GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: The Heart-Healthy Polypill - Simplifying Secondary Prevention of Cardiovascular Death and Complications after Myocardial Infarction

The Heart-Healthy Polypill: Simplifying Secondary Prevention of Cardiovascular Death and Complications after Myocardial Infarction

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Polypill Strategy in Secondary Cardiovascular Prevention

Castellano JM, Pocock SJ, Bhatt DL, et al. Polypill Strategy in Secondary Cardiovascular Prevention [published online ahead of print, 2022 Aug 26]. *N Engl J Med.* 2022; 10.1056/NEJMoa2208275. doi:10.1056/NEJMoa2208275

KEY TAKEAWAY: A polypill for secondary cardiovascular prevention reduces the risk of cardiovascular death and complications more than usual care.

STUDY DESIGN: Multinational, phase three, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Though effective medication regimens exist for the secondary prevention of cardiovascular disease, a lack of adherence to these regimens has been associated with poor outcomes. The polypill increases medication adherence by simplifying these regimens and has been studied in primary prevention of cardiovascular disease with promising results.

PATIENTS: Older adults who have had a type one myocardial infarction within the last six-months

INTERVENTION: Polypill

CONTROL: Usual care

PRIMARY OUTCOME: Composite of cardiovascular death, non-fatal type 1 myocardial infarction, nonfatal ischemic stroke, or urgent coronary revascularization

Secondary Outcome: Composite of cardiovascular death, nonfatal type 1 myocardial infarction, or nonfatal ischemic stroke

METHODS (BRIEF DESCRIPTION):

- Older adults who had had a type 1 myocardial infarction, defined as myocardial infarction from coronary plaque rupture or erosion followed by superimposed thrombosis, within six months were included in the trial.
  - Patients were at least 75 years old or at least 65 years old with risk factors (diabetes mellitus, chronic kidney disease, prior vascular events, etc.).
  - Patients who were on oral anticoagulants were excluded.
- Patients were recruited over the course of three years, and ultimately 2,499 out of 4,003 screened patients were both eligible and agreeable to participate in the trial.
- The trial occurred in 113 centers in Europe, including Spain, Italy, France, Germany, Poland, the Czech Republic, and Hungary.
- Patients were randomly assigned to either an intervention group or a usual care group via a centralized online system.
- Patients in the intervention group were assigned a combination pill containing aspirin (100 mg), ramipril (2.5, 5, or 10 mg), and atorvastatin (20 or 40 mg) and were compared to participants receiving usual care based on the current European Society of Cardiology guidelines.
- Medication adherence was measured using the Morisky Medication Adherence Scale at six- and 24-month visits. Scores ranged from 0 to 8 with higher scores representing better adherence.
- Treatment satisfaction was measured using the Treatment Satisfaction Questionnaire for Medication at baseline and 24-month visits.

INTERVENTION (# IN THE GROUP): 1,237

COMPARISON (# IN THE GROUP): 1,229

FOLLOW UP PERIOD: 48 months

RESULTS:

Primary Outcome –

- Patients receiving polypill therapy had a lower risk for the primary composite outcome compared to usual care (9.5% vs 13%, respectively; HR 0.76; 95% CI, 0.60–0.90; NNT=31).

Secondary Outcome –

- Patients receiving polypill therapy had a lower risk for the secondary composite outcome compared to usual care (8.2% vs 12%, respectively; HR 0.70; 95% CI, 0.54–0.90; NNT=29).

LIMITATIONS:

- Participants were not blinded.
- The sample was not representative of the population, with Black patients being underrepresented, thus limiting generalizability.

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Could Dabigatran Replace Warfarin Prophylaxis in Valvular Atrial Fibrillation?

Comparison of Dabigatran versus Warfarin Treatment for Prevention of New Cerebral Lesions in Valvular Atrial Fibrillation

Cho MS, Kim M, Lee SA, et al. Comparison of Dabigatran Versus Warfarin Treatment for Prevention of New Cerebral Lesions in Valvular Atrial Fibrillation. *Am J Cardiol*. 2022; 175:58-64. doi:10.1016/j.amjcard.2022.03.050

KEY TAKEAWAY: Dabigatran is noninferior to warfarin in decreasing the risk of developing new cerebral lesions in patients with significant valvular heart disease and atrial fibrillation (AF).

STUDY DESIGN: Randomized, prospective, open-label, single center, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Warfarin has been the standard therapy for anticoagulation in valvular atrial fibrillation, being the most studied and cost-effective treatment of choice. However, studies have yet to analyze the safety profile and efficacy of warfarin in comparison to non-vitamin K antagonist oral anticoagulants (NOACs) in the treatment of valvular AF.

