

# Racecadotril Efficacy in the Symptomatic Treatment of Adult Acute Diarrhoea: A Systematic Review and Meta-Analysis

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## Abstract

The efficacy of racecadotril (RC), an intestinal antisecretory drug acting via an enkephalinase inhibition, was reviewed in paediatric acute diarrhoea but not yet in adults. Objective: To estimate the effectiveness of RC in the symptomatic treatment of acute diarrhoea in adults. Data Sources: A systematic review of MedLine, Cochrane Controlled Trials Register, DARE, and Embase (up to November 2013). Additional studies were identified by contacting clinical experts and the manufacturer. Study Selection and Appraisal: Randomized Controlled Trials performed in adults suffering from acute diarrhoea using RC in one treatment arm. Independent extraction of articles using predefined data fields, and methodological quality measurement assessment. All randomised trials performed in adults suffering from acute diarrhoea with RC as the studied group. Statistics: The main efficacy endpoint was diarrhoea duration defined as time to recovery compared between groups by survival techniques and converted into hazard ratio (HR). We exclusively used a random-effect meta-analytic model. Constipation proportion was the main safety endpoint, evaluated between treatments by the Relative Risks (RR). Results: Twelve randomised trials (2619 patients) met inclusion criteria. Duration of diarrhoea was much shorter in the RC group, the proportion of patients having recovered at any time of the treatment period was 65% higher in the RC group, compared with placebo (HR = 1.65 [1.38 - 1.97],  $p < 0.00001$ ,  $n = 1001$ ). Duration of diarrhoea was similar in the RC and loperamide groups (HR = 1.08 [0.95 - 1.22],  $p = 0.24$ ,  $n = 1618$ ). The proportions of constipated patients were similar in the RC and placebo groups 0.95 [0.24 - 3.68],  $p = 0.97$ , however, about 3 times more constipated patients were found in the loperamide group compared with the RC group (RR = 0.34 [0.22 - 0.51],  $p < 0.0001$ ). Conclusions: Compared

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to placebo, RC is characterized by a clinically relevant earlier remission of diarrhoea. When compared to loperamide, diarrhoea duration was similar, however, significantly fewer secondary constipation adverse effects were observed.

## Keywords

Acute Diarrhoea, Meta-Analysis, Racecadotril

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## 1. Introduction

### 1.1. Rationale

Acute diarrhoea is a source of plenty common ideas, such as paediatrics is the only matter of concern, it is a self-limited condition that does not need medical intervention and if the patients wish a symptomatic treatment, an OTC agent will be sufficient. For the first point, the mortality induced by acute diarrhoea does occur mainly in infants, especially in the developing world. But in the developed countries, the mortality in adults, especially in elderly, is underestimated because it occurs after a delay due to visceral failure secondary to dehydration [1] Almost acute gastroenteritis resolve spontaneously within a miscellaneous period of time, depending of epidemiological conditions. In this active population, shortening the period of incapacity can be a major concern because it induces a huge cost [2].

There is a need for a drug, with a safe profile, that means, in particular, devoid of antimotility action, and with an established efficacy in order to reduce the diarrhoea duration.

Racecadotril is an antidiarrhoeal drug whose safety is well established, both in paediatrics [3] and in adults [4]. It acts via an enkephalinase inhibition, thus it reinforces the intestinal antisecretory effect of enkephalins [5] and has no antimotility effect [6]. Its efficacy has been recently reviewed in an individual patient data meta-analysis in paediatrics [7]. But a review of its efficacy in an adult population is still lacking.

### 1.2. Objectives

To examine whether RC reduces diarrhoea duration, we reviewed randomized, controlled trials that assessed the efficacy of this drug for the symptomatic treatment of acute diarrhoea compared to any comparator in adults.

## 2. Methods

### 2.1. Eligibility Criteria

*Participants* above 18 years old, male or female, with acute diarrhoea (AD) were considered, whatever the presumed cause of AD except cholera, healthy volunteers, paediatric patients, patients with chronic HIV-related diarrhoea, or due to anticancerous chemotherapy. The *intervention* was RC, adult formulation, without dosage restriction. *Comparators* were any control group admitted, placebo or any antidiarrhoeal drug except another formulation of RC. *Outcomes* were diarrhoea duration (DD) from treatment onset to the last unformed stools, and safety, in particular treatment related constipation adverse effect. Study design: all randomized controlled trials (RCT), either double-blind or single blind studies. *Reports* were any published data, without any restriction of language, year of publication, abstract as well as full publication.

### 2.2. Information Sources, Key Words

Studies were identified by searching electronic databases (up to November 2013): Medline (via PubMed and Ovid), Embase, ClinicalTrials.gov, Cochrane and DARE (Database of Abstracts of Reviews of Effectiveness). Besides, we contacting the authors of each identified study and questioned the manufacturer (Bioprojet Pharma), in particular on possibilities of unpublished studies. We used the following search terms to search all trials registers and databases: (“acetorphan OR racecadotril”) and “Acute diarrh\*” with the following limits: Humans, Clinical Trial, Adult.

### 2.3. Study Selection

Eligibility assessment was performed independently by 2 reviewers (JV, PL). Disagreements between reviewers

were resolved by consensus. To assess the methodological quality of RCTs, a qualitative checklist for each trial was completed and independently evaluated by each reviewer [8]. The checklist comprised seven items assessing internal validity, five items of external validity, and five items of statistical validity (see Addendum A.2. Methodological Quality Questionnaire).

