Top studies of 2021 relevant to primary care

From the PEER team

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Abstract

Objective To summarize 10 high-quality studies or guidelines from 2021 that have strong relevance to physicians in comprehensive family practice.

Selecting the evidence Routine literature surveillance of abstracts in high-impact journals and EvidenceAlerts was completed by the PEER (Patients, Experience, Evidence, Research) team, a group of health care professionals with a research interest in evidence-based medicine and primary care. Abstracts were screened, selected, and ranked by the PEER team.

Main message The articles from 2021 that are most likely to impact primary care practice discuss the following topics: empagliflozin for heart failure with preserved ejection fraction; semaglutide for weight loss; stopping antidepressants in primary care; inhaled budesonide for COVID-19; acetylsalicylic acid for preeclampsia prevention; quarter-dose blood pressure medications for hypertension; aggressive blood pressure control for elderly patients; kangaroo care for low-birth-weight infants; footwear for knee osteoarthritis; and delayed antibiotics for pediatric respiratory infections. Two "honourable mention" studies are also briefly reviewed.

Conclusion Research from 2021 produced several high-quality studies in cardiovascular care but also addressed a variety of conditions relevant to primary care including weight loss, depression, and COVID-19.

Each year, an overwhelming number of medical articles are published, making it challenging for family physicians to keep up to date on the literature. We have summarized our selection of the top 10 articles from 2021, along with 2 "honourable mentions," that we believe will offer value for physicians in comprehensive family practice.

Selecting the evidence

The PEER (Patients, Experience, Evidence, Research) team identified studies and guidelines by routine surveillance of the tables of contents from high-impact medical journals (eg, *New England Journal of Medicine* and *The Lancet*). We also regularly reviewed EvidenceAlerts[1] and the American College of Physicians Journal Club,[2] both of which identify highly rated articles relevant to primary care. The studies were ranked by our team. All results are statistically significant unless otherwise noted.

Main message

Does empagliflozin reduce cardiovascular outcomes in patients who have heart failure with preserved or mildly reduced ejection fraction (>40%)?

Bottom line: In patients with chronic heart failure and ejection fraction greater than 40%, empagliflozin reduces the risk of hospitalization for heart failure regardless of the presence of diabetes.

Editor's key points

- Staying apprised of the vast amount of new literature relevant to primary care presents a considerable challenge. The authors of this review summarize what they believe were the top 10 studies or guidelines (and 2 honourable mentions) of 2021 that could have meaningful effects on comprehensive family medicine practice.
- Studies relate to a variety of conditions and topics commonly encountered in primary care, including cardiovascular disease, weight loss, depression, COVID-19, prenatal and neonatal care, knee osteoarthritis, and antibiotic prescribing.
- Honourable mentions include effects of salt substitutes on cardiovascular outcomes and psilocybin for moderate to severe depression.

Methods: A double-blind randomized controlled trial (RCT) (N=5988) compared 10 mg of empagliflozin with placebo in patients with chronic heart failure and ejection fraction greater than 40% (mean age 72; 49% had diabetes; 82% had New York Heart Association class II heart failure; 67% had an ejection fraction ≥50%).[3]

Results: At 26 months, empagliflozin reduced the primary composite outcome (cardiovascular death or hospitalization for heart failure) to 13.8% compared with 17.1% with placebo (number needed to treat [NNT]=31). Benefit was driven by the reduction in hospitalizations for heart failure, with no impact on all-cause death (14.1% vs 14.3%), and was similar in those with or without diabetes. Empagliflozin increased risk of hypotension (10.4% vs 8.6%; number needed to harm [NNH]=56), urinary tract infections (9.9% vs 8.1%; NNH=56), and genital infections (2.2% vs 0.7%; NNH=67).

Does semaglutide help with weight loss?

Bottom line: Semaglutide reduces weight in patients with obesity, but weight is regained after stopping the medication.

