

Appendix to
Lumiracoxib (COX189) Background Document for Novartis
Presentation to FDA Advisory Committee
(February 16-18, 2005)

**Errata: Comparison of document released on January 13, 2005 with
the updated version released on February 3, 2005**

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Change: Novartis has performed a standard and cumulative meta-analysis of the cardiovascular safety of lumiracoxib for all doses, including suprathreshold doses (100 mg to 1200mg od), of all completed randomized controlled trials of lumiracoxib \geq 1 week duration.

To: Novartis has performed a standard and cumulative meta-analysis of the cardiovascular safety of lumiracoxib for all doses, including suprathreshold doses (100 mg to 1200mg od), of all randomized controlled trials of lumiracoxib \geq 1 week duration **completed by December 31, 2004.**

Change: (44 patient – years compared with 9796 patient-years for patients taking lumiracoxib for treatment of the signs and symptoms of either osteoarthritis or rheumatoid arthritis)

To: (44 patient – years compared with **9797** patient-years for patients taking lumiracoxib for treatment of the signs and symptoms of either osteoarthritis or rheumatoid arthritis)

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Change: A total of 33,933 patients were included in the safety population used for the analyses; of these, 17339 patients (9796.4 patient-years exposure) were randomized to lumiracoxib and 16594 patients were allocated to controls (8824.5 patient-years exposure). Prospective adjudication for the components of Antiplatelet Trialist's Collaboration (APTC) endpoint occurred for 15,678.7 of the total 18,620.9 patient-years exposure. ... Four trials continued for one year (TARGET, and trials 112, 2335, and 2361 with their extensions) totaling 22,781 safety patients (16,526.1 patient-years exposure).

To: A total of 33,933 patients were included in the safety population **from these trials used for the analyses**; of these, 17339 patients (**9797** patient-years exposure) were randomized to lumiracoxib and 16594 patients were allocated to controls (**8824.6** patient-years exposure). Prospective adjudication for the components of Antiplatelet Trialist's Collaboration (APTC) endpoint occurred for **15,679.3** of the total **18,621.6** patient-years exposure. ... Four trials continued for one year (TARGET, and trials 112, 2335, and 2361 with their extensions) totaling 22,781 safety patients (**16,526.7** patient-years exposure).

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Change: Table 1-2 Relative risk of APTC endpoint with lumiracoxib and comparators from a stratified meta-analysis

Comparisons	Contrasts	Risk ratio	95% CI for risk ratio	Interaction p-value
All comparators	all Lumiracoxib - all control	1.14	(0.83,1.57)	
Type of control	Lumiracoxib - placebo	0.88	(0.34,2.25)	0.6172
	Lumiracoxib - Non Naproxen NSAID	0.83	(0.46,1.51)	
	Lumiracoxib - Naproxen	1.49	(0.94,2.36)	
Duration	>3 months: Lumiracoxib - control	1.18	(0.84,1.67)	0.6121
	<=3 months: Lumiracoxib - control	0.93	(0.38,2.29)	
External Adjudication	external: Lumiracoxib - control	1.08	(0.75,1.54)	0.5562
	no external: Lumiracoxib - control	1.36	(0.66,2.80)	
Dose*	Lumiracoxib high dose -control	1.17	(0.84,1.65)	0.5379
	Lumiracoxib low dose -control	0.99	(0.57,1.71)	

To:

Comparisons	Contrasts	Risk ratio	95% CI for risk ratio	Interaction p-value
All comparators	all Lumiracoxib -all control	<u>1.12</u>	<u>(0.82,1.55)</u>	
Type of control	Lumiracoxib - placebo	<u>1.08</u>	<u>(0.41,2.86)</u>	<u>0.9102</u>
	Lumiracoxib - non-naproxen NSAID	0.83	(0.46,1.51)	
	Lumiracoxib - Naproxen	1.49	(0.94,2.36)	
<u>Indication</u>	<u>RA: Lumiracoxib - control</u>	<u>1.59</u>	<u>(0.61,4.13)</u>	<u>0.4360</u>
	<u>OA: Lumiracoxib - control</u>	<u>1.08</u>	<u>(0.77,1.51)</u>	
Duration	>3 months: Lumiracoxib - control	<u>1.15</u>	<u>(0.82,1.61)</u>	<u>0.8162</u>
	<=3 months: Lumiracoxib - control	<u>1.02</u>	<u>(0.41,2.57)</u>	
External Adjudication	external: Lumiracoxib - control	<u>1.06</u>	<u>(0.74,1.51)</u>	<u>0.5274</u>
	no external: Lumiracoxib - control	<u>1.36</u>	<u>(0.66,2.80)</u>	
Dose	Lumiracoxib high dose -control	<u>1.15</u>	<u>(0.82,1.61)</u>	<u>0.5506</u>
	Lumiracoxib low dose -control	<u>0.98</u>	<u>(0.57,1.69)</u>	

Change: **Table 1-3 Relative risk of MI with lumiracoxib and comparators from a stratified meta-analysis**