PATIENTS: Adults with valvular atrial fibrillation

INTERVENTION: Dabigatran

CONTROL: Warfarin or aspirin

PRIMARY OUTCOME: Clinical stroke, new cerebral lesion

METHODS (BRIEF DESCRIPTION):

- Men (69%) and women (mean age 61 years old) who have moderate to severe native left-sided valvular heart disease and AF (for a mean of 6.6 years) with a $CHA_2DSVASc$ score ≥2 or 1 with left atrial enlargement were included.
- Adults with a history of stroke within two weeks, creatinine clearance (CrCl) <30 mL/min, increased risk of bleeding, thrombocytopenia <80,000, or anemia with Hgb <10 were excluded.
- Patients were randomized to:
  - 150 mg dabigatran twice daily (BID), reduced to 110 mg BID if CrCl was 30–49 mL/min
  - Control group with $CHA_2DSVASc$ score ≥2 and MS given warfarin targeting international normalized ratio (INR) of 2–3.
  - Control group with $CHA_2DSVASc$ score of one given warfarin or aspirin 100 mg once daily.
- Patients were followed every three months to evaluate medication adherence and clinical assessment.
- Primary endpoint was measured with brain magnetic resonance imaging (MRI), identifying newly developed silent brain infarction or microbleeds.
  - Changes were measured by obtaining a baseline then randomized at various follow-up points and at 12 months follow-up.
- Interpretation was relayed by independent neuroradiologists blinded to patient groups, with a second interpretation from a radiologist with good interobserver variability.

INTERVENTION (# IN THE GROUP): 59

COMPARISON (# IN THE GROUP): 60

FOLLOW UP PERIOD: 24 months

RESULTS:

- Dabigatran did not reduce the risk of stroke or silent brain lesion compared to the control group (34% vs 40%, respectively; RR 0.87; 95% CI, 0.59–1.3).
- Dabigatran did not reduce the risk of microbleeds at one year compared to the control group (4% vs 7%, respectively; RR 0.66; 95% CI, 0.21–2.1).

LIMITATIONS:

- Limited data on mitral stenosis severity was not clearly stratified.
- Race was vaguely reported in the study, therefore limiting generalizability.
- Small sample size and relatively short follow-up duration.

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Pain in the Tuchus: Intragluteal vs Intra-Articular Knee Injections

Effect of Intramuscular vs Intra-Articular Glucocorticoid Injection on Pain Among Adults with Knee Osteoarthritis: The KIS Randomized Clinical Trial

Wang Q, Mol MF, Bos PK, et al. Effect of Intramuscular vs Intra-articular Glucocorticoid Injection on Pain Among Adults with Knee Osteoarthritis: The KIS Randomized Clinical Trial. *JAMA Netw Open*. 2022 Apr 1;5(4):e224852. doi: 10.1001/jamanetworkopen.2022.4852.

KEY TAKEAWAY: At four weeks, intramuscular (IM) injections are inferior to intra-articular (IA) injections in improving pain from knee osteoarthritis. At eight and 24 weeks, IM injections are noninferior to IA for managing knee osteoarthritis in the primary care setting.

STUDY DESIGN: Multisite, noninferiority, unblinded randomized trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to unblinded procedure and lack of placebo)

BRIEF BACKGROUND INFORMATION: Studies on IA glucocorticoid injections reveal improved knee pain with some risks for cartilage loss and septic arthritis. The effect of IM glucocorticoid injections is unknown in this population. In patients with rotator cuff disease and hand osteoarthritis, IM glucocorticoid injections have been found to improve pain.

PATIENTS: Adults with knee osteoarthritis

INTERVENTION: IM glucocorticoid injection

CONTROL: IA glucocorticoid injection

PRIMARY OUTCOME: Pain at four weeks

Secondary Outcomes: Pain at two, eight, 12, and 24 weeks, adverse events

METHODS (BRIEF DESCRIPTION):

- Patients ≥45 years old from the southwest region of the Netherlands diagnosed with knee osteoarthritis in the past five years were included.
- Participants had osteoarthritis diagnosed by a general practitioner with symptoms for three months with moderate to severe pain in the past week (pain rated 0–10 with higher scores indicating more pain).
- Patients were excluded if they had inflammatory rheumatic disease, were using oral glucocorticoids, or received an IA injection within six months.
- The mean age was 67 years old with an average BMI of 29.
- The average knee injury and osteoarthritis score pain subscale (KOOS, range 0–100, 0 indicating extreme pain) was 55.
- 94 women and 51 men were included.
- The intervention group received a single IM injection of triamcinolone acetonide 40 mg in the ipsilateral ventrogluteal region.
- The comparison group received a single IA injection of triamcinolone acetonide 40 mg in the symptomatic knee.
- The primary pain outcome was measured via KOOS (with –7 noninferiority margin) at four weeks after injection.
- The secondary pain outcome was measured via KOOS pain score at two, eight, 12, and 24 weeks.
- Adverse events were measured at two weeks.