Methods: Two double-blind RCTs examined the effect of semaglutide (2.4 mg/wk, subcutaneously) on weight loss in patients without diabetes (mean age 46; 21% to 26% male; baseline body mass index of about 38 kg/m^2). One RCT (N=1961) compared semaglutide with placebo for 68 weeks,[4] and the other (N=803) gave semaglutide for 20 weeks followed by randomization to continuation of semaglutide or to placebo for 48 weeks.[5]

Results: At 68 weeks, semaglutide reduced weight (-15.3 kg) compared with placebo (-2.6 kg; difference of 12.7 kg), leading to more patients with a 10% or greater loss of their body weight (69.1% vs 12.0%; NNT=2).[4] Semaglutide increased gastrointestinal adverse effects (74% vs 48%; NNH=4) and stopping medication owing to adverse events (7% vs 3%; NNH=25).[4] In the second RCT, after a mean 11-kg weight loss at 20 weeks, continuing semaglutide further reduced weight (-7.1 kg), whereas weight gain occurred after discontinuation (gain of 6.1 kg; difference of 13.2 kg).[5]

Is discontinuing antidepressants safe in patients with depression who are in remission?

Bottom line: In patients taking long-standing antidepressants who are in remission, discontinuing treatment results in more patients relapsing at 1 year compared with continuing treatment.

Methods: In a multicentre, double-blind, primary care RCT (N=478), adults with a long-standing history of depression (mean age 54; 93% had had ≥3 depressive episodes; 70% had been taking antidepressants for ≥3 years) who were feeling well enough to consider stopping were randomized to continuing or discontinuing (using placebo) treatment.[6] Patients had been taking a common antidepressant (citalopram, sertraline, fluoxetine, or mirtazapine) for at least 9 months.

Results: At 1 year, relapse occurred in 39% of those in the continuation group and in 56% of those in the discontinuation group (NNH=6). Discontinuation was also associated with more withdrawal symptoms and higher depression and anxiety scores. These results are similar to those of previous studies.[7]

Are inhaled steroids effective in community patients with COVID-19?

Bottom line: Among outpatients with COVID-19 infection, inhaled budesonide may shorten time to recovery and reduce need for health services.

Methods: An open-label trial randomized nonhospitalized patients whose test results were positive for COVID-19 and who were aged 65 years or older, or 50 years and older with comorbidities, to 800 µg of inhaled budesonide twice daily for 14 days or to usual care (N=1856; mean age 64; about 80% had comorbidities).[8] A smaller RCT also randomized patients to inhaled budesonide or usual care (N=146; generally lower risk; mean age 45).[9]

Results: Both trials suggested that budesonide improves recovery at 14 days compared with usual care, with a recovery rate of 32% versus 22% (NNT=10) in the larger trial.[8] Budesonide also shortened time to recovery (12 vs 15 days)[8] and reduced urgent care and higher-acuity visits (3% vs 15%; NNT=9).[9] Budesonide had a positive but not statistically significant effect on hospitalizations or death (6.8% vs 8.8%).[8]

Does low-dose acetylsalicylic acid (ASA) prevent preeclampsia and related complications?

Bottom line: In pregnant women at increased risk of preeclampsia, daily low-dose ASA reduces risk of preeclampsia, perinatal mortality, preterm birth, and small-for-gestational-age birth weight, with no evidence of harms.

Methods: The US Preventive Services Task Force conducted a systematic review and meta-analysis of 18 RCTs of daily low-dose ASA (50 to 150 mg) in pregnant women at increased risk of preeclampsia (N=15,908; mean ages 24 to 33).[10]

Results: The ASA (100 mg/d was most frequently used) was usually started between weeks 11 and 18 and continued until delivery or near term. Use of ASA resulted in less preeclampsia (9.6% vs 11.3%; NNT=60), perinatal mortality (2.1% vs 2.7%; NNT=179), and preterm birth (17.9% vs 22.4%; NNT=23), and fewer small-for-gestational-age infants (8.5% vs 10.4%; NNT=54), with no increase in maternal or perinatal harms.

The US Preventive Services Task Force recommends ASA (81 mg/d) after 12 weeks' gestation in women at high risk of preeclampsia.[11]

Does a single pill combining 4 low-dose medications reduce blood pressure (BP) more than a higher-dose single agent?

