

## ORIGINAL ARTICLE

# Levonorgestrel Intrauterine System versus Medical Therapy for Menorrhagia

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## ABSTRACT

**BACKGROUND**

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Menorrhagia is a common problem, yet evidence to inform decisions about therapy is limited. In a pragmatic, multicenter, randomized trial, we compared the levonorgestrel-releasing intrauterine system (levonorgestrel-IUS) with usual medical treatment in women with menorrhagia who presented to their primary care providers.

**METHODS**

We randomly assigned 571 women with menorrhagia to treatment with levonorgestrel-IUS or usual medical treatment (tranexamic acid, mefenamic acid, combined estrogen–progestogen, or progesterone alone). The primary outcome was the patient-reported score on the Menorrhagia Multi-Attribute Scale (MMAS) (ranging from 0 to 100, with lower scores indicating greater severity), assessed over a 2-year period. Secondary outcomes included general quality-of-life and sexual-activity scores and surgical intervention.

**RESULTS**

MMAS scores improved from baseline to 6 months in both the levonorgestrel-IUS group and the usual-treatment group (mean increase, 32.7 and 21.4 points, respectively;  $P < 0.001$  for both comparisons). The improvements were maintained over a 2-year period but were significantly greater in the levonorgestrel-IUS group than in the usual-treatment group (mean between-group difference, 13.4 points; 95% confidence interval, 9.9 to 16.9;  $P < 0.001$ ). Improvements in all MMAS domains (practical difficulties, social life, family life, work and daily routine, psychological well-being, and physical health) were significantly greater in the levonorgestrel-IUS group than in the usual-treatment group, and this was also true for seven of the eight quality-of-life domains. At 2 years, more of the women were still using the levonorgestrel-IUS than were undergoing the usual medical treatment (64% vs. 38%,  $P < 0.001$ ). There were no significant between-group differences in the rates of surgical intervention or sexual-activity scores. There were no significant differences in serious adverse events between groups.

**CONCLUSIONS**

In women with menorrhagia who presented to primary care providers, the levonorgestrel-IUS was more effective than usual medical treatment in reducing the effect of heavy menstrual bleeding on quality of life. (Funded by the National Institute of Health Research Health Technology Assessment Programme; ECLIPSE Controlled-Trials.com number, ISRCTN86566246.)

\*The members of the Effectiveness and Cost-Effectiveness of Levonorgestrel-Containing Intrauterine System in Primary Care against Standard Treatment for Menorrhagia (ECLIPSE) Trial Collaborative Group are listed in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

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**H**EAVY MENSTRUAL BLEEDING, OR MENORRHAGIA, is a common problem that can have a significant effect on women's lives and can burden both patients and health care systems.<sup>1,2</sup> Menorrhagia accounts for 18.5% of gynecologist office visits in the United States<sup>3</sup> and for 20% in the United Kingdom<sup>4</sup>; more than 5% of women who are 30 to 49 years of age consult family physicians each year in the United Kingdom with this problem.<sup>5</sup> Rates of surgical procedures for menorrhagia are 17.8 per 10,000 women 25 to 44 years of age in the United States<sup>6</sup> and 14.3 per 10,000 women 24 to 59 years of age in the United Kingdom.<sup>7</sup>

There is substantial discordance between objective measures of menstrual-blood loss and women's perception of the amount of bleeding.<sup>8,9</sup> Only about half the women with menorrhagia who present to health care providers have blood loss greater than the traditional clinical threshold of 80 ml per menstrual cycle.<sup>8</sup> Measurement of the hemoglobin level in menstrual blood collected in sanitary protective materials is inconvenient and often unacceptable for women.<sup>10</sup> Diary-based assessments of bleeding<sup>11</sup> also fail to reflect women's experience of what is burdensome for them.<sup>12</sup> Clinical guidelines now advocate a shift in emphasis from the amount of menstrual-blood loss to the more patient-centered definition of heavy menstrual bleeding that interferes with a woman's physical, emotional, and social life.<sup>10,12</sup>

Several nonhormonal and hormonal medical treatments are available for women with menorrhagia. Since 2009 in the United States, and earlier in Europe, the levonorgestrel-releasing intrauterine system (levonorgestrel-IUS) (Mirena, Bayer HealthCare) has been available to treat this problem. Although developed as a contraceptive, the levonorgestrel-IUS also reduces menstrual-blood loss.<sup>13</sup> In 2007, U.K. guidelines<sup>10</sup> introduced the option of the levonorgestrel-IUS for menorrhagia on the basis of limited evidence.<sup>14</sup> Updated meta-analyses, including the results of nine small, randomized trials (involving a total of 783 women) of the levonorgestrel-IUS as compared with nonhormonal and hormonal treatments, showed that the levonorgestrel-IUS resulted in a greater reduction in menstrual-blood loss at 3 to 12 months of follow-up.<sup>13,14</sup> However, it is not clear whether these short-term benefits persist, particularly since the rates of discontinuation of the levonorgestrel-IUS are as

high as 28% at 2 years,<sup>15</sup> and the effects of this therapy on bleeding-related quality of life are not known.

