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Javier Molina Infante, Belen Perez Gallardo, Miguel Fernandez Bermejo, Moises Hernandez Alonso, Gema Vinagre, Carmen Dueñas, Jose Maria Mateos Rodriguez, Guadalupe Gonzalez Garcia, Elena Garcia Abadia, Javier P Gisbert

► **To cite this version:**

Javier Molina Infante, Belen Perez Gallardo, Miguel Fernandez Bermejo, Moises Hernandez Alonso, Gema Vinagre, et al.. Clinical trial: clarithromycin vs. levofloxacin in first-line triple and sequential regimens for Helicobacter pylori eradication. *Alimentary Pharmacology and Therapeutics*, 2010, 10.1111/j.1365-2036.2010.04274.x . hal-00552534

HAL Id: hal-00552534

<https://hal.science/hal-00552534>

Submitted on 6 Jan 2011

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Clinical trial: clarithromycin vs. levofloxacin in first-line triple and sequential regimens for *Helicobacter pylori* eradication

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|-------------------------------|---|
| Journal: | <i>Alimentary Pharmacology & Therapeutics</i> |
| Manuscript ID: | APT-0061-2010.R1 |
| Manuscript Type: | Clinical Trial |
| Date Submitted by the Author: | 17-Feb-2010 |
| Complete List of Authors: | Molina Infante, Javier; Hospital San Pedro de Alcantara, Gastroenterology perez gallardo, belen; Hospital San Pedro de Alcantara, Gastroenterology Fernandez Bermejo, Miguel; Gastroenterology; Hospital San Pedro de Alcantara, Gastroenterology Hernandez Alonso, Moises; Hospital San Pedro de Alcantara, Gastroenterology Vinagre, Gema; Hospital San Pedro de Alcantara, Gastroenterology Dueñas, Carmen; Hospital San Pedro de Alcantara, Gastroenterology Mateos Rodriguez, Jose Maria; Hospital San Pedro de Alcantara, Gastroenterology Gonzalez Garcia, Guadalupe; Hospital San Pedro de Alcantara, Gastroenterology Abadia, Elena; Hospital San Pedro de Alcantara, Gastroenterology Gisbert, Javier; Hospital de la Princesa, Gastroenterology |
| Keywords: | H. pylori < Topics, Gastritis < Topics, Stomach and duodenum < Organ-based, Microbiology < Topics |
| | |

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3 **Clinical trial: clarithromycin vs. levofloxacin in first-line triple and**
4 **sequential regimens for *Helicobacter pylori* eradication**
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10 **SHORT TITLE:** Clarithromycin vs. levofloxacin for *H. pylori*
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35 **ABBREVIATIONS:** *Helicobacter pylori* (*H. pylori*), OCA (triple standard
36 therapy); OLA (triple therapy with levofloxacin); OACM (sequential therapy with
37 clarithromycin); OALM (modified sequential therapy with levofloxacin); intention to treat
38 (ITT); per protocol (PP); 95% confidence interval (95%CI).
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58 **CORRESPONDENCE**

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3 **BACKGROUND:** *Helicobacter pylori* eradication rates with standard triple therapy have
4 declined to unacceptable levels.
5

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7 **AIM:** To compare clarithromycin and levofloxacin in triple and sequential first-line
8 regimens.
9

10 **METHODS:** 460 patients were randomized into four 10-day therapeutic schemes (115
11 patients per group): (1) standard OCA, omeprazole, clarithromycin and amoxicillin; (2)
12 triple OLA, omeprazole, levofloxacin and amoxicillin; (3) sequential OACM, omeprazole
13 plus amoxicillin for 5 days, followed by omeprazole plus clarithromycin plus
14 metronidazole for 5 days, and (4) modified sequential OALM, using levofloxacin instead
15 of clarithromycin. Eradication was confirmed by 13C-urea breath test. Adverse effects
16 and compliance were assessed by a questionnaire.
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18

19 **RESULTS:** Per protocol cure rates were: OCA (66%; 95%CI: 57-74%), OLA (82.6%;
20 75-89%), OACM (80.8%; 73-88%), and OALM (85.2%; 78-91%). Intention to treat cure
21 rates were: OCA (64%; 55-73%), OLA (80.8%; 73-88%), OACM (76.5%; 69-85%), and
22 OALM (82.5%; 75-89%). Eradication rates were lower with OCA than with all the other
23 regimens ($p < 0.05$). No differences in compliance or adverse effects were demonstrated
24 among treatments.
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27 **CONCLUSIONS:** Levofloxacin-based and sequential therapy are superior to standard
28 triple scheme as first-line therapy in a setting with high clarithromycin resistance.
29 However, all of these therapies still have a 20% failure rate.
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40 **KEY WORDS:** *Helicobacter pylori*, sequential therapy, triple therapy,
41 clarithromycin, levofloxacin.
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51 INTRODUCTION

