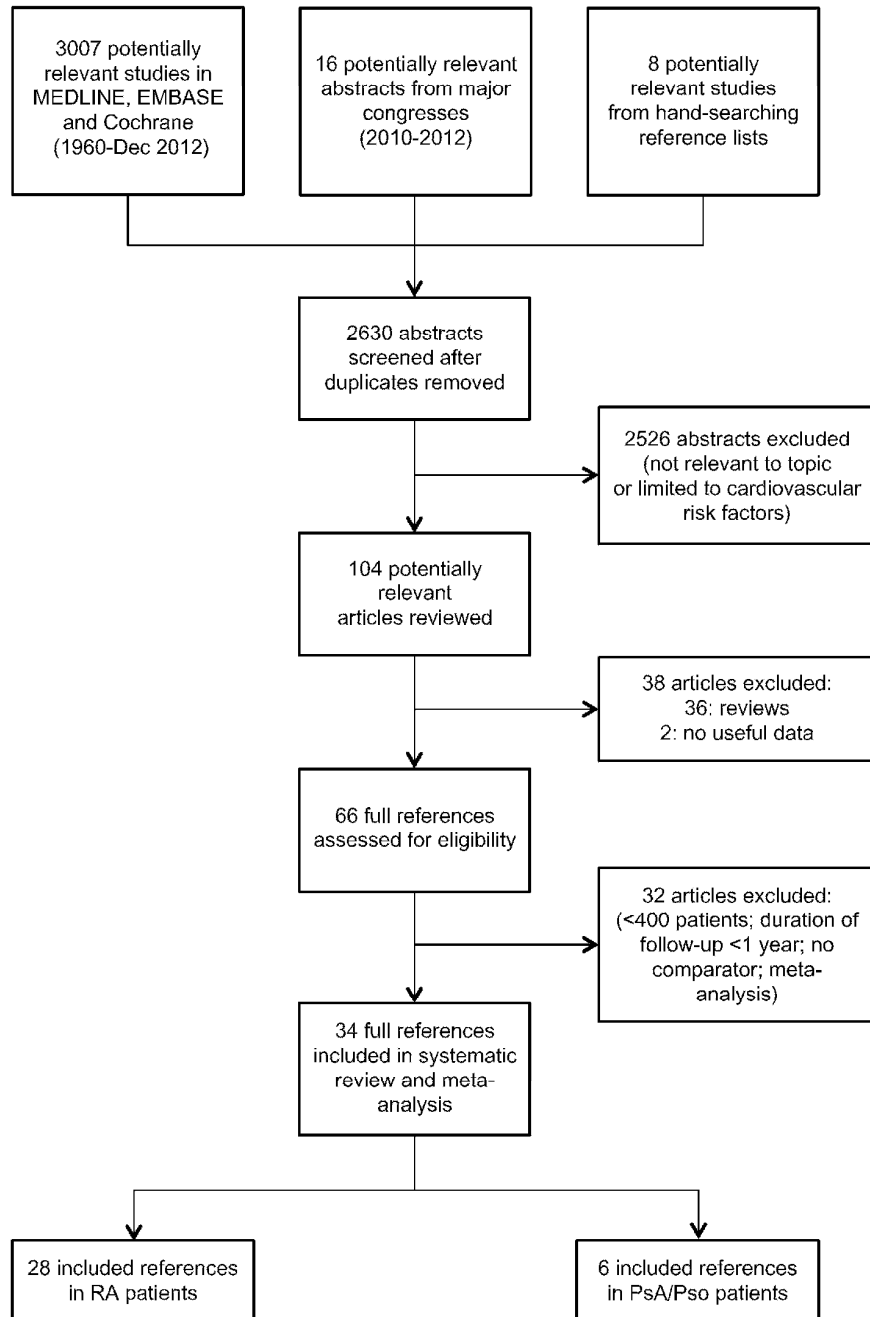


**Figure 1. Search and selection of studies for systematic review and meta-analysis.**



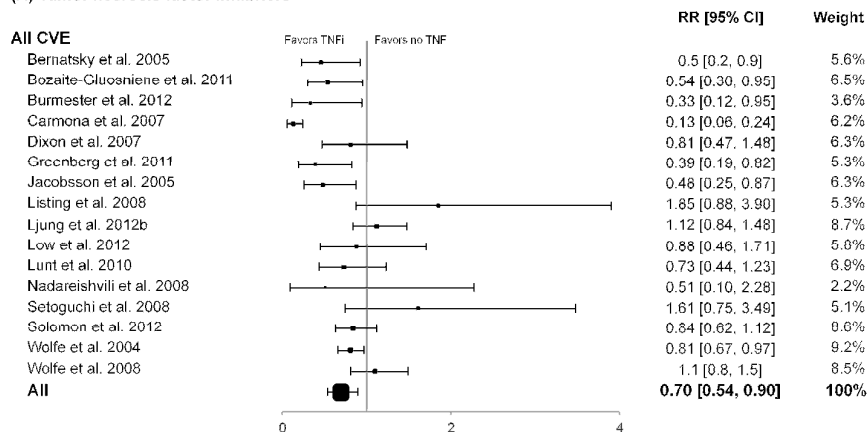
**Figure 2. Meta-analyses of all cardiovascular events and individual cardiovascular events in rheumatoid arthritis patients treated with (A) tumor necrosis factor inhibitors; (B) methotrexate; (C) non-steroidal anti-inflammatory drugs; or (D) corticosteroids in controlled studies.**

Size of data markers indicates relative weight of the study (from random-effects analysis).

CI = confidence interval; COX-2 = cyclo-oxygenase-2; CVE = cardiovascular event;

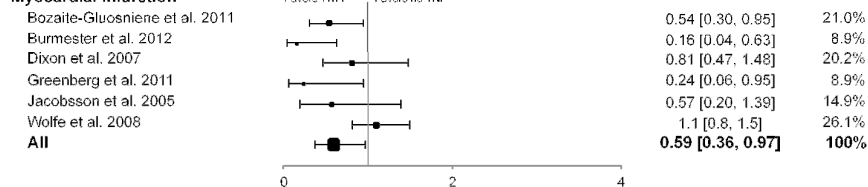
