	2001	40875
Ellis et al.	2002	39613
Akkerhuis et al.	2002	39184
Brener et al.	2002	44449
Kini et al.(2)	2004	45154
Cavallini et al.	2005	44528
Andron et al.	2008	44158
Jang et al.	2008	46215
Lindsey et al.	2011	41675



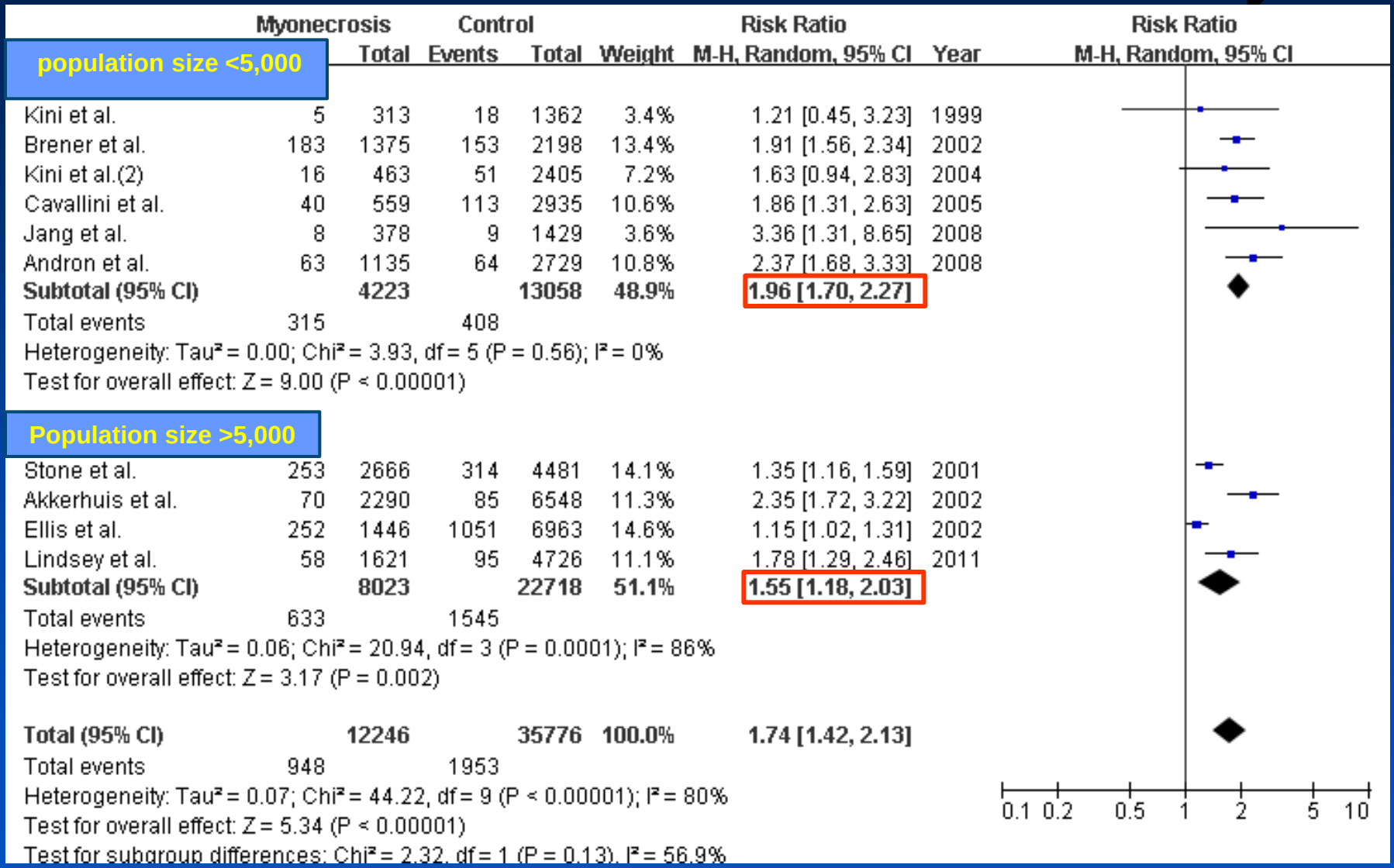
Cumulative Analysis of Included Studies
CK-MB >1-fold elevation on Mortality

