GEMs of the Week

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Hypertensive Medications and Their Effects on Blood Pressure Based on Age and Ethnicity

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

First Line Drug Treatment for Hypertension and Reductions in Blood Pressure According to Age and Ethnicity: Cohort Study in UK Primary Care

Sinnott SJ, Douglas IJ, Smeeth L, Williamson E, Tomlinson LA. First line drug treatment for hypertension and reductions in blood pressure according to age and ethnicity: cohort study in UK primary care. *BMJ*. 2020;371:m4080. Published 2020 Nov 18. doi:10.1136/bmj.m4080

KEY TAKEAWAY: CCB and ACEi/ARBs similarly reduce systolic blood pressure regardless of age and race.
STUDY DESIGN: Propensity score matched cohort study
LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: High blood pressure is a modifiable risk factor for mortality that affects 25% of the global population. In the UK, clinical guidelines are unique from other countries because they have recommendations for initiating hypertension (HTN) medications based on age and ethnicity which do not follow other guidelines. There is conflicting evidence on whether age and ethnicity should be used to influence treatment recommendations.

PATIENTS: UK patients with a new prescription for either a CCB or ACEi/ARB
INTERVENTION: ACEi/ARB
CONTROL: CCB
PRIMARY OUTCOME: Change in systolic blood pressure

METHODS (BRIEF DESCRIPTION):

- Researchers used Clinical Practice Research Database (CPRD-GOLD) to collect anonymized patient data from the electronic health record. The data collected were from UK patients from 2007 to 2017 who started a new prescription for either a CCB or ACEi/ARB who did not take any of these prescriptions within the past year of study enrollment.
- Patients received either a CCB or ACEi/ARB and systolic blood pressures were reported at 12, 26, and 52 weeks.
- Data was analyzed using a logistic regression model which included multiple covariates to estimate the propensity of being prescribed a CCB vs ACEi/ARB medication.

INTERVENTION (# IN THE GROUP): 87,440
COMPARISON (# IN THE GROUP): 67,274

FOLLOW UP PERIOD: 52 weeks

RESULTS:

- CCB and ACEi/ARBs had similar effects on systolic blood pressure in those less than 55 years old at 52 weeks (mean difference –0.53 mmHg; 99% CI, –2.0 to 0.91).
- CCB and ACEi had similar effects on systolic blood pressure in those greater than 55 years old at 52 weeks (mean difference 0.85 mmHg; 99% CI, –0.11 to 1.8).
- CCB and ACEi had similar effects on systolic blood pressure in non-Black patients at 52 weeks (mean difference 0.08 mmHg; 99% CI, –0.81 to 0.96).
- CCB and ACEi had similar effects on systolic blood pressure in Black patients at 52 weeks (mean difference 2.3 mmHg; 99% CI, –5.4 to 9.9).

LIMITATIONS:

- Cannot confirm causality due to nature of a cohort study.
- Comparison between ethnicity groups was only between Black vs non-Black leading to wide margins of uncertainty.
- Small number of Black patients were started on ACEi/ ARB which added to a level of uncertainty to comparisons between ethnicity groups.

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Remdesivir was Useful in Canada!

Remdesivir for the Treatment of Patients in Hospital with COVID-19 in Canada: A Randomized Controlled Trial

Ali K, Azher T, Baqi M, et al. Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: a randomized controlled trial. *CMAJ*. 2022;194(7):E242-E251. doi:10.1503/cmaj.211698

KEY TAKEAWAY: Remdesivir IV added to standard care significantly reduces the likelihood that hospitalized patients with COVID-19 will need mechanical ventilation; however, it does not reduce mortality, length of hospital stay, or oxygen-free and ventilator-free days.

STUDY DESIGN: Multi-center, open label randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Remdesivir, an antiviral mediation, has shown some benefit in treating COVID-19; however, clinical guidelines vary and its impact on clinical outcomes remains unclear. With the ongoing need to find safe and effective ways to treat COVID-19 globally, understanding the efficacy of Remdesivir in treating hospitalized patients is critically important.

PATIENTS: Hospitalized with COVID-19 in Canada

INTERVENTION: Remdesivir IV for 10 days plus standard care

CONTROL: Standard care

PRIMARY OUTCOME: In-hospital mortality

Secondary Outcome: 60-day mortality, new need for mechanical ventilation, hospital length of stay, oxygen-free and ventilator-free days at day 28, new hepatic dysfunction, new need for dialysis

METHODS (BRIEF DESCRIPTION):

- Canadian treatments for COVID-19 (CATCO) compared multiple agents to standard care, which was a sub-study of the World Health Organization Solidarity RCT which studied Remdesivir in many countries across the world.
- This study was done in conjunction with the Solidarity study and analyzed the results of 1,282 patients randomized to standard care vs. standard care plus Remdesivir.
- Patients were randomized to IV 200 mg (Day 0) and 100 mg (Days 1-9) of Remdesivir plus standard care or standard of care alone.
- Primary outcome was in-hospital mortality.
- Secondary outcomes were new need for mechanical ventilation, length of hospital stay, and change in clinical severity measured at days three, five, eight, 11, 15, 29 and 60. Safety outcomes, such as renal and hepatic dysfunction, were evaluated.