MACE = major adverse cardiac event; MTX = methotrexate; RR = relative risk; TNFi = tumor necrosis factor inhibitor.

**(A) Tumor necrosis factor inhibitors**



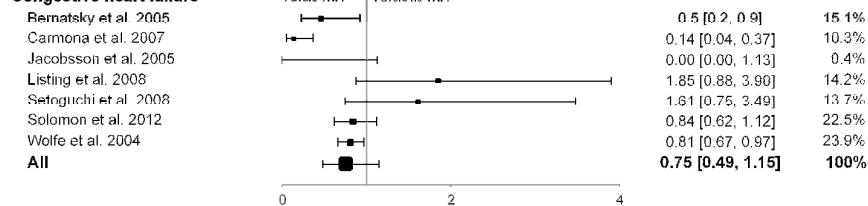
Heterogeneity:  $Tau^2=0.17$ ;  $Chi^2=65.48$ ,  $df=15$  ( $p<0.00001$ );  $I^2=77%$   
 Test for overall effect:  $Z=2.81$  ( $p=0.005$ )

**Myocardial infarction**



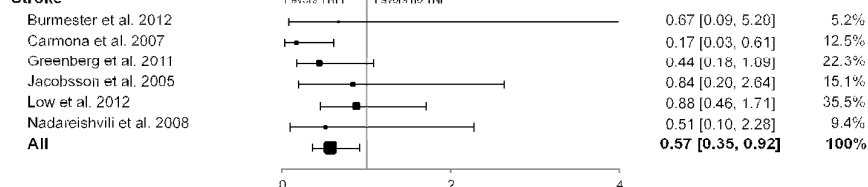
Heterogeneity:  $Tau^2=0.22$ ;  $Chi^2=14.70$ ,  $df=5$  ( $p=0.01$ );  $I^2=66%$   
 Test for overall effect:  $Z=2.08$  ( $p=0.04$ )

**Congestive heart failure**



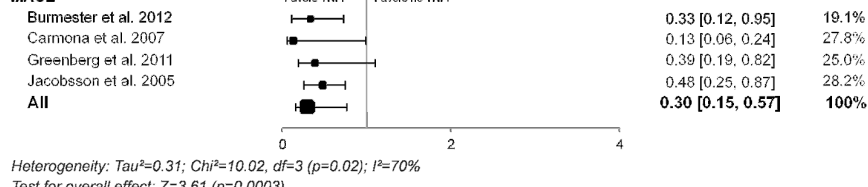
Heterogeneity:  $Tau^2=0.19$ ;  $Chi^2=25.66$ ,  $df=6$  ( $p=0.0003$ );  $I^2=77%$   
 Test for overall effect:  $Z=1.31$  ( $p=0.19$ )