Comparisons	Contrasts	Risk ratio	95% CI for risk ratio	Interaction p-value
All comparators	all Lumiracoxib -all control	1.28	(0.78, 2.12)	
Type of control	Lumiracoxib - placebo	1.06	(0.20, 6.69)	0.7484
	Lumiracoxib - Non Naproxen NSAID	0.80	(0.28, 2.25)	
	Lumiracoxib - Naproxen	1.69	(0.82, 3.48)	
Duration	>3 months: Lumiracoxib - control	1.30	(0.75, 2.27)	0.9191
	<=3 months: Lumiracoxib - control	1.39	(0.41, 4.72)	
External Adjudication	external: Lumiracoxib - control	1.20	(0.67, 2.16)	0.7152
	no external: Lumiracoxib - control	1.48	(0.54, 4.05)	
Dose	Lumiracoxib high dose -control	1.34	(0.79, 2.29)	0.5799
	Lumiracoxib low dose -control	1.07	(0.46, 2.49)	

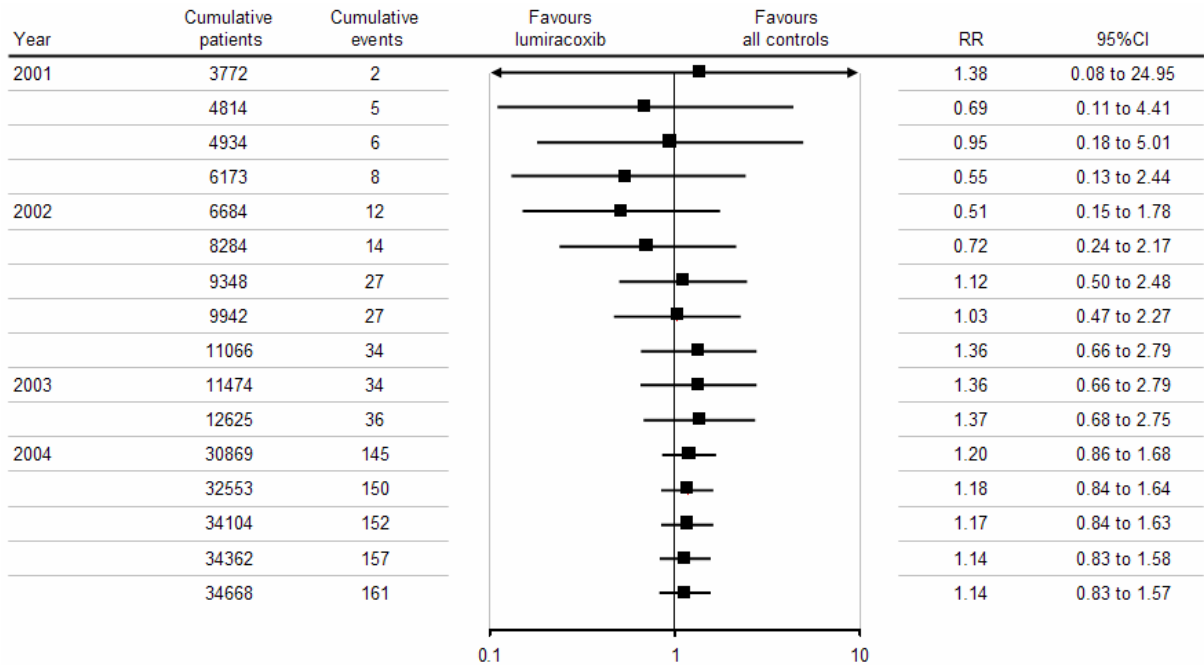
To:

Comparisons	Contrasts	Risk ratio	95% CI for risk ratio	Interaction p-value
All comparators	all Lumiracoxib -all control	1.28	(0.78,2.12)	
Type of control	Lumiracoxib - placebo	1.27	(0.25,6.56)	0.9010
	Lumiracoxib - non-naproxen NSAID	0.80	(0.28,2.25)	
	Lumiracoxib - Naproxen	1.69	(0.82,3.48)	
Indication	RA: Lumiracoxib - control	2.32	(0.43,12.4)	0.4407
	OA: Lumiracoxib - control	1.20	(0.71,2.05)	
Duration	>3 months: Lumiracoxib - control	1.30	(0.75,2.27)	0.9189
	<=3 months: Lumiracoxib - control	1.39	(0.41,4.72)	
External Adjudication	external: Lumiracoxib - control	1.20	(0.67,2.16)	0.7151
	no external: Lumiracoxib - control	1.48	(0.54,4.05)	
Dose	Lumiracoxib high dose -control	1.34	(0.79,2.29)	0.5859
	Lumiracoxib low dose -control	1.07	(0.46, 2.50)	

