GOOD EVIDENCE MATTERS

GEMs of the Week

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Turning the Tide on Tough Blood Pressure: Baxdrostat's Promise

Efficacy and Safety of Baxdrostat in Uncontrolled and Resistant Hypertension

Flack JM, Azizi M, Brown JM, et al. Efficacy and Safety of Baxdrostat in Uncontrolled and Resistant Hypertension. *N Engl J Med*. 2025;393(14):1363-1374. doi:10.1056/NEJMoa2507109

KEY TAKEAWAY: Baxdrostat reduces seated systolic blood pressure (SBP) compared to placebo in individuals with uncontrolled or resistant hypertension (HTN).

STUDY DESIGN: Multicenter, multinational, double-blind, randomized, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Uncontrolled HTN and resistant HTN has been a long-standing issue in primary care. There are several medications being explored to achieve optimal blood pressure goals. Baxdrostat is a selective aldosterone synthase inhibitor being studied as an add-on agent. This study aimed to review the efficacy of Baxdrostat, specifically, in combating uncontrolled or resistant HTN.

PATIENTS: Adults on antihypertensive medications with uncontrolled or resistant HTN

INTERVENTION: Baxdrostat at 1 mg and 2 mg

CONTROL: Placebo

PRIMARY OUTCOME: Change in seated SBP

Secondary Outcome: Seated SBP from baseline from week 24–32, SBP from baseline to week 12 in the resistant HTN subpopulation, seated diastolic blood pressure (DBP) from baseline to week 12, adverse events

METHODS (BRIEF DESCRIPTION):

- Adults with SBP >140 and <170 mmHg currently taking at least two antihypertensives for uncontrolled HTN or at least three antihypertensives for resistant HTN and included a diuretic at least four weeks before screening were considered.
- Patients were included after a two-week run-in period for those who had a seated SBP ≥135 mmHg and ≥80% adherence to background antihypertensives.
- Patients were randomized 1:1:1 to either Baxdrostat 1 mg, Baxdrostat 2 mg, or placebo.
- Baxdrostat was administered orally once daily at 1 mg and 2 mg doses in three parts of the trial:
  - Part 1: Weeks 0–12, double blind, placebo-controlled treatment period.
  - Part 2: Open-label extension with 2-mg Baxdrostat for all patients.
  - Part 3: Randomized withdrawal; patients on 2 mg Baxdrostat were re-randomized to continue Baxdrostat 2 mg or switch to placebo for eight weeks.
- Placebo was administered once daily.
- The primary outcome measured the change in seated SBP from weeks 0–12
- The secondary outcomes measured the change in seated SBP from week 24–32, change in seated SBP from baseline to week 12 in the resistant HTN subpopulation, and change in the seated DBP from baseline to week 12.
- Safety outcomes included adverse evets, vital signs, laboratory tests, and major adverse cardiovascular events.

INTERVENTION (# IN THE GROUP):

- 1 mg: 264
- 2 mg: 266

COMPARISON (# IN THE GROUP): 264

FOLLOW-UP PERIOD:

- Part 1: 12 weeks
- Part 2: 12–24 weeks
- Part 3: 24–32 weeks
- Part 4: 32–52 weeks

RESULTS:

Primary Outcome –

- Baxdrostat 1 mg and 2 mg reduced seated SBP from baseline to week 12.
  - 1 mg (least squares mean difference –8.7 mmHg; 95% CI, –12 to –5.8)
  - 2 mg (least squares mean difference –9.8 mmHg; 95% CI, –13 to –7.0).

Secondary Outcome –

- Baxdrostat 2 mg reduced seated SBP from week 24–32 (least squares mean difference –5.1 mmHg; 95% CI, –8.3 to –1.9), however Baxdrostat 1 mg did not.