**Stroke**



Heterogeneity:  $Tau^2=0.05$ ;  $Chi^2=5.85$ ,  $df=5$  ( $p=0.32$ );  $I^2=15%$   
 Test for overall effect:  $Z=2.29$  ( $p=0.02$ )

**MACE**

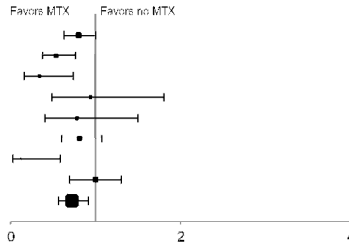


Heterogeneity:  $Tau^2=0.31$ ;  $Chi^2=10.02$ ,  $df=3$  ( $p=0.02$ );  $I^2=70%$   
 Test for overall effect:  $Z=3.61$  ( $p=0.0003$ )

**(B) Methotrexate**

**All CVE**

Bernatsky et al. 2005
Bozaite-Gluosniene et al. 2011
Choi et al. 2002
Greenberg et al. 2011
Nadareishvili et al. 2008
Suissa et al. 2006
van Halm et al. 2006
Wolfe et al. 2008
<b>All</b>

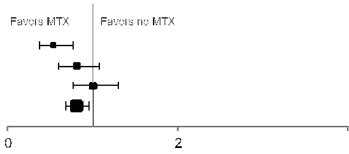


RR [95% CI]	Weight
0.8 [0.6, 1.0]	20.5%
0.54 [0.37, 0.77]	15.8%
0.3 [0.2, 0.7]	6.8%
0.94 [0.49, 1.80]	8.7%
0.78 [0.40, 1.50]	8.6%
0.81 [0.60, 1.08]	18.3%
0.12 [0.02, 0.59]	2.0%
1.0 [0.7, 1.3]	19.2%
<b>0.72 [0.57, 0.91]</b>	<b>100%</b>

Heterogeneity:  $Tau^2=0.06$ ;  $Chi^2=17.68$ ,  $df=7$  ( $p=0.01$ );  $I^2=60\%$   
Test for overall effect:  $Z=2.69$  ( $p=0.007$ )

**Myocardial infarction**

Bozaite-Gluosniene et al. 2011
Suissa et al. 2006
Wolfe et al. 2008
<b>All</b>

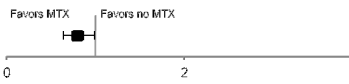


0.54 [0.37, 0.77]	22.3%
0.81 [0.61, 1.08]	35.3%
1.00 [0.77, 1.30]	42%
<b>0.81 [0.68, 0.96]</b>	<b>100%</b>

Heterogeneity:  $Chi^2=7.47$ ,  $df=2$  ( $p=0.02$ );  $I^2=73\%$   
Test for overall effect:  $Z=2.45$  ( $p=0.01$ )

**Congestive heart failure**

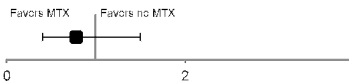
Bernatsky et al. 2005
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<b>0.8 [0.6, 1.0]</b>	<b>100%</b>
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**Stroke**

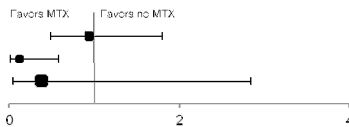
Nadareishvili et al. 2008
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<b>0.78 [0.40, 1.50]</b>	<b>100%</b>
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**MACE**

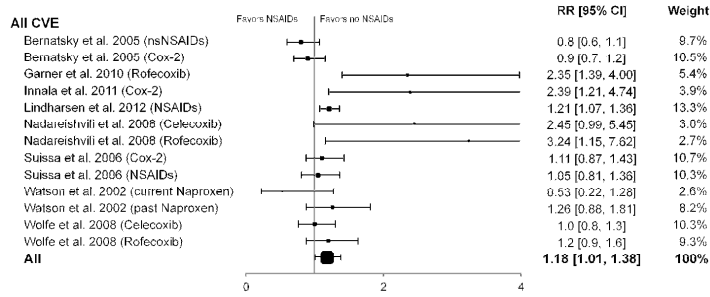
Greenberg et al. 2011
van Halm et al. 2006
<b>All</b>



