INHIBITORS OF COX-2 AND RISK FOR HEART FAILURE DECOMPENSATION: SYSTEMATIC REVIEW

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ABSTRACT

Objective: To review the relation between treatment with selective COX-2 inhibitors and risk for Heat Failure (HF) decompensation.

Methods: A PubMed® search was performed from inception to July 2014. Studies with any cohort or case-control designs were eligible for the systematic review if they addressed the association between COX-2 inhibitors exposure and HF decompensation, defined by hospital admission or death. Each study was characterized regarding: first author and publication year; study population; study design; drug exposure and daily dose; outcome; measure of association and respective variance estimates; and control for confounding.

Results: The systematic review included 9 studies, published from 1999 to 2014. Etoricoxib exhibited a Hazard Ratio of 1.21 (95% CI: 1.035 – 1.402) for HF hospitalization. Rofecoxib showed an Odds Ratio of 1.58 (95% CI: 1.190 – 2.110) and Celecoxib revealed a Hazard Ratio of 1.54 95% (CI: 1.170 – 2.040) for HF decompensation.

Conclusion: Coxibs increase the risk for heart failure decompensation.

KEYWORDS

Coxibs, Heart Failure, Cohort Studies, Case-Control Studies, Systematic Review.

ABBREVIATIONS

HF – Heart Failure; Coxibs – COX-2 inhibitors; NSAID – Non Steroidal Anti-Inflammatory Drug; ASA – Acetylsalicylic Acid; GP – General Population; CC – Case-control design; Co – Cohort design; HA – Hospital Admission due heart failure; OR – Odds Ratio; HR – Hazard Ration; ll – Low Limit; ul – Up Limit; OA - Osteoarthritis patients; RA - Rheumatoid Arthritis patients; CV – Cardiovascular risk; NA – Not Available.

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INTRODUCTION

Heart failure (HF) constitutes an increasing public health issue, with high prevalence and growing incidence, poor clinical prognosis and high hospital admission rates[1]. Patients with HF remain asymptomatic for extended periods if compensatory mechanisms and/or treatments are sufficient to balance the cardiac dysfunction. Factors that commonly disturb this balance include treatment noncompliance, uncontrolled hypertension, atrial fibrillation, renal dysfunction, asthma or chronic obstructive pulmonary disease, anaemia, acute respiratory infections, drug or alcohol abuse, myocardial ischemia or infarction and the use of some types of drugs, like nonsteroidal anti-inflammatory drugs[2,3].

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are used by millions of people worldwide to reduce pain and inflammation[4]. However, long-term use of such drugs and particularly use of selective COX-2 inhibitors (Coxibs) has been reported to increase cardiovascular risk[4,5]. NSAIDs may precipitate heart failure through renal dysfunction in patients with a decreased effective circulating volume by inhibiting prostaglandin synthesis. Consequently, water and sodium retention take place, and decreases in renal blood flow and glomerular filtration rate may occur, affecting the unstable cardiovascular homeostasis. In patients with pre-existing heart failure, this may lead to cardiac decompensation[1,5,6].

The identification of factors that lead to acute cardiac decompensation and subsequent hospitalization or death has a considerable clinical interest and may contribute to improve the management of HF. However, the assessment of factors for a deleterious condition requires non-experimental methods instead the randomized clinical trials methods.

Therefore, we aimed to review systematically the published evidence of the relation between treatment with selective COX-2 inhibitors and death or hospitalization for HF assessed by non-experimental study designs.

METHODS

Search strategy

A PubMed® (http://www.ncbi.nlm.nih.gov/entrez) search was performed, from inception to July 2014, under the expression [("heart failure" OR “diastolic heart failure” OR “systolic heart failure” OR "cardiac failure" OR "chronic heart failure" OR “congestive heart failure”) AND (“coxibs” OR “COX-2 inhibitors” OR “Celecoxib” OR “Rofecoxib” OR “Etoricoxib” OR “Lumiracoxib” OR “Parecoxib” OR “Valdecoxib”)]. Titles and abstracts of the citations identified were screened and full reports of potentially eligible studies retrieved for further assessment.

Studies published as full papers or abstracts were considered as long as relevant data could be extracted.