The Effectiveness and Cost-Effectiveness of Levonorgestrel-Containing Intrauterine System in Primary Care against Standard Treatment for Menorrhagia (ECLIPSE) trial was a pragmatic, multicenter, randomized trial that compared the clinical effectiveness of the levonorgestrel-IUS with that of usual medical treatment in the primary care setting.

## METHODS

### PATIENTS

Women between 25 and 50 years of age who presented to their primary care physicians with menorrhagia involving at least three consecutive menstrual cycles were eligible to participate. Women were excluded if they intended to become pregnant over the next 5 years, were taking hormone-replacement therapy or tamoxifen, had intermenstrual bleeding (between expected periods) or postcoital bleeding or findings suggestive of fibroids (abdominally palpable uterus equivalent in size to that at 10 to 12 weeks' gestation) or other disorders, or had contraindications to or a preference for either the levonorgestrel-IUS or usual medical treatments. Women with heavy, irregular bleeding were ineligible unless the results of endometrial biopsy were reported to be normal; no further investigations were mandated by the protocol. All patients provided written informed consent.

### RANDOMIZATION

Patients were assigned to a study group by telephone or a Web-based central randomization service at the University of Birmingham Clinical Trials Unit. A computerized, minimized randomization procedure was used to achieve balance between the groups with respect to age (<35 years or ≥35 years), body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) (≤25 or >25), duration of symptoms (<1 year or ≥1 year), need for contraception (yes or no), and menorrhagia alone or menorrhagia accompanied by menstrual pain.

### STUDY INTERVENTIONS AND COMPLIANCE

Eligible women who provided written informed consent were randomly assigned to either the levonorgestrel-IUS or usual medical treatment. Usual-

treatment options included mefenamic acid, tranexamic acid, norethindrone, a combined estrogen-progestogen or progesterone-only oral contraceptive pill (any formulation), or medroxyprogesterone acetate injection and were chosen by the physician and patient on the basis of contraceptive needs or the desire to avoid hormonal treatment.<sup>10,16</sup> The particular medical treatment to be used was specified before randomization. Subsequently, treatments could be changed (from one medical treatment to another, from the levonorgestrel-IUS to medical treatment, or from medical treatment to the levonorgestrel-IUS) or could be discontinued because of a perceived lack of benefit, side effects, a change in the need for contraception, referral for endometrial ablation or hysterectomy, or other reasons, according to usual practice.<sup>10,16</sup> Treatment changes reported by patients were confirmed with the primary care physician.

#### OUTCOME MEASURES AND FOLLOW-UP

The primary outcome measure was the condition-specific Menorrhagia Multi-Attribute Scale (MMAS),<sup>17,18</sup> which is designed to measure the effect of menorrhagia on six domains of daily life (practical difficulties, social life, psychological health, physical health, work and daily routine, and family life and relationships). Summary scores, which range from 0 (severely affected) to 100 (not affected), were assessed at 6, 12, and 24 months. The MMAS has a high degree of reliability and internal consistency,<sup>17</sup> has good content and construct validity,<sup>19,20</sup> is responsive,<sup>21,22</sup> and is acceptable to respondents.<sup>17,18,21,22</sup>

Secondary outcome measures included general health-related quality of life and sexual activity. To assess quality of life, we used three instruments: the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), version 2 (with scores ranging from 0 [severely affected] to 100 [not affected]); the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D) descriptive system (with scores ranging from -0.59 [health state worse than death] to 100 [perfect health state]); and the EQ-5D visual-analogue scale (with scores ranging from 0 [worst health state imaginable] to 100 [most perfect health state imaginable]). The validated Sexual Activity Questionnaire measures pleasure (with scores ranging from 0 [lowest level] to 18 [highest level]), discomfort (with scores ranging from 0 [greatest] to 6 [none]), and frequency

(assessed relative to perceived usual activity as an ordinal response).<sup>23</sup> Scores were obtained before randomization and by mail at 6 months, 1 year, and 2 years after randomization. Data were collected from participating clinicians regarding all serious adverse events, defined as adverse events that resulted in death, disability, or hospitalization. Patients were also asked to report any hospitalizations and adverse events leading to discontinuation of the study drug.

#### STUDY OVERSIGHT

Study oversight was provided by an independent steering committee and an independent data and safety monitoring committee, whose three reviews of interim data provided no reason to modify the trial protocol on the basis of pragmatic stopping criteria.<sup>24</sup> The study was conducted in accordance with the protocol, which is available with the full text of this article at NEJM.org. Approval of the study was obtained from the South-West England Multicenter Research Ethics Committee, and clinical trial authorization was received from the Medicines and Healthcare Products Regulatory Authority. The writing committee vouches for the accuracy and completeness of the data and analyses. (For a list of members of the writing committee, as well as the trial team, see the Supplementary Appendix, available at NEJM.org.) All medications and devices were prescribed by providers through the National Health Service. The manufacturers of the levonorgestrel-IUS and other therapeutic agents used in the study were not involved in any aspect of the trial.