INTERVENTION (# IN THE GROUP): 72

COMPARISON (# IN THE GROUP): 66

FOLLOW UP PERIOD: 24 weeks

RESULTS:

Primary Outcome –

- IM treatment was inferior to IA treatment for pain reduction at four weeks (mean difference [MD] –3.4; 95% CI, –10 to –3.3).

Secondary Outcomes –

- IM treatment was noninferior for pain reduction at eight and 24 weeks.
  - Eight weeks: MD 0.7 (95% CI, –6.5 to 7.8)
  - 24 weeks: MD 1.6 (95% CI, –5.7 to 9.0)
- IM treatment was inferior for pain reduction at two and 12 weeks compared to IA treatment.
  - Two weeks: MD –1.8 (95% CI, –8.8 to 5.3)
  - 12 weeks: MD –1.6 (95% CI, –8.8 to 5.7)
- Adverse events were similar in both groups except for hot flushes (10% in IM group vs 21% in IA group).
- Rate of repeat injections was lower in the IM group compared to the IA group (0% vs 6%, respectively).

LIMITATIONS:

- Participants and providers were unblinded.
- The study lacked a placebo group.
- The clinical margin of noninferiority was subjectively chosen.

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Can Anything Be Done to Improve Healthcare Access in Rural Communities?

Rural Patient Experiences of Accessing Care for Chronic Conditions: A Systematic Review and Thematic Synthesis of Qualitative Studies

Golembiewski EH, Gravholt DL, Torres Roldan VD, et al. Rural Patient Experiences of Accessing Care for Chronic Conditions: A Systematic Review and Thematic Synthesis of Qualitative Studies. *Ann Fam Med*. 2022;20(3):266-272. doi:10.1370/afm.2798

KEY TAKEAWAY: Self-reported barriers to healthcare in rural areas include perceived suboptimal quality, financial and social support, and cultural mores such as self-sufficiency and not seeing the need for formal healthcare. Further understanding of these barriers can help decrease the mortality gap between rural and suburban patients suffering from chronic illness.

STUDY DESIGN: Systematic review and thematic synthesis of 62 qualitative studies (N=1,354)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to variability in outcomes and small studies)

BRIEF BACKGROUND INFORMATION: Rural communities have long struggled to access healthcare for their chronic medical conditions. Due to a lack of quantitative clinical research, qualitative synthesis could point to recurring themes in rural settings regarding healthcare access.

PATIENTS: Patients with chronic diseases

INTERVENTION: Living in a rural setting

CONTROL: General U.S. population

PRIMARY OUTCOME: Themes associated with limited access to healthcare

METHODS (BRIEF DESCRIPTION):

- Data was captured through interviews and focus groups.
- Qualitative studies from 2010 to 2019 in Embase, MEDLINE, PsycInfo, CINAHL, and Scopus were chosen based on inclusion of adult patients, qualitative data, participants living in rural U.S., and presence of one diagnosed chronic health condition.
- Four primary analytic themes were determined through independent coding of quotes and responses from participants and study authors' interpretive statements.
  - Theme 1: Navigating the rural environment; Theme 2: navigating the healthcare system; Theme 3: financing chronic disease; Theme 4: culture of rural life
- Chronic conditions in participants surveyed: cancer (24%), behavioral health (16%), HIV/AIDS (15%), type 1 or 2 diabetes (13%), any or multiple chronic diseases (13%), other (32%)

INTERVENTION (# IN THE GROUP): 1,354

COMPARISON (# IN THE GROUP): The general U.S. population

FOLLOW UP PERIOD: Not applicable

RESULTS: In the quantitative analysis, four themes were identified on the associations between living in a rural setting and having limited access to health care.

- Theme 1: Navigating the rural environment
  - 48 studies discussed the financial burden and cost of lengthy travel.
  - 45 studies discussed the barrier of suboptimal social support.
  - 27 studies discussed the barrier of willingness to travel.
- Theme 2: Navigating the healthcare system
  - 22 studies discussed delays in care.
  - 33 studies discussed miscommunications in care continuity.
  - 29 studies discussed complexities of healthcare systems' structures.
- Theme 3: Financing chronic disease
  - 31 studies discussed the additional costs of rural living.
  - 26 studies discussed the barrier of competing expenses.
  - 14 studies discussed the barrier of their baseline economic condition.
- Theme 4: Culture of rural life
  - 13 studies discussed the barrier of close communities and lack of privacy.
  - 12 studies discussed the perceived lack of need for healthcare.
  - 12 studies discussed the lack of cultural sensitivity.

LIMITATIONS:

- Definition variability of *rural*, *access*, and *chronic health conditions*.
- Few studies analyzed telemedicine, but this has changed significantly since the onset of the COVID-19 pandemic.

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