GOOD EVIDENCE MATTERS

GEMs of the Week

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A New Era in CVD Risk Prediction: The AHA PREVENT Equations

Development and Validation of the American Heart Association's PREVENT Equations

Khan SS, Matsushita K, Sang Y, et al. Development and Validation of the American Heart Association's PREVENT Equations. *Circulation*. 2024;149(6):430-449. doi:10.1161/CIRCULATIONAHA.123.067626

KEY TAKEAWAY: The AHA PREVENT equations accurately predict 10- and 30-year risk of cardiovascular disease (CVD) and heart failure (HF) using routinely available clinical variables, providing a more equitable and precise tool for risk assessment in primary care.

STUDY DESIGN: Multicenter, retrospective and prospective cohort study (derivation and external validation of risk prediction models), using data sets from both research and health systems (N=6,612,004)

LEVEL OF EVIDENCE: STEP 2 (prognosis-inception cohort studies with >80% follow-up)

BRIEF BACKGROUND INFORMATION: CVD risk prediction is essential for guiding primary prevention, but existing models like the Pooled Cohort Equations often lack accuracy in diverse populations and do not account for HF or kidney disease risk. These limitations can lead to suboptimal risk assessment, particularly in patients with cardiovascular-kidney-metabolic (CKM) conditions. There is a need for more comprehensive and equitable risk prediction tools. This study aimed to develop and validate the AHA PREVENT equations to improve CVD risk prediction in US adults.

PATIENTS: Adults 30–79 years old without known CVD

INTERVENTION: Risk prediction using the newly developed AHA PREVENT equations

CONTROL: Existing risk prediction models (e.g., Pooled Cohort Equations)

PRIMARY OUTCOME: Incidence of CVD

METHODS (BRIEF DESCRIPTION):

- Individual-level data from 46 US-based cohort data set (25 for derivation, 21 for validation) from 1992–2017.
- Adults 30–79 years old with no baseline atherosclerotic cardiovascular disease (ASCVD) or HF and had available data on key risk factors including systolic blood pressure (SBP), total cholesterol (TC), body mass index (BMI), estimated glomerular filtration rate (eGFR) were included in the study.
- Patients with missing predictor data (SBP, TC, BMI, eGFR) or extreme clinical values were excluded from the study.
- Predictors: The PREVENT equations incorporated traditional CVD risk factors (age, sex, SBP, non-HDL cholesterol, HDL cholesterol, diabetes, smoking status, antihypertensive and statin use) and eGFR; optional models included urine albumin-to-creatinine ratio (UACR), hemoglobin A1c (HbA1c), and social deprivation index (SDI).
- Primary outcome was incident total CVD, defined as a composite of fatal and nonfatal ASCVD and HF.
- Models were sex-specific, did not include race as a predictor, and were adjusted for competing risk of non-CVD death using Cox proportional hazards models with age as the time scale.
- Model performance was assessed by discrimination (Harrell C-statistic), calibration (slope of observed vs. predicted risk), and net reclassification improvement (NRI).
- Additional analyses evaluated the impact of adding UACR, HbA1c, and SDI to the base model and compared PREVENT performance to the Pooled Cohort Equations (PCEs).

INTERVENTION (# IN THE GROUP):

- Derivation: 3,281,919 (1,839,828 female, 1,442,091 male)
- Validation: 3,330,085 (1,894,882 female, 1,435,203 male)

COMPARISON (# IN THE GROUP): Same as above (external validation compared PREVENT to PCEs in the same populations)

FOLLOW-UP PERIOD: Mean 4.8 years (SD 3.1) in derivation; mean 4.6 years (SD 3.2) in validation

RESULTS:

Primary Outcome –

- The PREVENT equations demonstrated good to excellent discrimination for predicting total CVD with a C-statistic (interquartile interval: 25–75th percentile) of 0.79 for females and 0.76 for males in the validation cohort.