INTERVENTION (# IN THE GROUP): 634

COMPARISON (# IN THE GROUP): 647

FOLLOW UP PERIOD: 60 days

RESULTS:

Primary Outcome –

- Remdesivir treatment did not reduce in hospital mortality compared to standard care (19% vs 23%, respectively; RR 0.83; 95% CI, 0.67–1.0).

Secondary Outcomes –

- Remdesivir treatment did not reduce 60-day mortality compared to standard care (25% vs 28%, respectively; RR 0.88; 95% CI, 0.72–1.1).
- Remdesivir (in patients not mechanically ventilated at baseline) statistically decreased the need for mechanical ventilation compared to standard care (8% vs 15%, respectively; RR 0.53; 95% CI, 0.38–0.75).
- Hospital length of stay was similar between the two groups (median 10 in the Remdesivir group and 9 in the control group).
- Remdesivir did not significantly affect oxygen-free or ventilator-free status compared to standard of care.
- Remdesivir did not prevent new hepatic dysfunction or dialysis compared to standard of care.

LIMITATIONS:

- Patients were recruited from August 2020 until April 2021; therefore, the dominant COVID-19 variant in the study may be different than current or future variants.
- Overall, the study was underpowered to show a statistically significant difference for patient-oriented outcomes like in-hospital mortality and 60-day mortality.
- At the time of publication, there was no data available on the cost effectiveness of Remdesivir.

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PRP Injections vs Other intraarticular Injections for Knee Osteoarthritis

PRP Injections vs Other Intraarticular Injections for Knee Osteoarthritis: A Meta-Analysis of Randomized Controlled Trials

Filardo G, Previtali D, Napoli F, et al. PRP Injections for the Treatment of Knee Osteoarthritis: A Meta-Analysis of Randomized Controlled Trials. *Cartilage*. 2021 Dec;13: 364S-375S.

KEY TAKEAWAY: Platelet rich plasma (PRP) intraarticular knee injections result in greater patient-perceived benefit compared to placebo and other injectable treatments.
STUDY DESIGN: Meta-analysis of 34 RCTs (N=2,829)
LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: PRP is becoming popular in treating OA due to low side-effect profile and the possibility to delay the progression of OA. But it is unclear how much these benefits are perceived by the patient when comparing to placebo or other intraarticular injections treatments.

PATIENTS: Patients with knee osteoarthritis
INTERVENTION: Intraarticular knee injection with platelet-rich-plasma (PRP)
CONTROL: Placebo or other injection treatments
PRIMARY OUTCOME: Patient-perceived benefit
Secondary Outcomes: Short-term benefit, pain, stiffness

METHODS (BRIEF DESCRIPTION):

- This was a meta-analysis of RCTs that compared PRP knee injection vs. placebo (saline) or other injection treatments such as hyaluronic acid (HA), corticosteroids (CS), ozone, or prolotherapy (dextrose).
  - Articles that were duplicates, non-RCT or no-injection in control groups were excluded.
- Authors used the PRISMA guidelines while selecting articles and measured the quality of the studies using the GRADE guidelines.
- Patient-perceived benefit compared the overall Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at six- and 12-month follow up after injections.
  - WOMAC quantifies pain (score range 0 to 20), stiffness (0 to 8), and function (0 to 68) in patients with hip or knee OA. A score of zero represents the best health status.
- Secondary outcomes compared the WOMAC overall score at one- and three-month follow up; WOMAC subscores that assessed pain, stiffness and function at six-month follow up; pain measured on the Visual Analogue Scale (VAS, score range 0 to 10, 10 being the worst) at six-month follow up and Osteoarthritis Outcome Score (KOOS, score range 0 to 100, 0 being the worst) at six-month follow up.

INTERVENTION (# IN THE GROUP): 1,403
COMPARISON (# IN THE GROUP): 1,426

- Placebo: 195
- HA: 977
- CS: 174
- Ozone: 59
- Dextrose: 21

FOLLOW UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- PRP injections improved perceived patient benefit at 12 months compared to placebo (3 trials, N=129; mean difference [MD] –19; 95% CI, –36 to –2.7). However, no significant minimal clinically important difference (MCID=6.4).
- There was no short-term benefit at six months (6 trials, N=not available; MD –13; 95% CI, –26 to 0.6).
- PRP injections significantly improved perceived patient benefit at six- and 12- months compared to HA.
  - Six-months (10 trials, N=790; MD –7.1; 95% CI, –9.7 to –4.7)
  - 12-months (7 trials, N=553; MD –11; 95% CI, –4.8 to –7.9)

Secondary Outcomes –

- PRP did not give short-term improvement at one- and three-months compared to placebo.
- PRP improved short-term benefits at one- and three-months compared to HA.
  - One-month (5 trials, N=338; MD –2.6; 95% CI, –3.5 to –1.8)
  - Three-months (5 trials, N=356; MD –4.6; 95% CI, –9 to –0.3)
- PRP improved perceived patient benefit in pain and stiffness but not in function compared to placebo at six-months.
  - Pain (5 trials, N=210; MD –3.1; 95% CI, –5.5 to –0.65). Not clinically significant (MCID=1.5).
  - Stiffness (5 trials, N=210; MD –1.3; 95% CI, –2.6 to –0.05). Not clinically significant (MCID=0.6).