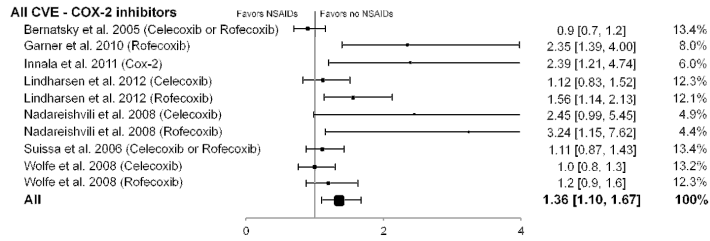
0.94 [0.49, 1.80]	58.5%
0.12 [0.02, 0.59]	41.5%
<b>0.38 [0.05, 2.84]</b>	<b>100%</b>

Heterogeneity:  $Tau^2=1.73$ ;  $Chi^2=5.50$ ,  $df=1$  ( $p=0.02$ );  $I^2=82\%$   
Test for overall effect:  $Z=0.94$  ( $p=0.35$ )

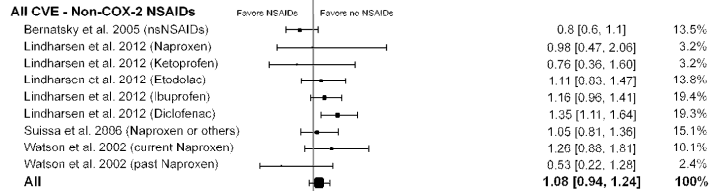
**(C) Non-steroidal anti-inflammatory drugs (NSAIDs)**



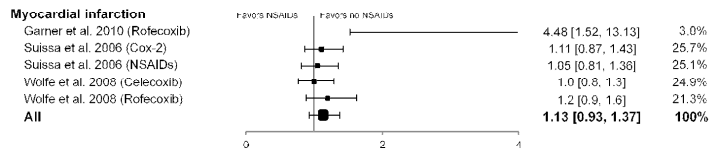
Heterogeneity:  $Tau=0.04$ ;  $Chi^2=35.64$ ,  $df=9$  ( $p=0.0004$ );  $I^2=66\%$   
 Test for overall effect:  $Z=2.08$  ( $p=0.04$ )



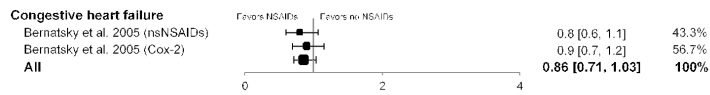
Heterogeneity:  $Tau=0.07$ ;  $Chi^2=28.40$ ,  $df=9$  ( $p=0.0008$ );  $I^2=68\%$   
 Test for overall effect:  $Z=2.87$  ( $p=0.004$ )



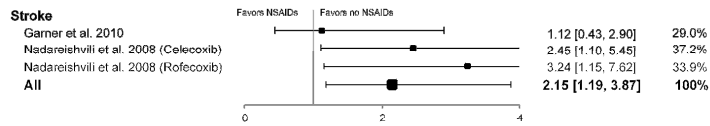
Heterogeneity:  $Tau=0.02$ ;  $Chi^2=13.46$ ,  $df=8$  ( $p=0.10$ );  $I^2=41\%$   
 Test for overall effect:  $Z=1.08$  ( $p=0.28$ )



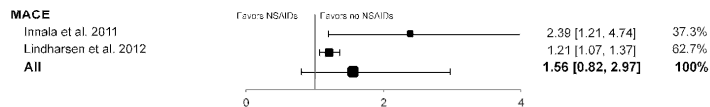
Heterogeneity:  $Tau=0.02$ ;  $Chi^2=7.49$ ,  $df=4$  ( $p=0.11$ );  $I^2=47\%$   
 Test for overall effect:  $Z=1.25$  ( $p=0.21$ )



Heterogeneity:  $Tau=0.00$ ;  $Chi^2=0.36$ ,  $df=1$  ( $p=0.55$ );  $I^2=0\%$   
 Test for overall effect:  $Z=1.62$  ( $p=0.11$ )