## 2.4. Data Collection Process

For each selected trial, a pre-defined list of items was extracted (Addendum A1) by one review author [JV] and checked by another [PL]. Disagreements were resolved by discussion between the two review authors; if no agreement could be reached, consensus was reached by vote on all the authors. If needed, study authors were contacted for clarification.

## 2.5. Assessment of Risk of Bias in Individual Studies

The methodological quality of the studies was assessed using a domain-based evaluation of three domains: internal, external, and statistical validity. We assessed the internal validity of generation of random allocation sequence, concealment of the allocation sequence, blinding of participants, health care providers, data collectors, and outcome adjudicators, proportion of patients lost to follow-up; stopping of trials early for benefit, and whether the analysis followed the intention-to-treat principle. An overall Methodological Quality Score was derived from the summary table through a principal components analysis (see Addendum A3. Construction and calculation of the Methodological Quality Index).

## 2.6. Statistical Analysis

The main endpoint was diarrhoea duration (DD) and was compared between treatment groups within each study by the Hazard Ratio HR. Frequency of constipation was defined according to study authors, whatever their own criteria.

We pooled treatment effects and calculated a weighted average risk ratio for all outcomes in the treatment and control groups by using a random-effects model [9]. We tested for between study heterogeneity in calculating the percentage of total variation across studies due to heterogeneity  $I^2$  [11] [12].

The main endpoint was expected to be reported on various ways necessitating indirect calculation for estimating the Hazard Ratios: If Cox proportional Hazard was used, results are provided in terms of HR or Log(HR). Median values were converted into HR by assuming exponential models, similarly an approximation of conversion between Log rank value and HR was used. Finally, the approximation of Var(HR) was made possible through of exponential distribution (Addendum A5). 95% confidence intervals are uniformly reported. The statistical analysis was performed with help of R statistical package (version 2.10.1).

The risk of bias across studies was studied by the following analyses: The publication bias was tested by means of funnel plots [10], funnel plot regression [13]. Year of publication was considered as a predictor in a meta-regression model to examine a possible time-lag bias [14]. The significance of the observed difference of treatment between sponsored and non-sponsored trials was assessed. We also tested the same difference between published and non published trials. We assessed the sensitivity of our results in regressing the results according to the Methodological quality index.

## 3. Results

### 3.1. Study Selection

Overall, 28 studies were identified through database searching and 4 additional studies were found from authors and Pharma sources (Bioprojet Pharma and Smith and Beecham international). The excluded studies were: duplicate or translation of previous published trials [15], and review or meta-analysis [16]-[18], studies performed in infants or in children, in patients suffering from cholera [19], from HIV-related chronic diarrhoea [20] [21] or from subacute or recurrent diarrhoea induced by anticancerous chemotherapy [22]-[26] studies comparing 100 mg capsules RC to domestic Chinese 100 mg RC [27], to the RC isomer, dexecadotril [28], and to 175 mg tablets RC [29]-[31], due to the lack of a third comparator.

Further to these exclusions (see **Table 1**), 15 studies were included in qualitative synthesis. Two studies [32]

**Table 1.** Excluded studies.

Study	Year	Country	Reason for exclusion
Alam NH [19]	2003	Bangladesh	Diarrhoea due to cholera
Ang ER [16]	2009	Philippines	Meta-analysis
Baldi F [17]	2009	Italy	Review
Baumer P [21]	1995	France	Chronic HIV-related diarrhoea
Beaugerie L [20]	1996	France	Diarrhoea due to AIDS
Bouhnik Y [30]	2008	France	Comparator = racecadotril 175*
Coffin B [29]	2008	France	Comparator = racecadotril 175*
Coffin B [31]	2008	France	Comparator = racecadotril 175*
Dorval ED [22]	1995	France	Diarrhoea due to chemotherapy
Frexinos J [32]	1996	France	Abstract with low methodological score
Freyer G [24]	2000	France	Diarrhoea due to Chemotherapy
Eberlin M [17]	2012	Germany	Review
Gendre JP [28]	1996	France	Comparator = dexecadotril*
Goncalves E [23]	1995	France	Anticancerous chemotherapy
Lin Sanren (SB011) [27]	2001	China	Comparator was other RC formulation
Mehta S [34]	2012	India	Open study—no duration data
Saliba F [26]	1998	France	Anticancerous chemotherapy
Yao P [33]	2011	China	Abstract with low methodological score
Ychou M [25]	2000	France	Anticancerous chemotherapy

[33] were published only as short abstracts and were characterized by low methodological scores (see Addendum A4. Individual results of the methodology quality questionnaire (recoded results). At last, a third study [34] has no data at all on DD. These last three studies were excluded from the quantitative synthesis. In final, 12 studies were included in the quantitative analysis (see **Table 2**).

### 3.2. Study Characteristics

The selected trials included a total of 2717 adults (intention to treat population): 1422 were assigned to RC and 1295 to control, the per protocol population was 2619 (1378 in RC groups and 1241 in control groups). Five studies were considered as placebo-controlled, four with a placebo arm [35] [36], Vetel & Coffin: personal data], one with a *Saccharomyces boulardii* arm [37] and seven were loperamide-controlled [35] [39]-[42], [Lin Sanren & Coulden: personal data]. Control group, design and population for each study are listed in **Table 2**.