	Year	Cumulative N	Cumulative measure	P value
Kini et al.	1999	1675	0.19 (-0.92; 1.3)	0.74
Stone et al.	2001	8822	0.28 (-0.21; 0.77)	0.26
Ellis et al.	2002	17231	0.22 (-0.14; 0.58)	0.23
Akkerhuis et al.	2002	26069	0.39 (0.08; 0.69)	0.01
Brener et al.	2002	29642	0.45 (0.18; 0.72)	0
Kini et al.(2)	2004	32510	0.45 (0.2; 0.71)	0
Cavallini et al.	2005	36004	0.48 (0.24; 0.71)	0
Andron et al.	2008	39868	0.52 (0.3; 0.74)	0
Jang et al.	2008	41675	0.55 (0.34; 0.77)	0
Lindsey et al.	2011	48022	0.55 (0.35; 0.76)	0



Mortality according to Population size

CK-MB >1-fold elevation on Mortality



	Myonecrosis		Control			Risk Ratio	
	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
population size <5,000							
Kini et al.	5	313	18	1362	3.4%	1.21 [0.45, 3.23]	1999
Brener et al.	183	1375	153	2198	13.4%	1.91 [1.56, 2.34]	2002
Kini et al.(2)	16	463	51	2405	7.2%	1.63 [0.94, 2.83]	2004
Cavallini et al.	40	559	113	2935	10.6%	1.86 [1.31, 2.63]	2005
Jang et al.	8	378	9	1429	3.6%	3.36 [1.31, 8.65]	2008
Andron et al.	63	1135	64	2729	10.8%	2.37 [1.68, 3.33]	2008
Subtotal (95% CI)		**4223**		**13058**	**48.9%**	**1.96 [1.70, 2.27]**	
Total events	315		408				
Heterogeneity: Tau² = 0.00; Chi² = 3.93, df = 5 (P = 0.56); I² = 0%							
Test for overall effect: Z = 9.00 (P < 0.00001)							
Population size >5,000							
Stone et al.	253	2666	314	4481	14.1%	1.35 [1.16, 1.59]	2001
Akkerhuis et al.	70	2290	85	6548	11.3%	2.35 [1.72, 3.22]	2002
Ellis et al.	252	1446	1051	6963	14.6%	1.15 [1.02, 1.31]	2002
Lindsey et al.	58	1621	95	4726	11.1%	1.78 [1.29, 2.46]	2011
Subtotal (95% CI)		**8023**		**22718**	**51.1%**	**1.55 [1.18, 2.03]**	
Total events	633		1545				
Heterogeneity: Tau² = 0.06; Chi² = 20.94, df = 3 (P = 0.0001); I² = 86%							
Test for overall effect: Z = 3.17 (P = 0.002)							
Total (95% CI)		**12246**		**35776**	**100.0%**	**1.74 [1.42, 2.13]**	
Total events	948		1953				
Heterogeneity: Tau² = 0.07; Chi² = 44.22, df = 9 (P < 0.00001); I² = 80%							
Test for overall effect: Z = 5.34 (P < 0.00001)							
Test for subgroup differences: Chi² = 2.32, df = 1 (P = 0.13), I² = 56.9%							

