

## Diclofenac: Increase of Myocardial Infarctions at low Doses?

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A few months ago an important article, widely read and intensively quoted, appeared in this journal: Varas-Lorenzo et al. [1] 'Myocardial infarction and individual non-steroidal and inflammatory drugs meta-analysis of observational studies'.

The investigation described was supported by the EMA [1]. It refers to this article in its recent evaluation of diclofenac containing medicines and makes this article in addition to the manuscript published by Bhala et al. [2] the basis of their recent PRAC (Pharmacovigilance Risk Assessment Committee) recommendations (EMA/353084/2013). Indeed, the study deserves specific attention: It appears especially credible since it has been funded by European governmental organizations and not by drug industry. For the same reason it deserves scrutiny and caution. The statement in the abstract of the publication that 'for diclofenac... the risk of acute myocardial infarctions, AMI, was increased at low and high doses' has found worldwide attention. It stigmatizes diclofenac as comparatively dangerous even in low doses with respect to cardiovascular events. Indeed, diclofenac would deserve specific risk precautions if the conclusions of this article would be correct, consistent and plausible.

Therefore we investigated the publication cautiously with respect to the specific role of diclofenac in this analysis. Unexpectedly, we believe to have found major errors and flaws which discredit the use of this publication as a cornerstone of additional safety deliberations concerning diclofenac and other drugs. The central problem is evidenced in figure 2 of the publication by Varas-Lorenzo et al. [1]. In this figure (Table 1 of this manuscript) relative risks from studies employing low (OTC) as compared to high doses of the same drug or as compared to other widely used cyclooxygenase-inhibitors. If one compares the risk ratios (RRs) given in Table 1, i.e., in figure 2 of the publication by Varas-Lorenzo et al. [1], for diclofenac several questions arise:

- Why show three of the six studies quoted no significant risk at 'low dose', whilst three other investigations [3-5] indicate such a risk?
- Why do two studies show a higher cardiovascular risk for low doses of diclofenac as compared to high doses [5,6]. Ray et al. [5] does not even discuss the astonishing difference in favor of the high dose. Varas-Lorenzo et al. [1] indicate that the small numbers of cases incorporated in their study might explain the surprising outcome.

Nevertheless, Varas-Lorenzo et al. [1] use their own (implausible) data in the present investigation without mitigating the claims in view of the acknowledged limited validity of the data. Scrutinizing the Ray-publication, one finds again that high doses are 'cardiosafe' and low doses are dangerous to the heart. Further doubts come when one investigates what the different authors define as 'high' or 'low' dose. For the three publications indicating a cardiovascular risk of low doses of diclofenac, I have compiled the definition of high and low dose in. Indeed, Andersohn regards doses of up to 100 mg as low, i.e., doses clearly above the OTC limit. Moreover, Ray defines high doses as those above 150 mg, whilst low doses are all up to 150 mg per day.

But 150 mg/day is the upper limit of doses allowed in man in most countries of the world.

Interesting is the third publication putatively indicating an AMI-risk of low doses of diclofenac. García Rodríguez et al. [4] investigate the full dose spectrum from 50, 75, 100 and 150 mg per day. They observe that low doses, 50 and 75 mg, do not go along with a significantly increased incidence of AMI. But these data did not make it into this publication, instead what García Rodríguez et al. [4] call 'medium high doses' are quoted as low dose by Varas-Lorenzo et al. [1]. These 'medium high doses' go along with an AMI-risk, but are relatively high and clearly above the OTC level.

In conclusion, I cannot find scientific evidence for the contention that diclofenac at low doses is associated with an increased risk of cardiovascular events. Still, the effort of Varas-Lorenzo and her co-workers should be acknowledged. It has however to be kept in mind that the data presented in this large and independent investigation are not of the quality which would allow to draw sound conclusions. This study should be seen in connection with the recent study of the CNT-Group [2]. These authors investigate the risk of common cyclooxygenase inhibitors at high doses in controlled prospective studies. The data by Baigent and his co-workers confirm that diclofenac, when compared to naproxen or ibuprofen, goes along with clearly less gastrointestinal toxicity and a slightly higher propensity to suffer from an acute myocardial infarction in long-term use of maximal doses.