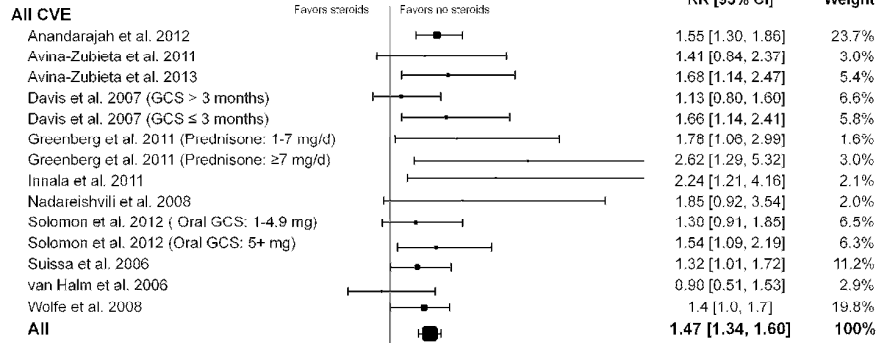


Heterogeneity:  $Tau=0.08$ ;  $Chi^2=2.79$ ,  $df=2$  ( $p=0.25$ );  $I^2=28\%$   
 Test for overall effect:  $Z=2.54$  ( $p=0.01$ )

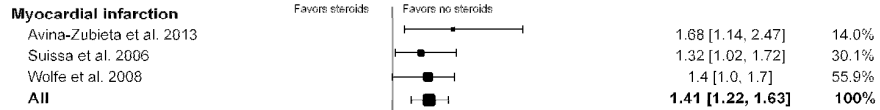


Heterogeneity:  $Tau=0.17$ ;  $Chi^2=3.68$ ,  $df=1$  ( $p=0.06$ );  $I^2=73\%$   
 Test for overall effect:  $Z=1.35$  ( $p=0.18$ )

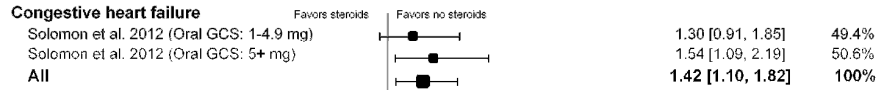
(D) Corticosteroids



Heterogeneity:  $Tau^2=0.00$ ;  $Chi^2=13.44$ ,  $df=12$  ( $p=0.34$ );  $I^2=11%$   
Test for overall effect:  $Z=7.60$  ( $p<0.00001$ )



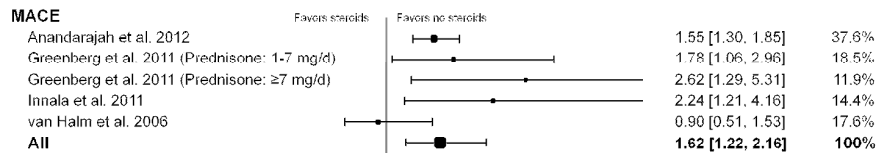
Heterogeneity:  $Tau^2=0.00$ ;  $Chi^2=1.03$ ,  $df=2$  ( $p=0.60$ );  $I^2=0%$   
Test for overall effect:  $Z=4.65$  ( $p<0.00001$ )



Heterogeneity:  $Tau^2=0.00$ ;  $Chi^2=0.44$ ,  $df=1$  ( $p=0.51$ );  $I^2=0%$   
Test for overall effect:  $Z=2.72$  ( $p=0.006$ )



Heterogeneity:  $Tau^2=0.00$ ;  $Chi^2=0.41$ ,  $df=1$  ( $p=0.52$ );  $I^2=0%$   
Test for overall effect:  $Z=2.17$  ( $p=0.03$ )



Heterogeneity:  $Tau^2=0.05$ ;  $Chi^2=7.75$ ,  $df=4$  ( $p=0.10$ );  $I^2=48%$   
Test for overall effect:  $Z=3.30$  ( $p=0.0010$ )

**Figure 3. Funnel plots for the meta-analysis of occurrence of cardiovascular events associated with treatment with (A) tumor necrosis factor inhibitors, (B)**

**methotrexate, (C) non-steroidal anti-inflammatory drugs and (D) corticosteroids.**

The importance (weight) of each study is proportional to the marker size.