Bottom line: A single pill with 4 low-dose antihypertensive agents decreased BP more effectively than a single agent at a higher dose.[12]

Methods: In a multicentre, blinded RCT, Australian adults with hypertension (N=591; mean age 59; baseline BP 141/85 mm Hg) were randomized to a once-daily "quad pill" (4 medications: 37.5 mg of irbesartan, 1.25 mg of amlodipine, 0.625 mg of indapamide, and 2.5 mg of bisoprolol) or to 150 mg of irbesartan once daily.

Results: At 12 weeks, patients taking quad pills had greater decreases in BP (7 mm Hg systolic and 6 mm Hg diastolic pressure), were more likely to achieve BP below 140/90 mm Hg (76% vs 58%; NNT=6), and were less likely to require add-on therapy (15% vs 40%; NNT=4) than patients taking the single agent. There were no statistically significant differences in serious adverse events or self-reported side effects. The study was limited by its short duration and because patient-oriented outcomes (eg, cardiovascular events) were not reported. The quad pill is not commercially available in Canada.

Does more-intensive BP control reduce cardiovascular outcomes compared with standard control in older patients with hypertension?

Bottom line: Targeting an office systolic pressure (SBP) of 110 to 130 mm Hg in patients 60 to 80 years of age reduces cardiovascular events compared with treating to a target SBP of 130 to 150 mm Hg.

Methods: A non-blinded RCT in China (N=8511) randomized patients with hypertension (mean age 66; 47% male; 19% had diabetes; 65% had Framingham 10-year risk scores ≥15%) to "intensive" (office SBP target of 110 to 130 mm Hg) versus "standard" (SBP of 130 to 150 mm Hg) BP control.[13]

Results: At 1 year, mean SBP was 128 mm Hg in the intensive arm compared with 135 mm Hg in the standard arm. At 3.3 years, 3.5% of participants in the intensive group developed the primary composite outcome (stroke, acute coronary syndrome, decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes) versus 4.6% in the control group (NNT=91). There was no statistically significant difference in death. The only adverse effect more common with intensive treatment was hypotension (3.4% vs 2.6%; NNH=125).

Does early kangaroo care reduce mortality compared with conventional care in low-birth-weight infants?

Bottom line: In developing countries, kangaroo care initiated as quickly as possible in low-birth-weight infants reduces infant mortality at 28 days. These results can be implemented in the developed world and did not show harm.

Methods: A multicentre RCT conducted in Africa and India compared immediate kangaroo care (skin-to-skin contact with infant on mother's chest) with conventional care (incubator until stable) in infants with birth weights of 1.0 to 1.8 kg (N=3211; mean birth weight 1.5 kg; mean gestational age 33 weeks).[14] Infants had to be spontaneously breathing by 1 hour after birth to be enrolled. Once stable for 24 hours, infants were transferred to the unit where continuous kangaroo care was provided to all.

Results: Kangaroo care was initiated earlier in the intervention group (1.3 vs 54 hours in the control group) and duration of skin-to-skin contact was longer (17 vs 1.5 hours per day). Infant mortality was reduced at 28 days (12% vs 15.7%; NNT=27). Sepsis-related mortality was lower with kangaroo care (4.4% vs 6.9%; NNT=40). Time to stabilization (about 74 hours) was not different between groups, contrary to previous studies.[15,16]

Do stable, supportive shoes improve knee osteoarthritis (OA) symptoms compared with flat, flexible shoes?

Bottom line: Stable, supportive shoes with elevated heels, arch support, and rigid soles improve knee OA pain when compared with flatter and more flexible shoes.

Methods: In this RCT (N=164), patients with moderate to severe knee pain and medial knee OA on radiographs (mean age 65; 38% male) were randomized to stable, supportive (heel thickness >3 cm, arch support, rigid sole) or flat, flexible (heel thickness <1.5 cm, no arch support, flexible sole) shoes.[17] Shoes were worn for about 8 hours per day.

Results: Baseline pain scores were 6.2 out of 10. At 6 months, pain improved more with stable, supportive shoes (2.1 points) than with flat, flexible shoes (1.1 points). More patients in the stable, supportive shoes arm achieved the prespecified minimally clinically important difference (1.8 points) in walking knee pain (58% vs 40%; NNT=6). Fewer patients in the stable, supportive arm (12% vs 32%) experienced adverse events (eg, foot or ankle pain).