- Calibration of the PREVENT equations was superior to the Pooled Cohort Equations (PCEs), with calibration slopes of 1.0 for females and 0.94 for males.
- Adding UACR, HbA1c, and SDI to the base model resulted in small but statistically significant improvements in discrimination (ΔC-statistic up to 0.005) and calibration, particularly in high-risk subgroups.
- The PREVENT equations outperformed the PCEs in both discrimination and calibration for total CVD, ASCVD, and HF.

Secondary Outcome –

- The addition of UACR to the base model improved calibration significantly among individuals with marked albuminuria (>300 mg/g), with a calibration slope improvement from 1.1 to 1.4 (*P*=.01).
- Similar improvements in discrimination and calibration were observed for ASCVD and HF-specific models when additional predictors were included.

LIMITATIONS:

- The study relied on electronic medical record (EMR) data, which may lack research-based measurements and outcome adjudication, potentially affecting data accuracy.
- The baseline data spanned over three decades, which could introduce variations in risk factor prevalence and treatment practices over time.
- The models used age as the time scale, which, while allowing flexibility, may lead to overestimation of 30-year risk.
- Individual-level social determinants of health were not consistently available across all data sets, limiting the ability to fully assess their impact.
- Biomarkers indicating target-organ damage or subclinical disease were not included, which could enhance risk prediction if incorporated in future models.

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Clipping the Risk: Left Atrial Appendage Closure Reduces Bleeding Without Sacrificing Stroke Protection After AF Ablation

Left Atrial Appendage Closure after Ablation for Atrial Fibrillation

Wazni OM, Saliba WI, Nair DG, et al. Left Atrial Appendage Closure after Ablation for Atrial Fibrillation. *N Engl J Med*. 2025;392(13):1277-1287. doi:10.1056/NEJMoa2408308

KEY TAKEAWAY: Following ablation for atrial fibrillation (AF) in patients at moderate to high risk for stroke, left atrial appendage closure (LAAC) is associated with fewer non-procedure related bleeding episodes compared to long term oral anticoagulation (OAC) and is noninferior to OAC with respect to the composite of all-cause death, stroke, or systemic embolism.

STUDY DESIGN: Multicenter, open-label randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Continued anticoagulation after AF ablation is recommended to reduce the risk of stroke. The efficacy and safety of LAAC with short term anticoagulation as an alternative to long term OAC for stroke prevention post-ablation is unknown. This trial sought to evaluate the safety and efficacy of LAAC with short term anticoagulation as a viable option for long term anticoagulation after ablation.

PATIENTS: Adults with AF treated with catheter ablation

INTERVENTION: LAAC

CONTROL: Long-term OAC

PRIMARY OUTCOME: Safety and efficacy

Secondary Outcome: Major bleeding either procedure or non-procedure related

METHODS (BRIEF DESCRIPTION):

- Patients included adults (mean age 69 years old) with non-valvular AF and a CHA_2DS_2-VASc score of ≥2 for men or ≥3 for women on a scale of 0–9 with higher number indicating greater risk of stroke, who have undergone catheter ablation either 90–180 days prior to or within 10 days after randomization.
- Patients were excluded if they required long-term anticoagulation for reasons other than AF, had ejection fraction (EF) of <30%, had a stroke or transient ischemic attack (TIA) within previous 14 days, or prior history of major bleeding event.
- Patients underwent 1:1 randomization to receive either LAAC or long-term OAC.
  - LAAC arm: Catheter ablation was performed before LAAC and patients received OAC + aspirin for 90 days, then aspirin alone for 12 months following the procedure.
  - OAC arm: Patients were treated with OAC.
- 95% of patients received a non-warfarin anticoagulant, most received either apixaban (59%) or rivaroxaba (27%). Choice of anticoagulants used was at physician's discretion.
- Follow up took place three, 12, 24, and 36 months after randomization.
- Primary safety endpoint was non-procedure related bleeding that was either major, as defined by the International Society on Thrombosis and Haemostasis (ISTH), or nonmajor bleeding that required medical intervention. Bleeding was defined as non-procedure related if it occurred ≥3 days after LAAC.
- Primary efficacy endpoint was a composite of death from any cause, stroke, or systemic embolism.
- All major bleeding episodes including procedure related as defined by ISTH. Bleeding was considered procedure related if it occurred <3 days after the procedure.