- Baxdrostat 1 mg and 2 mg reduced seated SBP from baseline to week 12 in the resistant HTN subpopulation.
  - 1 mg (least squares mean difference –9.1 mmHg; 95% CI, –13 to –5.7)
  - 2 mg (least squares mean difference –9.8 mmHg; 95% CI, –13 to –6.4)
- Baxdrostat 1 mg and 2 mg reduced seated DBP from baseline to week 12.
  - 1 mg (least squares mean difference –3.3 mmHg; 95% CI, –5.2 to –1.4)
  - 2 mg (least squares mean difference –3.9 mmHg; 95% CI, –5.7 to –2.0)
- Adverse events occurred about equally in all treatment groups. Hyperkalemia was cited in both Baxdrostat groups and not in the placebo group.

LIMITATIONS:

- Percentage of female and Black patients with HTN who were enrolled in the trial were lower than the percentage observed in the real world.
- Members of AstraZeneca were both supporting the study and creators of Baxdrostat, at risk for bias.

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The AGE Old Question: Does Socioeconomic Status Influence Polypharmacy?

Are There Socioeconomic Inequalities in Polypharmacy Among Older People? A Systematic Review and Meta-Analysis

Iqbal A, Richardson C, Iqbal Z, et al. Are There Socioeconomic Inequalities in Polypharmacy among Older People? A Systematic Review and Meta-analysis. *BMC Geriatr*. 2023;23(1):149. Published 2023 Mar 18. doi:10.1186/s12877-023-03835-z

KEY TAKEAWAY: Lower socioeconomic status is associated with significantly higher odds of polypharmacy among older adults.

STUDY DESIGN: Systematic review and meta-analysis of 54 observational studies (N=2,927,992)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to lack of generalizability)

BRIEF BACKGROUND INFORMATION: Polypharmacy is increasing globally and is associated with harm in older adults. Socioeconomic status may influence prescribing, adherence, multimorbidity, and healthcare access. This review examined whether socioeconomic status contributes to prevalence of polypharmacy.

PATIENTS: Adults ≥55 years old in any healthcare setting

INTERVENTION: Lower socioeconomic status (education, income, occupation, employment, wealth, social class, and deprivation)

CONTROL: Higher socioeconomic status

PRIMARY OUTCOME: Prevalence of polypharmacy (≥5 medications)

METHODS (BRIEF DESCRIPTION):

- Conducted a systematic review and meta-analysis following PRISMA guidelines.
- Searched four databases: Medline (OVID), Web of Science, Embase (OVID), and CINAHL (inception to July 2021)
- Search strategy based on three concepts: polypharmacy, socioeconomic status (SES), and ageing. Additional articles were identified through hand searching references. Articles published prior to 1990 were considered less relevant and not included in this study.
- All settings were considered irrespective of country or health care system. Study types included in the analysis were observational in nature (cohort and cross sectional).
- Articles were required to be available in the English language.
- Data extracted from the manuscripts included patient characteristics, socioeconomic measure, and polypharmacy.
- Eligibility criteria for studies to be included in the meta-analysis included (1) raw data on polypharmacy rates for an individual socioeconomic factor, and (2) information to identify total number of patients with or without polypharmacy for a specific socioeconomic factor being investigated.
- Contributing factors for socioeconomic status looked at in this study included education, income, wealth, occupation, employment, social class, socioeconomic categories and deprivation.
- A random-effects model was undertaken comparing polypharmacy (≥5 medications) against no polypharmacy, before pooled odds ratios, confidence intervals and standard errors were calculated for each study.

INTERVENTION (# IN THE GROUP): Not applicable

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: Not applicable

RESULTS:

Primary Outcome –

- Those with lower education backgrounds had significantly higher odds of receiving polypharmacy compared to those with higher education (38 studies, n=not available; odds ratio [OR] 1.2; 95% CI, 1.2–1.3).
- Those with lower wealth had significantly higher odds of polypharmacy compared to those with greater wealth (4 studies, n=not available; OR 1.4; 95% CI, 1.3–1.5).
- Those identified as being in lower social classes had significantly higher odds of polypharmacy compared to those in higher social classes (3 studies, n=not available; OR 1.3; 95% CI, 1.2–1.4).
- Those with lower income had no significant difference in polypharmacy compared to those with higher income (12 studies, n=not available; OR 1.1; 95% CI, 0.98–1.2).