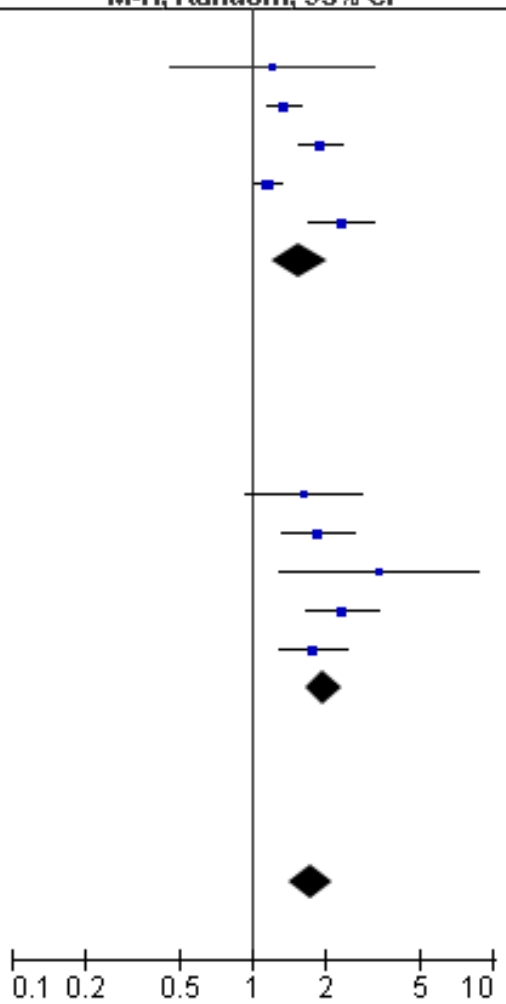
Risk Ratio M-H, Random, 95% CI

0.1 0.2 0.5 1 2 5 10

Mortality according to Publication year

CK-MB >1-fold elevation on Mortality

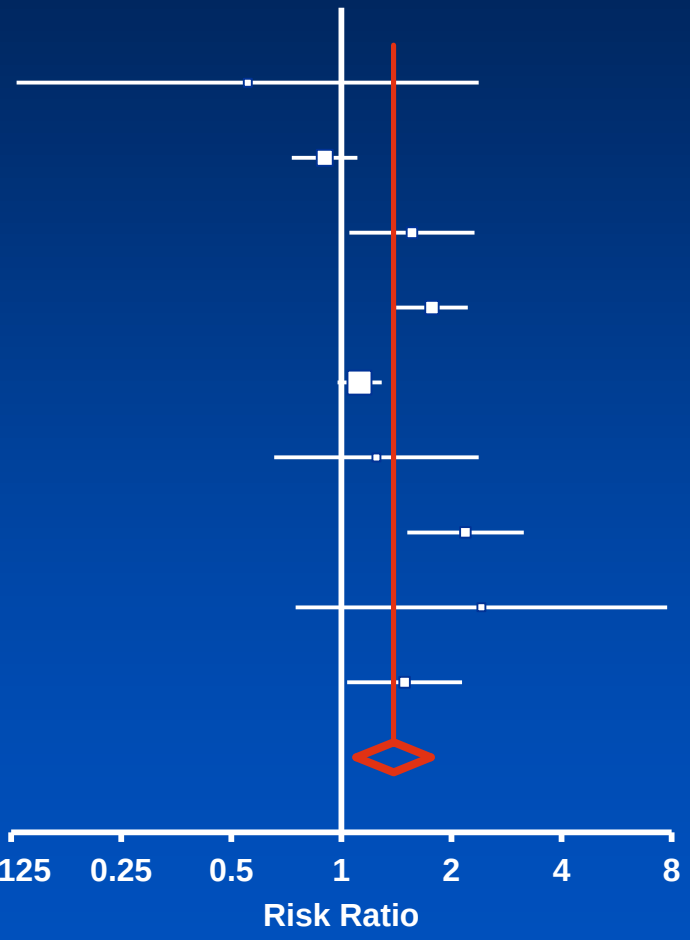
	Myonecrosis		Control			Risk Ratio	
	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	Risk Ratio M-H, Random, 95% CI
Before 2003							
Kini et al.	5	313	18	1362	3.4%	1.21 [0.45, 3.23]	1999
Stone et al.	253	2666	314	4481	14.1%	1.35 [1.16, 1.59]	2001
Brener et al.	183	1375	153	2198	13.4%	1.91 [1.56, 2.34]	2002
Ellis et al.	252	1446	1051	6963	14.6%	1.15 [1.02, 1.31]	2002
Akkerhuis et al.	70	2290	85	6548	11.3%	2.35 [1.72, 3.22]	2002
Subtotal (95% CI)		**8090**		**21552**	**56.7%**	**1.56 [1.19, 2.05]**	
Total events	763		1621				
Heterogeneity: Tau² = 0.07; Chi² = 28.96, df = 4 (P < 0.00001); I² = 86%							
Test for overall effect: Z = 3.25 (P = 0.001)							
After 2003							
Kini et al.(2)	16	463	51	2405	7.2%	1.63 [0.94, 2.83]	2004
Cavallini et al.	40	559	113	2935	10.6%	1.86 [1.31, 2.63]	2005
Jang et al.	8	378	9	1429	3.6%	3.36 [1.31, 8.65]	2008
Andron et al.	63	1135	64	2729	10.8%	2.37 [1.68, 3.33]	2008
Lindsey et al.	58	1621	95	4726	11.1%	1.78 [1.29, 2.46]	2011
Subtotal (95% CI)		**4156**		**14224**	**43.3%**	**1.98 [1.65, 2.37]**	
Total events	185		332				
Heterogeneity: Tau² = 0.00; Chi² = 3.28, df = 4 (P = 0.51); I² = 0%							
Test for overall effect: Z = 7.42 (P < 0.00001)							
Total (95% CI)		**12246**		**35776**	**100.0%**	**1.74 [1.42, 2.13]**	
Total events	948		1953				
Heterogeneity: Tau² = 0.07; Chi² = 44.22, df = 9 (P < 0.00001); I² = 80%							
Test for overall effect: Z = 5.34 (P < 0.00001)							
Test for subgroup differences: Chi² = 2.00, df = 1 (P = 0.16), I² = 50.0%							