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3 Evolving research has demonstrated the relationship of *Helicobacter pylori*
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5 infection with chronic gastritis, peptic ulcer disease and gastric adenocarcinoma and
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7 MALT lymphoma, as well as the importance of a prompt cure of the infection to change
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9 the natural history of these diseases. After the initial high efficacy (eradication rate >
10
11 90%) of triple standard regimens, we are witnessing within the last decade a
12
13 progressive decline in cure rates^{1,2}. The high prevalence of antimicrobial drug
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15 resistance, especially to clarithromycin and metronidazole, is believed to be the key
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17 factor. For this reason, consensus statements recommend empirical therapeutic
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19 regimens that achieve *H. pylori* cure rates higher than 80% on an intention-to-treat
20
21 (ITT) basis^{3,4}.
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26 Novel antibiotic regimens have been developed to overcome this troublesome
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28 scenario. One recent therapeutic innovation, postulated as an alternative to standard
29
30 triple therapy, is the so called "sequential" treatment⁵. Strictly speaking, it is not a new
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32 approach, as it uses well-known drugs with approved indication for *H. pylori*
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34 eradication. However, the administration strategy is innovative. The sequential regimen
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36 is a simple dual therapy including a PPI plus amoxicillin 1 g (both twice daily) given for
37
38 the first five days followed by a triple therapy including a PPI, clarithromycin 500 mg,
39
40 and tinidazole (all twice daily) for the remaining five days. Its rationale is based on an
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42 initial phase with amoxicillin which aims to lower the bacterial load in the stomach.
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44 Moreover, it has been speculated that amoxicillin may prevent the development of
45
46 efflux channels for clarithromycin. This induction phase, therefore, is believed to
47
48 amplify the efficacy of the second phase of therapy containing clarithromycin and
49
50 metronidazole. Italian studies regarding this clarithromycin-based sequential therapy
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52 have shown promising eradication rates higher than 90%, even in patients with risk
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54 factors for triple therapy failure (clarithromycin resistance, non ulcer dyspepsia,
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56 smoking or the absence of the gene CagA)^{6,7}. Furthermore, a recent meta-analysis has
57
58 shown that eradication rate with 10-day sequential therapy (93.4%) is notably higher
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3 than that for standard triple therapy (76.9%), with similar adherence in both groups⁸.
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5 Thus, it has been questioned whether sequential therapy should be the preferred first
6
7 line therapy for *H. pylori* infection⁹, albeit the global validation of the sequential scheme
8
9 out of Italy is awaited.
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13 On the other hand, levofloxacin, a fluoroquinolone with *in vivo* activity against *H.*
14
15 *pylori* strains resistant to clarithromycin and metronidazole, has also shown promising
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17 results in different first-line triple regimens in Italy, Spain and the Netherlands, with an
18
19 eradication rate on ITT ranging from 83% to 96%¹⁰⁻¹⁷. The efficacy of levofloxacin in a
20
21 sequential eradication scheme for *H. pylori* infection has been exclusively assessed in
22
23 a single recent study from Turkey¹⁸, with an 82% ITT cure rate. Moreover, a head-to-
24
25 head comparison between similar clarithromycin and levofloxacin regimens has not
26
27 been addressed yet. Therefore, we aimed to evaluate the cure rate of triple and
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29 sequential regimens containing clarithromycin or levofloxacin in a geographical area
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31 with a high failure rate of triple classical eradication therapy.
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36 37 **METHODS**

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41 This study is a prospective, open-label, single center, randomized trial. From
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43 January 2008 to August 2009, 460 consecutive *H. pylori* positive patients were
44
45 enrolled. The diagnosis of *H. pylori* was determined by at least a positive test among
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47 urea breath test, histology or rapid urease test. Written informed consent was obtained
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49 from all patients. The study was approved by the Ethics Committee of our Hospital.
50
51 Exclusion criteria were (1) age under 18 yr, (2) presence of severe comorbidities, (3)
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53 prior *H. pylori* eradication, (4) gastric surgery, (5) allergy of any of the antibiotics used
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55 in the study and (6) intake of antibiotics, proton pump inhibitors or nonsteroidal anti-
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57 inflammatory drugs within the last month.
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3 Using a computer-generated numeric sequence, patients were randomized to
4 receive one of the four first-line schemes for 10 days, having all high-dose acid
5 suppressive therapy¹⁹:
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- 8 - Standard triple OCA (n=115), omeprazole 20 mg, clarithromycin 500
9 mg and amoxicillin 1 g, all three twice a day.
10
- 11 - Triple OLA (n=115), omeprazole 20 mg, levofloxacin 500 mg and
12 amoxicillin 1 g, all three twice a day.
13
- 14 - Sequential OACM (n=115), omeprazole 20 mg and amoxicillin 1 g
15 both twice a day for 5 days followed by omeprazole 20 mg,
16 clarithromycin 500 mg and metronidazole 500 mg, all three twice a day
17 during the next 5 days.
18
- 19 - Modified sequential OALM (n=115), omeprazole 20 mg and
20 amoxicillin 1 g both twice a day for 5 days followed by omeprazole 20
21 mg, levofloxacin 500 mg and metronidazole 500 mg, all three twice a
22 day during the next 5 days.
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38 Compliance with therapy was determined from the interrogatory and the recovery
39 of empty envelopes of medications. Side effects were assessed by a specific
40 questionnaire completed at the time of post-treatment urea breath testing. Eradication
41 of *H. pylori* infection was defined as a negative urea breath test 8 weeks after
42 completion of treatment except for patients requiring a follow-up endoscopy due to
43 gastric ulcer, in which histological examination of four samples taken from the body and
44 the antrum stained with Giemsa was the diagnostic test.
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55 **Statistical analysis**

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The predetermination of the sample size in each group (n=115), assuming an
80% power at a 5% significance level, was performed to detect a 15% difference in

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3 eradication rates between triple standard therapy (control group) and any of the other
4 regimens (experimental group), in accordance to the most recent cure rates reported in
5 our setting (triple standard therapy 70%²⁰, sequential therapy 84%²¹).
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10 Categorical variables are described with percentages and continuous variables
11 are described with mean and standard deviation or median and range as appropriate.
12 The eradication rates and their 95% confidence intervals (95% CI) were obtained by
13 intention to treat (ITT) and per protocol (PP). Univariate and multivariate logistic
14 regression analysis were performed to evaluate independent predictive variables for
15 eradication of *H. pylori*. The magnitude of the effect is described with the odds ratios
16 (ORs) and 95% CI. Variables chosen to be introduced in predictive models depended
17 on statistical significance on univariate analysis. P-values lower than 0.05 were
18 considered statistically significant.
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42 RESULTS

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46 Four hundred and sixty patients were enrolled in the study. The baseline
47 demographic and clinical characteristics, indication for eradication and diagnostic
48 method for the infection of the total cohort and each therapeutic subgroup are listed in
49 table 1. The overall sample was balanced in gender, had a median age of 48 yrs and
50 33% smoked cigarettes. Dyspepsia was the most common indication for *H. pylori*
51 eradication (59%).
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59 The study flow chart is summarized in Figure 1. Eradication rates are shown in
60 Figure 2. ITT cure rates were: OCA (64%; 55-73%), OLA (80%; 73-88%), OACM (76%;

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3 69-85%), and OALM (82%; 75-89%). PP cure rates were: OCA (66%; 95%CI: 57-74%),
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5 OLA (82%; 75-89%), OACM (80%; 73-88%), and OALM (85%; 78-91%). ITT
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7 eradication rates were significantly higher with all the other regimens when compared
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9 to standard triple treatment (OLA OR (95%CI): 2.4 (1.3-4.5), $p < 0.05$, OACM OR
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11 (95%CI): 2.1 (1.1-3.9), $p < 0.05$, OALM OR (95%CI): 2.9 (1.5-5.6), $p < 0.05$). No
12
13 significant differences were demonstrated among OLA, OACM and OALM. Figure 3
14
15 shows the ITT eradication rates according to the indication. In patients with
16
17 noninvestigated dyspepsia, no relevant differences were observed among the four
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19 therapeutic regimens. Levofloxacin-based regimens were significantly more effective
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21 for patients suffering from functional dyspepsia when compared to OCA (OLA OR
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23 (95%CI): 4.7 (1.7-13), $p < 0.01$, OALM OR (95%CI): 3.5 (1.3-9.2), $p < 0.05$).
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25 Clarithromycin sequential regimen failed to improve significantly eradication rates
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27 compared to OCA in this subset of patients. (OR (95%CI): 1.8 (0.7-4.5). For patients
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29 with gastric or duodenal ulcer, OALM regimen was also significantly better than OCA
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31 (OR (95%CI): 4.1 (1.1-14)).
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36 In the univariate analysis, the efficacy of the therapy was influenced by the type
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38 of treatment (OCA 66% vs. 82% for the others, $p < 0.01$) but not by the indication (77%
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40 for dyspepsia vs. 82% for ulcer, $p = 0.18$), gender (82% for men vs. 75% for women,
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42 $p = 0.06$), age (eradicated 48 yrs (18-87) vs. non eradicated 49 yrs (18-71), $p = 0.4$) or
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44 smoking habit (smokers 81% vs. non-smokers 77%, $p = 0.28$). In the multivariate
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46 analysis, any of the therapeutic schemes different from OCA remained as independent
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48 predictor factor for *H. pylori* eradication (OR (95%CI): 2.5 (1.5-4)).
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51 Overall, 97% of the patients had complete adherence to antibiotic therapy, as
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53 shown in Figure 1. Three patients were lost to follow-up and nine patients discontinued
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55 therapy due to adverse events. Minor or mid side effects were reported by 129 patients
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57 (28%), without significant differences between therapeutic schemes. No major adverse
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59 events were observed. Side effects are summarized in table 2.
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DISCUSSION

