GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of April 5 - 9, 2021

SPOTLIGHT: No difference in effectiveness between chlorthalidone and hydrochlorothiazide?

- Once-weekly insulin for type 2 diabetes shows glucose-lowering effects
- Baby, hit the gym! Does exercise have an impact on gestational DM or BP issues in pregnancy?
- Vitamin D supplementation, omega-3 fatty acid supplementation, or strength-training exercise program in older adults - Is it necessary?

No Difference in Effectiveness between Chlorthalidone and Hydrochlorothiazide?

Comparison of Cardiovascular and Safety Outcomes of Chlorthalidone vs Hydrochlorothiazide to Treat Hypertension

Hripcsak G, Suchard M, Shea S, et al. Comparison of Cardiovascular and Safety Outcomes of Chlorthalidone vs Hydrochlorothiazide to Treat Hypertension. *JAMA*. 2020; 180(4):542–551.

KEY TAKEAWAY: In treatment-naïve hypertensive patients, chlorthalidone does not have a cardiovascular benefit and had more safety risks, such as hypokalemia and hyponatremia, compared to hydrochlorothiazide.
STUDY DESIGN: Retrospective, observational, comparative, new-user cohort study
LEVEL OF EVIDENCE: STEP 4

BRIEF BACKGROUND INFORMATION: Current American College of Cardiology and American Heart Association guidelines recommend the use of chlorthalidone over hydrochlorothiazide for first-line treatment of hypertension. Previous trials have demonstrated a reduction in cardiovascular disease with chlorthalidone.

PATIENTS: Patients from 3 Observational Health Data Sciences and Informatics (OHDSI) databases
INTERVENTION: Chlorthalidone any dose
CONTROL: Hydrochlorothiazide any dose
OUTCOME: Hospitalization for acute myocardial infarction, heart failure, ischemic or hemorrhagic stroke; composite cardiovascular disease outcomes; safety outcomes

METHODS (BRIEF DESCRIPTION):

- Patients were divided by factors such as age, sex, index year, index month, and medical history (i.e., adults newly diagnosed with hypertension)
- Eligibility criteria: observed in database for at least 365 days prior to starting treatment, no prior exposure to hypertension treatment, no diagnosis of the outcomes of interest
- Exclusion criteria: known prior use of antihypertensives or started another antihypertensive within 7 days of starting either chlorthalidone or hydrochlorothiazide
- Propensity scores and hazard ratios estimated treatment exposure and outcomes, calibrated with respect to confounders (large difference in group sizes)

INTERVENTION (# IN THE GROUP): 36,918
COMPARISON (# IN THE GROUP): 693,337

FOLLOW UP PERIOD: January 2001 – December 2018

RESULTS:
Chlorthalidone did not improve outcomes compared to hydrochlorothiazide:

- Composite cardiovascular disease (HR 1.0; 95% CI, 0.85–1.2)
- Myocardial infarction (HR 0.92; 95% CI, 0.64–1.3)
- Hospitalization for heart failure (HR 1.1; 95% CI, 0.82–1.3)
- Stroke (HR 1.1; 95% CI, 0.86–1.4)

Chlorthalidone caused greater risk of safety concerns compared to hydrochlorothiazide:

- Hypokalemia (HR 2.2; 95% CI, 1.9–2.6)
- Hyponatremia (HR 1.3; 95% CI, 1.2–1.5)
- Acute renal failure (HR 1.4; 95% CI, 1.2–1.6)
- Chronic kidney disease (HR 1.2; 95% CI, 1.1–1.4)
- Type 2 diabetes mellitus (HR 1.2; 95% CI, 1.1–1.3)

However, patients taking chlorthalidone had a lower risk of abnormal weight gain (HR 0.73; 95% CI, 0.61–0.86).

LIMITATIONS:

- Physicians chose which medications to give which patients (i.e. more subjects give hydrochlorothiazide than chlorthalidone)
- Irregularities in taking blood pressure measurements
- Other medications with known cardiovascular benefit used alongside the thiazide diuretic after the 7 days of initiation.

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Once-weekly insulin for type 2 diabetes shows glucose-lowering effects

Once-weekly insulin for type 2 diabetes without previous insulin treatment

Rosenstock J, Bajaj HS, Janež A, et al. Once-Weekly Insulin for Type 2 Diabetes without Previous Insulin Treatment. *N Engl J Med*. 2020; 383(22):2107-2116.

KEY TAKEAWAY: Once-weekly insulin icodec in adult with type 2 diabetes showed glucose-lowering efficacy similar to that of daily insulin glargine.

STUDY DESIGN: Multinational, randomized, double-blind, double dummy, treat-to-target, active-controlled, parallel group phase 2 trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: In patients with type 2 diabetes, adherence to medication regimens can be difficult, especially with insulin. Reducing frequency of basal insulin injections to once-weekly as compared to daily might increase treatment adherence.

PATIENTS: Insulin-naïve patients, aged 18-75 (mean = 59), with type 2 diabetes

INTERVENTION: Insulin icodec starting at 70 units

CONTROL: Insulin glargine U100 starting at 10 units daily

OUTCOME: Change in baseline A1C over 26 weeks. Secondary: changes in fasting plasma glucose level, time spent in tight glycemic range, and mean weekly insulin dose during last 2 weeks of treatment, adverse events, hypoglycemia

METHODS (BRIEF DESCRIPTION): Patients with type 2 diabetes diagnosed at least 180 days prior to study were enrolled. Glycated hemoglobin (A1C) ranged from 7.0 to 9.5%. Patients were on stable metformin dosages with or without a dipeptidyl peptidase 4 inhibitor (DPP4i). Approximately 20% of patients had a diabetic complication.

- Randomization occurred 1:1 using DPP4i use to stratify.
- Each group received 70 units of insulin per week, with weekly target-to-treat adjustment to 70-108 mg/dL
- Icodec group received daily placebo injections; glargine group received weekly placebo injections.
- Patients self-measured blood glucose using capillary blood glucose monitors. A1C values were drawn every 4 weeks with exception of the last value drawn after 6 weeks.
- All symptomatic and asymptomatic hypoglycemic events were reported.

INTERVENTION (# IN THE GROUP): 125

COMPARISON (# IN THE GROUP): 122

FOLLOW UP PERIOD: 26-week treatment, 5-week follow up

RESULTS:

Primary outcome: mean decrease of A1C

- Icodec: from 8.1% to 6.7%
- Glargine: from 8.0% to 6.9%
- No difference in change of A1c between groups (mean difference -0.18%; 95% CI -0.38 to 0.02)

Secondary outcomes

- Mean fasting plasma glucose: no statistically significant difference
- Icodec had incidence of greater symptomatic and asymptomatic hypoglycemic events than glargine.
- Glucose 54–70 mg/dL: (rate ratio 2.4; 95% CI, 1.5 to 3.9)
- Glucose < 54 mg/dL: (rate ratio 1.1; 95% CI, 0.45 to 2.7)

LIMITATIONS:

- This was an industry sponsored study.
- Icodec is in phase 2 trials (not available for immediate use).
- No significant difference in lowering A1C between icodec and glargine. Either icodec is noninferior to glargine, or hypoglycemic events with icodec contributed to A1C value.
- The sample size of the study was inadequately powered.
- Starting and adjustment doses of icodec and glargine were treated 1:1, but icodec's pharmacokinetics needs more investigation.

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Baby, Hit the Gym! Does exercise have an impact on gestational DM or BP issues in pregnancy?

Prenatal exercise for the prevention of gestational diabetes mellitus and hypertensive disorders of pregnancy: a systematic review and meta-analysis

Davenport MH, Ruchat SM, Poitras VJ, et al. Prenatal exercise for the prevention of gestational diabetes mellitus and hypertensive disorders of pregnancy: a systematic review and meta-analysis. *Br J Sports Med*. 2018; 52(21):1367–1375.

KEY TAKEAWAY: Exercise during pregnancy decreases the risk of developing gestational diabetes mellitus (DM), gestational hypertension (HTN), and pre-eclampsia.

STUDY DESIGN: Meta-analysis of 65 RCTs, 9 non-RCTs, 13 cohort, 11 cross-sectional, and 8 case-control studies

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Complications of pregnancy, including gestational diabetes, hypertension, and pre-eclampsia present significant risk for maternal and fetal morbidity and mortality. As such, interventions which prevent the development of these disorders of pregnancy can significantly affect the long-term health of both the maternal and fetal population.

PATIENTS: Pregnant women in any trimester

INTERVENTION: Exercise or exercise + intervention (dietary or lifestyle counseling)

CONTROL: No exercise

OUTCOME: Development of gestational diabetes, gestational HTN, or pre-eclampsia during pregnancy

METHODS (BRIEF DESCRIPTION):

- Patients included pregnant women without contraindications to exercise, such as PROM, placenta previa, cervical incompetence, IUGR, or other underlying serious maternal illness, and without a diagnosis of gestational hypertension, gestational diabetes, or pre-eclampsia at the initiation of the study.
- Intervention included various types of physical activity. Type of activity was not specified. Both long- and short-term exercise interventions were included. Exercise included any body movement that generated increased energy expenditure to level at rest.
- Criteria for measuring gestational DM was defined individually by each study with little consensus.
- Gestational HTN was defined as diastolic BP >90 on 2 measurements after 20 weeks gestational age. If a patient met criteria for gestational HTN and was found to have proteinuria, they were defined as having pre-eclampsia.

INTERVENTION (# IN THE GROUP): 4,236 exercise alone; 4,449 exercise + interventions

COMPARISON (# IN THE GROUP): 8,484

FOLLOW UP PERIOD: Unknown

RESULTS:

Women who exercise during pregnancy compared to no exercise during pregnancy are less likely to develop:

- Gestational DM (26 RCTs; N=6,934; OR 0.62; 95% CI, 0.52–0.75)
- Gestational HTN (22 RCTs; N=5,316; OR 0.61; 95% CI, 0.43–0.85)
- Pre-Eclampsia (15 trials; N=3,401; OR 0.59; 95% CI, 0.37–0.94)

LIMITATIONS:

- No studies examined the effect of exercise in different trimesters of pregnancy.
- Poor compliance
- Meta-analysis was unable to differentiate between different types of exercise
- Exercise-only interventions were consistently more effective at reducing the likelihood of developing the diseases in question than exercise + intervention, possibly due to increased compliance due to exercise supervision.

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Vitamin D Supplementation, Omega-3 Fatty Acid Supplementation, or Strength-Training Exercise Programs in Older Adults – Is It Necessary?

Effect of Vitamin D Supplementation, Omega-3 Fatty Acid Supplementation, or a Strength-Training Exercise Program on Clinical Outcomes in Older Adults

Bischoff-Ferrari HA, Vellas B, Rizzoli R, et al. Effect of Vitamin D Supplementation, Omega-3 Fatty Acid Supplementation, or a Strength-Training Exercise Program on Clinical Outcomes in Older Adults: The DO-HEALTH Randomized Clinical Trial. *JAMA*. 2020; 324(18):1855–1868.

KEY TAKEAWAY: Treatment with vitamin D3 (2000 IU/d), omega-3 fatty acids (1g/d), or a strength-training exercise program compared to control did not result in statistically significant differences in improvement in systolic or diastolic blood pressure (SBP and DBP), non-vertebral fractures, physical performance, infection rates, or cognitive function.

STUDY DESIGN: RCT

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Deficiencies in vitamin D or omega-3 fatty acids and a lack of exercise are often linked to poor outcomes in older adults. Despite this, many large studies have not shown these to be of significant benefit in otherwise healthy older adults.

PATIENTS: Adults ≥70 years with no major health events 5 years prior to enrollment

INTERVENTION: Vitamin D supplementation or omega-3 supplementation or strength training exercise

CONTROL: Placebo or joint flexibility exercise

OUTCOME: Change in blood pressure, muscular health, and cognitive health, as well as incidence of non-vertebral fractures and infections

METHODS (BRIEF DESCRIPTION):

Previously healthy adults were randomized into 8 treatment groups:

- One group received all three interventions
- Three groups received a combination of two of the interventions and one control
- Three groups received one intervention and two controls
- One group received only controls

Yearly clinical visits and telephone calls every 3 months assessed:

- Change in systolic blood pressure (SBP)
- Change in diastolic blood pressure (DBP)
- Incidence of non-vertebral fractures
- Change in muscle health via the Short Physical Performance Battery (SPPB): 3 component physical performance test with composite scores 0–12 (12 being best)
- Change in cognitive health via Montreal Cognitive Assessment (MoCA), with scores ranging from 0–30 (30 being best)
- Overall incidence of infections

INTERVENTION (# IN THE GROUP): 1,887 split into the 8 testing groups

COMPARISON (# IN THE GROUP): 270

FOLLOW UP PERIOD: 3 years

RESULTS:

- No combination of treatments compared to no treatment significantly changed systolic BP, diastolic BP, SPPB, MoCA, vertebral fractures, or infections.
- Participants taking only Omega-3 experienced a lower rate of:
  - Upper respiratory infections (IRR 0.90; 99% CI, 0.81–0.99)
  - Urinary tract infections (IRR 0.38; 99% CI, 0.23–0.62)

LIMITATIONS:

- A large portion of the participants were already healthy and engaged in physical activity at baseline, therefore additional exercise might have had minimal effect and explain why there were fewer number of fractures than expected and why the interventions had little effect on cognitive health
- Improvement in cognitive function may have been due to a learning effect
- Less than half the participants were actually deficient in vitamin D, thereby potentially masking its effects
- *P*=0.01 may not be a strong enough indicator of statistical significance given the large number of randomization groups and comparisons

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