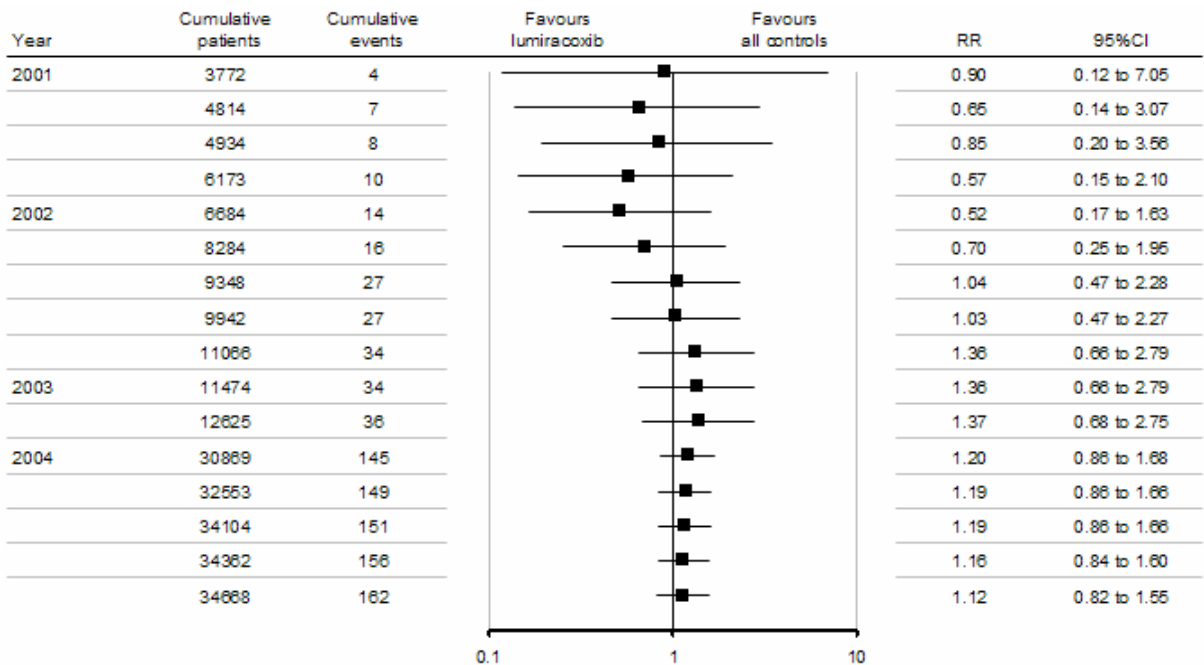
Change: The cumulative meta-analysis analyzed more than 34 000 patients with a total of 161 APTC events including 66 myocardial infarctions.

To: The cumulative meta-analysis analyzed more than 34 000 patients with a total of **162** APTC events including 66 myocardial infarctions.

Change: Figure 1-1 Cumulative stratified meta-analysis of APTC events in randomized trials comparing lumiracoxib with controls