This is the first randomized trial that compares clarithromycin to levofloxacin in triple and sequential schemes for *H. pylori* eradication. Since several recent meta-analyses^{8,22,23} have shown the advantage of sequential therapy over the standard triple scheme for clarithromycin-resistant strains, it has been suggested that sequential therapy should be advisable as a first-line therapy when the prevalence of clarithromycin resistance is high, as occurs presently in most developed countries. The present study shows that the eradication rate for clarithromycin sequential therapy was suboptimal (76%) in a setting with a high rate of failure for triple standard therapy (64%). Indeed, this is the lowest eradication rate reported to date for sequential therapy. Therefore, the sequential regimen may not lead to acceptable eradication rates in areas with a high prevalence of clarithromycin resistance. Indeed, ITT eradication rates for standard triple therapy (75-79%), in the aforementioned Italian studies, may be an indirect marker of medium clarithromycin resistance^{7,8}. Moreover, sequential therapy achieved a 75% eradication rate (41/55 patients) when exposed to documented clarithromycin-resistant strains in literature, whereas it was absolutely futile (0% eradication rate) in patients with dual resistance to clarithromycin and metronidazole⁵.

In this regard, the validation process of the sequential therapy regimen outside of Italy has led to controversial results. Similar successful eradication rates have been obtained in other settings such as Thailand (96%)²⁴ or Taiwan (92%)²⁵, whereas much more modest results have been recently obtained in Panama (85%)²⁶, France (85%)²⁷, Spain (84%)²¹ and Korea (80% and 77.9%)^{28, 29}. In fact, most of the studies regarding sequential therapy published during 2008 and 2009 had eradication rates lower than 90% eradication rates and, in some cases, even $\leq 80\%$ ²⁴⁻²⁸. Further controversy regarding sequential therapy has been provoked with the results of several studies

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3 performed outside of Italy that have been unable to demonstrate differences between
4 sequential and standard triple regimens²⁶⁻²⁹. Thus, studies validating both the cure rate
5 of sequential therapy and its advantage over triple standard therapy in settings with
6 different patterns of antimicrobial resistance are required before it can be widely
7 recommended in clinical practice. Attending to the results of the present study, it will be
8 especially mandatory in geographical areas with high rate of clarithromycin-resistant *H.*
9 *pylori* strains.
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18 Alternative therapeutic regimens are awaited in settings where empiric
19 therapies do not produce a $\geq 80\%$ cure rate on ITT basis. Besides the use of
20 levofloxacin-triple therapy in second and third-line regimens, encouraging cure rates (\geq
21 90%) have been obtained in first-line schemes in Italy^{10,11,13,14} and the Netherlands¹⁷.
22 More recently, a novel levofloxacin modified sequential therapy has been described for
23 the first time in Turkey with cure rates of 86% on PP and 82.5% on ITT¹⁸. In the present
24 study, levofloxacin-based triple (80%) and modified sequential scheme (82%) achieved
25 in the present study “adequate” cure rates. These results for the modified sequential
26 regimen are identical to those of the Turkish study. However, the overall results for
27 both levofloxacin regimens in the present study are to be considered poor. A first
28 course of antibiotic therapy for *H. pylori* infection should only be considered good if it
29 achieves a cure rate on ITT basis $> 90\%$ ³⁰. Indeed, fluoroquinolones resistance has
30 been rapidly increasing and this antibiotic family will probably become useless in the
31 short term^{20,30}. This trend is confirmed by our results using levofloxacin triple regimen in
32 first-line therapy for *H. pylori* since 2007 (84.4%¹⁵, 82.7%¹⁶ and 80.8% in the present
33 study). Moreover, another recent Spanish study³¹ could not demonstrate differences
34 either between standard triple therapy (75%) and levofloxacin triple therapy (72%) on
35 ITT basis. Similarly to our results with sequential therapy, the collective Spanish results
36 represent the lowest eradication rates reported for triple levofloxacin regimen in first-
37 line therapy, which contrast with cure rates $\geq 90\%$ reported in other settings.
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Therefore, the current prevalence of antibiotic resistance (clarithromycin,

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3 metronidazole and possibly levofloxacin) has probably increased to such an extent in
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5 some settings, such as Spain, that all patients should be considered as having
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7 resistant *H. pylori* infections to maintain acceptable cure rates³⁰. In this troublesome
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9 scenario, alternative regimens for initial treatment merit as well further evaluation, such
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11 as traditional bismuth-based quadruple therapy and concomitant therapy (non-bismuth-
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13 containing therapy giving the 4 constituent components of sequential therapy
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15 concurrently for 5-10 days)^{5,20,30}. Since bismuth-based quadruple therapy is not
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17 influenced by metronidazole or macrolide resistance, it has been recommended as the
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19 treatment of choice when clarithromycin resistance rates are $\geq 15\%$ in the
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21 community^{32,33}. Nevertheless, a recent meta-analysis failed to find a significant
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23 difference in the success rate in primary treatment between quadruple and standard
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25 triple therapy³⁴, which were both suboptimal (<80%). Additional disadvantages of
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27 bismuth quadruple therapy are that it is the most complex therapy, even despite a
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29 novel single capsule containing bismuth, metronidazole and tetracycline, and that
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31 bismuth salts are not available anymore in many countries^{5,32}.

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36 On the other hand, the advantage of concomitant therapy over triple therapy
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38 has been recently demonstrated, as well as its equal effectiveness and safety with less
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40 complexity compared to sequential therapy^{25,35}. The first randomized trial comparing
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42 concomitant and sequential therapies concluded that eradication rate was significantly
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44 better with concomitant therapy for clarithromycin-resistant strains (75% vs 57%) and
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46 dual clarithromycin and metronidazole resistant-strains (75% vs 33%)²⁵. Overall,
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48 clarithromycin-based sequential and concomitant therapies are encouraging novel
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50 regimens for primary *H. pylori* eradication but it remains to be elucidated whether both
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52 schemes are really effective in settings with a high prevalence of clarithromycin
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54 resistance, as occurs in most developed countries nowadays.

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57 The present study has several shortcomings. A major drawback is the lack of
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59 pretreatment susceptibility testing for clarithromycin and levofloxacin. Prevalence of
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clarithromycin resistance has been reported to be < 15% in adults in our country^{36,37}.

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3 Nonetheless, more recent studies have highlighted an increasing trend in its
4 prevalence in adults and children (22%)³⁸, with primary *H. pylori* resistant-strains in
5 children as high as 49% for clarithromycin and 32% for metronidazole³⁹. On the
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10 contrary, levofloxacin seems to have a relatively low resistance rate (<6%) in our
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12 country^{38,40}, which contrasts with the increasing trend in other settings, ranging from
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14 14% to 22%⁴¹. However, the higher cost of levofloxacin regimens is a major concern
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16 when dealing with a common disease as *H. pylori* infection. As such, it seems cautious
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18 to currently save levofloxacin for second and third line regimens.
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21 In conclusion, the efficacy of sequential therapy may be suboptimal (< 80%) in
22
23 areas with a high rate of failure for triple standard therapy. Sequential therapy is a
24
25 novel promising approach which deserves consideration, but its cure rates and its
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27 advantage over standard triple regimen require validation outside of Italy before a
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29 generalized change is recommended in clinical practice, especially in settings with high
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31 rate of clarithromycin-resistant *H. pylori* strains. At the present time, levofloxacin triple
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33 and modified sequential therapy are good alternatives, albeit burdened with a 20%
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35 failure rate and a higher cost. On this point, further studies addressing and comparing
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37 both sequential and concomitant quadruple schemes are warranted.
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42 **ACKNOWLEDGEMENTS**

43
44 We are indebted to the hard work and dedication of Juana Vicenta Molano, the nurse
45
46 who performed the post-therapy assessment. CIBEREHD is funded by the Instituto de
47
48 Salud Carlos III.
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53 **FINANCIAL DISCLOSURES:** none to declare.
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Table 1. Demographic and clinical characteristic of patients from the total cohort and in each therapeutic group after randomisation.

OCA: triple standard; OLA: levofloxacin triple therapy; OACM: sequential therapy with clarithromycin; OALM: modified sequential therapy with levofloxacin.

| | Total cohort | OCA | OLA | OACM | OALM |
|--|--------------|------------|------------|------------|------------|
| No. of patients | 460 | 115 | 115 | 115 | 115 |
| Gender (M/F) | 47%/53% | 47%/53% | 53%/47% | 47%/53% | 40%/60% |
| Age, yrs | 48 (18-84) | 44 (19-78) | 51 (18-84) | 49 (18-80) | 49 (19-79) |
| Smoking habit | 33% | 35% | 33% | 38% | 29% |
| Indication | | | | | |
| Noninvestigated dyspepsia | 95 (20.7%) | 30 (26.1%) | 23 (20%) | 25 (21.7%) | 20 (17.4%) |
| Functional dyspepsia | 180 (39.1%) | 42 (36.6%) | 47 (40.8%) | 42 (36.5%) | 51 (44.3%) |
| Gastric ulcer | 86 (18.7%) | 18 (15.6%) | 20 (17.4%) | 24 (20.8%) | 23 (20%) |
| Duodenal ulcer | 78 (17%) | 18 (15.6%) | 22 (19.1%) | 20 (17.4%) | 17 (14.8%) |
| Gastric cancer in first-degree relatives | 21 (4.5%) | 7 (6%) | 3 (2.6%) | 4 (3.5%) | 4 (3.5%) |
| Diagnostic method | | | | | |
| Urea breath test | 165 (35.8%) | 41 (35.6%) | 41 (35.6%) | 39 (33.9%) | 31 (26.9%) |
| Rapid urease test | 121 (26.3%) | 29 (25.2%) | 32 (27.8%) | 27 (23.4%) | 42 (36.5%) |
| Histology | 174 (37.8%) | 45 (39.1%) | 42 (36.5%) | 49 (42.6%) | 42 (36.5%) |

Table 2. Adverse events due to antibiotic therapy in patients from the total cohort and in each therapeutic group after randomisation.

OCA: triple standard; OLA: levofloxacin triple therapy; OACM: sequential therapy with clarithromycin; OALM: modified sequential therapy with levofloxacin.

| | Total cohort | OCA | OLA | OACM | OALM |
|----------------------|--------------|----------|----------|----------|----------|
| Side effects n, (%) | 129 (28%) | 29 (25%) | 32 (27%) | 29 (25%) | 29 (25%) |
| Diarrhea | 38 (8,2%) | 10 | 12 | 6 | 10 |
| Metallic taste | 30 (6,5%) | 7 | 4 | 7 | 2 |
| Epigastralgia/nausea | 24 (5,2%) | 7 | 3 | 8 | 6 |
| Myalgias | 17 (3,6%) | 0 | 8 | 0 | 9 |
| Aphthous stomatitis | 12 (2,6%) | 2 | 3 | 5 | 2 |
| Oral candidiasis | 4 (0,8%) | 2 | 2 | 0 | 0 |
| Skin rash | 3 (0,6%) | 1 | 0 | 2 | 0 |
| Lightheadedness | 1 (0,02%) | 0 | 0 | 1 | 0 |

Figure 1. Study flow chart.

ITT: intention to treat; OCA: triple standard; OLA: levofloxacin triple therapy; OACM: sequential therapy with clarithromycin; OALM: sequential therapy with levofloxacin

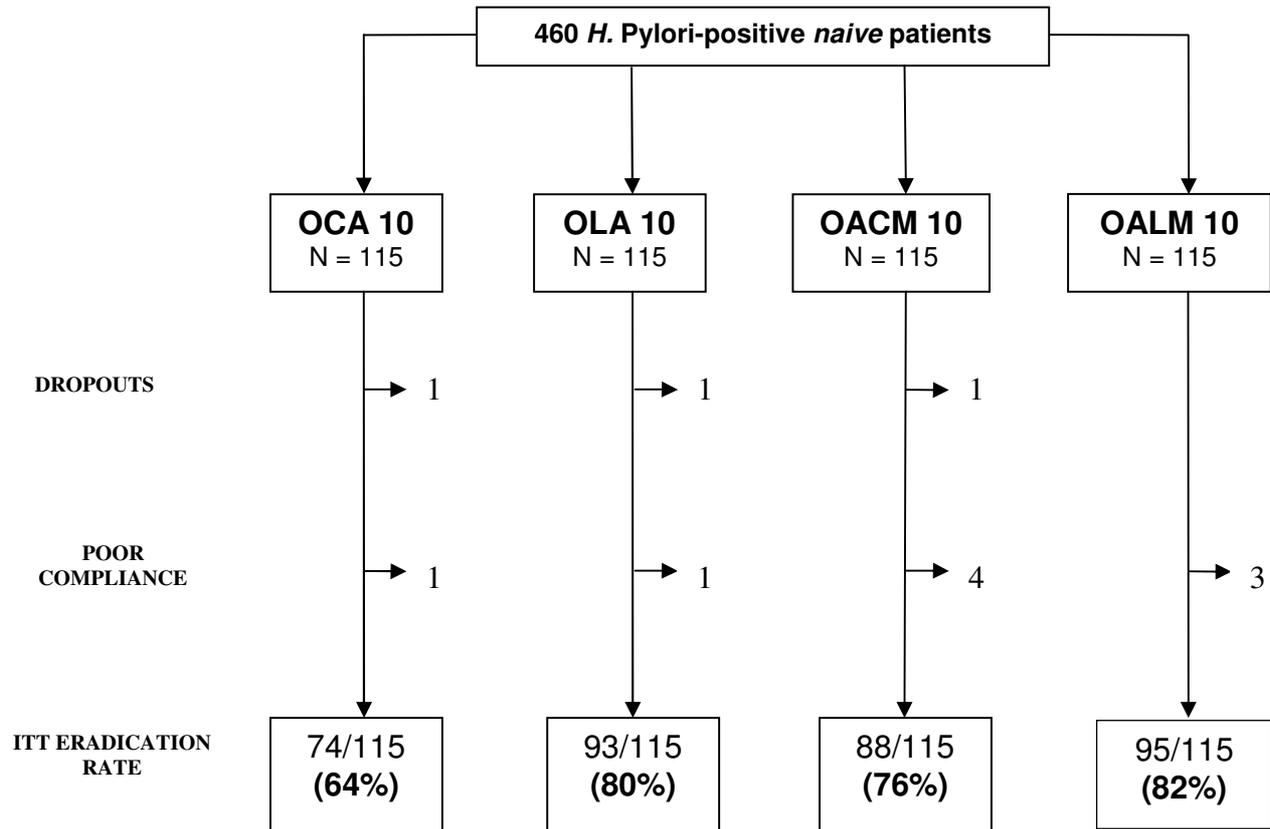


Figure 2. Eradication rates per protocol and per intention to treat analysis for 10-day clarythromycin and levofloxacin regimens. * $p < 0.05$

OCA: triple standard; OLA: levofloxacin triple therapy; OACM: sequential therapy with clarithromycin; OALM: modified sequential therapy with levofloxacin.

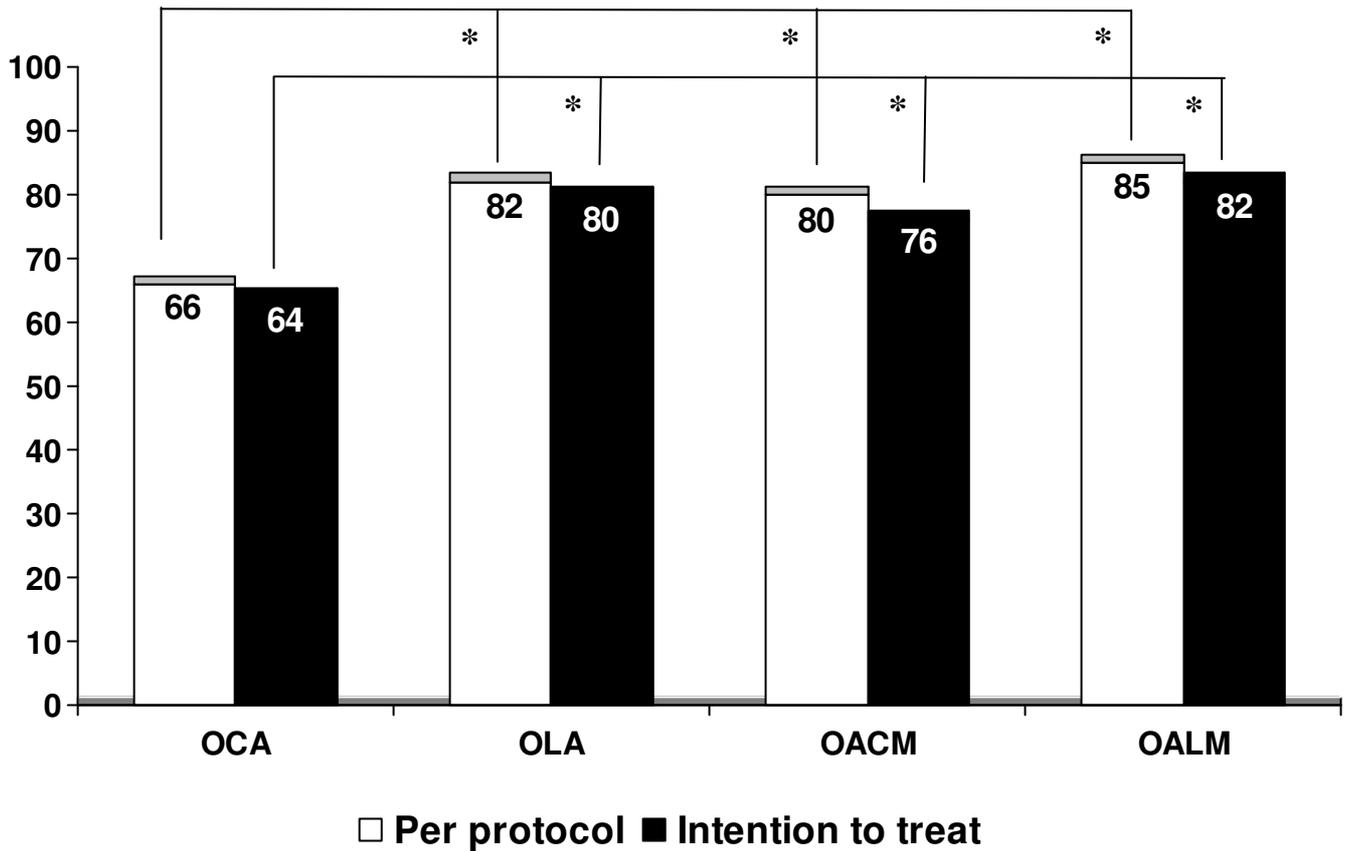
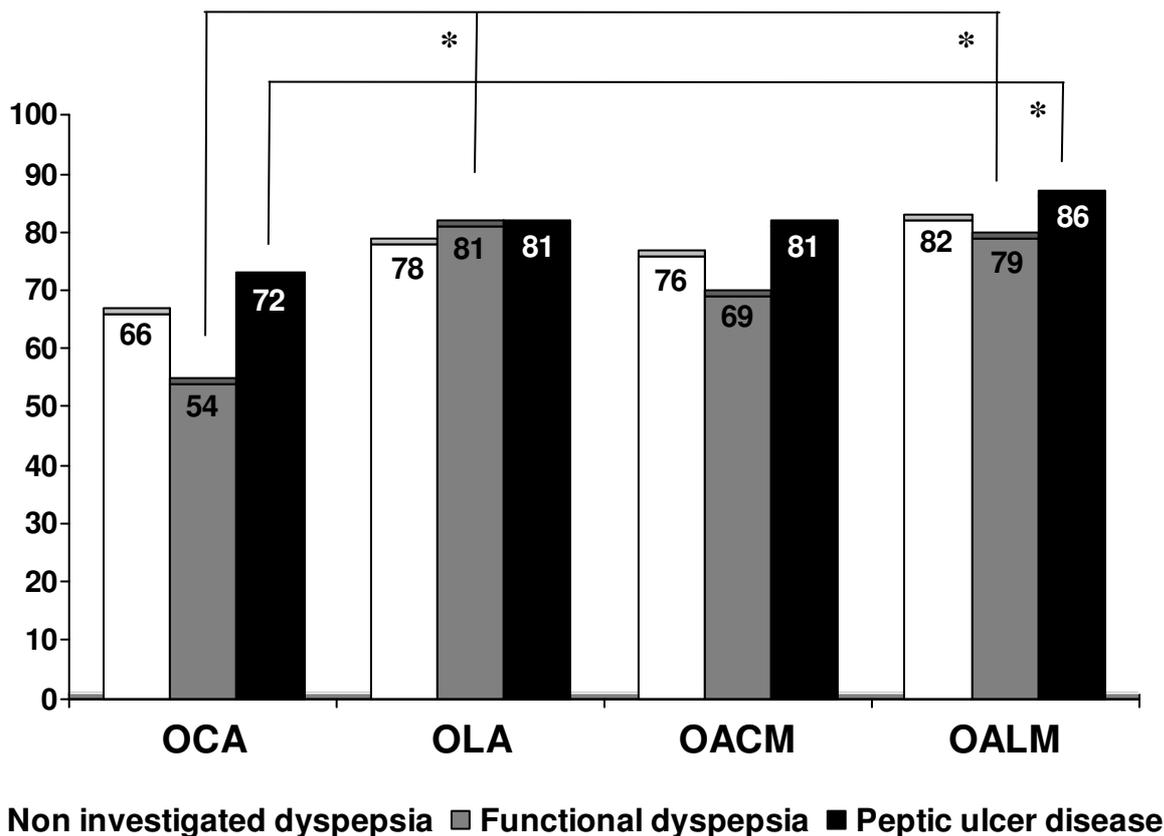