INTERVENTION (# IN THE GROUP): 803

COMPARISON (# IN THE GROUP): 797

FOLLOW-UP PERIOD: 36 months

RESULTS:

Primary Outcome –

- LAAC decreased the incidence of non-procedure-related major or clinically relevant non-major bleeding compared to OAC (hazard ratio [HR] 0.44; 95% CI, 0.33–0.59).
- There was no significant difference in composite endpoint of all-cause death, stroke, or systemic embolism with LAAC compared to OAC (HR 0.91; 95% CI, 0.59–1.4).

Secondary Outcome –

- LAAC with short term anticoagulation was noninferior to long term OAC for all major bleeding including procedure-related events (HR 0.77; 95% CI, 0.48–1.2; *P*<.001 for noninferiority).

LIMITATIONS:

- The manufacturer of the device funded the study.
- Exclusion of patients with LVEF ≤30% so results may not be valid for this group.
- Newer ablation techniques were not studied.
- Most of the patients were men.
- The open-label design may have led patients in the OAC group to seek medical attention more readily for bleeding symptoms, potentially inflating the bleeding event rate in that arm.

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Aspirin Alone is Good Enough After Coronary Artery Bypass Grafting

Ticagrelor and Aspirin or Aspirin Alone after Coronary Surgery for Acute Coronary Syndrome

Jeppsson A, James S, Moller CH, et al. Ticagrelor and Aspirin or Aspirin Alone after Coronary Surgery for Acute Coronary Syndrome. *N Engl J Med*. 2025;393(23):2313-2323. doi:10.1056/NEJMoa2508026

KEY TAKEAWAY: In patients undergoing coronary artery bypass grafting (CABG) for acute coronary syndrome (ACS), ticagrelor plus aspirin does not reduce death, myocardial infarction (MI), stroke, or repeat revascularization compared with aspirin alone at one year and increases the risk of bleeding and dyspnea.

STUDY DESIGN: Open-label, registry-based, randomized clinical trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to open label design and high discontinuation rate)

BRIEF BACKGROUND INFORMATION: Secondary prevention with dual antiplatelet therapy is standard after CABG for acute coronary syndrome. The guidelines extrapolated from percutaneous coronary intervention (PCI) populations recommend dual antiplatelet therapy (DAPT) for ACS, but evidence in CABG-specific cohorts has been limited. This trial assessed whether treatment with ticagrelor and aspirin improves outcomes after CABG for patients with ACS as compared to aspirin alone.

PATIENTS: Adults with ACS within six weeks prior to CABG

INTERVENTION: Ticagrelor and aspirin

CONTROL: Aspirin

PRIMARY OUTCOME: Composite of death, MI, stroke, or repeat revascularization at one year, and first major bleeding occurrence

Secondary Outcome: Composite net adverse clinical events including the primary outcome and major bleeding

METHODS (BRIEF DESCRIPTION):

- The trial was a multicenter, investigator-initiated, open-label, registry-based, randomized clinical trial performed at 22 Nordic centers.
- Participants were adults ≥18 years old who had CABG within six weeks of an ACS event.
- Those taking oral anticoagulants, on dialysis, with severe liver disease, bleeding disorder, other indication for DAPT or contraindication to either trial drug was excluded.
- Participants had a mean age of 66 years, 14% were women, 28% had diabetes, and the median operative risk was low. Indications for CABG included non-ST-segment elevation MI (58%), unstable angina (32%) and ST-segment elevation MI (10%).
- Participants were assigned in a 1:1 ratio to receive either open-label ticagrelor (90 mg twice daily) plus aspirin (75–100 mg daily), or aspirin alone (75–160 mg daily).
- The primary efficacy endpoint was a composite of death from any cause, MI, stroke, or repeat revascularization, evaluated as a time-to-event analysis at one year.
- The primary safety endpoint was time to first occurrence of major bleeding (defined as bleeding requiring hospitalization), evaluated as a time-to-event analysis at one year.
- The secondary endpoints included net adverse clinical events (components of the primary outcome or bleeding), individual components of the primary outcome, and first occurrence of major bleeding.