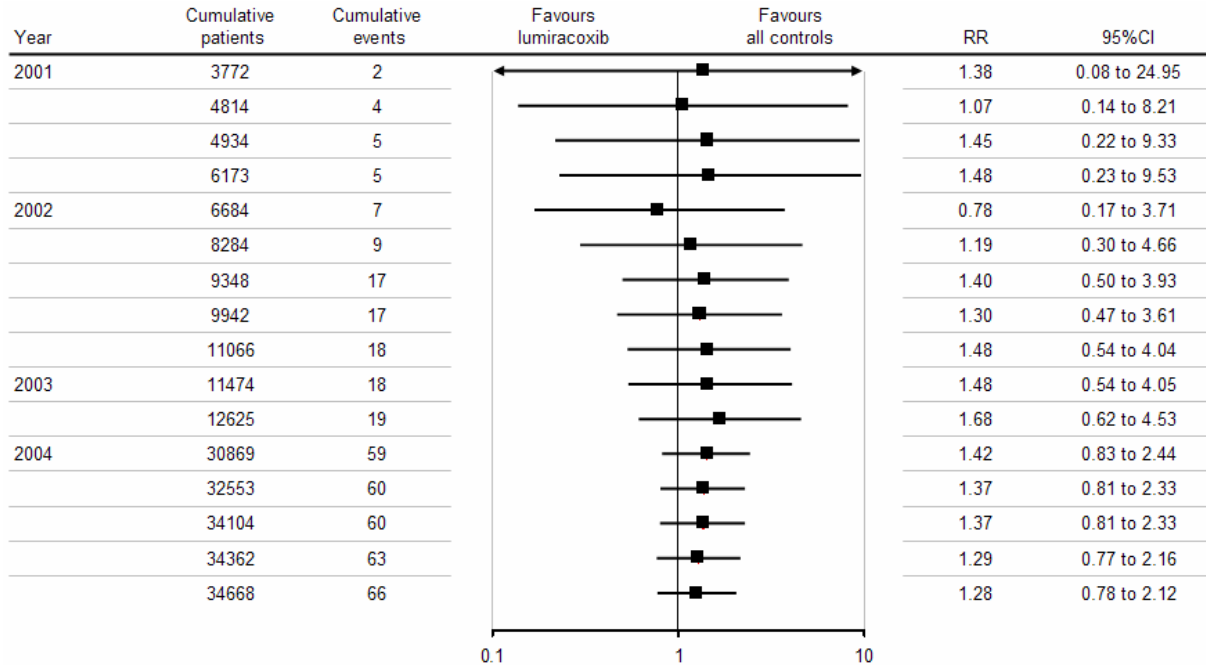


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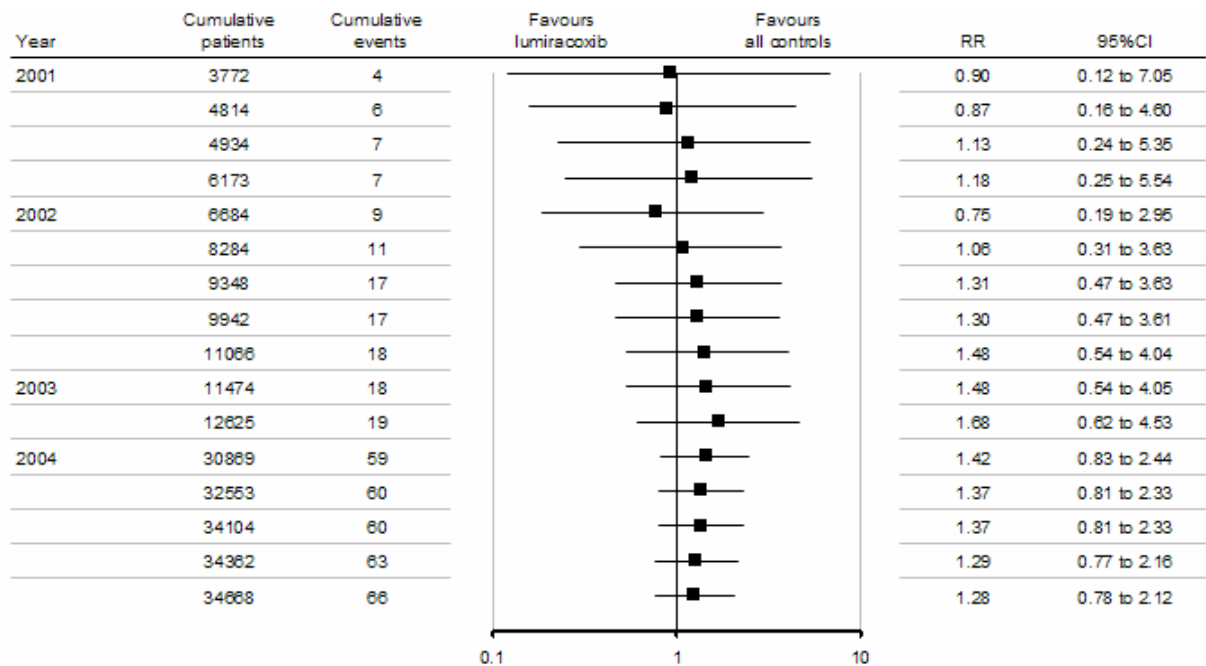


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Change: Figure 1-2 Cumulative stratified meta-analysis of MI in randomized trials comparing lumiracoxib with controls



To:

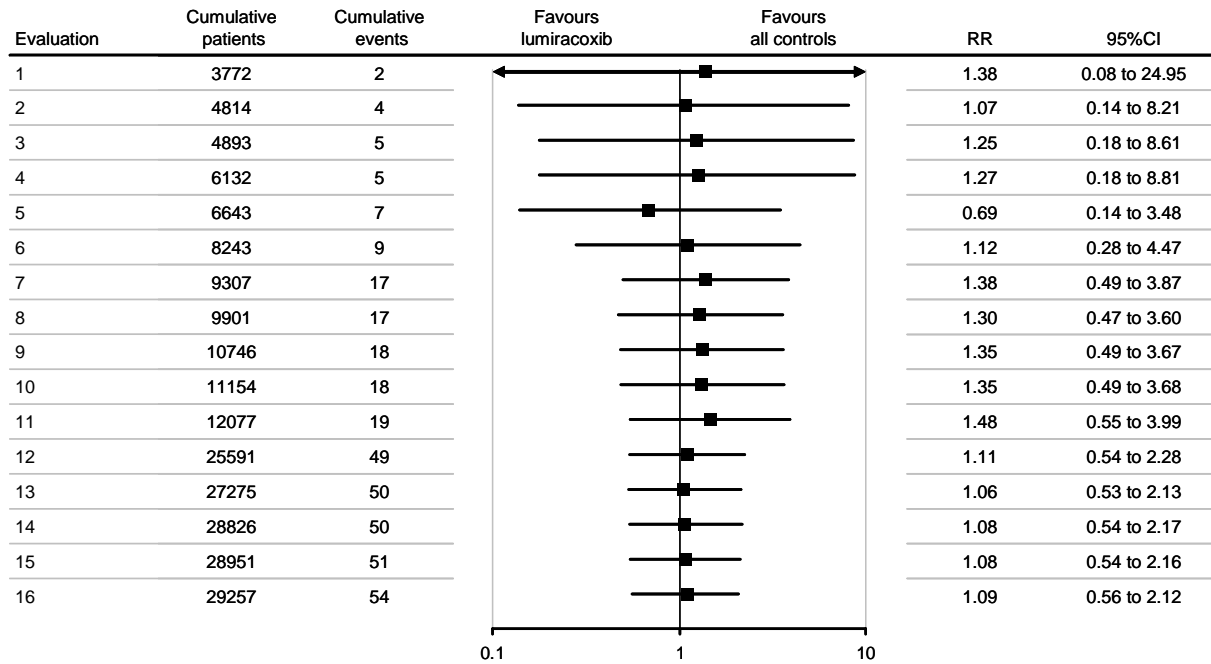


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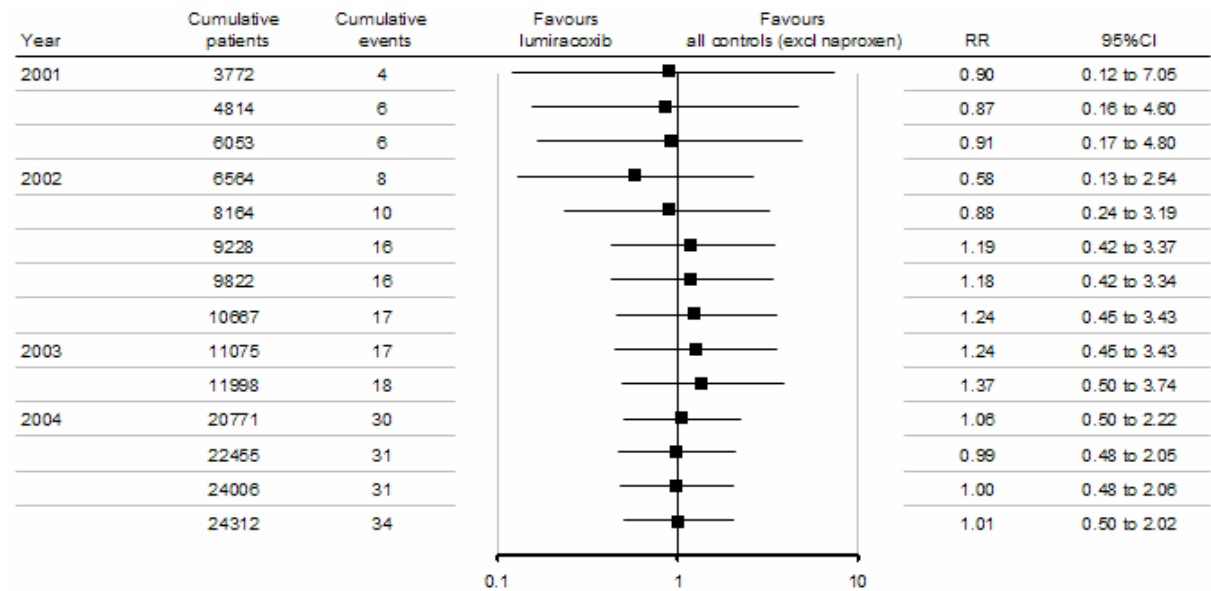
Change: When the analysis was done excluding naproxen, the risk decreased to 1.09 (95 % CI 0.56 – 2.12) which supports our assertion that naproxen at the high dose of 500 mg bid may have a antithrombotic effect (Figure 1-3 below)

To: When ~~the analysis was done excluding naproxen a stratified meta-analysis was performed comparing lumiracoxib to non-naproxen comparators~~, the risk decreased to **1.01** (95 % CI **0.50 – 2.02**) which supports our assertion that naproxen at the high dose of 500 mg bid may have **an** antithrombotic effect (Figure 1-3 below)

Change: Figure 1-3 Cumulative meta-analysis of MI in randomized trials comparing lumiracoxib with non-naproxen NSAIDs



To: Figure 1-3 Cumulative meta-analysis of MI in randomized trials comparing lumiracoxib versus all non-naproxen comparators



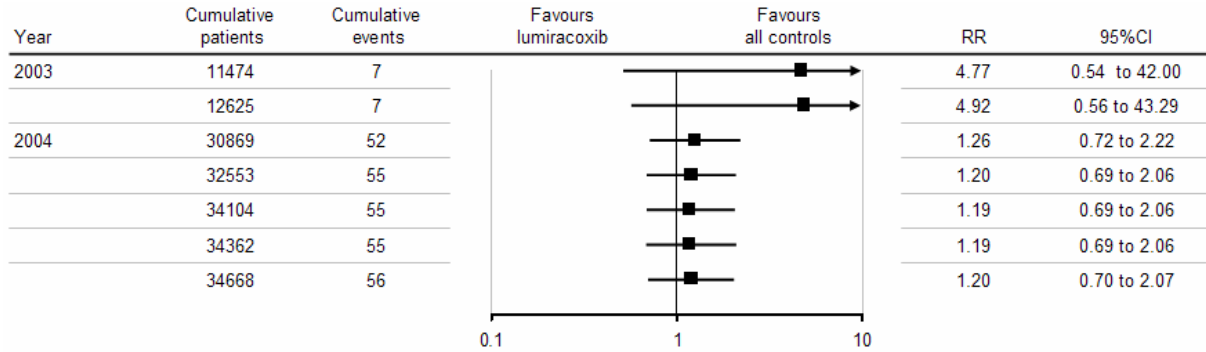
Change: **Table 1-4 Relative risk of stroke with lumiracoxib and comparators from a stratified meta-analysis**

Comparisons	Contrasts	Risk ratio	95% CI for risk ratio	Interaction p-value
All comparators	all Lumiracoxib - all control	1.20	(0.70, 2.07)	
Type of control	Lumiracoxib - placebo	0.89	(0.15, 5.08)	0.3174
	Lumiracoxib - Non Naproxen NSAID	0.91	(0.35, 2.35)	
	Lumiracoxib - Naproxen	1.46	(0.70, 3.07)	
Duration	>3 months: Lumiracoxib - control	1.18	(0.68, 2.06)	
	<=3 months: Lumiracoxib - control		not estimable	
External Adjudication	external: Lumiracoxib - control	1.06	(0.59, 1.88)	0.1424
	no external: Lumiracoxib - control	4.44	(0.51, 38.9)	
Dose	Lumiracoxib high dose - control	1.19	(0.67, 2.11)	0.8955
	Lumiracoxib low dose - control	1.12	(0.43, 2.92)	