Figure 3. Eradication rates in the ITT analysis depending on the indication for eradication among all the regimens. * p < 0.05
 OCA: triple standard; OLA: levofloxacin triple therapy; OACM: sequential therapy with clarithromycin; OALM: modified sequential therapy with levofloxacin.



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| PAPER SECTION And topic | Item | Descriptor Alimentary Pharmacology & Therapeutic | Reported on Page # |
|---|------|---|-------------------------------|
| 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 | 1 | <u>How participants were allocated to interventions</u> (e.g., "random allocation", "randomized", or "randomly assigned"). | 5 |
| TITLE & ABSTRACT | 2 | <u>Scientific background and explanation of rationale.</u> | 3-4 |
| INTRODUCTION Background | 3 | <u>Eligibility criteria for participants</u> and the <u>settings and locations where the data were collected.</u> | 5 |
| METHODS Participants | 4 | <u>Precise details of the interventions intended for each group and how and when they were actually administered.</u> | 5 |
| Interventions | 5 | <u>Specific objectives and hypotheses.</u> | 4 |
| Objectives | 6 | <u>Clearly defined primary and secondary outcome measures</u> and, when applicable, any <u>methods used to enhance the quality of measurements</u> (e.g., multiple observations, training of assessors). | 4 |
| Outcomes | 7 | <u>How sample size was determined</u> and, when applicable, <u>explanation of any interim analyses and stopping rules.</u> | 6 |
| Sample size | 8 | <u>Method used to generate the random allocation sequence, including details of any restrictions</u> (e.g., blocking, stratification) | 5 |
| Randomization -- Sequence generation | 9 | <u>Method used to implement the random allocation sequence</u> (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned. | |
| Randomization -- Allocation concealment | 10 | <u>Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.</u> | 5 |
| Randomization -- Implementation | 11 | <u>Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment.</u> If done, <u>how the success of blinding was evaluated.</u> | |
| Blinding (masking) | 12 | <u>Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses</u> , such as subgroup analyses and adjusted analyses. | 6 |
| Statistical methods | 13 | <u>Flow of participants through each stage</u> (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. <u>Describe protocol deviations from study as planned, together with reasons.</u> | Figure 1 |
| RESULTS Participant flow | 14 | <u>Dates defining the periods of recruitment and follow-up.</u> | 5 |
| Recruitment | 15 | <u>Baseline demographic and clinical characteristics of each group.</u> | Table 1 |
| Baseline data | 16 | <u>Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat".</u> State the results in absolute numbers when feasible (e.g., 10/20, not 50%). | Table 1 Figure 2 Page 7 |
| Numbers analyzed | 17 | <u>For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision</u> (e.g., 95% confidence interval). | Page 7 Figure 2 |
| Outcomes and estimation | 18 | <u>Address multiplicity by reporting any other analyses performed</u> , including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory. | Page 7 Figure 3 |
| Ancillary analyses | 19 | <u>All important adverse events or side effects in each intervention group.</u> | Table 2 Page 8 |
| Adverse events | 20 | <u>Interpretation of the results</u> , taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes. | Pages 9-10 |
| DISCUSSION Interpretation | 21 | <u>Generalizability (external validity) of the trial findings.</u> | Page 11 |
| Generalizability | 22 | <u>General interpretation of the results in the context of current evidence.</u> | Pages 9,11,12 |
| Overall evidence | | | |