- Those with lower occupation had no significant difference in polypharmacy compared to those in higher occupation (3 studies, n=not available; OR 1.2; 95% CI, 0.70–2.2).
- Unemployed individuals had no significant difference in polypharmacy compared to those who were employed (5 studies, n=not available; OR 1.3; 95% CI, 0.85–2.1).
- Those with lower SES had no significant difference in polypharmacy compared to those with higher socioeconomic status (2 studies, n=not available; OR 1.0; 95% CI, 0.67–1.6).

LIMITATIONS:

- Definition of "older adults" (≥55 years old) was arbitrary and may not align with all contexts or studies on ageing.
- High heterogeneity across included studies, partly because they came from a wide range of countries and healthcare systems (low-, middle-, and high-income), affecting generalizability.
- Variation in how SES was measured across studies (e.g., definitions of "high education" differed), making standardization challenging.
- Potential difficulty interpreting SES categories due to differing national systems and inconsistent reporting across studies.
- Unadjusted odds ratios were used in the meta-analysis, which do not account for other confounding factors.

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Turn Down for Lungs? Conservative Oxygen Therapy Does Not Affect Outcomes in Ventilated ICU Patients

Conservative Oxygen Therapy in Mechanically Ventilated Critically Ill Adult Patients: The UK-ROX Randomized Clinical Trial

Martin DS, Gould DW, Shahid T, et al. Conservative Oxygen Therapy in Mechanically Ventilated Critically Ill Adult Patients: The UK-ROX Randomized Clinical Trial. *JAMA*. 2025;334(5):398-408. doi:10.1001/jama.2025.9663

KEY TAKEAWAY: Conservative oxygen therapy does not significantly reduce 90-day all-cause mortality compared to usual oxygen therapy in mechanically ventilated adults in the intensive care unit (ICU).

STUDY DESIGN: Multicenter, nonblinded randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Supplemental oxygen is commonplace in intensive care settings, but few investigations into outcomes of conservative oxygen therapy exist. This study aimed to determine the difference in outcomes between conventional and conservative supplemental oxygen therapy in ventilated patients.

PATIENTS: Mechanically ventilated adults in the ICU

INTERVENTION: Minimum oxygen therapy needed to maintain SpO2 of 90%

CONTROL: Standard therapy at the treating physician's discretion

PRIMARY OUTCOME: 90-day all-cause mortality

Secondary Outcome: Length of stay, freedom from cardiovascular, respiratory, or renal support, and all-cause mortality at multiple intervals

METHODS (BRIEF DESCRIPTION):

- Patients were mechanically ventilated adult (≥18 years old) admitted to one of 97 participating ICUs in the UK from May 2021 to November 2024.
- Exclusion criteria included previous enrollment in the study, current recipient of extracorporeal membrane oxygenation, or intervention deemed clinically inappropriate by the treating physician.
- Patients randomized 1:1 ratio to receive conservative oxygen therapy or usual care.
    - Conservative therapy patients received the minimal FiO2 required to maintain an SpO2 of 90%.
    - Usual care patients received oxygen therapy at the treating physician's direction.
- The primary outcome of mortality rate at 90 days determined by linked data from the UK Civil Registry of Death.
- Secondary outcomes measured via:
    - Linked death registry date for mortality rates at ICU discharge, 60 days, and one year.
    - Linked chart information for length of ICU, acute care hospital stays, and number of days free of cardiovascular, respiratory, or renal support at 30 days.

INTERVENTION (# IN THE GROUP): 8,211

COMPARISON (# IN THE GROUP): 8,183

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- There was no significant difference in 90-day mortality for conservative oxygen therapy compared to usual oxygen therapy (35% vs 35%, respectively; risk difference [RD] 0.7 percentage points; 95% CI, –0.7 to 2.0).

Secondary Outcome –

- Conservative therapy did not significantly affect length of ICU stay, length of hospital stays, number of days free of organ support at 30 days, mortality rates at ICU discharge, mortality rates at 60 days, mortality rates at one year compared to usual oxygen therapy.

LIMITATIONS:

- The study intervention was unblinded.
- Treating clinicians deemed clinical appropriateness for patient enrollment which likely introduced selection bias.
- Study failed to adhere 42% of conservative therapy group to intervention parameters during 10% of total ICU hours.

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The views expressed herein are those of the author and do not necessarily reflect the official policy of the Department of the Air Force, Defense Health Agency, Department of Defense, or the U.S. Government.

Balancing Heat and Heart: Insights on Menopausal Hormone Therapy

Menopausal Hormone Therapy and Cardiovascular Diseases in Women with Vasomotor Symptoms: A Secondary Analysis of the Women's Health Initiative Randomized Clinical Trials

Rossouw JE, Aragaki AK, Manson JE, et al. Menopausal Hormone Therapy and Cardiovascular Diseases in Women with Vasomotor Symptoms: A Secondary Analysis of the Women's Health Initiative Randomized Clinical Trials. *JAMA Intern Med*. 2025;185(11):1330-1339. doi:10.1001/jamainternmed.2025.4510

KEY TAKEAWAY: Hormone therapy consisting of conjugated equine estrogens (CEE) alone and CEE + medroxyprogesterone acetate (MPA) in postmenopausal women 50–59 years old with vasomotor symptoms (VMS), reduces VMS with no increased effect on atherosclerotic cardiovascular (ASCVD) risk. However, in women ≥70 years old, CEE alone and CEE + MPA increases ASCVD risk. Women 60–69 years old have no statistically significant ASCVD risk for CEE alone.

STUDY DESIGN: Secondary analysis of two randomized clinical trials (RCTs) (n=27,347)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to secondary analysis)

BRIEF BACKGROUND INFORMATION: Hormone therapy provides relief to women experiencing menopausal VMS. Frequently patients and clinicians are hesitant to trial hormone therapy due to associated risks and adverse outcomes, including ASCVD, total cardiovascular disease (CVD), coronary heart disease (CHD), stroke, and venous thromboembolism (VTE). This study evaluated the risk of hormone therapy on CVD in women 50–79 years old with VMS.

PATIENTS: Postmenopausal women 50–79 years old

INTERVENTION: CEE or CEE + MPA

CONTROL: Placebo

PRIMARY OUTCOME: ASCVD and VMS

Secondary Outcome: Total CVD, a predefined global index of serious monitored hormone therapy-associated outcomes, all-cause mortality, CHD, stroke, and VTE

METHODS (BRIEF DESCRIPTION):

- Generally healthy postmenopausal women 50–79 years old were selected from the Women's Health Initiative trial in 40 US clinical centers in 1993–1998.
- Patients on hormone therapy at the pre-intervention visits were required to participate in and tolerate a three-month washout period.
- All patients completed a one-month placebo run-in.
- Patients were randomized to CEE or placebo in women with hysterectomy or CEE + MPA in women with an intact uterus.
    - The dose for CEE was 0.63 mg per day.
    - The dose for MPA was 2.5 mg per day.
- Both trials had 1:1 treatment allocation.
- Event rate comparisons were based on the intention-to-treat principle using failure time methods.
- The outcomes were measured by time to event analysis. This was defined as the number of days from randomization to the first diagnosis of the event or any components of the outcomes, including ASCVD, total CVD, a predefined global index of serious monitored hormone therapy-associated outcomes, all-cause mortality, CHD, stroke, and VTE.