INTERVENTION (# IN THE GROUP): 1,104

COMPARISON (# IN THE GROUP): 1,097

FOLLOW-UP PERIOD: One year

RESULTS:

Primary Outcome –

- There was no difference in the composite rate of death, MI, stroke, or repeat revascularization between the DAPT or aspirin groups (4.8% vs 4.6% events, respectively; hazard ratio [HR] 1.1; 95% CI, 0.72–1.6).
- More patients in the DAPT group had major bleeding compared to the aspirin group (4.9% vs 2.0%, respectively; HR 2.5; 95% CI, 1.5–4.1).

Secondary Outcome –

- More patients in the DAPT group had net adverse clinical events compared to the aspirin group (9.1% vs 6.4%, respectively; HR 1.5; 95% CI, 1.1–2.0).
- More patients in the DAPT group had severe dyspnea compared to the aspirin group (18% vs 6.4%, respectively; HR 3.1; 95% CI, 2.3–4.0).

- There were no significant differences in individual event rates for MI, stroke, repeat revascularization, or HF hospitalization.

LIMITATIONS:

- The event rate was lower than expected, reducing statistical power.
- The study was conducted only in Nordic countries, potentially limiting generalizability.
- The open-label study design confers potential adherence and reporting bias.
- One-third of patients discontinued ticagrelor early.

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Acupuncture Effective for Methadone Reduction?

Effect of Acupuncture for Methadone Reduction: A Randomized Clinical Trial

Lu L, Chen C, Chen Y, et al. Effect of Acupuncture for Methadone Reduction: A Randomized Clinical Trial. *Ann Intern Med*. 2024;177(8):1039-1047. doi:10.7326/M23-2721

KEY TAKEAWAY: Acupuncture treatment reduces methadone dosing and opioid cravings compared to sham acupuncture in patients with opioid use disorder (OUD).

STUDY DESIGN: Multicenter, randomized, sham-controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: OUD is highly prevalent, and methadone is used as a treatment, as it helps reduce symptoms of withdrawal when individuals stop taking opioids. However, methadone treatment has many side effects, and when lowering methadone doses, patients experience an increase in opioid withdrawal symptoms and are at risk for beginning opioids again. Acupuncture can reduce opioid cravings and reduce the doses of methadone needed to maintain opioid abstinence, and this study aimed to determine the effects of acupuncture on reducing methadone doses.

PATIENTS: Patients with OUD receiving methadone maintenance treatment

INTERVENTION: Acupuncture

CONTROL: Sham acupuncture

PRIMARY OUTCOME: Decrease in methadone dose by ≥20% and opioid cravings

Secondary Outcome: Opioid withdrawal symptoms, quality of sleep, anxiety, depression

METHODS (BRIEF DESCRIPTION):

- Patients with OUD between 18–65 years old, treated with methadone for >6 weeks were included in the study.
- Patients excluded were those who had received other treatment for pain/opioid use disorder, as well as those with mental health conditions.
- Patients were randomized 1:1 to either acupuncture or sham acupuncture.
    - Patients received three 30-minute sessions of acupuncture per week for eight weeks (24 total sessions).
    - Same acupoints were used for both groups.
- To measure the number of patients whose methadone dose decreased by at least 20%, all patients took methadone in the clinic every day. To measure opioid cravings, a visual analogue scale was used after eight weeks. Scores ranged from 0–100, with higher scores indicating more craving.
- Secondary outcomes:
    - Opioid withdrawal was assessed via the Clinical Opioid Withdrawal Scale. Scores range from 0–48, with higher scores indicating more withdrawal symptoms.
    - Quality of sleep was assessed via the Pittsburg Sleep Quality Index. Scores range from 0–21, with higher scores indicating worse sleep.
    - Anxiety was assessed via the Beck Anxiety Inventory Scale. Scores range from 0–63, with higher scores indicating worse anxiety symptoms.
    - Depression was assessed via the Beck Depression Inventory II scale. Scores range from 0–63, with higher scores indicating worse depression symptoms.