Risk of Death

1- to 5-fold elevation versus normal

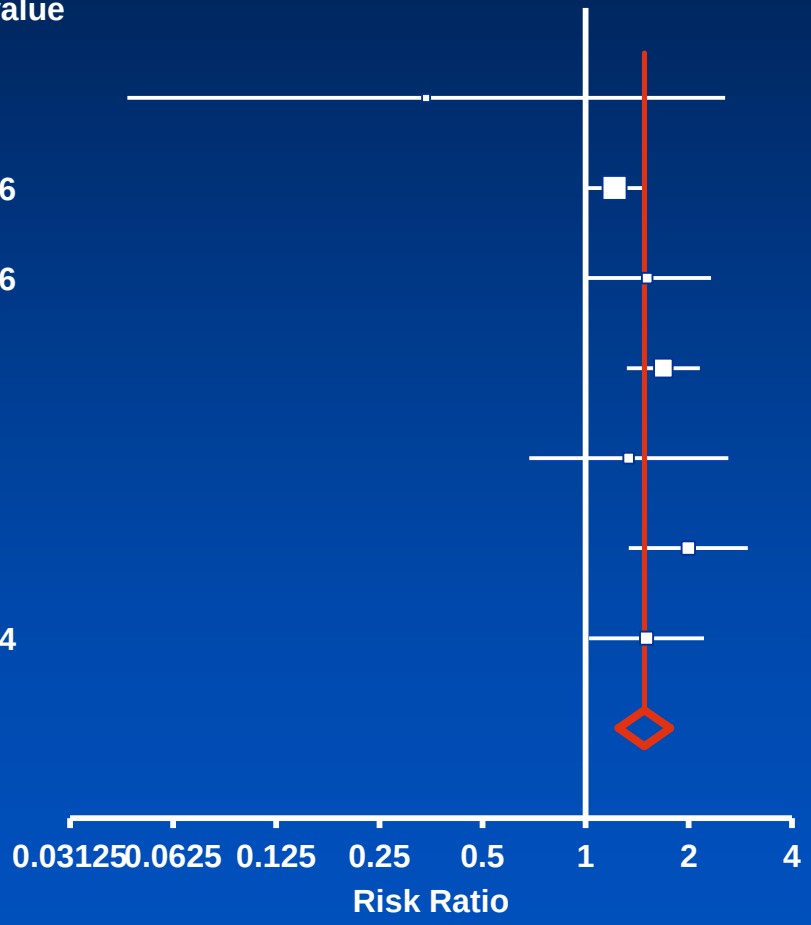
	Year	Weight %	Measure (CI)	P value
Kini et al.	1999	2.28%	0.55 (0.13; 2.38)	0.43
Stone et al.	2001	16.09%	0.9 (0.73; 1.11)	0.32
Akkerhuis et al.	2002	12.11%	1.56 (1.05; 2.31)	0.03
Brener et al.	2002	15.71%	1.77 (1.41; 2.22)	0
Ellis et al.	2002	17.26%	1.12 (0.98; 1.29)	0.11
Kini et al.(2)	2004	7.73%	1.25 (0.66; 2.37)	0.5
Andron et al.	2008	12.69%	2.18 (1.51; 3.15)	0
Jang et al.	2008	3.3%	2.41 (0.75; 7.78)	0.14
Lindsey et al.	2011	12.81%	1.49 (1.04; 2.14)	0.03
Synthesis		100%	1.39 (1.1; 1.76)	0.01