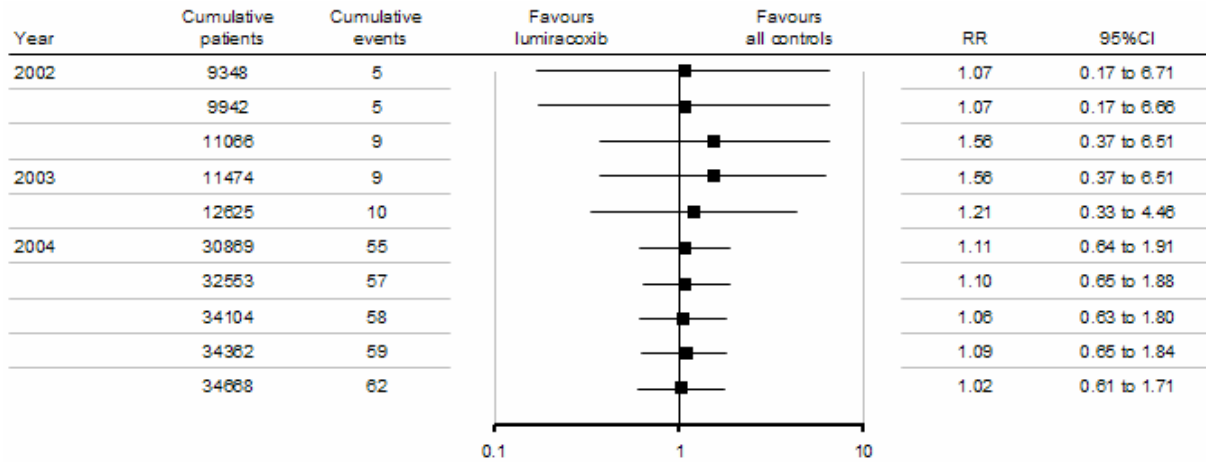
To:

Comparisons	Contrasts	Risk ratio	95% CI for risk ratio	Interaction p-value
All comparators	all Lumiracoxib -all control	<u>1.02</u>	<u>(0.61,1.71)</u>	
Type of control	Lumiracoxib - placebo	<u>0.59</u>	<u>(0.13,2.74)</u>	<u>0.8603</u>
	Lumiracoxib - non-naproxen NSAID	0.91	(0.35,2.35)	
	Lumiracoxib - Naproxen	<u>1.42</u>	<u>(0.70,2.91)</u>	
<u>Indication</u>	<u>RA: Lumiracoxib - control</u>	<u>2.32</u>	<u>(0.43,12.4)</u>	<u>0.2793</u>
	<u>OA: Lumiracoxib - control</u>	<u>0.93</u>	<u>(0.54,1.60)</u>	
Duration	>3 months: Lumiracoxib - control	<u>1.08</u>	<u>(0.64,1.84)</u>	<u>0.3445</u>
	<=3 months: Lumiracoxib - control	<u>0.38</u>	<u>(0.04,3.84)</u>	
External Adjudication	external: Lumiracoxib - control	<u>0.97</u>	<u>(0.56,1.68)</u>	<u>0.5705</u>
	no external: Lumiracoxib - control	<u>1.48</u>	<u>(0.36,6.13)</u>	
Dose	Lumiracoxib high dose -control	<u>1.01</u>	<u>(0.59,1.75)</u>	<u>0.9928</u>
	Lumiracoxib low dose -control	<u>1.02</u>	<u>(0.42,2.45)</u>	

Change: Figure 1-4 Cumulative stratified meta-analysis of stroke in randomized trials comparing lumiracoxib with controls



To:



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Change: **Table 1-5 Relative risk of peripheral vascular event with lumiracoxib and comparators from a stratified meta-analysis**

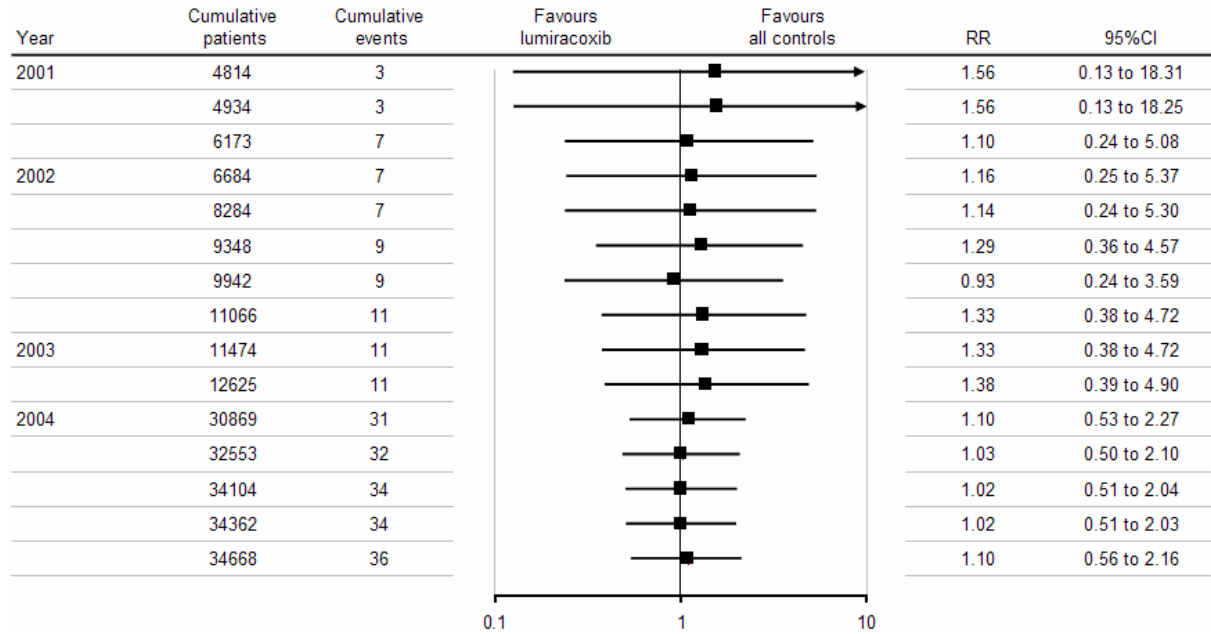
Comparisons	Contrasts	Risk ratio	95% CI for risk ratio	Interaction p-value
All comparators	all Lumiracoxib -all control	1.10	(0.56, 2.16)	
Type of control	Lumiracoxib - placebo	0.99	(0.25, 3.97)	0.1631
	Lumiracoxib - Non Naproxen NSAID	1.82	(0.44, 7.53)	
	Lumiracoxib - Naproxen	0.79	(0.26, 2.42)	
Duration	>3 months: Lumiracoxib - control	1.36	(0.62, 2.95)	0.3967
	<=3 months: Lumiracoxib - control	0.68	(0.16, 2.95)	
External Adjudication	external: Lumiracoxib - control	1.01	(0.45, 2.26)	0.7378
	no external: Lumiracoxib - control	1.30	(0.37, 4.57)	
Dose	Lumiracoxib high dose - control	0.98	(0.46, 2.09)	0.3570
	Lumiracoxib low dose - control	1.55	(0.61, 3.95)	