#### STATISTICAL ANALYSIS

The study was designed for 90% power (at  $P < 0.05$ ) to detect small-to-moderate (0.3 SD) differences in the primary outcome at any one time point.<sup>25</sup> This required an enrollment of 470 patients; we increased the sample size to 570 to allow for up to 20% loss to follow-up. Primary analyses were performed according to the intention-to-treat principle. Continuous measures were compared with the use of multilevel repeated-measures models,<sup>26</sup> including all assessment time points and with adjustment for baseline scores. All available data were included in this analysis, and any missing follow-up study questionnaires were assumed to be missing at random. Treatment-by-subgroup interaction was included to test for

differences in efficacy within prespecified subgroups. Changes from baseline scores within treatment groups were compared with the use of paired t-tests. Several sensitivity analyses were also performed on the primary outcome measure to test the robustness of the results. These included an analysis that accounted for missing responses with the use of a multiple-imputation approach,<sup>27</sup> as well as an analysis that excluded women who crossed over from the assigned study treatment to the other study treatment, assuming the best score for women who no longer had menstrual bleeding (and felt they could not complete the MMAS appropriately) and the worst score for missing responses.<sup>27,28</sup> Kaplan–Meier plots were constructed for time to first treatment change; a Cox proportional-hazards model was used to calculate hazard ratios. Effect sizes are presented with 95% confidence intervals and two-sided P values. SAS software, version 9.2 (SAS Institute), was used for analyses. Additional information regarding the statistical analyses is included in the Supplementary Appendix.

## RESULTS

### PATIENTS AND FOLLOW-UP

Between February 2005 and July 2009, a total of 571 women with menorrhagia from 63 U.K. centers were randomly assigned to either the levonorgestrel-IUS (285 women) or usual medical treatment (286 women). Baseline characteristics were similar between the two treatment groups (Table 1). For 215 (75%) of the women assigned to usual medical treatment, the initial prescription was for mefenamic acid, tranexamic acid, or a combination of the two drugs (Table S1 in the Supplementary Appendix); 55 (19%) of the women in the usual-treatment group required contraception. Study-questionnaire booklets were returned by 478 (84%) of the patients at the 2-year time point (Fig. 1); 45 of these women (9%) could not complete the MMAS appropriately because their menstrual bleeding had ceased, but they completed other parts of the booklet, and this information was used to inform the sensitivity analysis.

Of the 285 women randomly assigned to levonorgestrel-IUS, 24 (8%) did not have the IUS inserted: 10 chose usual medical treatment, 6 chose no treatment, and 8 underwent unsuccessful insertion of the system and were subsequently given usual medical treatment (Fig. 1). Women

**Table 1. Characteristics of the Patients.\***

Characteristic	Usual Medical Treatment	Levonorgestrel-IUS
No. of patients	286	285
Age		
≥35 yr — no. of patients (%) †	255 (89)	257 (90)
Mean — yr	41.8±5.5	42.1±5.0
Body-mass index ‡		
>25 — no. of patients (%) †	200 (70)	200 (70)
Mean	29.3±6.7	29.1±6.1
Race — no. of patients (%) §		
White	246 (86)	225 (79)
Asian	23 (8)	28 (10)
Black	12 (4)	18 (6)
Mixed	4 (1)	9 (3)
Other	1 (<1)	4 (1)
Duration of menorrhagia ≥1 yr — no. of patients (%) †	229 (80)	231 (81)
Menstrual pain — no. of patients (%) †	211 (74)	213 (75)
Contraceptive requirement — no. of patients (%) †	55 (19)	55 (19)
Copper or nonhormonal coil in place — no. of patients (%)	10 (3)	9 (3)

\* Plus–minus values are means ±SD. There were no significant differences between groups for any of the characteristics. Levonorgestrel-IUS denotes levonorgestrel-releasing intrauterine system.