Heterogeneity: Tau^2=0.08, Chi^2=34.52, df=8 (p<0.001); I^2=77%
Test for overall effect: Z=2.75 (p=0.006)

Risk of Death
1- to 3-fold elevation versus normal

	Year	Weight %	Measure (CI)	P value
Kini et al.	1999	0.74%	0.34 (0.05; 2.55)	0.3
Stone et al.	2001	28.94%	1.22 (0.99; 1.49)	0.06
Akkerhuis et al.	2002	12.22%	1.51 (0.98; 2.32)	0.06
Brener et al.	2002	24.43%	1.69 (1.32; 2.15)	0
Kini et al.(2)	2004	5.93%	1.34 (0.68; 2.61)	0.4
Andron et al.	2008	13.52%	1.99 (1.34; 2.98)	0
Lindsey et al.	2011	14.22%	1.51 (1.02; 2.22)	0.04
Synthesis		100%	1.48 (1.25; 1.77)	0

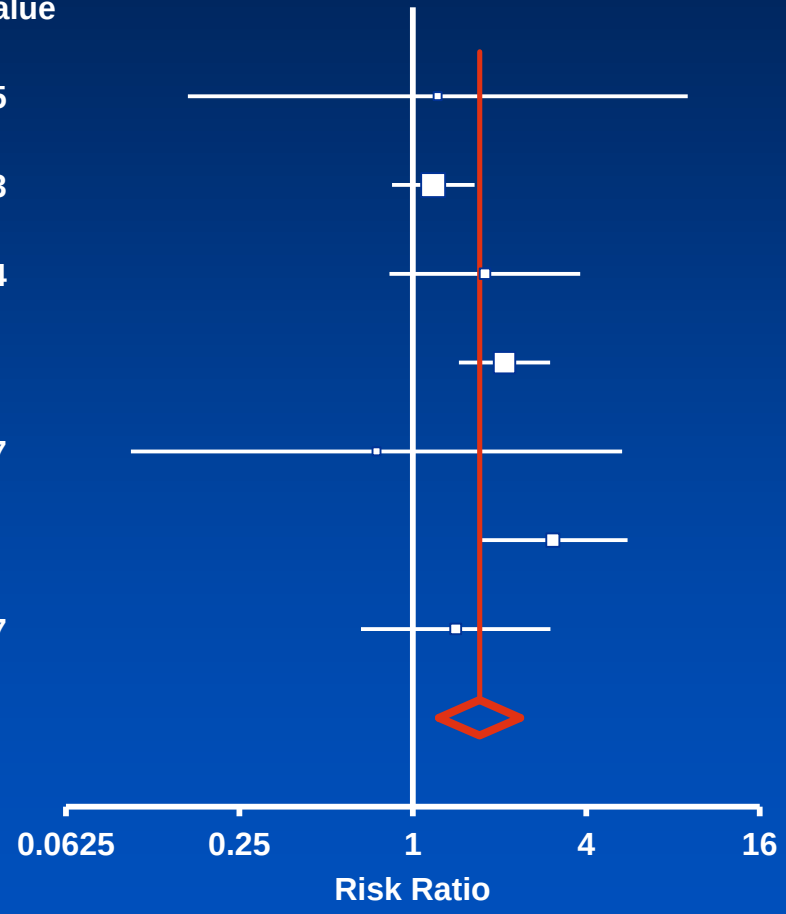


Heterogeneity: Tau^2=0.02, Chi^2=8.95, df=6 (p=0.18); I^2=33%
Test for overall effect: Z=4.44 (p<0.001)