INTERVENTION (# IN THE GROUP): 60

COMPARISON (# IN THE GROUP): 58

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- Acupuncture resulted in a decrease in methadone dose by ≥20% compared to control (62% vs 29%, respectively; $p<.001$).
- Acupuncture reduced opioid cravings compared to control (mean difference [MD] –12; 95% CI, –19 to –4.8).

Secondary Outcome –

- Acupuncture improved quality of sleep compared to control (MD –2.3; 95% CI, –3.4 to –1.2).
- There were no significant differences in opioid withdrawal, anxiety, or depression for acupuncture compared to control.

LIMITATIONS:

- Because this study was performed in China, there may be cultural differences in pain perception, thus limiting the generalizability.
- The acupuncture treatment points were limited. In addition, all patients had the same acupuncture points treated, but in real life, acupuncture treatments can be individualized for different patients.
- People can experience opioid withdrawal symptoms differently, and some may have a greater tolerance for withdrawal symptoms than others, which would lead to differences in methadone doses.
- The short 12-week period in which patients were followed did not fully show the long-term effects of the acupuncture treatment.
- The relatively small sample size may limit the statistical power of the study and reduce the generalizability of the findings.

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Surprise? Semaglutide with Automated Insulin Delivery in Type 1 Diabetes

Subcutaneous Weekly Semaglutide with Automated Insulin Delivery in Type 1 Diabetes: A Double-blind, Randomized, Crossover Trial

Pasqua MR, Tsoukas MA, Kobayati A, Aboznadah W, Jafar A, Haidar A. Subcutaneous Weekly Semaglutide with Automated Insulin Delivery in Type 1 Diabetes: A Double-blind, Randomized, Crossover Trial. *Nat Med*. 2025;31(4):1239-1245. doi:10.1038/s41591-024-03463-z

KEY TAKEAWAY: Semaglutide significantly increases the percentage of time spent in ideal blood glucose ranges in patients with type 1 diabetes mellitus (T1DM).

STUDY DESIGN: Randomized, double-blind crossover trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: While the benefits of glucagon-like peptide receptor agonists (GLP-1RAs) in type 2 diabetes have been well-documented, clinical trials in patients with T1DM have been scarce. Insulin therapy for T1DM uses automated systems that integrate continuous glucose monitoring with algorithm-driven dose adjustments along with an insulin pump. However, many patients using these devices still face trouble reaching their goal of Hemoglobin A1c (HbA1c) of <7%, often due to reduced glycemic control after meals. Given the success of GLP-1RAs in improving glycemic control in type 2 diabetes, this study aimed to determine whether weekly GLP-1RA therapy can similarly enhance outcomes for patients with T1DM using automated insulin delivery (AID) systems.

PATIENTS: Patients ≥18 years old with T1DM

INTERVENTION: Subcutaneous semaglutide for 11 weeks titrated to 1 mg or max tolerated dose + AID

CONTROL: Placebo _ AID

PRIMARY OUTCOME: Percentage of time in ideal range blood glucose (3.9–10 mmol l-1) during last four weeks of intervention

Secondary Outcome: Time spent in hypoglycemia (<3.9 mmol l-1), time spent in hyperglycemia (>10 mmol l-1), daily insulin requirements, adverse events

METHODS (BRIEF DESCRIPTION):