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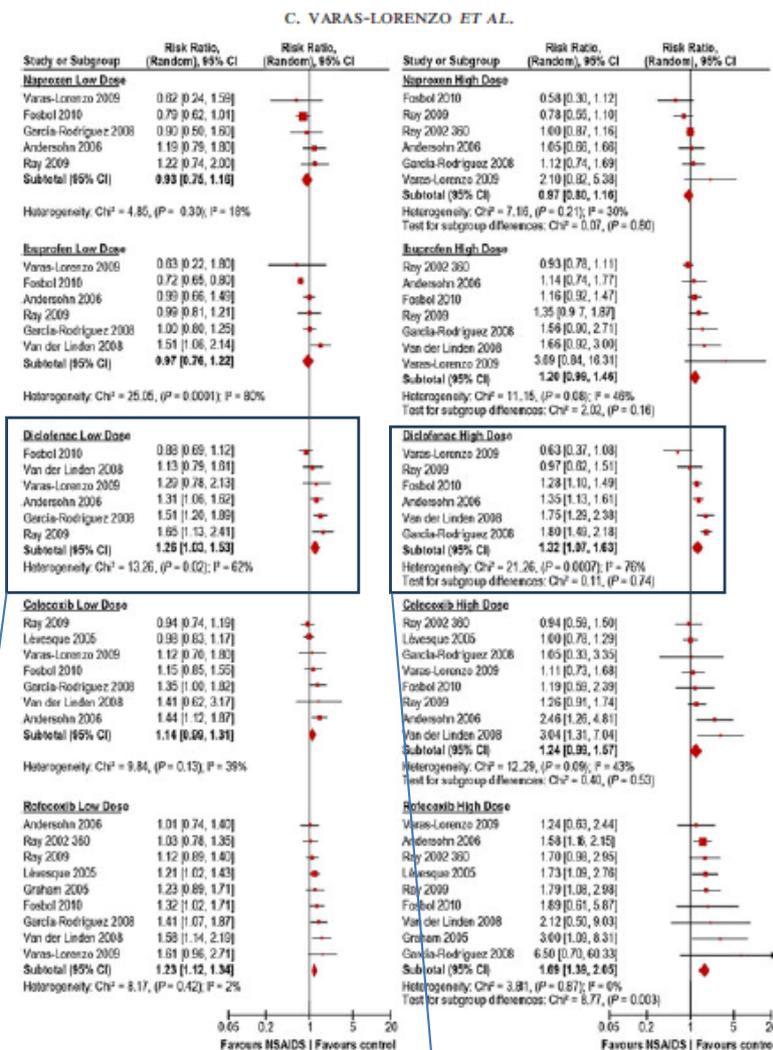
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AMI = acute myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; RR = relative risk.

Figure 2. Pooled relative risk (random effects) of acute myocardial infarction associated with current use of individual NSAIDs relative to NSAID nonuse, according to dose group. AMI = acute myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; RR = relative risk

<b>Diclofenac Low Dose</b>		
Fosbol 2010	0.88 [0.69, 1.12]	
Van der Linden 2008	1.13 [0.79, 1.61]	
Varas-Lorenzo 2009	1.29 [0.78, 2.13]	
Andersohn 2006	1.31 [1.06, 1.62]	
García-Rodríguez 2008	1.51 [1.20, 1.89]	
Ray 2009	1.65 [1.13, 2.41]	
<b>Subtotal (95% CI)</b>	<b>1.26 [1.03, 1.53]</b>	
Heterogeneity: Chi <sup>2</sup> = 13.26, (P = 0.02); I <sup>2</sup> = 62%		

<b>Diclofenac High Dose</b>		
Varas-Lorenzo 2009	0.63 [0.37, 1.08]	
Ray 2009	0.97 [0.62, 1.51]	
Fosbol 2010	1.28 [1.10, 1.49]	
Andersohn 2006	1.35 [1.13, 1.61]	
Van der Linden 2008	1.75 [1.29, 2.38]	
García-Rodríguez 2008	1.80 [1.49, 2.18]	
<b>Subtotal (95% CI)</b>	<b>1.32 [1.07, 1.63]</b>	
Heterogeneity: Chi <sup>2</sup> = 21.26, (P = 0.0007); I <sup>2</sup> = 76%		
Test for subgroup differences: Chi <sup>2</sup> = 0.11, (P = 0.74)		

Table 1: From the original publication of Varas-Lorenz et al. It delineates the relative risks calculated for putative high and low dose of drugs. The table demonstrates the inconsistency outlined in the text.

Study/Author	Low Dose / RR	High dose / RR	Comments
Andersohn 2006	≤ 100 mg/day 1.31 (1.06-1.62)	> 100 mg/day 1.35 (1.13-1.61)	OTC-dose not investigated
García-Rodriguez 2008	≤ 50 mg/day 1.12 (0.8-2.21) ≤ 75 mg/day 1.31 (0.8-2.16)	≥ 100 mg/day 1.65 (1.26-2.18) ≤ 100 mg* 1.51 (1.20-1.89)	No signific increase of risk at OTC-doses. (50 mg/75 mg) but at high dose ≥ 100 mg  Termed 'low medium dose'!? (used in the SOS-study as 'low dose')
Ray 2009	< 150 mg/day 1.65 (1.13-2.42)	≥ 150 mg/day 0.97 (0.62-1.50) (?)	Probably a calculation/transcription error

**Table 2:** The publications quoted as supporting the claim that diclofenac at low and high doses increase the risk of AMI do not support this contention: The doses going along with an increase in AMI are all above OTC-doses. The values in the study of Ray are probably flawed. (High risk at low dose but low risk at high dose).

\*from the manuscripts quoted by Varas-Lorenzo et al. [1]