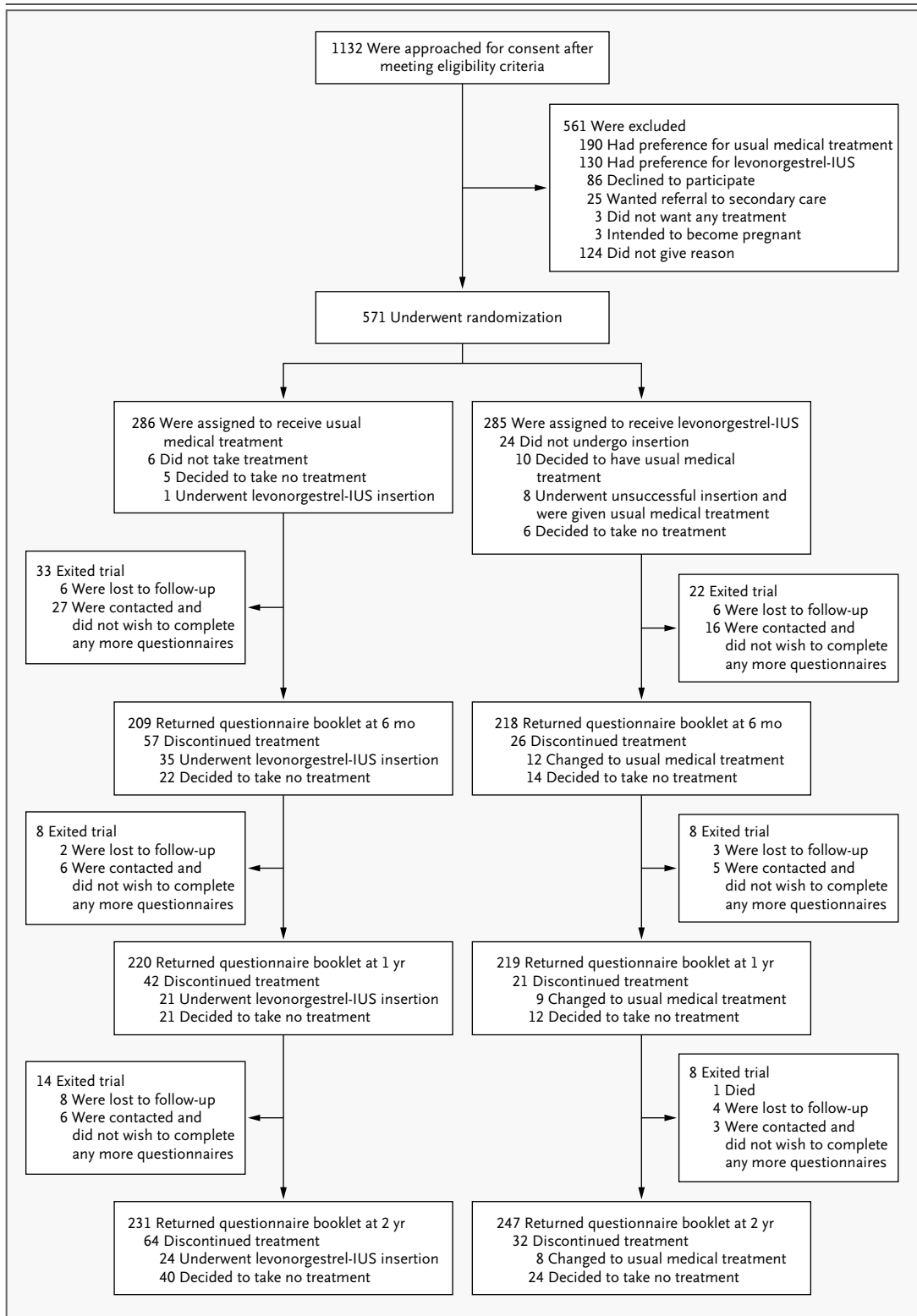
† This characteristic was a stratification variable and was assessed in predefined subgroup analyses.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Race was self-reported, with one response not given in the levonorgestrel-IUS group.

in the levonorgestrel-IUS group were almost twice as likely as those in the usual-treatment group to still be receiving their assigned treatment at 2 years (64% vs. 38%,  $P<0.001$ ) (Fig. 2). The most common reasons cited for discontinuation of the levonorgestrel-IUS were lack of effectiveness (37%) and irregular or prolonged bleeding (28%). Of the 163 women who discontinued usual medical treatment, 80 (49%) switched to levonorgestrel-IUS. The most common reason for discontinuation of usual medical therapy was lack of effectiveness (53%).

There was no significant difference between the two groups in the frequency of serious adverse events (58 in the usual-treatment group and 49 in the levonorgestrel-IUS group,  $P=0.59$ ). There was one death in the levonorgestrel-IUS group;



**Figure 1. Enrollment, Randomization, and Follow-up of the Study Patients.**

Reasons for discontinuation of treatment can be found in Tables S3a and S3b in the Supplementary Appendix. Levonorgestrel-IUS denotes levonorgestrel-releasing intrauterine system.



the cause of death was recorded by the coroner as inconclusive, and the levonorgestrel-IUS was not in situ. Serious adverse events and reasons for discontinuing therapy are summarized in Tables S2 and S3, respectively, in the Supplementary Appendix.

**PRIMARY OUTCOME**

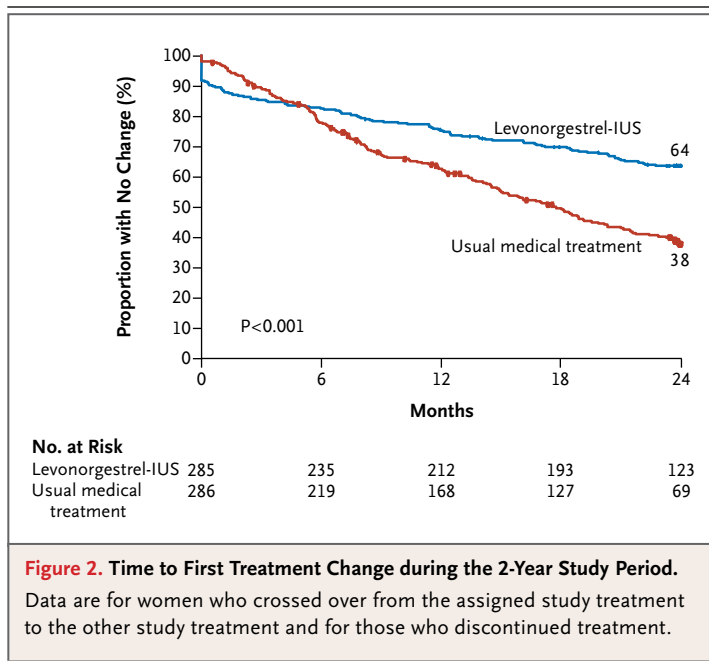
Total scores on the MMAS improved significantly in both groups at 6 months and at 1 year and 2 years, as compared with baseline scores (Fig. 3) (see Tables S4 and S5 in the Supplementary Appendix for full details, including responses to the individual domains of the survey), but improvements in these scores were significantly greater among women assigned to levonorgestrel-IUS than among those assigned to usual treatment (mean difference in scores over the course of 2 years, 13.4 points; 95% confidence interval [CI], 9.9 to 16.9;  $P < 0.001$ ). All six domains of the MMAS favored the levonorgestrel-IUS at every time point ( $P < 0.001$  with the use of a test for trend) (Table S5 in the Supplementary Appendix).