INTERVENTION (# IN THE GROUP):

- CEE alone: 5,310
- CEE + MPA: 8,506

COMPARISON (# IN THE GROUP):

- Placebo for CEE alone: 5,429
- Placebo for CEE + MPA: 8,102

FOLLOW-UP PERIOD: Median follow-up was 7.2 years for CEE alone and 5.6 years for CEE + MPA

RESULTS:

Primary Outcome –

- CEE alone decreased VMS across all age groups (overall relative risk [RR] 0.59; 95% CI, 0.53–0.66).
- CEE + MPA reduced VMS in women 50–59 years old (RR 0.41; 95% CI, 0.35–0.48), less effective among women 60–69 years old (RR 0.72; 95% CI, 0.61–0.85), and no clear benefit among women 70–79 years old (RR 1.2; 95% CI, 0.91–1.6).
- CEE alone did not significantly reduce ASCVD risk in women with VMS 50–59 years old compared to placebo (hazard ratio [HR] 0.85; 95% CI, 0.53–1.4; 13 fewer events per 10,000 person-years).
- CEE + MPA did not significantly reduce ASCVD risk in women with VMS 50–59 years old compared to

placebo (HR 0.84; 95% CI, 0.44–1.6; 6 fewer events per 10,000 person-years).

- CEE alone did not significantly reduce ASCVD risk in women with VMS 60–69 years old compared to placebo (HR 1.3; 95% CI, 0.90–1.9; 74 excess events per 10,000 person-years).
- CEE + MPA did not significantly reduce ASCVD risk in women with VMS 60–69 years old compared to placebo (HR 0.84; 95% CI, 0.51–1.4; 40 fewer events per 10,000 person-years).
- CEE alone increased the risk of ASCVD in women with VMS ≥70 years old compared to placebo (HR 2.0; 95% CI, 1.1–3.6; 217 excess events per 10,000 person-years).
- CEE + MPA increased the risk of ASCVD in women with VMS ≥70 years old compared to placebo (HR 3.2; 95% CI, 1.4–7.6; 382 excess events per 10,000 person-years).
- CEE alone did not significantly reduce ASCVD risk in women 50–59 years old or within 10 years of menopause compared to placebo (HR 0.85; 95% CI, 0.53–1.4).
- CEE + MPA did not significantly reduce ASCVD risk in women 50–59 years old or within 10 years of menopause compared to placebo (HR 0.84; 95% CI, 0.44–1.6).
- CEE alone did not significantly increase the risk of ASCVD in women ≥20 years since menopause compared to placebo (HR 1.5; 95% CI, 1.0–2.1).
- CEE + MPA did not significantly reduce ASCVD risk in women ≥20 years since menopause compared to placebo (HR 1.8; 95% CI, 0.85–3.9).

Secondary Outcome –

- CEE alone did not significantly reduce the risk of total CVD, global index events, and all-cause mortality in women with VMS 50–59 years old compared to placebo.
- CEE + MPA did not significantly reduce the risk of total CVD and global index events and decreased the risk of all-cause mortality in women with VMS 50–59 years old compared to placebo.
- CEE + MPA increased the risk of total CVD in women with VMS 70–79 years old compared to placebo (HR 2.2; 95% CI, 1.1–4.4).
- CEE + MPA increased the risk of global index events in women with VMS 70–79 years old compared to placebo (HR 2.7; 95% CI, 1.4–5.6).
- CEE alone increased the risk of CHD in women with VMS 70–79 years old compared to placebo (HR 5.0; 95% CI, 1.6–16; 157 excess events per 10,000 person-years).
- CEE + MPA increased the risk of CHD in women with VMS aged 70–79 years old compared to placebo (HR 6.2; 95% CI, 1.4–28; 242 excess events per 10,000 person-years).
- CEE alone increased the risk of CHD in women with VMS ≥20 years since menopause compared to placebo (HR 2.2; 95% CI, 1.2–4.1).
- CEE + MPA did not significantly increase the risk of CHD in women with VMS ≥20 years since menopause compared to placebo.

LIMITATIONS:

- VMS prevalence may have been lower than in the general population.
- This is a re-analysis of two RCTs, one with only women with CEE alone and the other with women with CEE + MPA.
- ASCVD and total CVD were used to increase study power but were not designated primary trial outcomes.
- Only oral CEEs and MPA at fixed doses were included in the trial.
- Non-CVD outcomes were not evaluated.

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