Selection criteria

Studies with any cohort design or case-control design were eligible for the systematic review if they addressed the association between COX-2 inhibitors exposure and HF decompensation, defined by hospital admission or death. Studies evaluating patients with different pathologies, including heart failure, were considered eligible only if providing specific results for heart failure patients.

Additionally, the reference lists provided by papers previously identified and considered eligible for the review were searched and forward citation tracking was conducted for all articles selected, using Scopus® (http://www.scopus.com) and Web of Science® (http://www.webofknowledge.com).

Data extraction and synthesis

Data was extracted independently by the two authors (GC and EF), using a standardized data-extraction form. Discrepancies in the evaluation of the articles were settled by consensus.

Each study was characterized regarding: first author and publication year; study population (general population or heart failure patients); study design (cohort or case-control); exposure (drug exposure and daily dose); outcome (heart failure hospitalization or death); measure of association (relative risk or odds ratio) and respective variance estimates; and control of confounding.

When stratum-specific estimates according to potentially effect modifying factors were available, they were considered separately as if obtained from different studies.

There were no language restrictions.

RESULTS

The electronic database search yielded 144 potentially relevant articles, published from 1999 to 2014. From those, 60 were excluded on the basis of title and abstract and 84 were retrieved for evaluation. After exclusion of 70 articles, 14 were further assessed. From those, 6 were rejected, which 3 did not provided specific data for HF decompensation[7–9], one had repeated results from another study[10] and 2 did not combine the relation between HF and Coxibs use[11,12]. One additional report[13] was added after the screening of the reference lists of all studies included in the review (backward citation tracking). Furthermore, none were found after forward citation tracking using Scopus® (http://www.scopus.com) or Web of Science® (http://www.webofknowledge.com). No studies had to be excluded based on the language in which they were written.

The systematic review included 9 studies[6,13–20], as described in the detailed flow-chart (Figure 1).

From the 9 articles included in the systematic review, 7 studies were cohort design[6,14–19] and 2 were case-control design[13,20]. Target population in 3 of the studies[14,16,19] was general population and in the other 6 was specific HF patients[6,13,15,17,18,20]. All studies defined exposure as Coxibs use. No study has been found that evaluates the exposure to Parecoxib or Valdecoxib. Concerning the outcome assessed (HF decompensation), 8 studies evaluated hospitalization due HF[6,13–17,19,20]and only one evaluated HF hospitalization or death[18]. Four studies considered for systematic review provided estimates adjusted for different potentially confounding factors. One considered concomitant use of ASA[14], two considered patients with osteoarthritis and/or patients with rheumatoid arthritis[16,19] and one considered exposure of traditional NSAIDs[18]. Two studies were conducted in Australia[19,20], 2 in Europe[13,15], one in Japan[16], 2 in Canada[17,18] and 2 were a multinational studies[6,14].

The Table 1 presents the characteristics of the non-experimental studies that evaluated the relation between selective COX-2 inhibitors and heart failure decompensation.

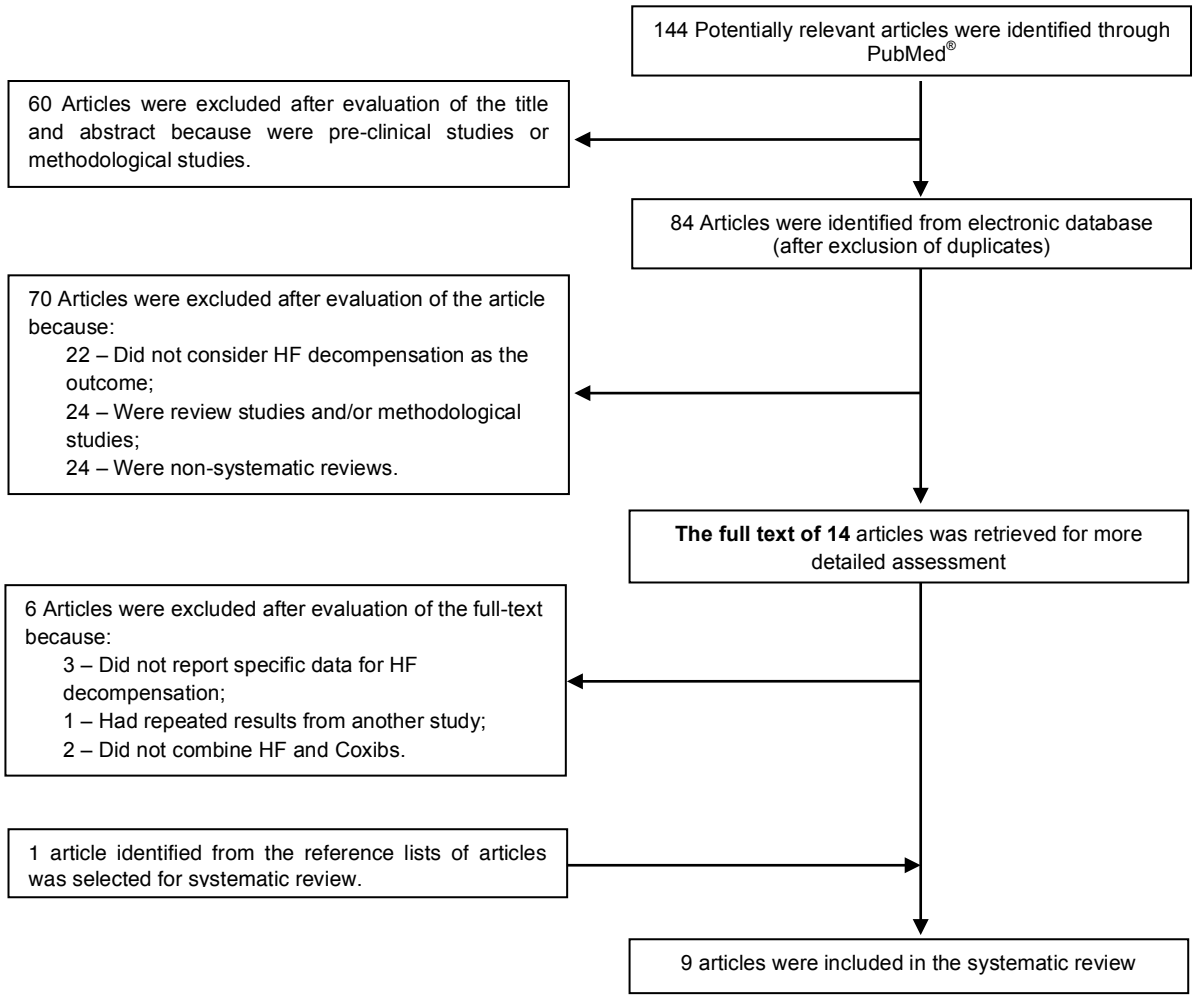

Figure 1 - Systematic review flow-chart.

Table 1 - Characteristics of the studies that evaluated the association between selective COX-2 inhibitors and heart failure decompensation.

Author, year	Study population	Study design	Age group	Drug exposure	Daily dose	Outcome	Measure of association	Hazard Ratio (95% CI)	ll	ul	Confounding
Mangoni 2009	HF	CC	≥ 65 yrs.	Coxibs (*)	NA	HA	OR	**0,96**	**0,930**	**0,990**	
McGettigan 2008	HF	CC	> 70 yrs.	Celecoxib	NA	HA	OR	1,47	0,860	2,530	
McGettigan 2008	HF	CC	> 70 yrs.	Rofecoxib	NA	HA	OR	1,29	0,780	2,130	
Hirayama 2014	OA	Co	≥ 65 yrs.	Celecoxib	200 mg	HA	HR	0,80	0,370	1,740	OA; RA
Hirayama 2014	RA	Co	≥ 65 yrs.	Celecoxib	400 mg	HA	HR	0,80	0,370	1,740	OA; RA
Gislason 2009	HF	Co	≥ 30 yrs.	Rofecoxib	NA	HA	HR	**1,40**	**1,260**	**1,550**	
Gislason 2009	HF	Co	≥ 30 yrs.	Rofecoxib	≤ 25 mg	HA	HR	**1,33**	**1,200**	**1,490**	
Gislason 2009	HF	Co	≥ 30 yrs.	Rofecoxib	> 25 mg	HA	HR	**1,86**	**1,460**	**2,350**	
Gislason 2009	HF	Co	≥ 30 yrs.	Celecoxib	NA	HA	HR	**1,24**	**1,120**	**1,390**	
Gislason 2009	HF	Co	≥ 30 yrs.	Celecoxib	≤ 200 mg	HA	HR	**1,24**	**1,090**	**1,410**	
Gislason 2009	HF	Co	≥ 30 yrs.	Celecoxib	> 200 mg	HA	HR	**1,26**	**1,040**	**1,530**	
Krum 2009	GP	Co	≥ 50 yrs.	Etoricoxib	90 mg	HA	HR	**1,88**	**1,130**	**3,100**	AO; RA
Krum 2009	RA	Co	≥ 50 yrs.	Etoricoxib	90 mg	HA	HR	1,94	0,990	3,800	
Krum 2009	OA	Co	≥ 50 yrs.	Etoricoxib	90 mg	HA	HR	1,83	0,880	3,820	
Krum 2009	OA	Co	≥ 50 yrs.	Etoricoxib	60 mg	HA	HR	1,28	0,640	2,550	

Table 1 – Characteristics of the studies that evaluated the association between selective COX-2 inhibitors and heart failure decompensation.

Author, year	Study population	Study design	Age group	Drug exposure	Daily dose	Outcome	Measure of association	Hazard Ratio (95% CI)	ll	ul	Confounding
Farkouh 2007	GP	Co	≥ 50 yrs.	Lumiracoxib	400 mg	HA	HR	0,92	0,310	2,740	ASA Non-User, ibuprofen
Farkouh 2007	GP Low CV risk	Co	≥ 50 yrs.	Lumiracoxib	400 mg	HA	HR	0,60	0,180	2,050	ASA Non-User, ibuprofen
Farkouh 2007	GP High CV risk	Co	≥ 50 yrs.	Lumiracoxib	400 mg	HA	HR	-	-	-	ASA Non-User, ibuprofen
Farkouh 2007	GP	Co	≥ 50 yrs.	Lumiracoxib	400 mg	HA	HR	3,26	0,880	12,050	ASA User, ibuprofen
Farkouh 2007	GP Low CV risk	Co	≥ 50 yrs.	Lumiracoxib	400 mg	HA	HR	1,48	0,250	8,870	ASA User, ibuprofen
Farkouh 2007	GP High CV risk	Co	≥ 50 yrs.	Lumiracoxib	400 mg	HA	HR	7,19	0,860	59,940	ASA User, ibuprofen
Farkouh 2007	GP	Co	≥ 50 yrs.	Lumiracoxib	400 mg	HA	HR	1,86	0,540	6,360	ASA Non-User, naproxen
Farkouh 2007	GP Low CV risk	Co	≥ 50 yrs.	Lumiracoxib	400 mg	HA	HR	1,77	0,420	7,400	ASA Non-User, naproxen
Farkouh 2007	GP High CV risk	Co	≥ 50 yrs.	Lumiracoxib	400 mg	HA	HR	2,17	0,200	24,190	ASA Non-User, naproxen
Farkouh 2007	GP	Co	≥ 50 yrs.	Lumiracoxib	400 mg	HA	HR	1,14	0,380	3,380	ASA User, naproxen
Farkouh 2007	GP Low CV risk	Co	≥ 50 yrs.	Lumiracoxib	400 mg	HA	HR	-	-	-	ASA User, naproxen
Farkouh 2007	GP High CV risk	Co	≥ 50 yrs.	Lumiracoxib	400 mg	HA	HR	0,87	0,260	2,840	ASA User, naproxen
Bäck 2011	HF	Co	≥ 18 yrs.	Celecoxib	187 - 213 mg	HA	HR	0,84	0,697	1,019	
Bäck 2011	HF	Co	≥ 18 yrs.	Etoricoxib	39 - 48 mg	HA	HR	**1,21**	**1,035**	**1,402**	

Table 1 – Characteristics of the studies that evaluated the association between selective COX-2 inhibitors and heart failure decompensation.