In a sensitivity analysis that excluded women who crossed over from the assigned treatment to the other study treatments, improvement with the levonorgestrel-IUS, as compared with usual medical treatment, increased (mean difference in scores over the course of 2 years, 17.8 points; 95% CI, 14.1 to 21.5;  $P < 0.001$ ). Other sensitivity analyses yielded results that were not materially different from the results of the primary analysis ( $P < 0.001$  for all comparisons). (Table S6 in the Supplementary Appendix).

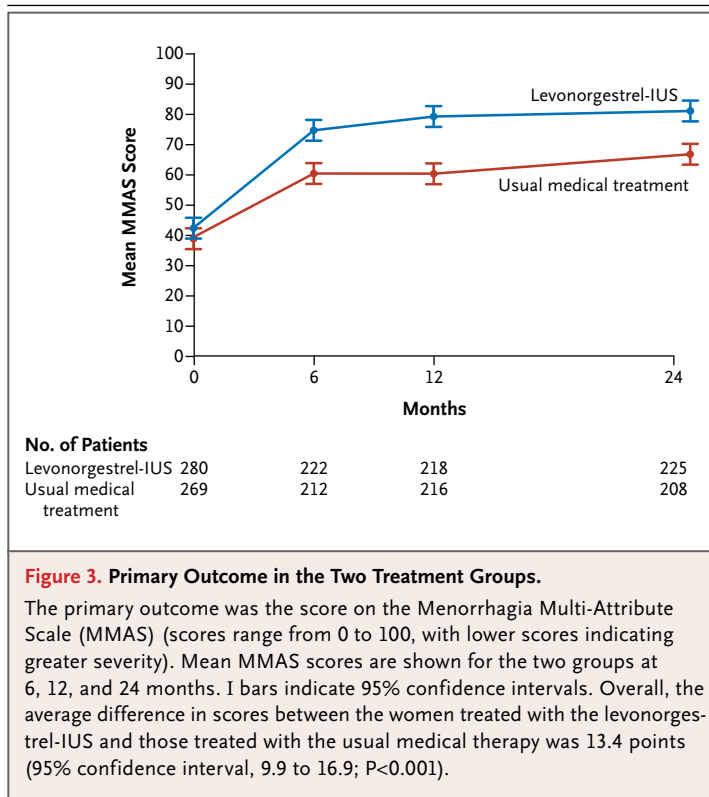
In subgroup analyses, there was a significant interaction between treatment and BMI ( $P = 0.004$ ). The benefit of the levonorgestrel-IUS was greater in women with a BMI above 25 (16.7 MMAS points; 95% CI, 12.6 to 20.9;  $P < 0.001$ ) than in those with a BMI of 25 or less (5.4 MMAS points; 95% CI, -1.0 to 11.8;  $P = 0.10$ ) This finding appeared to be attributable to the superior outcome with usual medical treatment in leaner women (Fig. S1 in the Supplementary Appendix). Improvements with the levonorgestrel-IUS were similar in both subgroups. None of the other tests for subgroup interaction were significant ( $P > 0.10$ ).

**GENERAL QUALITY OF LIFE AND SEXUAL ACTIVITY**

SF-36 domains were generally significantly improved from baseline in both groups at all time points, although the scores for women in the levo-



**Figure 2. Time to First Treatment Change during the 2-Year Study Period.**  
Data are for women who crossed over from the assigned study treatment to the other study treatment and for those who discontinued treatment.



**Figure 3. Primary Outcome in the Two Treatment Groups.**  
The primary outcome was the score on the Menorrhagia Multi-Attribute Scale (MMAS) (scores range from 0 to 100, with lower scores indicating greater severity). Mean MMAS scores are shown for the two groups at 6, 12, and 24 months. I bars indicate 95% confidence intervals. Overall, the average difference in scores between the women treated with the levonorgestrel-IUS and those treated with the usual medical therapy was 13.4 points (95% confidence interval, 9.9 to 16.9;  $P < 0.001$ ).

norgestrel-IUS group were better than for those in the usual-treatment group in seven of the eight domains in the analysis over all time points

**Table 2. Scores on the Quality-of-Life and Sexual-Activity Questionnaires at Baseline, and Mean Between-Group Difference over 2 Years.\***

Questionnaire	Score at Baseline		Between-Group Difference in Score over 2 Years (95% CI)†	P Value
	Usual Medical Treatment	Levonorgestrel-IUS		
SF-36‡				
Physical functioning	77.8±24.7	80.0±20.4	2.7 (0.0 to 5.4)	0.05
Physical role	68.9±26.2	72.1±24.7	5.9 (2.6 to 9.1)	<0.001
Emotional role	69.8±26.8	71.9±25.1	4.6 (1.3 to 8.0)	0.007
Social functioning	62.4±25.9	64.3±24.5	5.1 (2.0 to 8.1)	0.001
Mental health	59.0±19.8	60.3±19.3	1.5 (−1.0 to 3.9)	0.23
Energy and vitality	40.8±21.7	40.7±20.9	5.3 (2.5 to 8.2)	<0.001
Pain	49.5±24.9	54.2±24.9	7.8 (4.5 to 11.0)§	<0.001
Perception of general health	60.3±21.9	61.8±21.4	2.9 (−0.3 to 5.4)	0.03
EQ-5D descriptive system¶	0.714±0.276	0.756±0.243	0.013 (−0.016 to 0.042)	0.38
EQ-5D visual-analogue scale	69.7±19.8	70.3±19.1	2.0 (−0.5 to 4.6)§	0.12
Sexual Activity Questionnaire**				
Pleasure	10.9±4.9	10.8±4.9	0.4 (−0.3 to 1.1)	0.26
Discomfort	4.62±1.69	4.65±1.48	−0.07 (−0.30 to 0.16)	0.55

\* Plus–minus values are means ±SD.

† Estimated values greater than zero favor the levonorgestrel-IUS. These are summary results only; see the Supplementary Appendix for the complete results and for details of the repeated-measures model used to calculate these values.

‡ The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) is a general health-related quality-of-life questionnaire. Scores in each of the eight domains range from 0 (severely affected) to 100 (not affected).

§ There is some evidence of a time-by-treatment effect ( $P \leq 0.05$ ); see the Supplementary Appendix for full details of the estimates at each time point.

¶ The EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D) descriptive system is a general health-related quality-of-life questionnaire. Scores range from −0.59 (state of health worse than death) to 1.00 (perfect state of health).

|| Scores on the EQ-5D visual-analogue scale range from 0 (worst health state imaginable) to 100 (most perfect health state imaginable).

\*\* The Sexual Activity Questionnaire is designed to assess the possible effect of treatment on sexual functioning. Scores for pleasure range from 0 (lowest level) to 18 (highest level), and scores for discomfort range from 0 (greatest) to 6 (none).

(Table 2); mental health was the only domain for which there were no significant between-group differences. The improvements appeared to be greatest at 6 months but had lessened by the 2-year follow-up assessment (Table S7 in the Supplementary Appendix). No significant differences were seen between treatments with respect to the EQ-5D instrument; scores were significantly improved from baseline in both groups at 2 years but not at earlier assessments (Table S8 in the Supplementary Appendix). Nor did the treatments differ significantly with respect to the scores for the pleasure, discomfort, and frequency domains of the Sexual Activity Questionnaire (Table S9 in the Supplementary Appendix).

#### SURGICAL INTERVENTIONS

The frequency of surgical interventions for heavy menstrual bleeding within 2 years did not differ significantly between the two groups. Hysterectomy was performed in 6% of the women in each group; endometrial ablations were performed in 4% of women in the levonorgestrel-IUS group and in 6% of those in the usual-treatment group ( $P=0.44$ ).

#### DISCUSSION

The results of this trial show that levonorgestrel-IUS, as compared with usual medical therapies for menorrhagia, leads to greater improvement

in women's assessments of the effect of heavy menstrual bleeding on their daily routine, including work, social and family life, and psychological and physical well-being.

At baseline, the women were substantially affected by heavy menstrual bleeding, as assessed with the use of condition-specific (MMAS) and general (SF-36) health-related scales. The scores improved significantly over a period of 2 years in both the levonorgestrel-IUS group and the usual-treatment group. However, improvements in average scores and residual symptoms for all six MMAS domains were greater with the levonorgestrel-IUS than with usual medical treatment. The average between-group difference in the overall MMAS score over 2 years of follow-up was 13.4 points, with greater improvement in the levonorgestrel-IUS group than in the usual-treatment group — a difference that was both statistically significant and clinically meaningful. The between-group difference was more than 0.5 SD, which is the minimum clinically important difference identified in a systematic review of studies reporting such data for health-related quality-of-life measures.<sup>29</sup> A 13.4-point difference represents a change in two or three MMAS domains: from being substantially to minimally affected by menorrhagia (e.g., from frequent to occasional disruptions of work and daily routine) or from being minimally affected to being unaffected (e.g., from experiencing some strain in family life to experiencing no strain in family life). The between-group difference reported here is also greater than that reported in an observational study comparing women who did and those who did not undergo surgery for menorrhagia.<sup>21</sup>