To:

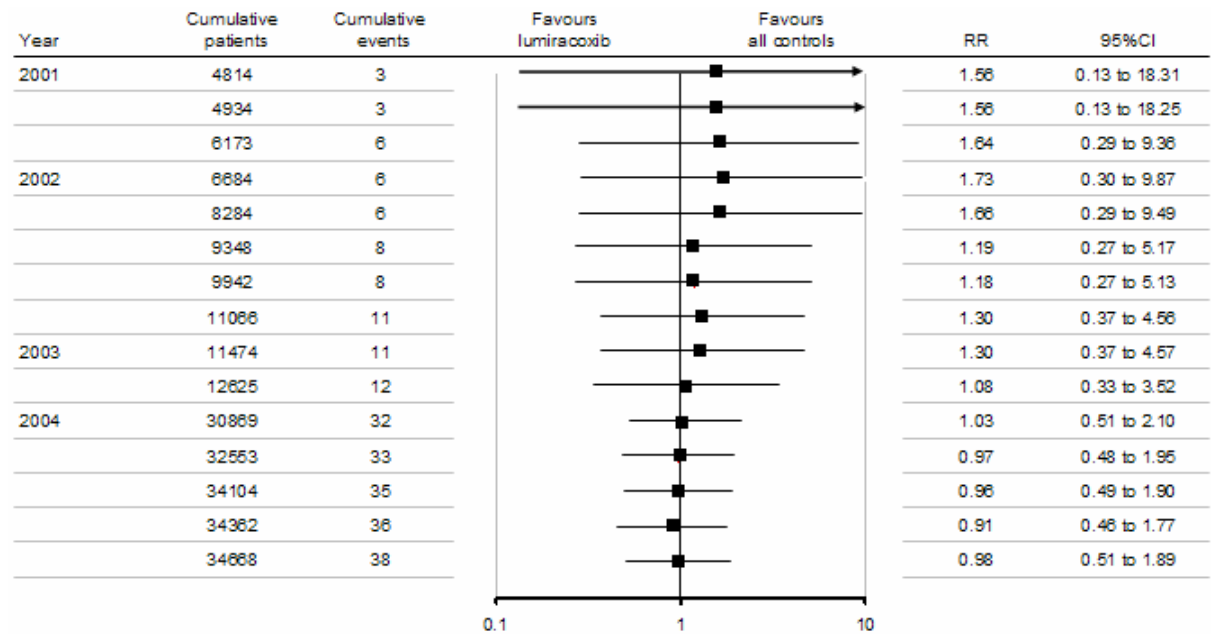
Comparisons	Contrasts	Risk ratio	95% CI for risk ratio	Interaction p-value
All comparators	all Lumiracoxib -all control	<u>0.98</u>	<u>(0.51,1.89)</u>	
Type of control	Lumiracoxib - placebo	<u>0.74</u>	<u>(0.21,2.61)</u>	<u>0.1086</u>
	Lumiracoxib - non-naproxen NSAID	1.82	(0.44,7.53)	
	Lumiracoxib - Naproxen	<u>0.69</u>	<u>(0.23,2.05)</u>	
<u>Indication</u>	<u>RA: Lumiracoxib - control</u>	<u>0.93</u>	<u>(0.22,3.84)</u>	<u>0.8982</u>
	<u>OA: Lumiracoxib - control</u>	<u>1.03</u>	<u>(0.49,2.14)</u>	
Duration	>3 months: Lumiracoxib - control	<u>1.15</u>	<u>(0.55,2.41)</u>	<u>0.5175</u>
	<=3 months: Lumiracoxib - control	0.68	(0.16,2.95)	
External Adjudication	external: Lumiracoxib - control	<u>0.87</u>	<u>(0.40,1.88)</u>	<u>0.5815</u>
	no external: Lumiracoxib - control	1.30	(0.37,4.57)	
Dose	Lumiracoxib high dose -control	<u>0.89</u>	<u>(0.43,1.86)</u>	<u>0.3986</u>
	Lumiracoxib low dose -control	<u>1.35</u>	<u>(0.54,3.38)</u>	

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Change: Figure 1-5 Cumulative stratified meta-analysis of peripheral vascular events in randomized trials comparing lumiracoxib with controls



To:



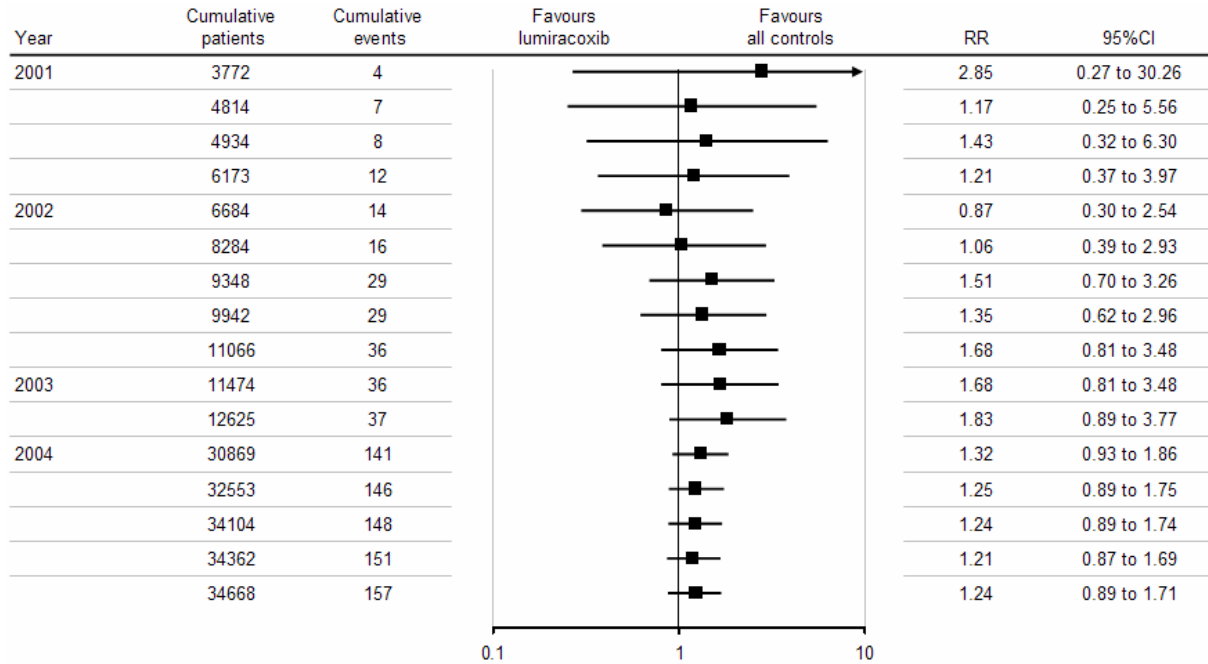
Change: **Table 1-8 Relative risk for MI / all strokes / peripheral vascular events – combined, with lumiracoxib and comparators from a stratified meta-analysis**

Comparisons	Contrasts	Risk ratio	95% CI for risk ratio	Interaction p-value
All comparators	all Lumiracoxib -all control	1.24	(0.89, 1.71)	
Type of control	Lumiracoxib - placebo	0.97	(0.39, 2.41)	0.5519
	Lumiracoxib - Non Naproxen NSAID	1.05	(0.56, 1.98)	
	Lumiracoxib - Naproxen	1.40	(0.88, 2.23)	
Duration	>3 months: Lumiracoxib - control	1.29	(0.9, 1.83)	0.6445
	<=3 months: Lumiracoxib - control	1.04	(0.43,2.50)	
External Adjudication	external: Lumiracoxib - control	1.12	(0.78, 1.62)	0.3034
	no external: Lumiracoxib - control	1.69	(0.82, 3.50)	
Dose	Lumiracoxib high dose -control	1.22	(0.86, 1.73)	0.9485
	Lumiracoxib low dose -control	1.24	(0.73, 2.11)	

To: **Table 1-6 Relative risk for MI / all strokes / peripheral vascular events – combined, with lumiracoxib and comparators from a stratified meta-analysis**

Comparisons	Contrasts	Risk ratio	95% CI for risk ratio	Interaction p-value
All comparators	all Lumiracoxib -all control	<u>1.13</u>	<u>(0.82,1.54)</u>	
Type of control	Lumiracoxib - placebo	<u>0.80</u>	<u>(0.35,1.84)</u>	<u>0.4585</u>
	Lumiracoxib - non-naproxen NSAID	1.05	(0.56,1.98)	
	Lumiracoxib - Naproxen	<u>1.34</u>	<u>(0.85,2.12)</u>	
<u>Indication</u>	<u>RA: Lumiracoxib - control</u>	<u>1.62</u>	<u>(0.67,3.95)</u>	<u>0.3769</u>
	<u>OA: Lumiracoxib - control</u>	<u>1.07</u>	<u>(0.77,1.50)</u>	
Duration	>3 months: Lumiracoxib - control	<u>1.19</u>	<u>(0.84,1.67)</u>	<u>0.5184</u>
	<=3 months: Lumiracoxib - control	<u>0.89</u>	<u>(0.38,2.07)</u>	
External Adjudication	external: Lumiracoxib - control	<u>1.04</u>	<u>(0.73,1.49)</u>	<u>0.4004</u>
	no external: Lumiracoxib - control	<u>1.44</u>	<u>(0.72,2.86)</u>	
Dose	Lumiracoxib high dose -control	<u>1.12</u>	<u>(0.80,1.58)</u>	<u>0.9647</u>
	Lumiracoxib low dose -control	<u>1.14</u>	<u>(0.68,1.90)</u>	

Change: Figure 1-6 Cumulative stratified meta-analysis for MI / all strokes / peripheral vascular events – combined, in randomized trials comparing lumiracoxib with controls



To:

