MAYO CLINIC

Uterine Fibroids 2024

Elizabeth (Ebbie) Stewart, M.D.
Professor of Obstetrics and Gynecology
Mayo Clinic College of Medicine and Science

Disclosures (24 months)

- **Consulting Fee (e.g., Advisory Board):**
  Analyn, AbbVie

Objectives

- To review the data for fertility sparing medical treatment of fibroids with oral GnRH antagonist combinations
- To articulate the long-term risks of hysterectomy, even when performed with bilateral ovarian conservation

Extreme heterogeneity of size, number and location makes study and treatment difficult.

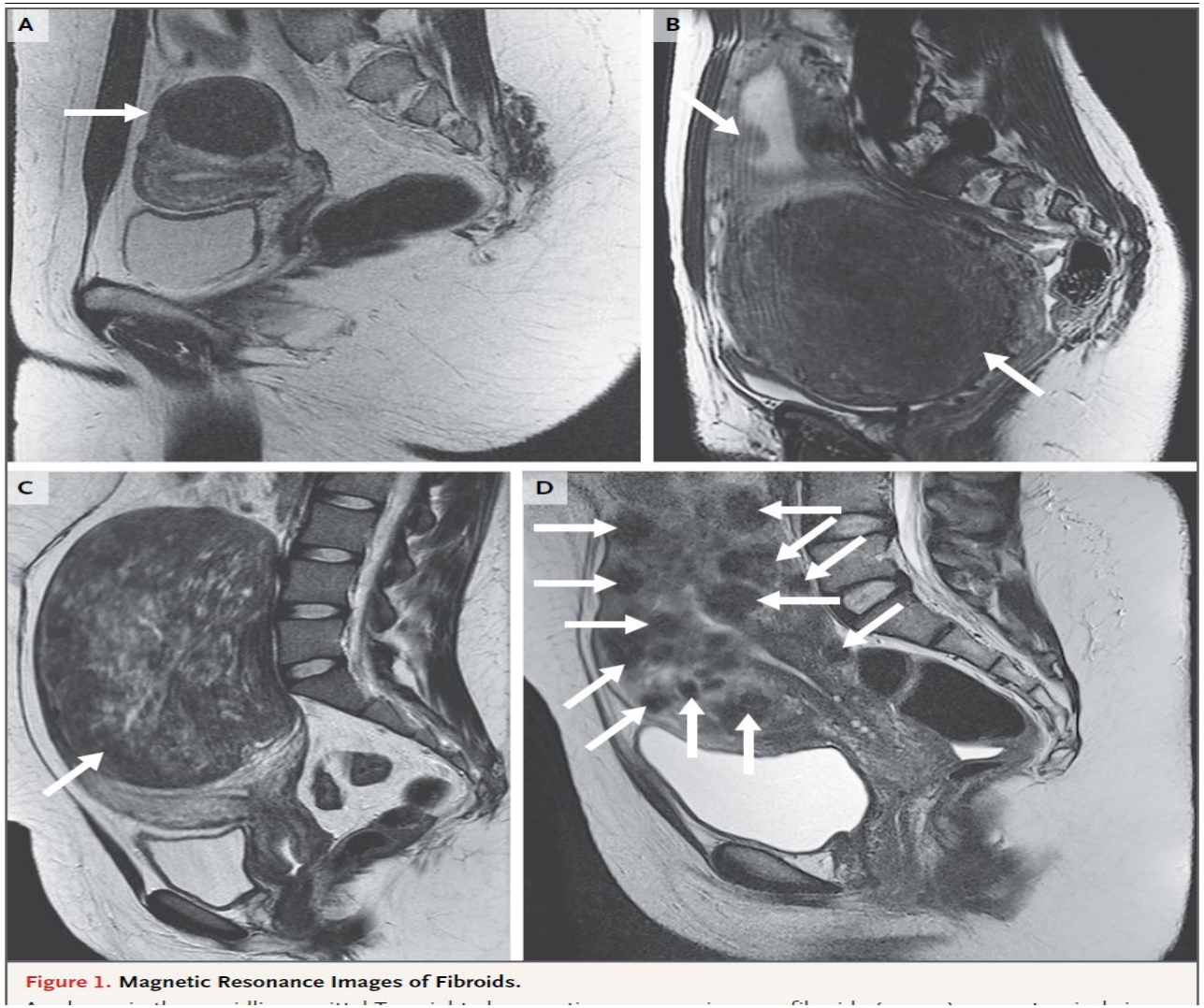


Figure 1. Magnetic Resonance Images of Fibroids.

MAYO CLINIC

Stewart E.A.: NEJM 372:17 1646-55, 2015

Heterogeneity of Symptoms

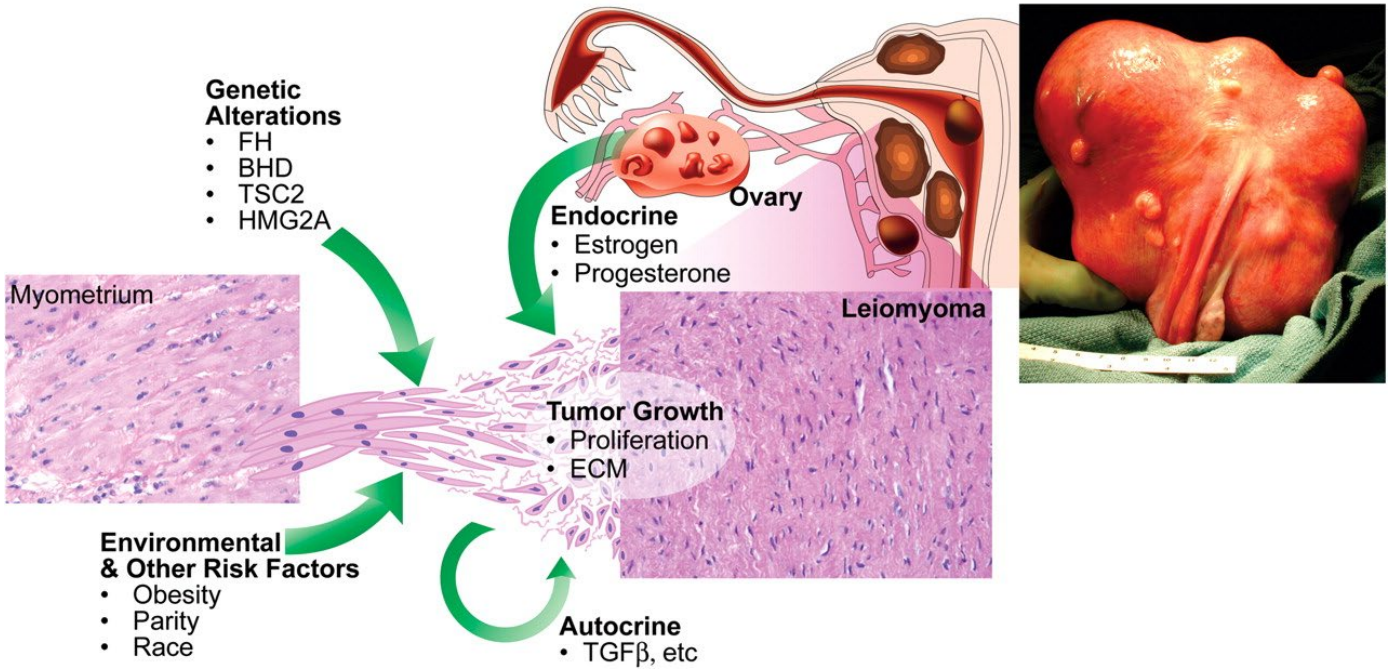
- Heavy or prolonged menses
- Abdominal protrusion
- Pelvic pain or discomfort
- Bladder of bowel problems
- Infertility, recurrent miscarriage, pregnancy complications

Many Fibroid Symptoms are Unrecognized or Attributed to Other Issues

- **“I pee every hour, but I drink a lot of water”**
- **“ All the women in my family have periods that last 10 days”**
- **“I’ve always been anemic”**
- **“I had a colonoscopy because of the anemia.”**
- **“ I’m a nurse so I have back pain from lifting patients.”**
- **“ My husband has erectile dysfunction so I think that’s why we can’t have sex.”**

MAYO CLINIC

Heterogeneous etiology of uterine fibroids



C. L. Walker and E. A. Stewart., Science 308, 1589 -1592 (2005)

Published by AAAS

Science AAAS

There is limited evidence for the efficacy of most first line medical therapies for fibroids

- A 52-mg LNG-IUD can be considered for the treatment of AUB-L. (Level B)
- Tranexamic acid can be considered for the treatment of AUB-L (Level B)
- Contraceptive steroid hormones (estrogen/progestin combinations and progestins alone) can be considered for the treatment of AUB-L (Level C)

Objectives

- To review the data for fertility sparing medical treatment of fibroids with oral GnRH antagonist combinations
- To articulate the long-term risks of hysterectomy, even when performed with bilateral ovarian conservation

Beyond “birth control”: More effective medical therapy is now available

Old	New
GnRH Agonist (leuprolide)	GnRH Antagonist (elagolix, relugolix, linzagolix)
Shots	Pills
“Flare” at start	Immediate shut down
Medication alone	Medication with low dose estrogen and progestin
Menopausal hormone level so symptoms like hot flashes, bone loss are common	Low normal hormone levels so symptoms uncommon

Oral GnRH Antagonists

With and Without Low Dose Hormonal Add-Back

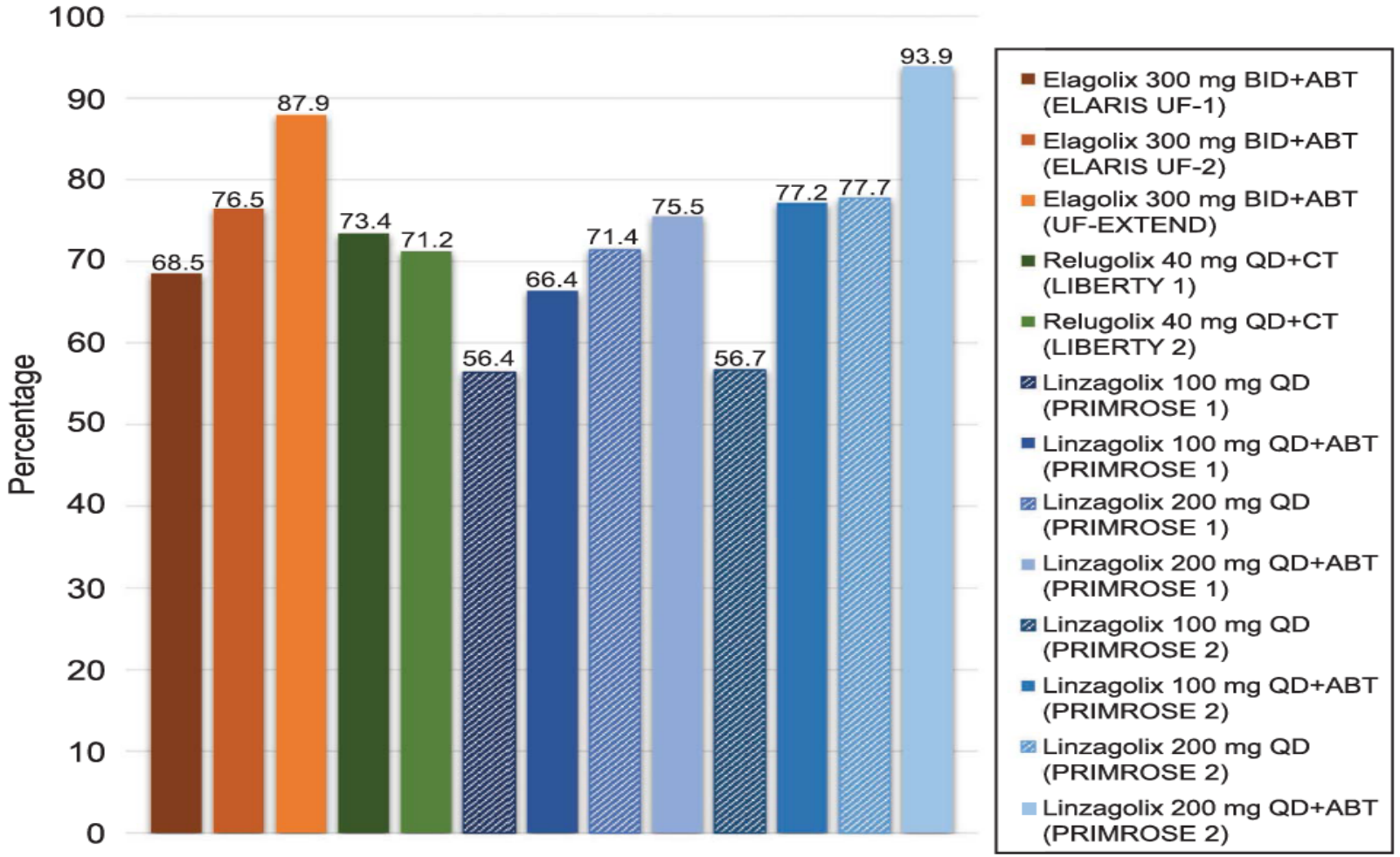
Table 1. Oral Gonadotropin-Releasing Hormone Antagonists Approved for the Treatment of Uterine Leiomyomas

Compound	Half-Life (h)	Dose (mg)	Dosing Frequency (/d)	Add-Back or Combination Therapy (mg)	FDA Approval	U.S. Indication and Duration	EU Indication and Duration
Elagolix	5.9	300	Twice	Yes 1 E2/0.5 NETA	Yes (2020)	HMB associated with uterine leiomyomas for up to 24 mo	Not approved
Relugolix	61.5	40	Once	Yes 1 E2/0.5 NETA	Yes (2021)	HMB associated with uterine leiomyomas for up to 24 mo	Moderate-to-severe symptoms of uterine leiomyomas, unlimited duration
Linzagolix	15	100 200	Once	Optional 1 E2/0.5 NETA	No	NA	Moderate-to-severe symptoms of uterine leiomyomas, unlimited duration for both doses with ABT and 100 mg without ABT, up to 6 months for 200 mg without ABT when volume reduction desired

FDA, U.S. Food and Drug Administration; EU, European Union; NETA, norethindrone acetate; HMB, heavy menstrual bleeding; ABT, add-back therapy; NA, not applicable.

Neblett & Stewart Obstet Gynecol 141:901-10, 2023

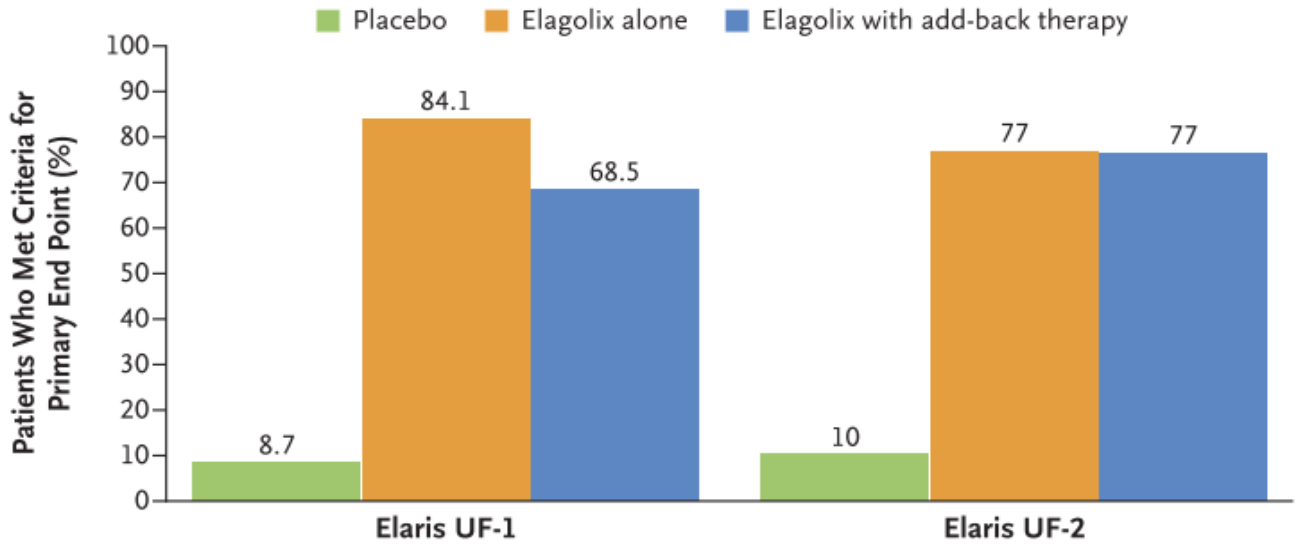
With and without hormones, oral GnRH Antagonists are effective treatment for HMB



MAYO CLINIC

Neblett & Stewart Obstet Gynecol 141:901-10, 2023

Elagolix, An Oral GnRH Antagonist, is Safe and Effective Treatment of Uterine Fibroids

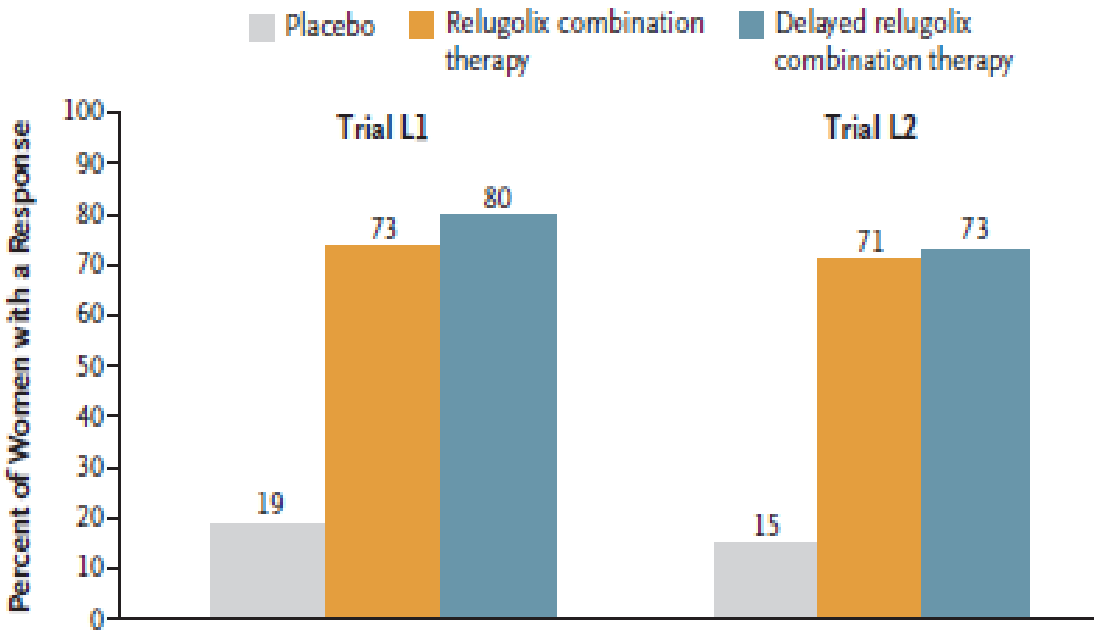


Difference from placebo — % (95% CI)		75.4 (66.2–84.6)	59.8 (51.1–68.5)		66.4 (55.5–77.3)	66.0 (57.1–75.0)
Risk ratio (95% CI)		9.7 (5.0–18.9)	7.9 (4.1–15.5)		7.1 (3.8–13.4)	7.2 (3.9–13.5)
Two-sided P value			<0.001			<0.001
No. of women	102	104	206	94	95	189
No. imputed by multiple imputation	8	3	16	6	11	12

Figure 1. Reduction in Heavy Menstrual Bleeding in Women with Uterine Fibroids.

Schlaff WD *et al*. *N Engl J Med*. 2020;382(4):328-340.

Relugolix is also Safe and Effective Treatment of Uterine Fibroids



	Trial L1			Trial L2		
No. of Patients	127	128	132	129	125	127
Difference vs. Placebo — percentage points (95% CI)		55 (44–65)	61 (51–70)		56 (46–66)	58 (49–68)
P Value vs. Placebo		<0.001			<0.001	

Figure 1. Participants with Reduction in Heavy Menstrual Bleeding.

Al-Hendy *et al*. *N Engl J Med*. 2021;384:630-42.

Elagolix Demonstrated Improvement in other Secondary Endpoints

Adapted from Table 2	Significant in both trials
Volume of menstrual blood loss	**Yes**
Suppression of bleeding at 1, 3, 6 and final month	**Yes**
Correction of anemia if present at start	**Yes**

Schlaff WD *et al*. *N Engl J Med*. 2020;382(4):328-340.

Relugolix Demonstrated Improvement in Most other Secondary Endpoints

Adapted from Table 2	Significant in both trials
No periods in last 35 days of treatment	Yes
Percentage decrease in menstrual blood loss	Yes
Decrease in Pelvic Discomfort Score	Yes
Correction of anemia if present at start	Yes
Pain ≤ 1 over last 35 days of treatment	Yes
Decrease in volume of largest fibroid	No
Decrease in uterine volume	Yes

Al-Hendy *et al*. *N Engl J Med*. 2021;384:630-42.

Side effects, including hot flashes, are low

Table 2. Adverse Events From Phase III Oral Gonadotropin-Releasing Hormone Antagonist Trials Compared With Placebo

Percent (%)	Regimens With Low-Dose Gonadal Steroid Add-Back (%)		
	Elagolix With ABT (Placebo)	Relugolix CT (Placebo)	Linzagolix 100 mg+ABT (Placebo)
Commonly reported adverse events			
Hot flushes	19.9–20.4 (4.3–8.8)	5.6–10.9 (3.9–7.9)	2.8–7.8 (3.8–6.7)
Nausea	7.4–11.2 (9.6–9.8)	3.1–4.8 (4.7–7.8)	2.9–3.7 (0.0–1.9)
Headache	8.3–10.6 (5.3–8.8)	8.7–10.9 (11.6–15.0)	4.9–5.5 (5.7–5.8)
Serious adverse events			
Any serious adverse event	1.5–3.7 (1.1–4.9)	0.8–5.5 (1.6–3.1)	0.0–4.9 (1.9)
Any serious adverse event leading to discontinuation	8.5–10.7 (5.3–7.8)	2.4–5.5 (3.9-4.7)	6.9–9.2 (6.7–9.6)

Percent (%)	Regimens With Low-Dose Gonadal Steroid Add-Back (%)	Regimens With GnRH Antagonist Monotherapy (%)	
	Linzagolix 200 mg+ABT (Placebo)	Linzagolix 100 mg (Placebo)	Linzagolix 200 mg (Placebo)
Commonly reported adverse events			
Hot flushes	6.5–12.9 (3.8–6.7)	6.0–14.1 (3.8–6.7)	31.7–34.9 (3.8–6.7)
Nausea	1.0–2.8 (0.0–1.9)	1.0–2.0 (0.0–1.9)	2.9–7.5 (0.0–1.9)
Headache	6.9–8.4 (5.7–5.8)	4.0–8.0 (5.7–5.8)	10.4–13.5 (5.7–5.8)
Serious adverse events			
Any serious adverse event	1.0–2.8 (1.9)	1.0–3.0 (1.9)	0.0–1.0 (1.9)
Any serious adverse event leading to discontinuation	6.9–9.3 (6.7–9.6)	7.0–7.1 (6.7–9.6)	10.4–10.6 (6.7–9.6)

GnRH, gonadotropin-releasing hormone; ABT, add-back therapy; CT, combination therapy.

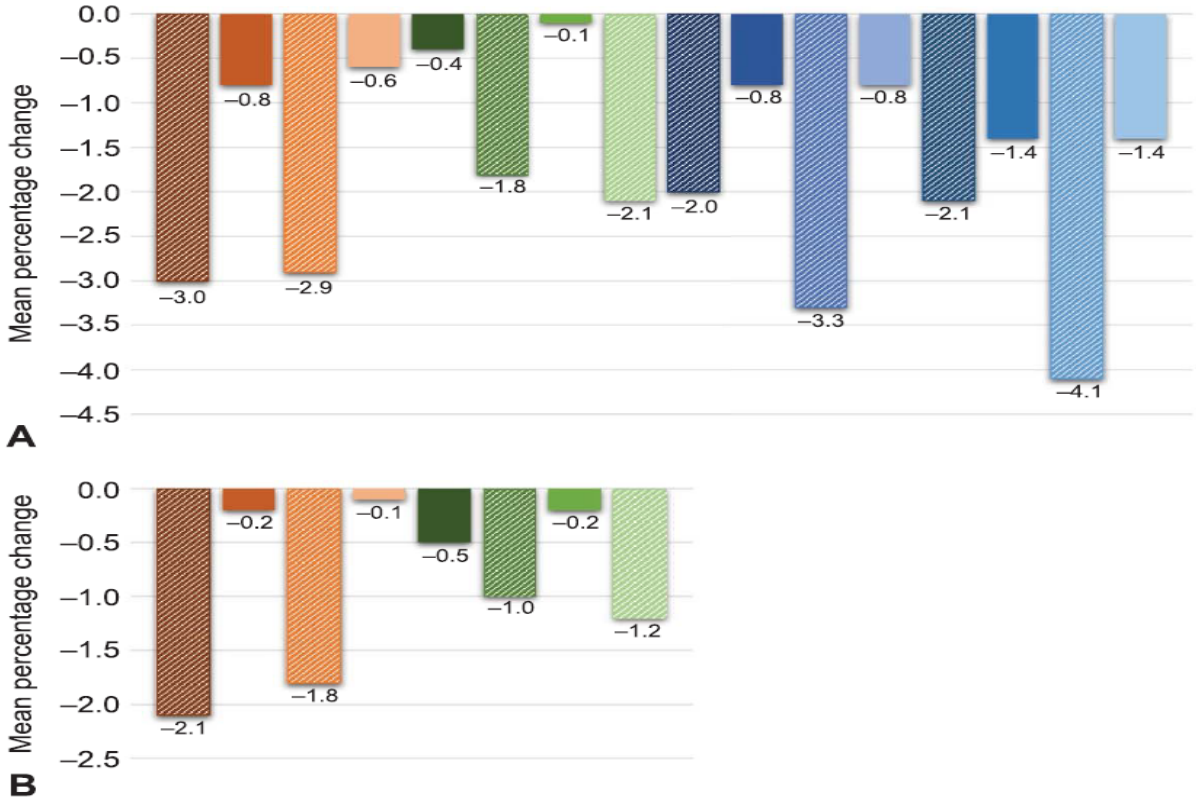
MAYO CLINIC

Neblett & Stewart Obstet Gynecol 141:901-10, 2023

Black Box Warning: Thromboembolic Disorders

- “Class Warning” because of estrogen and progestin components
- No thrombotic events reported in any of the 3 Phase III clinical trials
- Hormone levels consistent with early follicular phase, therefore lower hormone levels across cycle
- Oral administration may stimulate first pass effect

Bone loss is mitigated by low dose hormones

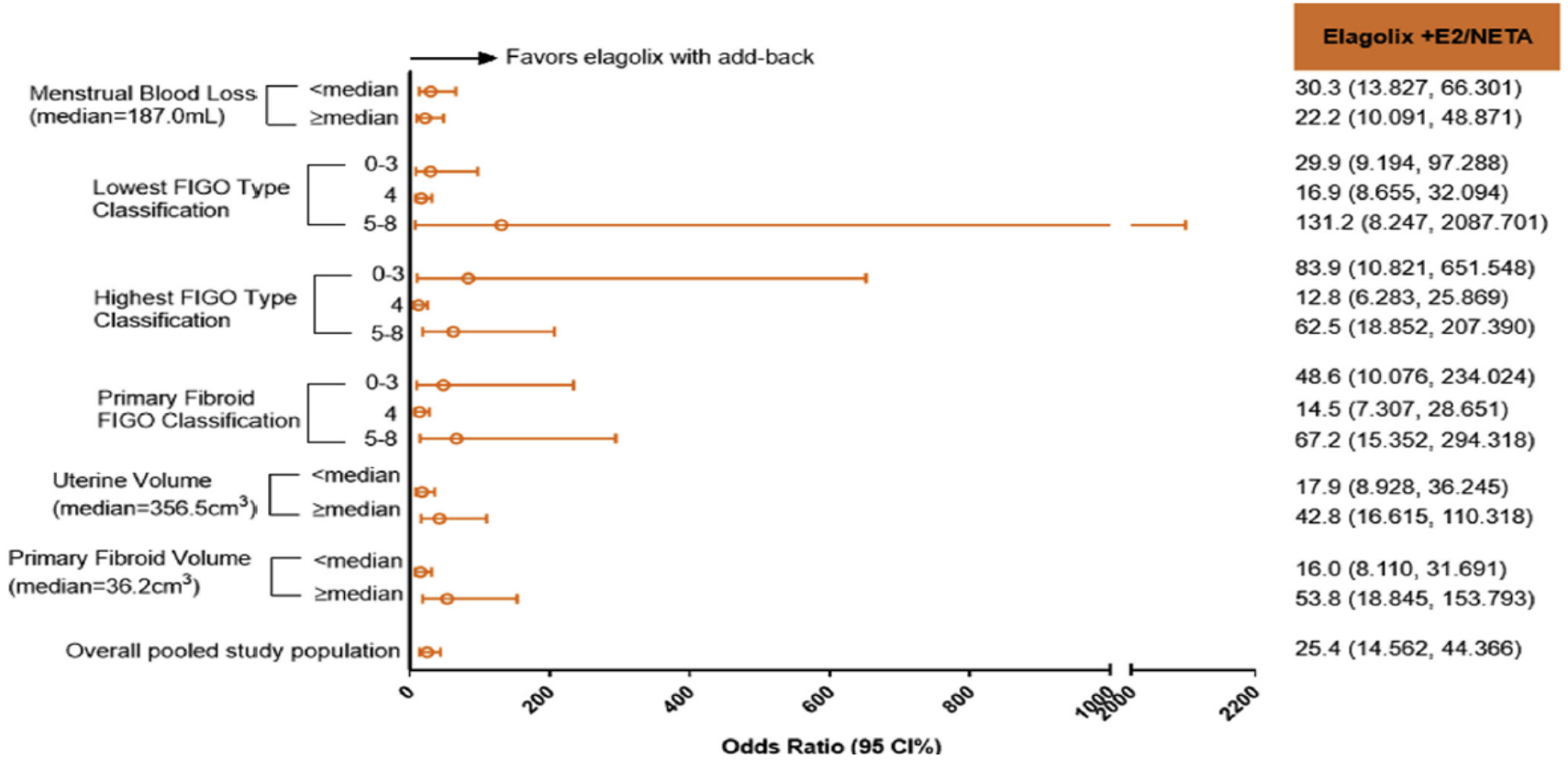


MAYO CLINIC

Neblett & Stewart Obstet Gynecol 141:901-10, 2023

Elagolix Response Appears Consistent Across Clinical Parameters

FIGURE 1
Odds ratios for primary endpoint by factors contributing to disease severity



Al-Hendy *et al*. Am J Ob Gyn. 2021; 224:72.e1-50.

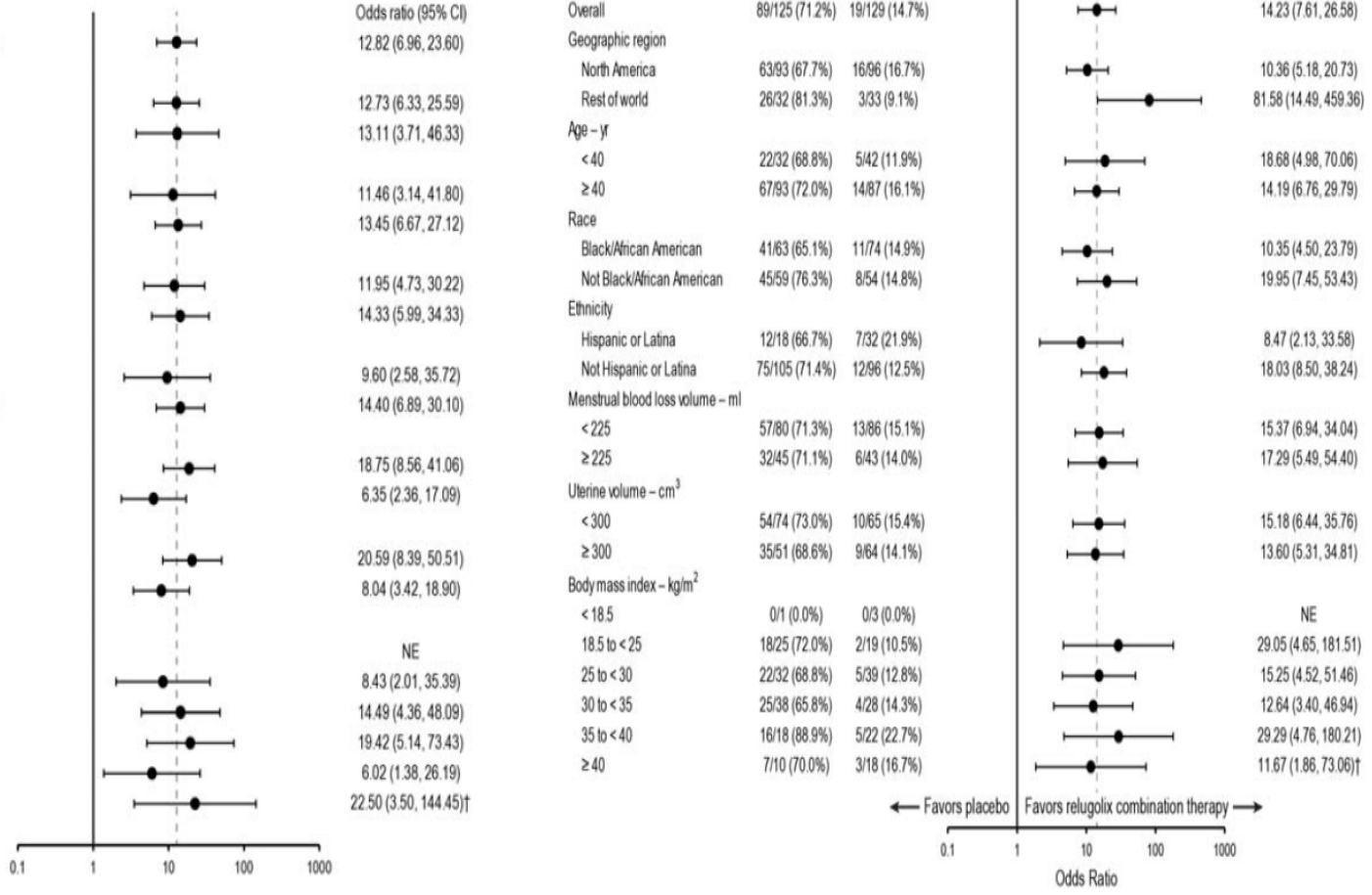
Relugolix Response Appears Consistent Across Clinical Parameters

LIBERTY 1

	Responder n/group n (%)		
	Relugolix Combination Therapy	Placebo	Odds ratio (95% CI)
Overall	94/128 (73.4%)	24/127 (18.9%)	12.82 (6.96, 23.60)
Geographic region			
North America	69/98 (70.4%)	16/98 (16.3%)	12.73 (6.33, 25.59)
Rest of world	25/30 (83.3%)	8/29 (27.6%)	13.11 (3.71, 46.33)
Age – yr			
< 40	19/30 (63.3%)	6/36 (16.7%)	11.46 (3.14, 41.80)
≥ 40	75/98 (76.5%)	18/91 (19.8%)	13.45 (6.67, 27.12)
Race			
Black/African American	36/59 (61.0%)	8/67 (11.9%)	11.95 (4.73, 30.22)
Not Black/African American	58/69 (84.1%)	16/60 (26.7%)	14.33 (5.99, 34.33)
Ethnicity			
Hispanic or Latina	29/34 (85.3%)	8/23 (34.8%)	9.60 (2.58, 35.72)
Not Hispanic or Latina	64/92 (69.6%)	16/103 (15.5%)	14.40 (6.89, 30.10)
Menstrual blood loss volume – ml			
< 225	67/84 (79.8%)	15/85 (17.6%)	18.75 (8.56, 41.06)
≥ 225	27/44 (61.4%)	9/42 (21.4%)	6.35 (2.36, 17.09)
Uterine volume – cm^3			
< 300	59/74 (79.7%)	11/64 (17.2%)	20.59 (8.39, 50.51)
≥ 300	35/53 (66.0%)	13/63 (20.6%)	8.04 (3.42, 18.90)
Body mass index – kg/m^2			
< 18.5	1/1 (100.0%)	0/0 (0.0%)	NE
18.5 to < 25	18/24 (75.0%)	6/21 (28.6%)	8.43 (2.01, 35.39)
25 to < 30	27/36 (75.0%)	6/33 (18.2%)	14.49 (4.36, 48.09)
30 to < 35	27/35 (77.1%)	4/27 (14.8%)	19.42 (5.14, 73.43)
35 to < 40	9/16 (56.3%)	6/29 (20.7%)	6.02 (1.38, 26.19)
≥ 40	12/16 (75.0%)	2/17 (11.8%)	22.50 (3.50, 144.45)†

LIBERTY 2

	Relugolix Combination Therapy	Placebo	Odds ratio (95% CI)
Overall	89/125 (71.2%)	19/129 (14.7%)	14.23 (7.61, 26.58)
Geographic region			
North America	63/93 (67.7%)	16/96 (16.7%)	10.36 (5.18, 20.73)
Rest of world	26/32 (81.3%)	3/33 (9.1%)	81.58 (14.49, 459.36)
Age – yr			
< 40	22/32 (68.8%)	5/42 (11.9%)	18.68 (4.98, 70.06)
≥ 40	67/93 (72.0%)	14/87 (16.1%)	14.19 (6.76, 29.79)
Race			
Black/African American	41/63 (65.1%)	11/74 (14.9%)	10.35 (4.50, 23.79)
Not Black/African American	45/59 (76.3%)	8/54 (14.8%)	19.95 (7.45, 53.43)
Ethnicity			
Hispanic or Latina	12/18 (66.7%)	7/32 (21.9%)	8.47 (2.13, 33.58)
Not Hispanic or Latina	75/105 (71.4%)	12/96 (12.5%)	18.03 (8.50, 38.24)
Menstrual blood loss volume – ml			
< 225	57/80 (71.3%)	13/86 (15.1%)	15.37 (6.94, 34.04)
≥ 225	32/45 (71.1%)	6/43 (14.0%)	17.29 (5.49, 54.40)
Uterine volume – cm^3			
< 300	54/74 (73.0%)	10/65 (15.4%)	15.18 (6.44, 35.76)
≥ 300	35/51 (68.6%)	9/64 (14.1%)	13.60 (5.31, 34.81)
Body mass index – kg/m^2			
< 18.5	0/1 (0.0%)	0/3 (0.0%)	NE
18.5 to < 25	18/25 (72.0%)	2/19 (10.5%)	29.05 (4.65, 181.51)
25 to < 30	22/32 (68.8%)	5/39 (12.8%)	15.25 (4.52, 51.46)
30 to < 35	25/38 (65.8%)	4/28 (14.3%)	12.64 (3.40, 46.94)
35 to < 40	16/18 (88.9%)	5/22 (22.7%)	29.29 (4.76, 180.21)
≥ 40	7/10 (70.0%)	3/18 (16.7%)	11.67 (1.86, 73.06)†



Al-Hendy *et al*. *N Engl J Med*. 2021;384:630-42, Supplemental material.

Hemorrhage with Type 0 Submucosal Fibroids: Relugolix without addback

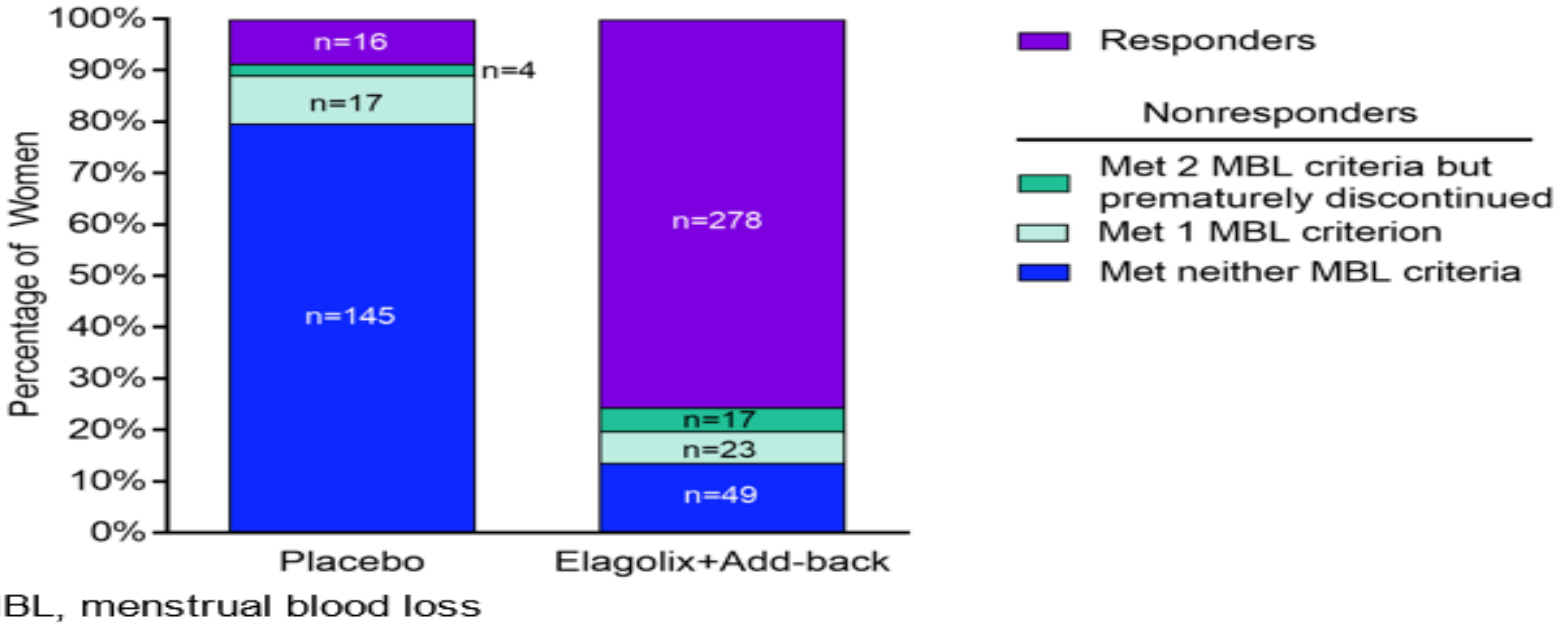
- 17 women with submucosal fibroids
- Relugolix 40 mg qd
- 2/17 had FIGO type 0 fibroids
- Both presented with vaginal hemorrhage and had the fibroid prolapsing through the vagina.

MAYO CLINIC

Wada *et al.* BMC Women's Health (2023) 23:110

Among Women Categorized as Nonresponders in Elagolix-ABT Phase 3 Trials, Almost Half had Some Improvement in HMB

Figure 1.

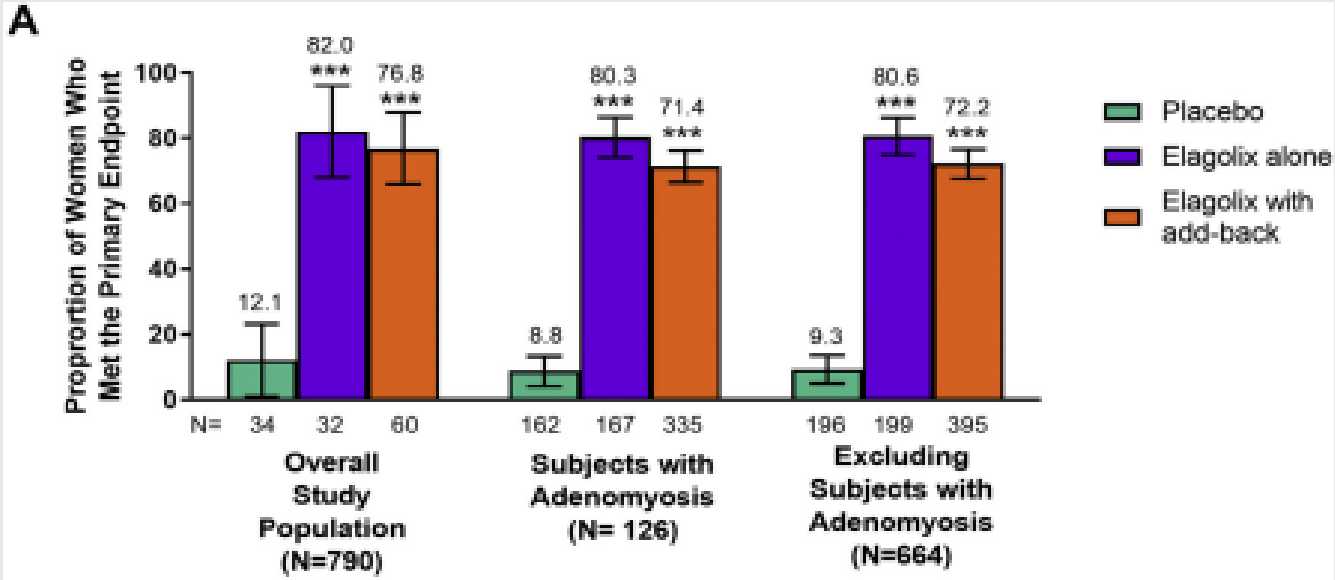


MBL, menstrual blood loss

Stewart *et al.* J Women's Health. 2022. 31:698-705

Concomitant Adenomyosis Does Not Decrease Elagolix-ABT Efficacy

FIGURE 1



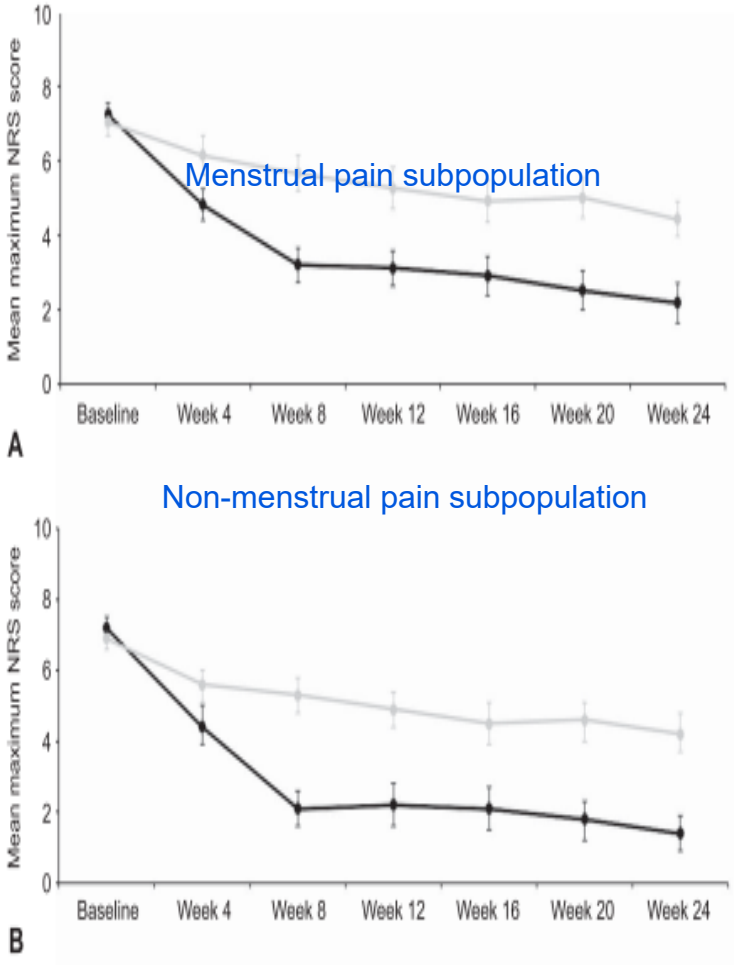
Odds Ratios (95% CI) for Women Who Met the Primary Endpoint

	Subjects with Adenomyosis	Excluding Subjects with Adenomyosis)
Elagolix alone	33.7 (8.0, 139.9)	43.1 (21.5, 86.7)
Elagolix with Add-back	24.4 (7.2, 82. 2)	26.3 (14.0, 49.4)

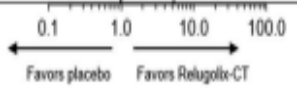
MAYO CLINIC

Muneyyirci-Delale *et al.* Fertil Steril Rep 2: 2666-3341, 2021

Relugolix–CT Significantly Decreases Menstrual and Non-menstrual Pain

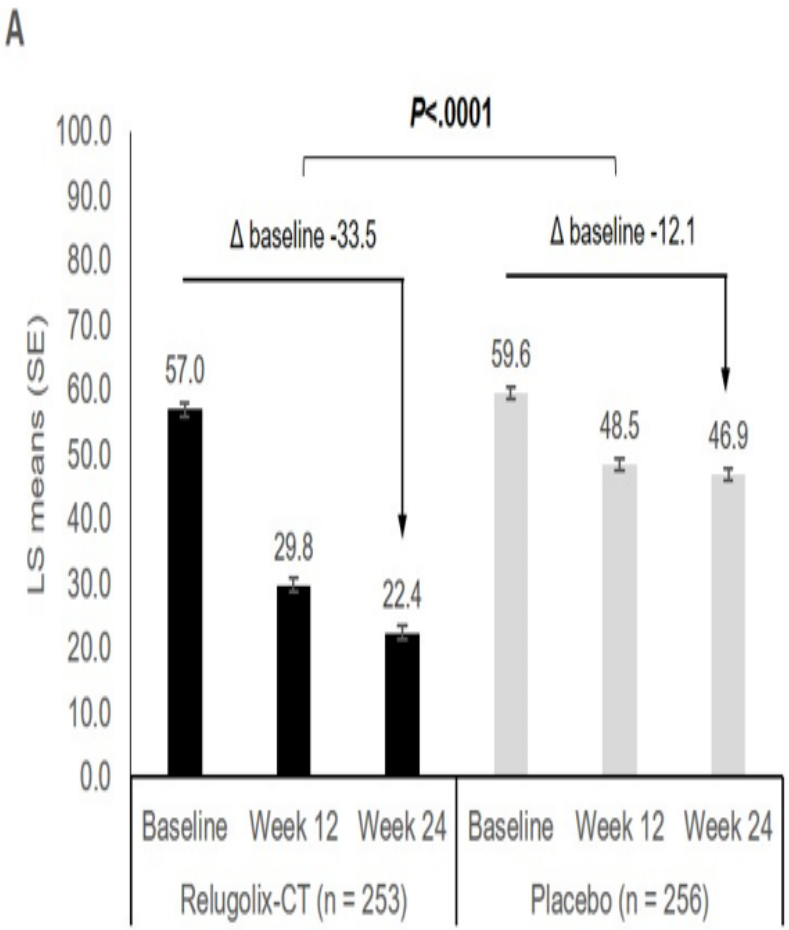


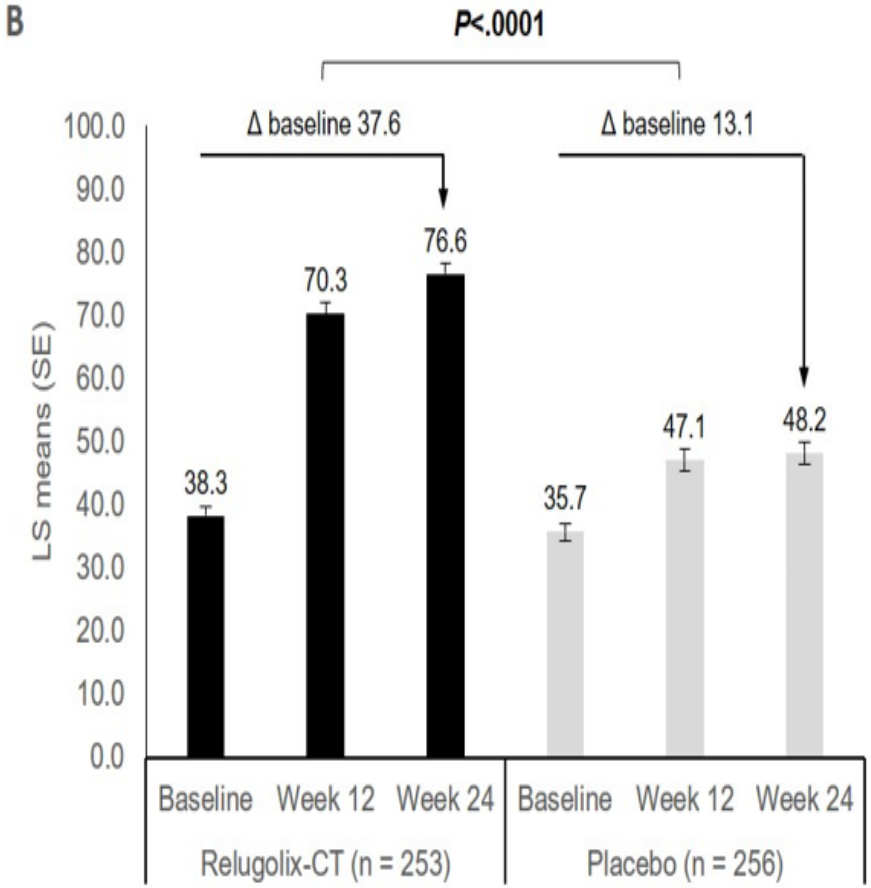
Subgroup	Relugolix-CT (n=126)	Placebo (n=151)	Odds ratio (95% CI)*
Overall	57 (45.2)	21 (13.9)	5.3 (3.0–9.6)
Age (y)			
<40	6 (21.4)	4 (9.8)	2.7 (0.7–11.3)
≥40	51 (52.0)	17 (15.5)	6.1 (3.1–11.7)
Race			
Black/African American	28 (45.9)	16 (20.0)	3.7 (1.7–8.1)
Not Black/African American	29 (44.6)	5 (7.1)	10.2 (3.6–28.9)
Ethnicity			
Hispanic/Latino	14 (46.7)	2 (6.3)	14.7 (2.6–82.1)
Not Hispanic/Latino	43 (44.8)	19 (16.2)	4.5 (2.4–8.7)
Geographic region			
North America	43 (44.8)	19 (17.0)	4.1 (2.2–7.9)
Rest of world	14 (46.7)	2 (5.1)	16.9 (3.4–83.8)
BMI (kg/m²)			
<30	21 (38.9)	8 (11.4)	5.0 (2.0–12.6)
≥30	36 (50.7)	13 (16.0)	5.8 (2.7–12.5)
MBL (mL)			
<225	40 (49.4)	13 (13.0)	6.4 (3.1–13.3)
≥225	17 (37.8)	8 (15.7)	3.6 (1.3–9.9)
UF volume (cm³)			
<25	28 (45.9)	16 (20.0)	7.4 (3.1–17.5)
≥25	29 (44.6)	5 (7.1)	3.9 (1.7–8.7)
Uterine volume (cm³)			
<300	36 (49.3)	9 (12.2)	7.2 (3.1–16.7)
≥300	21 (39.6)	12 (15.6)	3.6 (1.6–8.4)



Stewart *et al.* Obstet Gynecol. 2022. 139:1070-1081

Relugolix Decreases Symptoms and Improves Quality of Life Scales (UFS-QOL)





Stewart *et al.* AJOG 2023. 228 320.e1-320e11

Relugolix Efficacy Continues Through 52 weeks

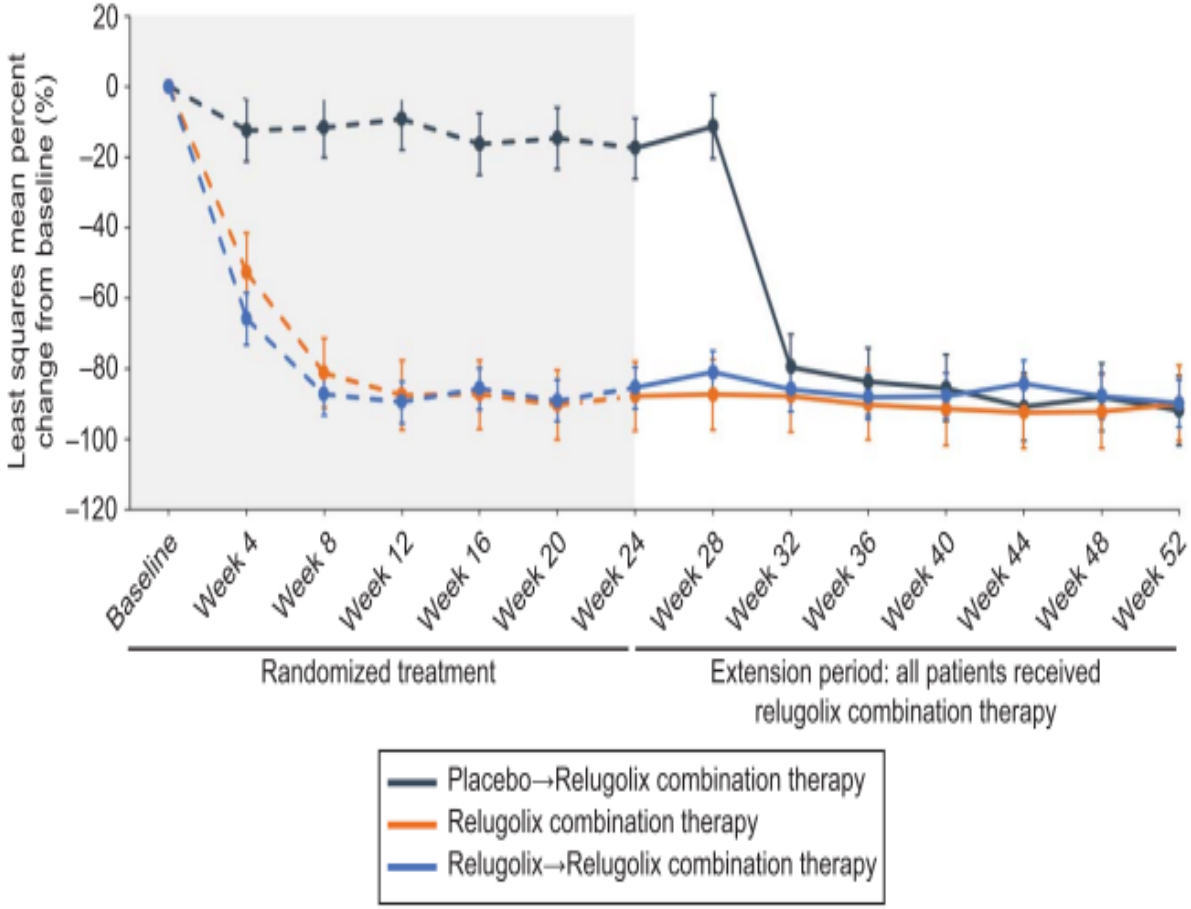
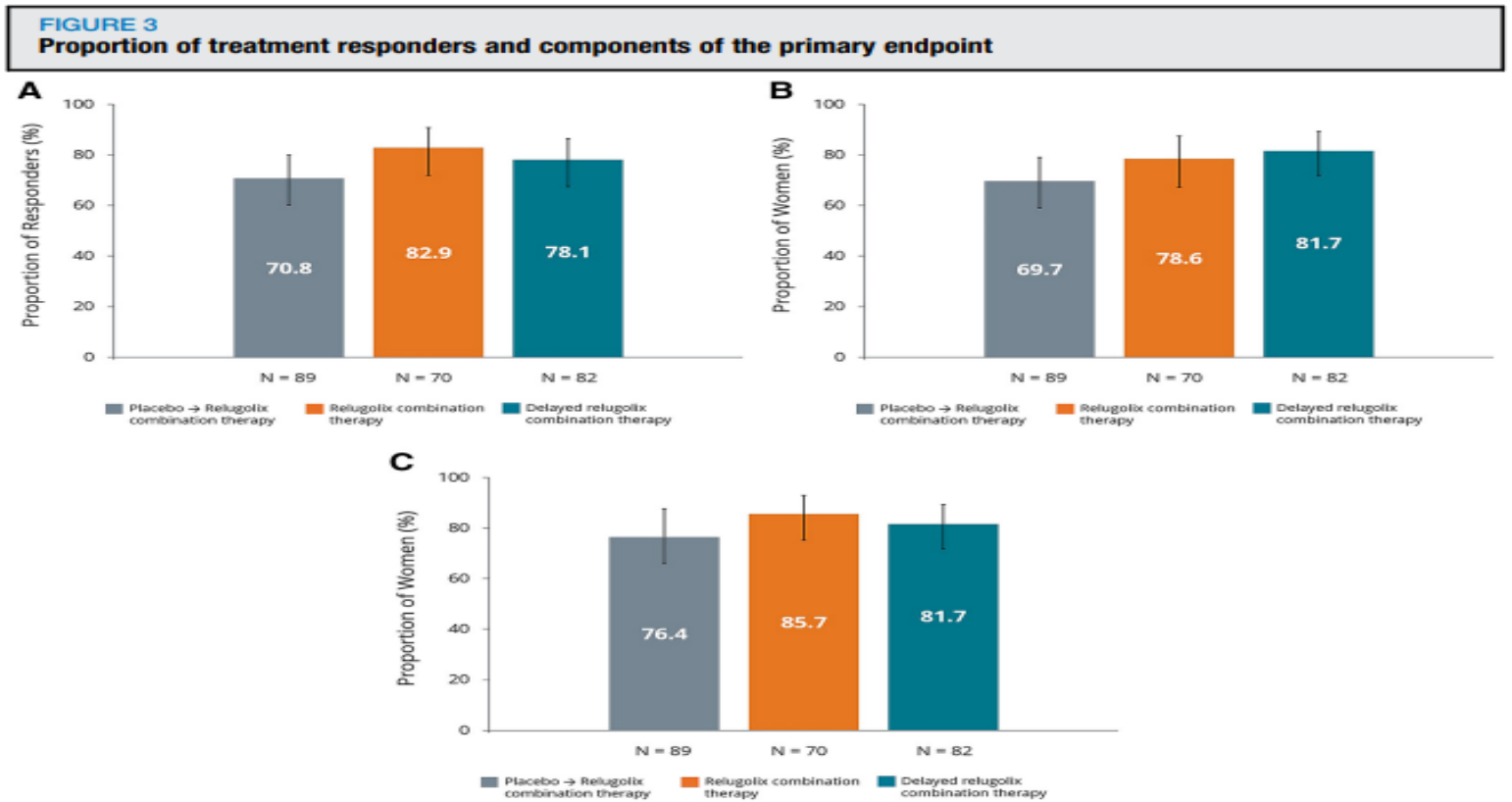


Fig. 2. Least squares percent change in menstrual blood loss volume from baseline to week 52. *Error bars* show 95% CIs.

Al-Hendy. Long-term Relugolix in Uterine Leiomyomas. Obstet Gynecol 2022.

Relugolix Combination Therapy is as Effective for Black/African American Women as the Population as a Whole



A, Proportion of responders. **B,** Proportion of women with an MBL of <80 mL over the last 35 days of treatment. **C,** Proportion of women with ≥50% reduction from baseline in MBL volume over the last 35 days of treatment. Treatment responder (MBL) = proportion of women who achieved or maintained an MBL volume of <80 mL and a ≥50% reduction in MBL volume from pivotal study baseline to the last 35 days of treatment. *Error bars* show 95% confidence intervals.

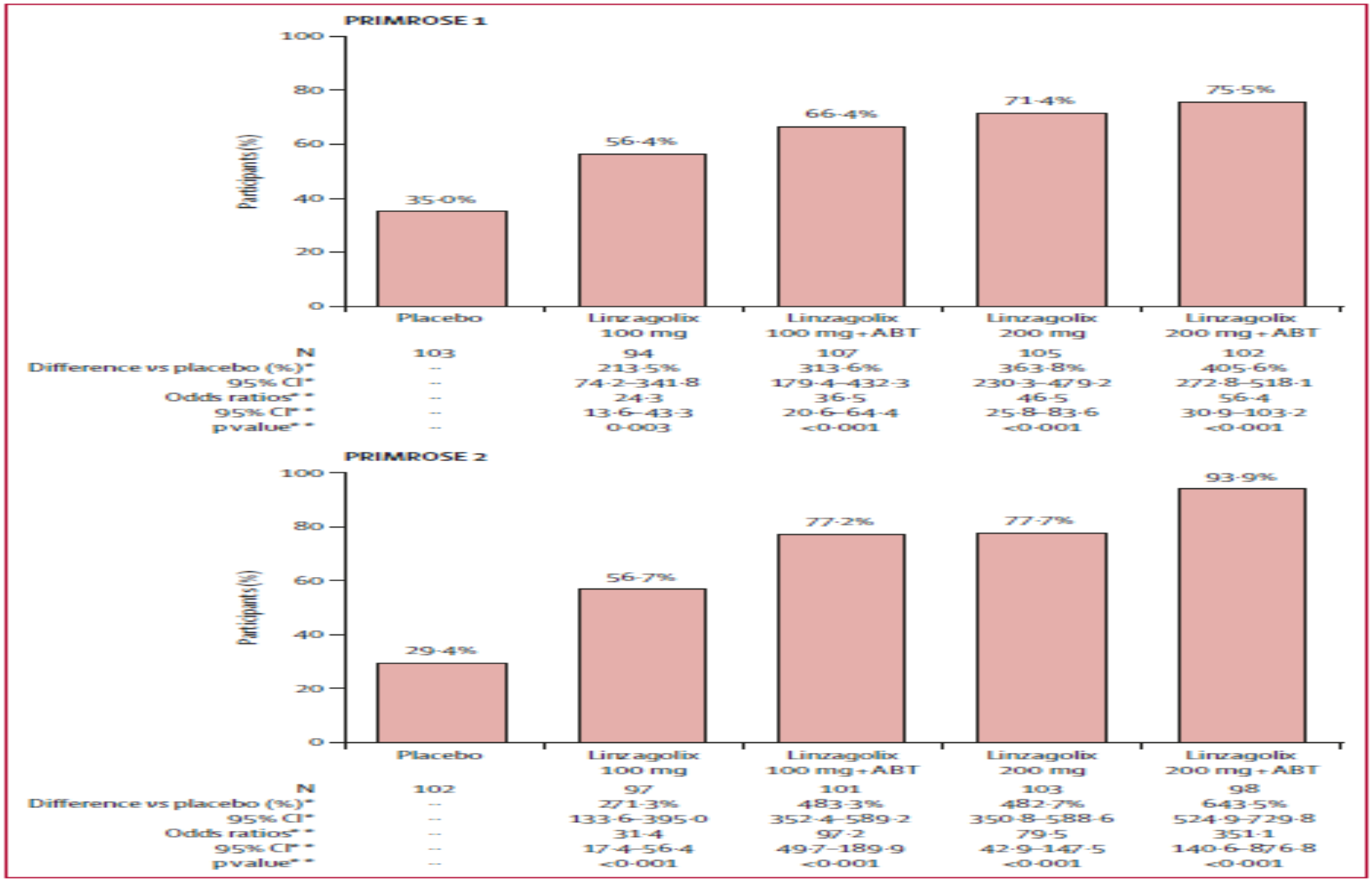
EOT, end of treatment; *LTE*, long-term extension; *MBL*, menstrual blood loss.

Stewart. Relugolix combination therapy in Black/African American women with uterine fibroids. Am J Obstet Gynecol 2024.

MAYO CLINIC

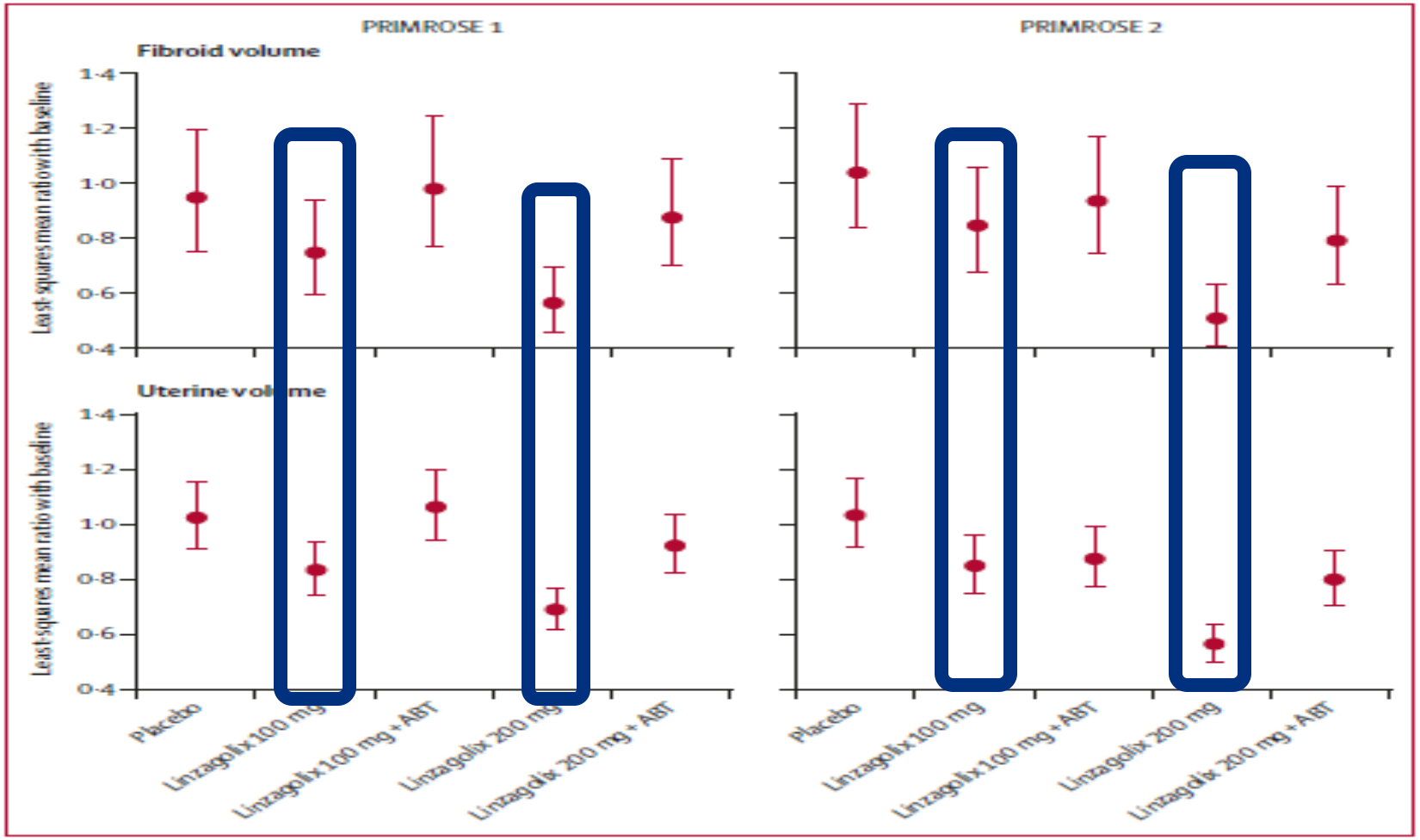
Stewart *et al.* Am J Ob Gyn. 2024. 230: 237e1-11

Linzagolix reduces heavy menstrual bleeding similarly with and without addback



Donnez *et al.* Lancet 400:896-907, 2022

Linzagolix Volume Reduction is Maximized without Hormonal Add-Back



Donnez *et al.* Lancet 400:896-907, 2022

FDA Approval for Treatment of Fibroid-Related HMB

- Elagolix 300 mg/Estradiol 1 mg/ NETA 0.5 mg q AM and elagolix 300 q PM -Approved May 2020
- Relugolix 40 mg/Estradiol 1 mg/ NETA 0.5 mg qd -Approved May 2021

No Linzagolix formulation is FDA approved, but 4 formulations (2 doses with and without add back) are approved in the European Union (https://www.ema.europa.eu/en/medicines/human/EPAR/yselty)

ACOG
The American College of Obstetricians and Gynecologists

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 228

(Replaces Practice Bulletin Number 96, August 2008)

Committee on Practice Bulletins—Gynecology. This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins–Gynecology in collaboration with Elizabeth A. Stewart, MD; Marisa R. Adelman, MD; and Vanessa L. Jacoby, MD, MAS.

Management of Symptomatic Uterine Leiomyomas

"An oral GnRH antagonist with hormonal add-back therapy can be considered for the treatment of AUB-L for up to 2 years." (Level B Evidence)

Objectives

- To review the data for fertility sparing medical treatment of fibroids with oral GnRH antagonist combinations
- To articulate the long-term risks of hysterectomy, even when performed with bilateral ovarian conservation

Hysterectomy

The one-size-fits-all solution

Why do anything else?

While hysterectomy eliminates new fibroid formation, it is not a risk-free option:

This is a topic many women are not hearing about

Reassessing Hysterectomy

Lifetime risk in US: 45 %

Only 8% are for cancers

- **Uterine (Endometrial & sarcomas)**
- **Cervix**
- **Ovary and fallopian tube**
- **Breast**

Stewart EA, Shuster LT, Rocca WA. *Minn Med*. 2012;95(3):36-39.

MAYO CLINIC

THE BOSTON GLOBE
MONDAY, AUGUST 8, 2005

ILLUSTRATION BY JACK GALLAGHER

Hysterectomy done more than necessary

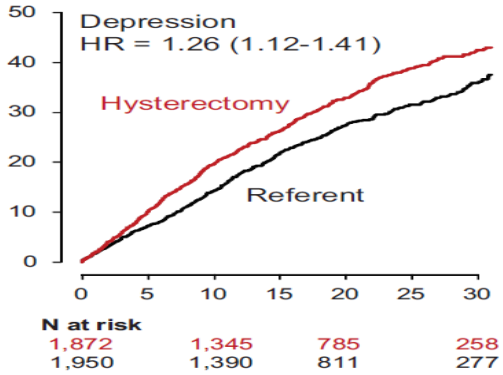
After about 20 years of followup, women undergoing hysterectomy with conservation of both ovaries have:

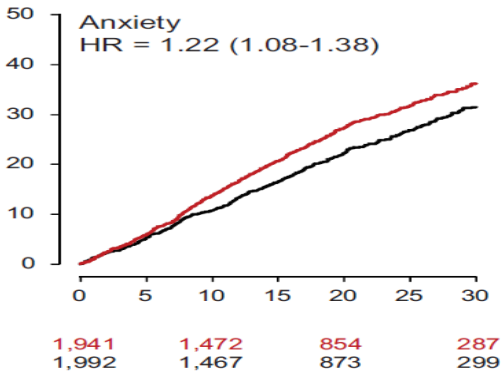
- 13% increased risk of hypertension
- 14% increased risk of hyperlipidemia
- 17% increased risk of cardiac arrhythmias
- 18% increased risk of obesity
- 33% increased risk of coronary artery disease

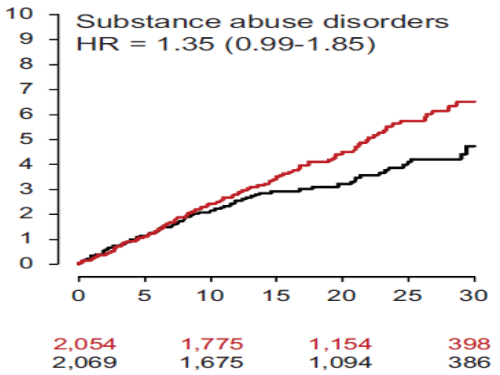
Laughlin-Tommaso SK et al. *Menopause*. 2016;23(2):121-128.

Diagnosis of Mental Health Conditions is Increased Following Hysterectomy with Ovarian Conservation

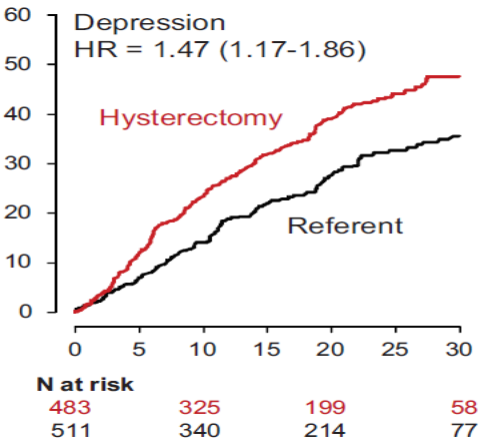
All

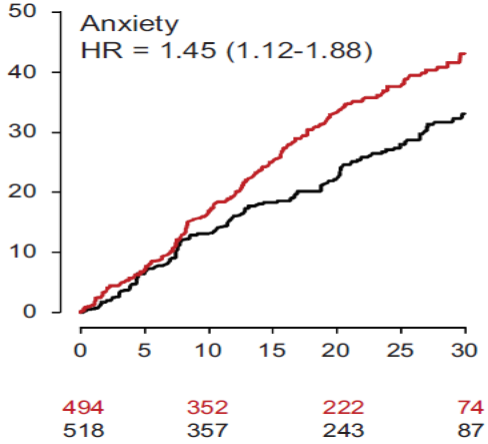


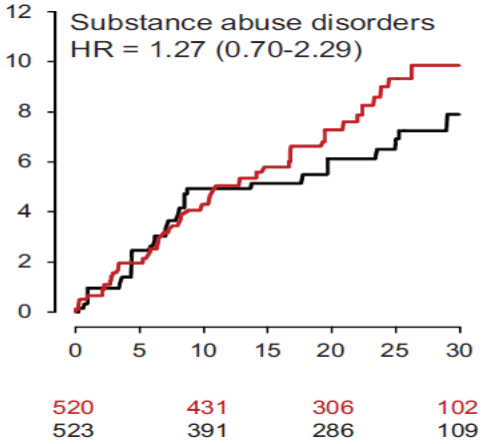




Women ≤ 35







Laughlin-Tommaso SK et al. *Menopause*. 2020;27(1):33-42.

Risk and Benefits of Hysterectomy with Ovarian Conservation: Educating Patients and Providers

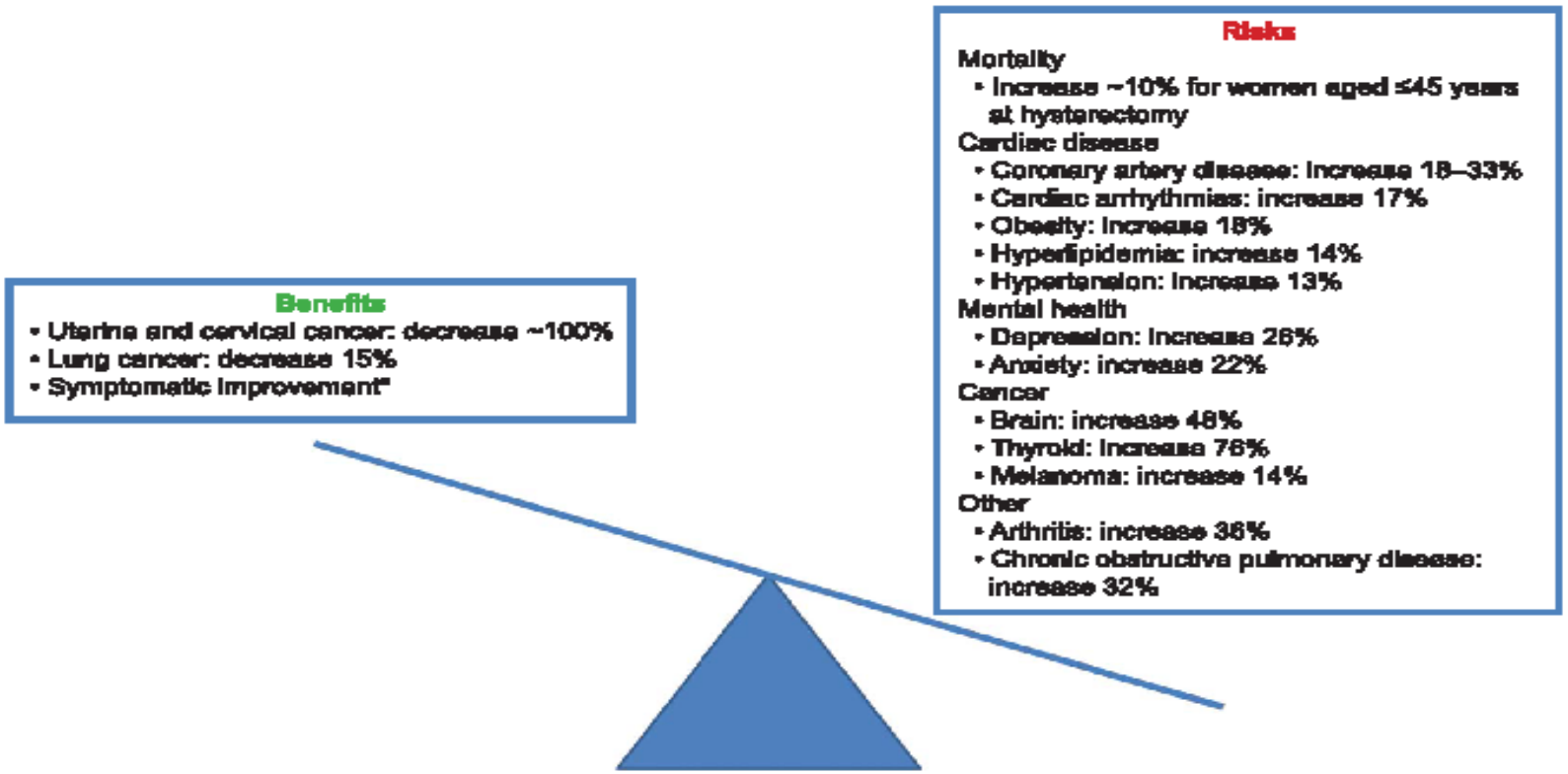


Fig. 1. Risks and benefits associated with hysterectomy with bilateral ovarian conservation at any age.[9–11,56–58]
*Although symptoms may be alleviated with other less invasive treatment options.

Laughlin-Tommaso & Stewart. Ob Gyn 132: 961-71, 2018

Western Australian Data Linkage Branch (WADLB)

- 666,588 Women
- 553,958 Without surgery
- 73,145 Hysterectomy with Ovarian Conservation
- 18,558 Hysterectomy with BSO
- 6,164 Hysterectomy with USO

Tuesley KM *et al.* Am J Ob Gyn 223:723.e1-e16, 2020

WADLB: Increase in mortality following hysterectomy based on age and ovaries

	All Cause Mortality	CVD Mortality	Cancer Mortality	Other Mortality
Hysterectomy alone, Age <35	**1.31 (1.21-1.42)**	**1.33 (1.09-1.63)**	**1.16 (1.03-1.31)**	**1.49 (1.30-1.69)**
Hysterectomy/ BSO, Age <35	**1.43 (1.11-1.85)**	**1.67 (0.92-3.02)**	**0.63 (0.37-1.08)**	**2.58 (1.85-3.60)**
Hysterectomy/ BSO, Age 35-44	**1.19 (1.06-1.34)**	**1.22 (0.95-1.56)**	**1.09 (0.92-1.30)**	**1.19 (0.98-1.45)**

MAYO CLINIC

Tuesley KM *et al*. Am J Ob Gyn 223:723.e1-e16, 2020

MAYO CLINIC

PERSPECTIVE AND CONTROVERSY

Moving Beyond Reflexive and Prophylactic Gynecologic Surgery

Check for updates

Elizabeth A. Stewart, MD; Stacey A. Missmer, ScD; and Walter A. Rocca, MD, MPH

Although recent data have documented the declining rate of hysterectomy, hysterectomy with and without concomitant oophorectomy and salpingectomy remains the second most com-

Data from the Mayo Clinic Cohort Study of Oophorectomy and Aging (MOA), starting in 2006, and the Nurse's Health Study, starting in 2009, appropriately focused the medical community on the risks of hysterec-

From the Division of Reproductive Endocrinology and Infertility, Department of Obstetrics

"We are now seeing the unintended consequences of assuming that the uterus and ovaries are only reproductive organs. Although women with high risk of future disease –such as those with BRCA1 and BRCA2 genetic variants- require prophylactic surgery, extending this practice to women at average risk of ovarian and fallopian tube cancer is not evidence based…"