### 3.3. Synthesis of Results

DD was first compared between RC and Placebo (**Figure 1(a)**) on the basis of 5 RCTs ( $n = 1001$ ): 65% more patients were observed to recover in the RC group compared with placebo (Hazard Ratio HR = 1.65 [1.38 - 1.97],  $p < 0.00001$ ). This result was found reasonable homogeneous between study ( $I^2 = 27\%$ , heterogeneity test  $Q = 5.48$ ,  $p = 0.24$ ).

In as second step, DD was compared between RC and loperamide (**Figure 1(b)**) on the basis of 7 RCTs ( $n = 1618$ ). A slightly higher but non significant proportion of recovered patients was found in RC group (HR = 1.08 [0.95 - 1.22],  $p = 0.24$ ), this result found homogeneous between studies ( $I^2 = 0$ ,  $Q$  test = 5.48,  $p = 0.55$ ).

Post-treatment constipation constituted our main safety endpoint. The proportion of constipation was found

**Table 2.** Included studies.

Author	Control group	Design	ITT sample size			PP sample size		
			RC	Control	Total	RC	Control	Total
Baumer P [35]	Placebo	DB	96	102	198	96	102	198
Hamza H [36]	Placebo	DB	32	39	71	32	38	71
Vetel JM (multidose)*	Placebo	DB	173	54	112	173	54	112
Moraes E [36]	<i>Sb</i>	SB	207	197	404	175	161	404
Coffin B & Rampal P*	Placebo	DB	86	87	173	83	87	173
Rogé J [38]	Loperamide	DB	40	36	76	37	32	76
Vetel JM [39]	Loperamide	DB	82	75	157	77	70	157
Prado D [40]	Loperamide	SB	473	472	945	473	471	945
Coulden S*	Loperamide	SB	60	60	120	60	60	120
Lin Sanren SB006*	Loperamide	SB	112	111	223	111	104	223
Wang HH [41]	Loperamide	SB	31	31	62	31	31	62
Gallelli L [42]	Loperamide	DB	30	31	61	30	31	61
All studies versus placebo (n = 5)			594	479	1073	559	442	1001
All studies versus loperamide (n = 7)			828	816	1 644	819	799	1618
All studies (n = 12)			1422	1295	2717	1378	1241	2619

RC = racecadotril; *Sb* = *Saccharomyces boulardii*; DB = double-blind; SB = single-blind. \*None publication (even as abstract), but available data from author/sponsor: Vetel JM = P.90 - 08 study (multidose) performed in France, clinical report from Bioprojet (1991): patients treated with 30 mg (n = 59), 100 mg (n = 58) or 300 mg (n = 56) racecadotril; Coulden S = SB004 study performed in India, Clinical report by Coulden S (SBI, 2001); Lin Sanren = SB006 study performed in China, Clinical report by Hue R & Sun J (SBI, 2003); Coffin B & Rampal P = P.05-04 study performed in France, Clinical report from Bioprojet (2007).

similar between RC and Placebo (**Figure 1(a)**), RR = 0.95 [0.24 - 3.68],  $p = 0.97$ ), however, a significantly lower proportion was observed in the RC group compared with loperamide (**Figure 2(b)**), RR = 0.34 [0.22 - 0.51,  $p < 0.0001$ ), these two results found reasonably homogeneous between studies ( $I^2 = 10\%$  and  $30\%$ , respectively, Q test,  $p > 0.5$ ).

### 3.4. Risk of Bias across Studies

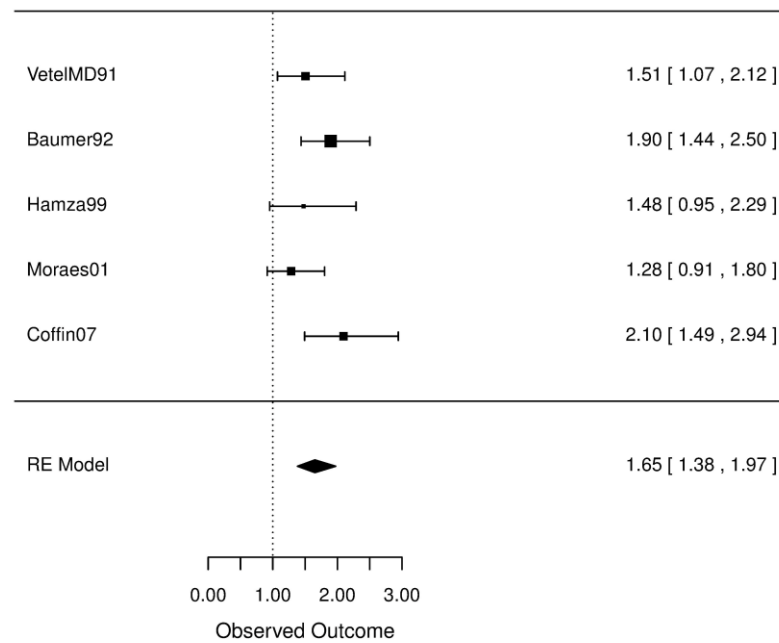
Through a Funnel plot (**Figure 3**), we failed to identify a publication bias on the main efficacy endpoint, or in the safety endpoints (both for study comparing loperamide or placebo). For the four meta-analyses, we conducted separate meta-regression on Year of publication, Sponsored versus non-sponsored trials, and Published versus non published trials. For all these analyses, no significant effect of any of these regressors was found.

## 4. Discussion

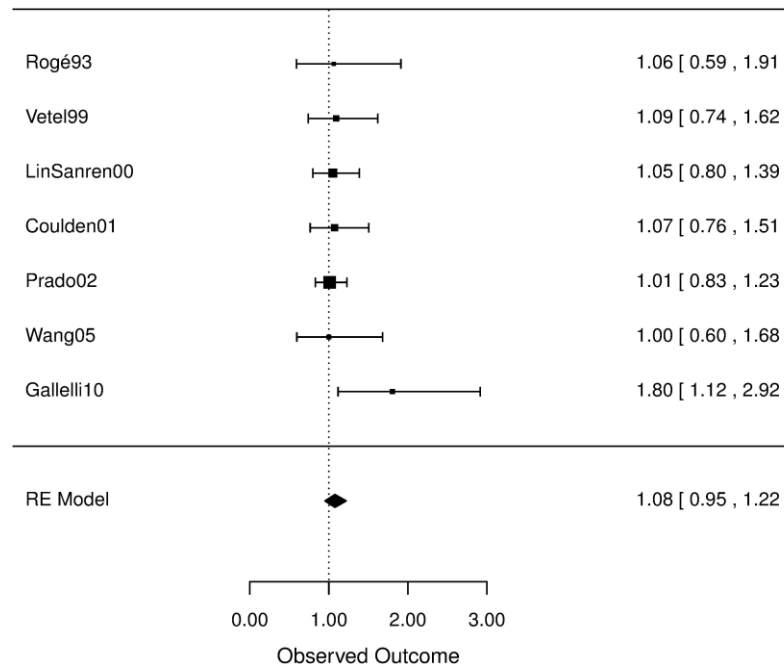
### 4.1. Summary of Evidence

#### 4.1.1. Discussion on DD Definition and Its Clinical Relevance

Definition of DD can be a matter of questions. A duration is a time interval between a startpoint and an endpoint. In all the studies, the DD startpoint was when the first therapeutic dose is taken instead of the beginning of the AD, in order to answer to a practical question: is it worthwhile to prescribe a drug while a patient visit, whatever the AD starts. The common DD endpoint definition was when the last unformed stool is recorded, that means followed by 12 hours with no stools or two consecutive normal stools. The first formed stools can not be chosen as a recovery definition because it can be preceded by a time without any stool. The relevance of DD reduction as to be expressed not only statistically but clinically too. As compared to placebo, no-one can affirm the minimal relevant difference of DD reduction in term on a number of hours, especially because DD may varies within placebo groups according to epidemiological conditions. Overall, RC induced a 65% reduction of DD:



(a)



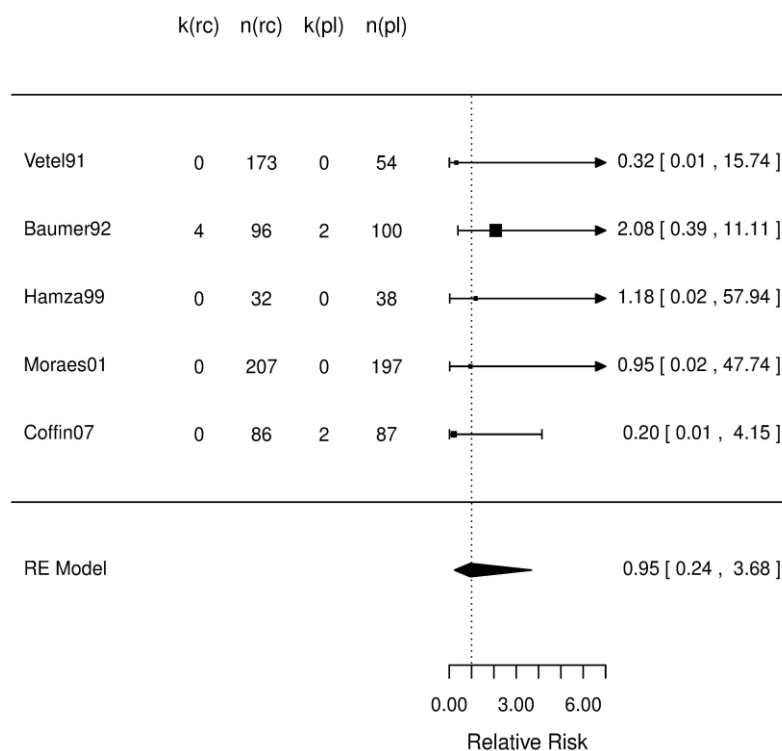
(b)

**Figure 1.** Diarrhoea Duration Forest Plot. Comparing Racecadotril (RC) *versus* placebo (on the left 1(a)) and RC *versus* Loperamide (on the right 1(b)), using Randomized Der Simonian and Laird Model, Risk Ratio.

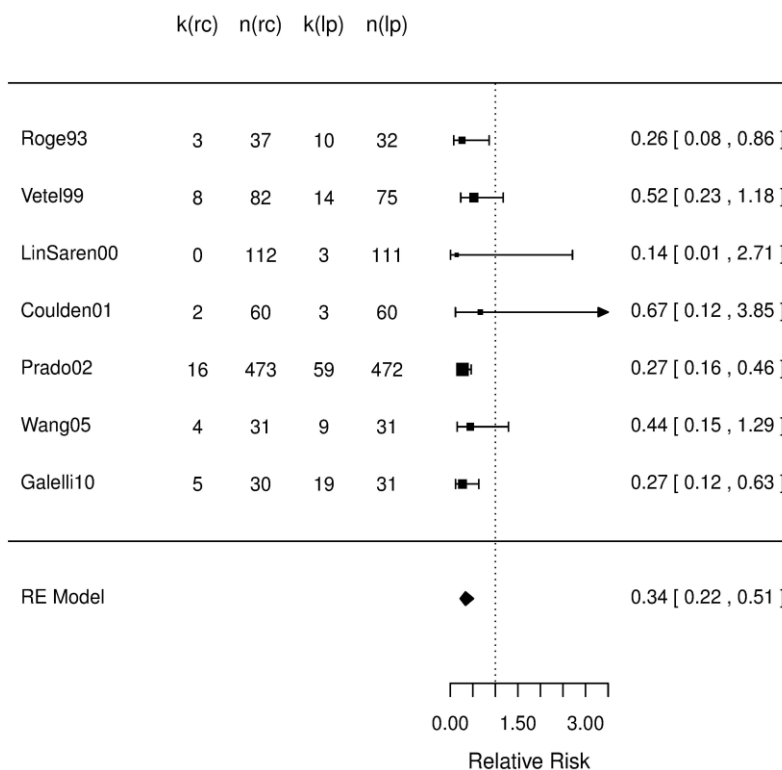
this is available whatever these epidemiological conditions.

#### 4.1.2. Discussion on Different Antitransit Effects

During the clinical development of loperamide, its activity was demonstrated by its constipation effect in normal volunteers: 4 mg single dose or 3 mg b.i.d for 5 days of loperamide were significantly superior to placebo in in-

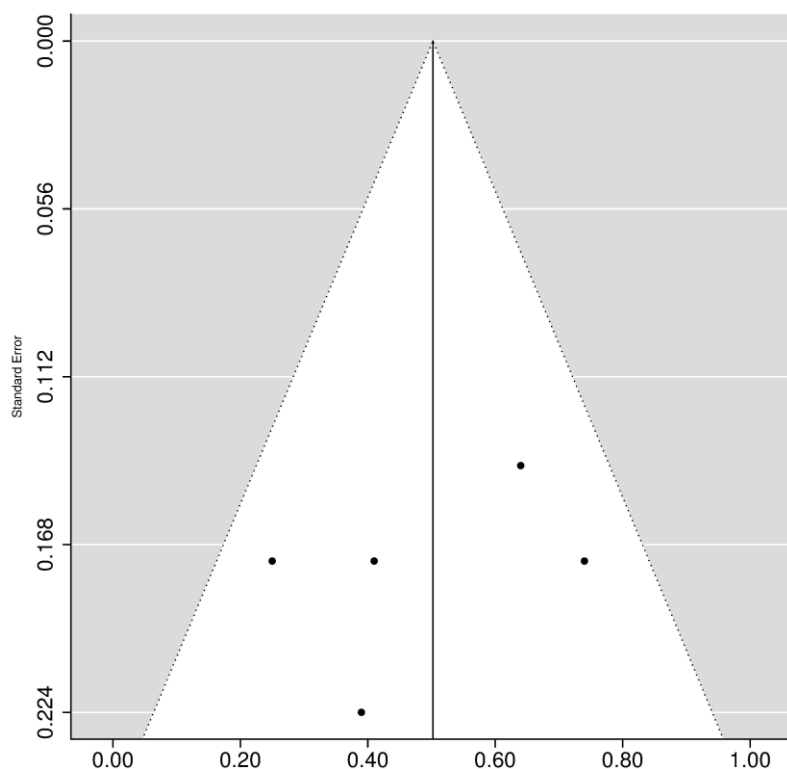


(a)



(b)

**Figure 2.** Constipation occurrences Forest Plot. Comparing Racecadotril (RC) versus placebo (on the left 2(a)) and RC versus Loperamide (on the right 2(b)), using Randomized Der Simonian and Laird Model, Risk Ratio.



**Figure 3.** Funnet plot.

ducing constipation [43]. As compared to placebo, loperamide prolonged significantly the oro-caecal transit time (breath hydrogen test after ingestion of lactulose) [44] [45].

At the opposite, RC did not induce a significant change of transit times at the large bowel level as well as at the oro-caecal level, as demonstrated by a double-blind cross over study conducted with the therapeutic dose given for one week [6].

The clinical consequences are the significant differences in the constipation frequency, already shown by a review of RC safety [4], and complications frequency linked to this antitransit effect such as ileus [46] toxic megacolon [47]-[49] and colectasia occurring after therapeutic dose of loperamide, which may be facilitated by the concomitant intake of a calcium inhibitor [50] or of a muscle relaxant [51]. As a consequence, in addition to its lack of central nervous effect, RC has a safe profile, not different from placebo and better than loperamide, whatever the patients age [4].