The strengths of our randomized trial include its size (larger than prior trials of treatments for heavy menstrual bleeding), the multicenter design, the inclusion of patients ethnically representative of the U.K. population, the relatively low rates of loss to follow-up, and the assessment of outcomes over a period of 2 years rather than 6 or 12 months, as in previous studies.<sup>13,14</sup> In addition, previous trials have focused on the reduction of menstrual-blood loss, which does not reflect the full effect of menorrhagia on women's lives.<sup>13,14</sup> In contrast, our primary outcome measure was the patient-reported, psychometrically valid, condition-specific MMAS, which better reflects women's personal experience of the bur-

den of menorrhagia. Interference with the quality of life, rather than perceptions of heavy menstrual bleeding itself, appears to be the primary factor in women's decision to seek treatment.<sup>30</sup>

Some limitations of our study should be noted. The range of options available for medical treatment complicates any efforts to compare the levonorgestrel-IUS with individual agents. However, the choice among the various agents is representative of current clinical practice. In addition, substantial numbers of patients switched treatments over the course of the study; however, these crossovers would be expected to result in an underestimation of the benefits that might be achieved with perfect compliance. A range of sensitivity analyses did not change the conclusions. Although the interventions studied in this trial represent options available in primary care settings in the United Kingdom, insertion of intrauterine devices is not part of primary care in all health care settings, and in some circumstances, it requires consultation with a gynecologist.

The 21.4-point improvement from baseline in the average MMAS score at 6 months in the usual-treatment group, which was sustained throughout the 2 years of follow-up, was not explained by a switch in treatment, since similar improvements were noted when crossovers to the levonorgestrel-IUS were excluded from the analyses. The higher rate of discontinuation in the usual-treatment group than in the levonorgestrel-IUS group could reflect greater symptom relief with levonorgestrel-IUS, but another possible explanation is that discontinuation of usual medical treatment does not require consultation. Nonetheless, at 2 years, 36% of women in the levonorgestrel-IUS group had had the system removed, generally owing to lack of effectiveness or to irregular or prolonged bleeding, which are well-recognized reasons for discontinuing the levonorgestrel-IUS.<sup>31,32</sup> This proportion is consistent with the proportions of women who discontinued levonorgestrel-IUS treatment in smaller trials that compared it with hysterectomy<sup>33</sup> (31% of 117 women at 12 months) or with endometrial ablation (28% of 105 women at 2 years).<sup>31,34,35</sup>

In subgroup analyses, the levonorgestrel-IUS appeared to be less beneficial in women with a BMI of 25 or less than in those with a BMI of more than 25, an observation that was explained by an apparently greater efficacy of usual medical treatments in the leaner women. This analy-



sis was one of several subgroup analyses and should be interpreted with caution, since the findings may be explained by chance and require confirmation.

We expected fewer surgical interventions in the levonorgestrel-IUS group, but rates were similarly low in the two groups. This finding may reflect the eligibility criteria for the trial, since women who had fibroids or other disorders were excluded.

Finally, given the long natural history of menorrhagia, study outcomes need to be assessed over a period that is longer than 2 years; additional intention-to-treat analyses are planned at 5 and 10 years.

In conclusion, our study showed that both the levonorgestrel-IUS and usual medical treatments reduced the adverse effect of menorrhagia on women's lives over the course of 2 years, but the levonorgestrel-IUS was the more effective first choice, as assessed by the impact of bleeding on the women's quality of life.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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## REFERENCES