Author, year	Study population	Study design	Age group	Drug exposure	Daily dose	Outcome	Measure of association	Hazard Ratio (95% CI)	ll	ul	Confounding
Hudson 2007	HF	Co	≥ 66 yrs.	Rofecoxib	≥ 25 mg	HA	OR	**1,58**	**1,190**	**2,110**	
Hudson 2007	HF	Co	≥ 66 yrs.	Non exposed	NA	HA	OR	0,93	0,750	1,150	
Hudson 2005	HF	Co	≥ 66 yrs.	Celecoxib	200 mg	HA	HR	1,21	0,920	1,600	NSAID
Hudson 2005	HF	Co	≥ 66 yrs.	Rofecoxib	25 mg	HA	HR	1,17	0,960	1,420	Celecoxib
Hudson 2005	HF	Co	≥ 66 yrs.	Rofecoxib	25 mg	HA	HR	1,04	0,800	1,360	NSAID
Hudson 2005	HF	Co	≥ 66 yrs.	Celecoxib	200 mg	Death	HR	1,26	1,000	1,570	NSAID
Hudson 2005	HF	Co	≥ 66 yrs.	Rofecoxib	25 mg	Death	HR	**1,27**	**1,090**	**1,490**	Celecoxib
Hudson 2005	HF	Co	≥ 66 yrs.	Rofecoxib	25 mg	Death	HR	0,99	0,800	1,220	NSAID
Hudson 2005	HF	Co	≥ 66 yrs.	Celecoxib	200 mg	Death or HA	HR	**1,54**	**1,170**	**2,040**	NSAID
Hudson 2005	HF	Co	≥ 66 yrs.	Rofecoxib	25 mg	Death or HA	HR	**1,44**	**1,170**	**1,780**	Celecoxib
Hudson 2005	HF	Co	≥ 66 yrs.	Rofecoxib	25 mg	Death or HA	HR	1,07	0,820	1,390	NSAID

Abbreviations: HF – Heart Failure patients; GP – General Population; CC – Case-control design; Co – Cohort design; HA – Hospital Admission due heart failure; OR – Odds Ratio; HR – Hazard Ration; ll – Low Limit; ul – Up Limit; OA - Osteoarthritis patients; RA - Rheumatoid Arthritis patients; CV – Cardiovascular risk; NSAID – Non Steroidal Anti-Inflammatory Drug; NA – Not Available.

(*) Celecoxib, Lumiracoxib, and Rofecoxib

Table 2 - Relation between selective COX-2 inhibitors use and hospitalization due heart failure in osteoarthritis or rheumatoid arthritis patients.

Author, year	Study population	Age group	Drug exposure	Daily dose	Hazard Ratio (95% CI)	ll	ul
Hirayama 2014	OA	≥ 65 yrs.	Celecoxib	200 mg	0,80	0,370	1,740
Hirayama 2014	RA	≥ 65 yrs.	Celecoxib	400 mg	0,80	0,370	1,740
Krum 2009	RA	≥ 50 yrs.	Etoricoxib	90 mg	1,94	0,990	3,800
Krum 2009	OA	≥ 50 yrs.	Etoricoxib	90 mg	1,83	0,880	3,820
Krum 2009	OA	≥ 50 yrs.	Etoricoxib	60 mg	1,28	0,640	2,550

Abbreviations: HR – Hazard Ration; ll – Low Limit; ul – Up Limit; OA - Osteoarthritis patients; RA - Rheumatoid Arthritis patients.

Table 3 – Risk for heart failure decompensation in patients using Celecoxib.

Author, year	Study design	Age group	Celecoxib daily dose	Outcome	Measure of association	Hazard Ratio (95% CI)	ll	ul
McGettigan 2008	CC	> 70 yrs.	NA	HA	OR	1,47	0,860	2,530
Gislason 2009	Co	≥ 30 yrs.	NA	HA	OR	**1,24**	**1,120**	**1,390**
Gislason 2009	Co	≥ 30 yrs.	≤ 200 mg	HA	OR	**1,24**	**1,090**	**1,410**
Gislason 2009	Co	≥ 30 yrs.	> 200 mg	HA	OR	**1,26**	**1,040**	**1,530**
Bäck 2011	Co	≥ 18 yrs.	187 - 213 mg	HA	HR	0,84	0,697	1,019
Hudson 2005	Co	≥ 66 yrs.	200 mg	HA	HR	1,21	0,920	1,600
Hudson 2005	Co	≥ 66 yrs.	200 mg	Death	HR	1,26	1,000	1,570
Hudson 2005	Co	≥ 66 yrs.	200 mg	Death or HA	HR	**1,54**	**1,170**	**2,040**

Abbreviations: CC – Case-control design; Co – Cohort design; HA – Hospital Admission due heart failure; OR – Odds Ratio; HR – Hazard Ration; ll – Low Limit; ul – Up Limit.

Table 4 - Risk for heart failure decompensation in patients using Rofecoxib.

Author, year	Study design	Age group	Rofecoxib daily dose	Outcome	Measure of association	Hazard Ratio (95% CI)	ll	ul
McGettigan 2008	CC	> 70 yrs.	NA	HA	OR	1,29	0,780	2,130
Gislason 2009	Co	≥ 30 yrs.	NA	HA	OR	**1,40**	**1,260**	**1,550**
Gislason 2009	Co	≥ 30 yrs.	≤ 25 mg	HA	OR	**1,33**	**1,200**	**1,490**
Gislason 2009	Co	≥ 30 yrs.	> 25 mg	HA	OR	**1,86**	**1,460**	**2,350**
Hudson 2007	Co	≥ 66 yrs.	≥ 25 mg	HA	OR	**1,58**	**1,190**	**2,110**
Hudson 2005	Co	≥ 66 yrs.	25 mg	HA	HR	1,17	0,960	1,420
Hudson 2005	Co	≥ 66 yrs.	25 mg	Death	HR	**1,27**	**1,090**	**1,490**
Hudson 2005	Co	≥ 66 yrs.	25 mg	Death or HA	HR	**1,44**	**1,170**	**1,780**

Abbreviations: CC – Case-control design; Co – Cohort design; HA – Hospital Admission due heart failure; OR – Odds Ratio; HR – Hazard Ration; ll – Low Limit; ul – Up Limit.

All studies stratified the results by age. In older people, statistical significant associations have been observed between Rofecoxib use and the increased risk for HF decompensation (Table 1).

Farkouh and colleagues demonstrated that the exposure to Coxibs caused a greater risk for hospital admission in high-risk patients, defined as elevated cardiovascular score, than in low risk patients. Nevertheless, in none of the analyses was found significant results. Parallel to that find, concomitant use of low ASA dose or Naproxen or Ibuprofen use, seems to be a confounding factors of the relation between Coxibs exposure and HF hospitalization (Table 1).

The study of Bäck and colleagues exhibited a statistically significant increased in risk for HF hospitalization in patients using Etoricoxib (Hazard Ratio = 1.21; 95% CI: 1.035 – 1.402).

Hudson and colleagues founded a statistical significant risk for the exposure to Rofecoxib and the hospital admission due HF (Odds Ratio = 1.58; 95% CI: 1.190 – 2.110).

Table 2 shows that Etoricoxib exposure had a higher risk for hospital admission than Celecoxib, in HF patients that concomitantly had osteoarthritis or rheumatoid arthritis.

Table 3 displays, that in older people, Celecoxib at 200mg daily dose increased the risk for hospital admission or death (Hazard Ratio = 1.54; 95% CI: 1.170 – 2.040). All the studies analysed revealed that an increase in daily doses reflected an augmented risk for HF decompensation, however, not all values had statistical significance.

The raise of daily doses for Celecoxib or Rofecoxib augmented the risk for HF decompensation, showing the biological gradient effect (Tables 3 and 4).

All studies show in Table 4 evidenced that Rofecoxib, at any doses, increased the risk for HF decompensation (hospital admission or death).

DISCUSSION AND CONCLUSIONS

We found 9 articles that assessed the relation between Coxibs exposure and risk for HF decompensation.

The different Coxibs molecules analysed in this paper exhibit several degrees of COX-2 inhibition, consequently leading to different levels of risk for HF decompensation. However, more studies are needed to co-substantiate the findings expressed in this review. Also, it seems to be needed additional studies that evaluated our objective in populations with the same range of ages. Although data is not strong enough, the Coxib that displays a smallest risk of hospitalization due HF seems to be the Celecoxib at 200mg daily dose.

This work should progress towards a meta-analysis, in order to achieve an overall risk estimate.

Conclusions

The use of Coxibs increased the risk for heart failure decompensation, namely hospital admission or death.

The biological gradient effect was confirmed in all studied Coxibs, i.e. the raise of dose increased the risk for HF decompensation.

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