The number of patients involved in the comparison with loperamide, more than 1.6 thousand, was sufficient to point out a significant difference in term of a relatively frequent event, the constipation, but it is obviously too low to establish a difference in term of a rare event such as a complication.

#### 4.1.3. Implications for Practice and Research

To help physician to choose an antidiarrhoeal agent, many meta-analysis were published, but almost involved childhood studies. No conclusion can be drawn from the two meta-analyses of an antidiarrhoeal drug with adult patients: one meta-analysis included specific indications but not acute diarrhoea, due to the limited number ( $n = 2$ ) of randomized trials in this indication [52], the other meta-analysis mixed childhood trials ( $n = 56$ ) and adult trials ( $n = 7$ ) without separated results for adults [53]. Two Cochrane meta-analyses evaluated the efficacy of different oral rehydration solution (ORS): polymer-based ORS was tested versus glucose-based ORS in one meta-analysis [54], but the few trials performed in adults included patients positive for *V. cholerae*, and in the second meta-analysis, including a majority of adults, the two ORS with different osmolarity were studied in cholera [55].

Thus, up to now, no drug meta-analysis was devoted to adults suffering from acute diarrhoea, except one abstract [16] and a recent student dissertation [56].



## 4.2. Limitations

The dose differed between studies and sometimes from the Summary of Product Characteristics (SmPC) dosage. The initial dosing regimen of RC in the first randomized clinical trial performed in adults suffering from acute diarrhoea [35], was: “two capsules at first, followed by one capsule after each unformed stool, with treatment lasting until production of the first formed stool, up to 10 days”. This regimen differs from the dosages in the next trials and from recommended dosages in SmPC, but the number of RC capsules ingested, day by day, were very close to the number of capsules if SmPC dosage was prescribed:  $4.3 \pm 2.1$  on day 1 (instead of 4),  $2.8 \pm 1.9$  on day 2 (instead of 3). Overall, they took  $10.3 \pm 6.7$  capsules. As patients recovered after  $3.4 \pm 0.1$  days of treatment in the RC group (vs.  $4.4 \pm 0.1$  in the placebo group), the theoretical number of capsules according to SmPC schedule should be between 10 and 11 capsules overall.

Loperamide doses differ from SmPC dose and seem to be not optimized:

During Rogé study [35], loperamide doses (1.33 mg per capsule, two capsules initially, followed by 2 capsules during the next 12 hours, thereafter, one capsule 3 times a day until recovery) seem to be not optimized. But this dosage induced similar efficacy (for instance, time to recovery was  $2.2 \pm 0.2$  days in the RC group and  $2.3 \pm 0.2$  days in the loperamide group), and significantly worse tolerance as compared to RC group: secondary constipation was significantly more frequent in the loperamide group (31.3% vs. 8.1%,  $p < 0.02$ ). Duration of bloating lasted significantly longer ( $1.8 \pm 0; 3$  days vs.  $1.1 \pm 0.2$  days;  $p < 0.05$ ).

Dose during Prado study [40] (2 mg per capsule, 3 times a day until recovery) was also different from SmPC dose, but it induced equivalent efficacy, and significantly worse tolerance as compared to RC group: in terms of associated symptoms, changes from Visits 1 to 2, revealed a significant difference between the two therapeutic groups for abdominal pain ( $p = 0.024$ ) and abdominal distension ( $p = 0.035$ ). For instance, when comparing the two scheduled visits in this study, abdominal pain was still present in 3.0% of patients treated with RC versus 7.1% of loperamide patients. Abdominal distension deteriorated in 1.5% and 4.5% of patients, respectively. The median duration of abdominal distension was 5.4 hours and 24 hours respectively ( $p = 0.0001$ ). In terms of constipation incidence during the study, there were 74 patients (18%) in the RC group and 116 patients (29%) in the loperamide group who had a stool free period lasting 36 hours or more. This difference was statistically significant ( $p = 0.001$ ) between the two treatment groups.

*Saccharomyces boulardii* was assimilated to a placebo because there is no RCT performed in adults that demonstrated its advantage versus placebo [53].

The definition of constipation was not homogeneous among studies: there is no universal definition of constipation. Miscellaneous definitions were adopted within RCTs, from 48 hours without any stool [39] to a reported adverse event [35] [40]-[42], [Lin Sanren & Coulden: personal data]. As previously discussed, frequency of antitransit complications are too low to be compared within hundreds of patients.

Pharmacoeconomic evaluation: the diarrhoea reduction is a condition to reduce the period of time the patient has to stop working. But this data was not informed, thus the demonstration of a lower cost is lacking. Anyway the patient social condition was not reported, and an economical approach can not be performed although a pharmacoeconomic analysis was included in one study [42]: its conclusion was a fewer cost in the RC group as compared to the loperamide group.

The meta-analysis from literature collects the largest data as possible and is not limited to study with available individual patient data (IPD), but it can't look for baseline predictors and thus does not allow adjusting with these covariates.

## 5. Conclusion

Compared to placebo, racecadotril is characterized by a clinically relevant earlier remission of diarrhoea. When compared to loperamide, diarrhoea duration was similar, however, significantly fewer secondary constipation adverse effects were observed.

## Funding & Conflict of Interest Statement

This research received no specific grant from any funding agency in public, commercial or not-for-profit sectors. Authors have declared no competing interests exist.

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## Addendum

### A1. A Priori LIST of Requested Information for Each Study

Investigator: name.

Study centres: number, place (country).

Publication or report reference.

Studied period: dates of first enrolment and last completed.

Objectives.

Methodology: single- or double-blind

Number of patients: planned and analysed.

Diagnosis and main criteria for inclusion.

Test product, dose and mode of administration.

Duration of treatment.

Reference therapy, dose and mode of administration.

Efficacy criteria: including main criterion, secondary criteria and definition of recovery.

Safety: adverse events (AEs), such as secondary constipation.

Statistical methods.

Population included: number of patients, with sexe, age, characteristics of diarrhoea before inclusion (number of stool in the last 24 hrs, diarrhoea duration)

Efficacy results.

Safety results.

Conclusion from publication's or report's author.

### A2. Methodological Quality Questionnaire

Internal validity	
1. Was the assigned treatment adequately concealed prior to allocation?	X1
2. Were the outcomes of patients who withdrew or were excluded after allocation described and included in an intention to treat analysis?	X2
3. Were the outcome assessors blind to assignment status?	X3
4. Were the participants blind to assignment status following allocation?	X4
5. Were the treatment providers blind to assignment status?	X5
6. Were the care programs, other than the trial options, identical?	X6
7. Were the withdrawals <10% of the trial population?	X7
External validity	
1. Were the inclusion and exclusion criteria for entry clearly defined?	X8
2. Were the outcome measures used clearly defined?	X9
3. Were accuracy, precision, observer variation of measures adequate?	X10
4. Was the timing of the outcome measures appropriate?	X11
5. The quality of allocation concealment was graded?	X12
Statistical validity	
1. Was the main endpoint mentioned?	X13
2. Was the power analysis described?	X14
3. Baseline comparison reported?	X15
4. Statistical technique appropriate?	X16
5. Table and graphical results clear?	X17

### A.3. Construction and Calculation of the Methodological Quality Index

The MQ index was based on the following approach:

(a) a principal components analysis and internal consistency of the original items was performed to assess MQ dimensionality and correlation between items, in particular between internal validity, external validity and statistical characteristics, and assessment of weight of each item;

(b) search of alternative scores based on the dimensionality found in (a);

(c) obtaining the best classification of studies based on MQ items by hierarchical cluster analysis.

(d) the inter-rater variability was tested according a mixed model in testing the significance of the rater random factor for each each dimension. For each item possible responses were: 2 = adequate, 1 = unclear, 0 = inadequate, and undocumented (blank space). Each item was then recoded as a binary value: adequate (1) or not (0 = all responses except for “adequate”, thus incorporating previous codes 1 [unclear], 0 [inadequate, and undocumented]).

### A.4. Individual Results of the Methodology Quality Questionnaire (Recoded Results)

Methodology Quality Questionnaire			Internal Validity Questions (IV)							External Validity Questions (IV)							Statistical Validity Questions (SV)						
Author(s)	Year	Control group	X1	X2	X3	X4	X5	X6	X7	IVS*	X8	X9	X10	X11	X12	EVS*	X13	X14	X15	X16	X17	SVS*	MQS
Vetel JM (multidose)	1991	Placebo	1	1	0	1	1	1	1	0.43	1	0	0	1	0	0.20	1	0	1	1	1	0.40	0.34
Baumer P	1992	Placebo	1	1	0	1	1	1	1	0.43	1	0	0	1	0	0.20	1	0	1	1	1	0.40	0.34
Rogé J	1993	Loperamide	1	0	0	1	1	1	1	0.36	1	0	0	0	0	0.10	0	0	0	1	1	0.20	0.22
Frexinox J	1996	Loperamide oxide	1	0	0	1	1	1	0	0.29	1	0	0	1	0	0.20	0	0	0	0	0	0.00	<b>0.16</b>
Hamza H	1999	Placebo	1	0	0	1	1	1	1	0.36	1	1	1	1	0	0.40	1	1	0	1	1	0.40	0.39
Vetel JM	1999	Loperamide	1	0	0	1	1	1	1	0.36	1	1	1	1	0	0.40	1	1	1	1	1	0.50	0.42
Lin Sanren	2000	Loperamide	0	1	0	0	0	1	1	0.21	1	1	1	1	0	0.40	1	0	0	0	1	0.20	0.27
Coulden S	2001	Loperamide	0	0	0	0	0	1	1	0.14	1	1	1	1	0	0.40	1	0	0	1	1	0.30	0.28
Moraes E	2001	<i>Saccharomyces boulardii</i>	0	0	0	0	0	1	0	0.07	1	1	1	1	0	0.40	1	1	1	1	1	0.50	0.32
Prado D	2002	Loperamide	0	0	0	0	0	1	1	0.14	1	1	1	1	0	0.40	1	1	1	1	1	0.50	0.35
Wang HH	2005	Loperamide	0	1	0	0	0	1	1	0.21	1	1	1	1	0	0.40	1	0	0	1	1	0.30	0.30
Coffin B	2007	Dexecadotril Placebo	1	1	0	1	1	1	1	0.43	1	1	1	1	0	0.40	1	1	1	0	1	0.40	0.41
Gallelli L	2010	Loperamide	0	0	0	1	0	1	0	0.14	1	1	1	1	0	0.40	1	0	1	1	0	0.30	0.28
Yao P	2011	Oral rehydration solution	0	0	0	0	0	2	?	0.14	0	0	0	0	0	0.00	0	0	0	0	0	0.00	<b>0.05</b>
Mehta S	2012	Placebo octreotide	0	0	0	0	0	1	1	0.14	0	0	1	1	0	0.20	0	0	1	1	1	0.30	0.21
		Mean	0.47	0.33	0.00	0.53	0.47	1.07	0.73	0.26	0.87	0.60	0.67	0.87	0.00	0.30	0.73	0.33	0.53	0.73	0.80	0.31	0.29
		SD	0.5	0.47	0	0.50	0.50	0.25	0.41	0.12	0.34	0.49	0.47	0.34	0	0.13	0.44	0.47	0.50	0.44	0.40	0.15	0.10

### A.5. Statistical Addendum

Meta-analyses on survival technique, can be done in first calculating the HR o for each study to save the HR and its SE in a file HR. MTM and MTP require for each study the mesure  $Y_i$  and its variance  $Vari$  (thus not forget to calculate  $Vari = sei*sei$  in case where the SE is found). When only two variables are provided, MTM and MTP will consider these variables as  $Y_i$  and  $Vari$  in the order.

The values  $Y_i$  and  $Vari$  must sometimes be transformed: for proportions (thus calculation of RR, HR, etc.), the log transformed values must be provided for  $Y_i$  and  $Vari$ . Thus in the MTP command you must request/  $transf = exp$ . This is also true if you use MTM on log-transformed data.

Finally, this particular use with two variables can be used for a meta-analysis on one data: for instance, calculating the pooled value of a percentage, a market share, etc. over several studies.

#### Conversion Techniques

The compared studies may have been analyzed following various techniques:



0) The main endpoint of the study must be used even it is not the DD. In this case, an equivalence will be searched through a calibration with DD, through IPD techniques, and the CI will be corrected according to the correlation. If several endpoints are used, the arithmetic mean of the converted values will be used.

1) If Cox proportional Hazard was used, results are provided in terms of HR or Log(HR). However, values can also be provided as medians. An approximation assuming exponential models is that as in this model  $S(t) = \exp(-ht)$ , thus the median is such that  $0.5 = \exp(-ht)$ , thus  $\text{med} = \ln(2)/h$ , thus the median is inversely related with hazard  $h$ , and when knowing the medians  $m_s$  and  $m_r$ , the value  $m_r/m_s = h_s/h_r = \text{HR}$ .

2) It is also possible to convert Logrank values into HR. assuming that  $Z = (O-E)/V$  where  $O$ ,  $E$  and  $V$  are the sum of the observed, expected and variance of the difference  $O-E$ , HR can be found as  $\text{Log}(\text{HR}) = Z \sqrt{4/nd}$  where  $nd = \text{total number of events in both groups}$ . Because  $Z^2$  is provided instead of  $Z$  (in the case of R command Survival), the value  $\sqrt{Z^2}$  must be first calculated, thus the sign of  $Z$  is unknown, thus when HR is found, if expect  $\text{HR} < 1$  is expected,  $1/\text{HR}$  will be used.

3) Indirect equivalence from another endpoint. In some studies Stool Output was provided as the main endpoint. The relationship between SO and DD was calculated through a calibration  $\text{Log}(\text{DD}) = k_0 + k_1 \text{Log}(\text{SO})$ . The significance of  $k_0$  and  $k_1$  were calculated. The conversion from SO into DD was calculated as  $\text{HR} = \text{Exp}(k_0 + k_1 \text{Log}(\text{SO})/k_0 + k_1 \text{Log}(\text{SO})r)$ .

4) Calculating  $\text{Var}(\text{HR})$  is possible, still under assumption of exponential distribution. As  $S(t) = \exp(ht)$ , for each exponential curve corresponding to the two treatments, assuming that Median or Mean  $\mu$  and variance  $\sigma^2$ , it is known from exponential distribution that  $\mu = 1/h$  and  $\text{var} = 1/h^2$ . As  $\text{HR} = h_s/h_r$  we can calculate the  $\text{SE}(\text{HS})$  through  $\text{SE}(\log(\text{HS})) = \log(h_s) - \log(h_r)$ . If  $\sigma(h_s) = \sigma$ ,  $\text{var}(\log(h_s)) = \text{var}(h_s) |\text{Log}'(m)|$  where  $\text{Log}'()$  is the derivative of  $\text{Log}()$  at point  $m$ , thus  $1/h_s$  in this case.  $\Rightarrow \text{Var}(\log(h_s)) = \text{var}(h_s)/(1/m_s) = (1/m_s^2)/(1/m_s) = 1/m_s$ , further more the SE of  $\text{var}(h_s)$  is  $1/m_s \cdot 1/\sqrt{ns}$ . It follows that  $\text{SE}(\log(\text{HS})) = \sqrt{1/(m_s \cdot n_s) + 1/(m_r \cdot n_r)}$ .

## A6. Prisma Flow Diagram