Risk of Death

3- to 5-fold elevation versus normal

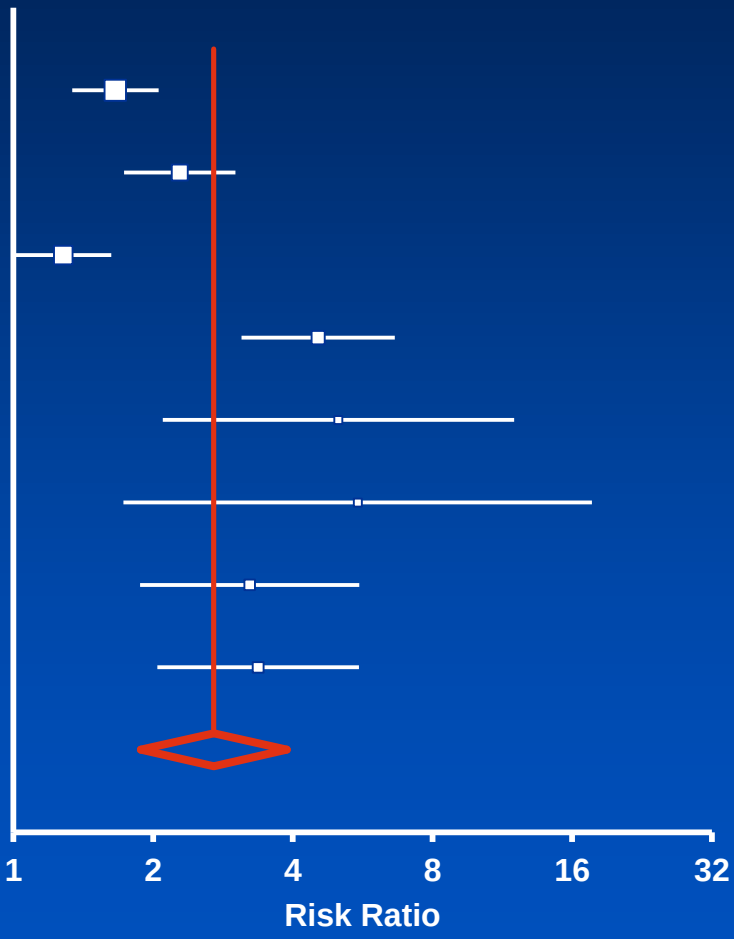
	Year	Weight %	Measure (CI)	P value
Kini et al.	1999	2.47%	1.22 (0.17; 9)	0.85
Stone et al.	2001	27.54%	1.18 (0.85; 1.64)	0.33
Akkerhuis et al.	2002	12.32%	1.78 (0.83; 3.81)	0.14
Brener et al.	2002	25.94%	2.08 (1.45; 3)	0
Kini et al.(2)	2004	2.55%	0.75 (0.11; 5.33)	0.77
Andron et al.	2008	16.74%	3.06 (1.69; 5.56)	0
Lindsey et al.	2011	12.44%	1.41 (0.66; 3.01)	0.37
Synthesis		100%	1.71 (1.23; 2.36)	0



Heterogeneity: Tau^2=0.07, Chi^2=10.81, df=6 (p=0.09); I^2=45%
Test for overall effect: Z=3.19 (p=0.001)

Risk of Death
>5-fold elevation versus normal

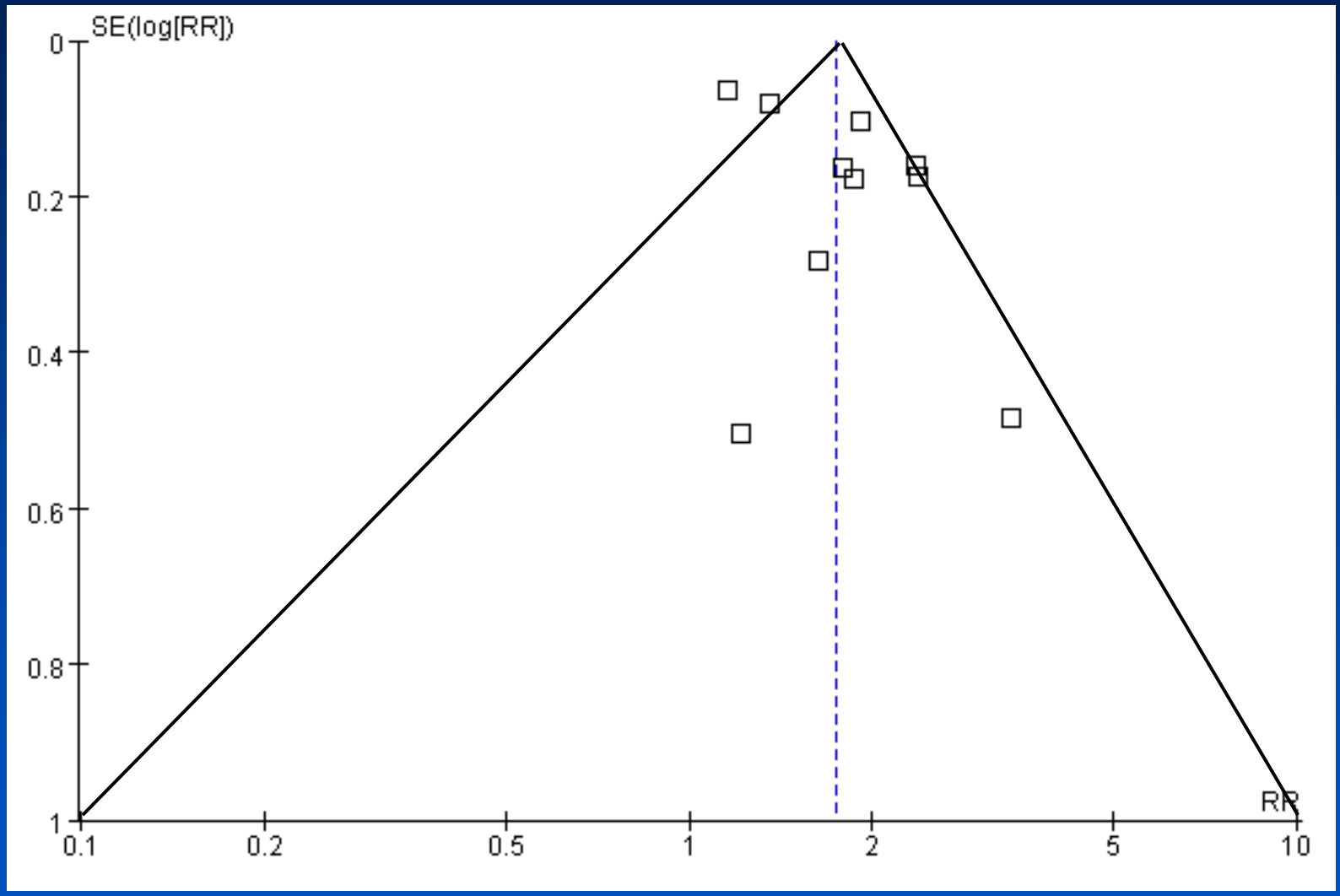
Author	Year	Weight %	Measure (CI)	P value
Stone et al.	2001	15.75%	1.66 (1.34; 2.06)	0
Brener et al.	2002	15.2%	2.28 (1.73; 3.01)	0
Ellis et al.	2002	15.56%	1.28 (1.01; 1.62)	0.04
Akkerhuis et al.	2002	14.08%	4.54 (3.1; 6.64)	0
Kini et al.(2)	2004	8.48%	5.02 (2.1; 12)	0
Jang et al.	2008	6.14%	5.52 (1.73; 17.66)	0
Andron et al.	2008	12.13%	3.23 (1.88; 5.56)	0
Lindsey et al.	2011	12.65%	3.37 (2.04; 5.56)	0
Synthesis		100%	2.7 (1.88; 3.88)	0



Heterogeneity: Tau^2=0.21, Chi^2=49.79, df=7 (p<0.001); I^2=86%
Test for overall effect: Z=5.36 (p<0.001)

Publication (Small Study) Bias

Funnel plot for CK-MB >1-fold elevation on Mortality



Study Limitations

- Observational cohort studies were analyzed.
- Included studies used various type revascularization tools:

  not fully powered to examine possible differences on degree of CK-MB elevations related with different PCI modalities.
- Methods of measurement and reference values of CK-MB were varied across the included studies.
- Patient level data were not available in all studies.
- Publication bias could not be completely ruled out.

Conclusions

- The results of our meta-analysis demonstrates that even a small increase in CK-MB levels after PCI is associated with significantly higher risk of late mortality.

- Efforts to routinely monitor periprocedural CK-MB level may help to improve the long-term clinical outcomes following PCI.