- Adult patients with T1DM who have been diagnosed for >1 year, with an HbA1c of ≤11%, and using AID for three months or more were included. Patients of reproductive age agreed to use highly effective methods of contraception or abstained during this study.
- The following patients were excluded:
  - Recent use of any non-insulin antihyperglycemic medication(s) in the last two weeks, severe low blood sugars within the last three months, or prior adverse reactions to GLP-1RAs
  - Pregnancy/breastfeeding or planned to do so
  - Hospitalized for diabetic ketoacidosis (DKA) or had bariatric surgery within the last six months
  - History of diabetic retinopathy, diabetic gastroparesis, gallbladder, pancreatic disease or multiple endocrine neoplasia 2 syndrome (MEN2), or medullary thyroid cancer
  - Body mass index (BMI) ≤21 kg/m^2
  - Chronic hydroxyurea use
- Initial visit was combined with a training visit involving diabetes management review and training on drug injection technique
- Patients were randomized into two groups: Placebo (saline 0.19 mL per week for 4 weeks, 0.37 mL per week for 4 weeks, then 0.74 mL per week for 4 weeks) then semaglutide (0.25 mg per week for 4 weeks, 0.5 mg per week for 4 weeks, 1 mg per week for 4 weeks) vs semaglutide then placebo.
- Researchers and participants were blinded to group distribution and medication allocation.
- Afterwards, an 11-week drug titration period consisted of 0.25 mg per week for 4 weeks (consistent volume 0.19 mL), 0.5 mg per week for 4 weeks (0.37 mL), then 1 mg (0.74 mL) afterwards) vs placebo weekly injections, with volume of injection consistent between groups to maintain blinding, began.
- Patients remained on pre-trial AID devices and insulin throughout this period.
- Side effect review and continuous glucose monitoring (CGM) reports occurred on days seven, 21, 32, 56, 63, and 77.
- After the drug titration period, patients then used a research-based AID system for the 28-day follow-up period to reduce potential selection bias.

- The percentage of time during follow-up in which each group was within 3.9–10 mmol l-1 blood glucose was then measured.
- Secondary outcomes included adverse events, coefficient of variation of glucose levels, time spent in hyperglycemia, time spent in hypoglycemia, and insulin requirements (pump data)
- Remote follow-ups during this time occurred on days four, seven, and 21.
- After the 28-day follow-up period, a washout period of two weeks was conducted before the groups switched to reduce carryover drug effects from the semaglutide.

INTERVENTION (# IN THE GROUP): 26
COMPARISON (# IN THE GROUP): 25

FOLLOW-UP PERIOD: 28 days

RESULTS:

Primary Outcome –

- Semaglutide administered to patients with T1DM increased time spent in target blood glucose range compared to placebo (74% vs 69%, respectively; difference 4.8 percentage points; *P*=.006).

Secondary Outcome –

- Semaglutide administered with AID to patients with T1DM did not significantly affect percentage time spent in hypoglycemia compared to placebo.
- Semaglutide administered with AID to patients with T1DM decreased percentage of time spent in hyperglycemia compared to placebo (24% vs 29%, respectively; difference –5 percentage points; *P*=.006).
- Semaglutide administered with AID decreased the following compared to placebo:
  - Total insulin use (46 Uday vs 62 Uday, respectively; difference –11 Uday; *p*<.001)
  - Basal insulin use (31 Uday vs 35 Uday, respectively; difference –3.5 Uday; *p*=.003)
  - Bolus insulin use (15 Uday vs 24 Uday, respectively; difference –6.2 Uday; *p*<.001)
- Gastrointestinal adverse drug reactions occurred more frequently in those administering semaglutide (72 ADRs in 23 patients administering semaglutide vs 14 ADRs in 7 placebo patients).
- Two patients had euglycemic ketosis without acidosis, which was resolved with carbohydrate intake and insulin alone.

LIMITATIONS:

- This study had a small sample size.
- Baseline characteristics involving 28 participants did not exclude those who withdrew from the study.
- The study has limited follow-up for a short period of 28 days.
- The crossover design of the trial contains a risk of carryover drug effects from semaglutide, even despite the washout period of two weeks.
- There was an increased number of patient follow-ups in the semaglutide group.

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