- PRP improved perceived patient benefit in pain, stiffness and function compared to HA at six-months.
    - Pain (9 trials, N=702; MD –1.3; 95% CI, –2.1 to –0.56)
    - Stiffness (8 trials, N=565; MD -0.3; 95% CI, –0.52 to –0.03)
    - Function (8 trials, N=605; MD –3.5; 95% CI, –5.2 to –1.8)
- PRP improved perceived patient benefit compared to CS at six-month.
    - VAS pain (4 trials, N=206; MD –2; 95% CI, –2.0 to –1.7)
    - KOOS pain (5 trials, N=170; MD 15; 95% CI, 6.1 to 24)
    - KOOS ADL (5 trials, N=170; MD 16; 95% CI, 9.7 to 21)
    - KOOS QoL (5 trials, N=170; MD 11; 95% CI, 6.9 to 15)

LIMITATIONS:

- Unable to obtain primary outcome with WOMAC for PRP compared to CS, ozone, or dextrose due to scarcity of data.
- Given these trials used as a self-administered questionnaire, there's likely a selective reporting bias.
- Some studies had unclear methods of allocation concealment.
- The level of evidence was low in some of the studies due to low power and high heterogeneity of results.
- There was a lack of standardization given the PRP manufacturing techniques were not the same between all the trials.

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Some Models of Intermittent Fasting are Effective for Short-Term Weight Loss

Intermittent Fasting and Obesity-Related Health Outcomes: An Umbrella Review of Meta-analyses of Randomized Clinical Trials

Patikorn C, Roubal K, Veettil SK, et al. Intermittent Fasting and Obesity-Related Health Outcomes: An Umbrella Review of Meta-analyses of Randomized Clinical Trials. *JAMA Netw Open.* 2021; 4(12):e2139558. Published 2021 Dec 1. doi:10.1001/jamanetworkopen.2021.

KEY TAKEAWAY: Modified alternate day fasting (MADF) and the 5:2 diet models of intermittent fasting are associated with weight loss and a reduction in cardiometabolic risk factors at three months. Zero calorie alternate-day fasting (ADF) and time restricted eating (TRE) studies were not associated with significant weight loss.

STUDY DESIGN: Systemic review of 11 meta-analyses of 130 RCTs (N=6,883)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Intermittent fasting recently gained popularity as a weight loss approach. Several RCTs have shown health benefits from intermittent fasting, however the identified aggregate studies focused on specific subtypes of intermittent fasting, and the strength of evidence towards obesity-related outcomes is limited.

PATIENTS: Adult participants from 11 meta-analyses of randomized controlled trials

INTERVENTION: Intermittent fasting (IF)

CONTROL: Continuous energy restriction or regular diet

OUTCOME: Weight loss

Secondary outcome: Cardiometabolic risk factors

METHODS (BRIEF DESCRIPTION):

- A comprehensive literature review of meta-analyses of RCTs. Studies included adults with any past medical history participating in intermittent fasting and examining obesity-related health outcomes compared to regular caloric restriction and/or regular diet was conducted.
- Intermittent fasting included the following subtypes: zero calorie alternate-day fasting (ADF), modified alternate-day fasting (MADF), 5:2 weekly fasting, and time restricted eating (TRE).
- Comparator group included continuous energy restriction, regular diet, and TRE.
- Outcomes were measured by AMSTAR-2 (a measurement tool to assess systematic reviews).
- 6 /11 RCTs were statistically significant and supported by high-moderate quality evidence.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW UP PERIOD: Average of three months (range of 2-6 months)

RESULTS:

- Two IF subtypes (MADF and 5:2 diet) were associated with statistically significant weight loss (-1.7 kg; 95% CI, −2.8 to −0.55).
- Reduction of BMI of healthy adults and those who were overweight and obese following the modified alternate-day fasting for 1-2 months as compared with regular diet (MD, -1.2 kg; 95% CI, -1.4 to -0.96).
- No statistically significant weight loss was associated with other subtypes of intermittent fasting, including zero calorie alternate-day fasting or time restricted eating.
- MADF was associated with improved cardiometabolic outcomes, including statistically significant reductions:
  - LDL (−5.1 mg/dL; 95% CI, −7.4 to −2.8)
  - Total cholesterol (−8.1 mg/dL; 95% CI, −16 to −0.46)
  - Triglycerides (−22 mg/dL; 95% CI, −39 to−3.9)
  - SBP (−4.4 mmHg; 95% CI, −7.4 to −1.5)

LIMITATIONS:

- Parameters of caloric restriction or regular diet were not defined, which could alter significance of results.
- Safety could not be assessed as adverse effects were not included in studied meta-analyses.
- Short length of follow-up and small number of participants in the RCTs.
- Long-term data is limited.

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