What is the impact of delayed antibiotic prescribing on patient outcomes in children?

Bottom line: Delayed antibiotic prescribing for common respiratory infections can substantially reduce antibiotic use in primary care without important negative consequences.

Methods: An RCT of children (N=436; mean age 6) presenting with respiratory infections (51% otitis media, 34% pharyngitis, 9% acute bronchitis, 6% rhinosinusitis) randomized them to immediate, delayed, or no antibiotics if the pediatrician had reasonable doubts that antibiotics were indicated.[18] Mean duration of symptoms at the first visit was 2.5 days.

Results: Antibiotic use was 96% in the immediate group, 25% in the delayed group, and 12% in the no-antibiotic group. Delayed prescriptions reduced antibiotic use by 71% compared with an immediate strategy (NNT=2). No differences were identified in most outcomes, including symptom duration, symptom severity,

follow-up visits, and parent satisfaction. A few outcomes, like cough score, were slightly worse with delayed versus immediate antibiotics (3 vs 2, on a 7-point scale). Results are consistent with a recent systematic review in adults and children that showed no difference in symptom severity, reconsultation, and complications.[19]

Honourable mentions

What impact do salt substitutes have on cardiovascular outcomes?

Bottom line: Switching to a salt substitute (by partially replacing sodium with potassium) may decrease the risk of stroke, major adverse cardiovascular events, and death in patients with history of stroke or those 60 years of age or older with elevated BP. Salt substitutes with potassium are available in Canada (eg, Half Salt).

Methods: In a cluster RCT (N=20,995; mean age 65; 88% had hypertension) in 600 rural villages in China,[20] patients with a history of stroke (73%) or who were aged 60 or older with elevated BP were randomized to a salt substitute (75% sodium chloride, 25% potassium chloride) or regular salt (100% sodium chloride) for cooking and preserving.

Results: Baseline BP was 154/89 mm Hg. Systolic BP was 3.3 mm Hg lower in the salt substitute group. Over 5 years, stroke was significantly reduced in the salt-substitute group (29 vs 34 events per 1000 person-years). The composite cardiovascular outcome (nonfatal stroke, nonfatal acute coronary syndrome, or death) was also reduced per 1000 person-years (49 vs 56 events), as was all-cause death (39 vs 45 events). Clinical hyperkalemia was not statistically different between groups, but potassium levels were not routinely measured during the trial.

Is psilocybin effective for moderate to severe depression compared with escitalopram?

Bottom line: Psilocybin may have a role in improving moderate to severe depression, but larger and longer trials are needed. If used, psilocybin will be resource intensive and require specialist referral. Psilocybin is currently available in Canada under the Special Access Program.

Methods: A double-blind RCT (N=59) compared psilocybin (2 doses of 25 mg, 3 weeks apart) with escitalopram (titrated to 20 mg/d).[21] Participants were adults (mean age 41; 66% male) with moderate to severe depression (mean duration of 19 years). Mental health professionals supported patients for 4 to 6 hours during the psilocybin sessions as well as before and after psilocybin dosing.

Results: The primary outcome was change from baseline on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (possible scores range from 0 to 27, with higher scores representing worse symptoms). At 6 weeks, psilocybin reduced scores by 8.0 points, which was not statistically different from escitalopram (6.0 points). However, remission (score ≤5) was achieved in 57% of psilocybin patients compared with 28% taking escitalopram (NNT=4). Patients reported more headache on day 1 of psilocybin (43% vs 17% with escitalopram; NNH=4). Dry mouth and anxiety were more common with escitalopram than psilocybin (14% vs 0% for both adverse effects; NNH=8) over 6 weeks.

Conclusion

Research from 2021 produced several high-quality studies in cardiovascular care but also addressed a variety of conditions relevant to primary care including weight loss, depression, and COVID-19.

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All authors contributed to the literature review and interpretation, and to preparing the manuscript for submission.

Competing interests

None declared

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