1. Frick KD, Clark MA, Steinwachs DM, et al. Financial and quality-of-life burden of dysfunctional uterine bleeding among women agreeing to obtain surgical treatment. *Womens Health Issues* 2009;19:70-8.
2. Roberts TE, Tsourapas A, Middleton LJ, et al. Hysterectomy, endometrial ablation, and levonorgestrel releasing intrauterine system (Mirena) for treatment of heavy menstrual bleeding: cost effectiveness analysis. *BMJ* 2011;342:d2202.
3. Nicholson WK, Ellison SA, Grason H, Powe NR. Patterns of ambulatory care use for gynecologic conditions: a national study. *Am J Obstet Gynecol* 2001;184:523-30.
4. Coulter A, Bradlow J, Agass M. Outcomes of referrals to gynecology outpatient clinics for menstrual problems: an audit of general practice records. *Br J Obstet Gynaecol* 1991;98:789-96.
5. Office of Population Census and Surveys. Morbidity statistics from general practice: fourth national morbidity study 1991-1992. London: Her Majesty's Stationery Office, 1995.
6. Whiteman MK, Kuklina E, Jamieson DJ, Hillis SD, Marchbanks PA. Inpatient hospitalization for gynecologic disorders in the United States. *Am J Obstet Gynecol* 2010;202(6):541.e1-541.e6.
7. Cromwell DA, Mahmood TA, Templeton A, van der Meulen JH. Surgery for menorrhagia within English regions: variation in rates of endometrial ablation and hysterectomy. *BJOG* 2009;116:1373-9.
8. Higham JM, Shaw RW. Clinical associations with objective menstrual blood volume. *Eur J Obstet Gynecol Reprod Biol* 1999;82:73-6.
9. Warner P, Critchley HO, Lumsden MA, Campbell-Brown M, Douglas A, Murray G. Referral for menstrual problems: cross sectional survey of symptoms, reasons for referral, and management. *BMJ* 2001;323:24-8.
10. National Collaborating Centre for Women's and Children's Health. Heavy menstrual bleeding. London: Royal College of Obstetricians and Gynaecologists, 2007 (guideline CG44).
11. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol* 1990;97:734-9.
12. Santer M, Wyke S, Warner P. What aspects of periods are most bothersome for women reporting heavy menstrual bleeding? Community survey and qualitative study. *BMC Womens Health* 2007;7:8.
13. Endrikat J, Vilos G, Muysers C, Fortier M, Solomayer E, Lukkari-Lax E. The levonorgestrel-releasing intrauterine system provides a reliable, long-term treatment option for women with idiopathic menorrhagia. *Arch Gynecol Obstet* 2012;285:117-21.
14. Stewart A, Cummins C, Gold L, Jordan R, Phillips W. The effectiveness of the levonorgestrel-releasing intrauterine system in menorrhagia: a systematic review. *BJOG* 2001;108:74-86.
15. Middleton LJ, Champaneria R, Daniels JP, et al. Hysterectomy, endometrial destruction, and levonorgestrel releasing intrauterine system (Mirena) for heavy menstrual bleeding: systematic review and meta-analysis of data from individual patients. *BMJ* 2010;341:c3929.
16. The initial management of menorrhagia: evidence based guidelines no. 1. London: Royal College of Obstetricians and Gynaecologists, 1998.
17. Shaw RW, Brickley MR, Evans L, Edwards MJ. Perceptions of women on the impact of menorrhagia on their health using multi-attribute utility assessment. *Br J Obstet Gynaecol* 1998;105:1155-9.
18. Pattison H, Daniels JP, Kai J, Gupta JK. The measurement properties of the menorrhagia multi-attribute quality-of-life scale: a psychometric analysis. *BJOG* 2011;118:1528-31.
19. Matteson KA, Boardman LA, Munro MG, Clark MA. Abnormal uterine bleed-

- ing: a review of patient-based outcome measures. *Fertil Steril* 2009;92:205-16.
20. Gibbons E, Mckintosh A, Fitzpatrick R. A structured review of patient-reported outcome measures for people undergoing elective procedures for benign gynaecological conditions of the uterus: report to the Department of Health. Oxford, United Kingdom: University of Oxford, 2010.
21. Habiba M, Julian S, Taub N, et al. Limited role of multi-attribute utility scale and SF-36 in predicting management outcome of heavy menstrual bleeding. *Eur J Obstet Gynecol Reprod Biol* 2010;148:81-5.
22. Protheroe J, Bower P, Chew-Graham C, Peters TJ, Fahey T. Effectiveness of a computerized decision aid in primary care on decision making and quality of life in menorrhagia: results of the MENTIP randomized controlled trial. *Med Decis Making* 2007;27:575-84.
23. Thirlaway K, Fallowfield L, Cuzick J. The Sexual Activity Questionnaire: a measure of women's sexual functioning. *Qual Life Res* 1996;5:81-90. [Erratum, *Qual Life Res* 1997;6:606.]
24. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer* 1976;34:585-612.
25. Cohen J. *Statistical power analysis for the behavioural sciences*. New York: Academic Press, 1977.
26. Verbeke G, Molenberghs G. *Linear mixed models for longitudinal data*. New York: Springer, 2000.
27. Rubin DB. *Multiple imputation for non-response in surveys*. New York: Wiley, 1987.
28. White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. *BMJ* 2011;342:d40.
29. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003;41:582-92.
30. Shapley M, Blagojevic M, Jordan K, Croft P. The spontaneous resolution of heavy menstrual bleeding in the perimenopausal years. *BJOG* 2012;119:545-53.
31. Shaw RW, Symonds IM, Tamizian O, Chaplain J, Mukhopadhyay S. Randomised comparative trial of thermal balloon ablation and levonorgestrel intrauterine system in patients with idiopathic menorrhagia. *Aust N Z J Obstet Gynaecol* 2007;47:335-40.
32. Ewies AA. Levonorgestrel-releasing intrauterine system — the discontinuing story. *Gynecol Endocrinol* 2009;25:668-73.
33. Hurskainen R, Teperi J, Rissanen P, et al. Quality of life and cost-effectiveness of levonorgestrel-releasing intrauterine system versus hysterectomy for treatment of menorrhagia: a randomised trial. *Lancet* 2001;357:273-7.
34. Busfield RA, Farquhar CM, Sowter MC, et al. A randomised trial comparing the levonorgestrel intrauterine system and thermal balloon ablation for heavy menstrual bleeding. *BJOG* 2006;113:257-63.
35. Kittelsen N, Istre O. A randomized study comparing levonorgestrel intrauterine system (LNG IUS) and transcervical resection of the endometrium (TCRE) in the treatment of menorrhagia: preliminary results. *Gynaecol Endosc* 1998;7:61-5.

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