

### 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 topics (and 5 runners-up) of 2018 that could have meaningful effects on comprehensive family medicine practice.

► Topics included primary prevention of cardiovascular disease, diets for weight loss, vulvovaginal symptoms in menopause, opioid versus nonopioid pain management, recurrent cystitis, omega-3 fatty acids, cardiovascular outcomes with icosapent, bath additives for eczema, febrile seizure, and glycemic targets.

► Runners-up included increasing inhaled steroids for pediatric and adult asthma; human papillomavirus testing versus cytology for Papanicolaou tests; the effect of remeasuring blood pressure; antibiotics versus appendectomy for appendicitis; and steroids versus night splints for carpal tunnel syndrome.

# Top studies relevant to primary care from 2018

## From PEER

Danielle Perry PharmD Samantha Moe PharmD Christina Korownyk MD CCFP  
Adrienne J. Lindblad ACPR PharmD Michael R. Kolber MD CCFP MSc  
Betsy Thomas PharmD Joey Ton PharmD Scott Garrison MD PhD CCFP  
G. Michael Allan MD CCFP FCFP

### Abstract

**Objective** To summarize high-quality studies for 10 topics from 2018 that have strong relevance to primary care practice.

**Quality of evidence** Study selection involved routine literature surveillance by a group of primary care health professionals. This included screening abstracts of important journals and Evidence Alerts, as well as searching *ACP Journal Club*.

**Main message** Topics of the 2018 articles include whether low-dose acetylsalicylic acid improves health outcomes like cardiovascular disease (CVD); whether a low-carbohydrate diet is better than a low-fat diet for weight loss (and whether genetics matter); whether vaginal estradiol is superior to placebo for vulvovaginal symptoms of menopause; whether opioid management is better than nonopioid management for chronic back or osteoarthritis pain; whether additional water intake will decrease recurrent urinary tract infections; whether omega-3 fatty acids prevent CVD or reduce dry eyes; whether the new drug icosapent improves CVD; whether bath additives help eczema; whether acetaminophen can prevent recurrent febrile seizures; and recommendations for glycemic targets in diabetes based on reviews of evidence and other guidelines. Five “runner-up” studies are also briefly reviewed.

**Conclusion** Research from 2018 produced several high-quality studies in CVD but also spanned the breadth of primary care including pediatrics, women's health, and pain management, among other areas.

**K**eeping apprised of the large volume of new medical literature relevant to primary care presents a virtually impossible challenge. In this annual article, we summarize the top 10 topics (and 5 runners-up) that we suspect could have meaningful effects on comprehensive family medicine practice.

### Quality of evidence

The studies are identified by first scanning the tables of content from selected high-impact medical journals (like the *New England Journal of Medicine* and *JAMA*). Second, we review Evidence Alerts,<sup>1</sup> a service that daily identifies highly rated articles relevant to primary care. Last, we review the *ACP Journal Club*, which is published every 6 weeks and identifies important and high-quality articles for general internal medicine. These articles are then ranked by the PEER (Patients, Experience, Evidence, Research) Group, comprising family physicians and primary care health practitioners focused on providing actionable evidence for primary care providers and their patients.

**Main message****Does daily low-dose acetylsalicylic acid (ASA) improve cardiovascular outcomes in primary prevention?**

**Bottom line:** Daily, low-dose (100 mg) ASA in primary prevention did not prevent cardiovascular disease (CVD)<sup>2,3</sup> or only slightly reduced it (1% over 7 years).<sup>4</sup> Any benefit in CVD was offset by an increased risk of bleeding. Additionally, there were no reductions in cancer, and 1 trial found increased mortality.<sup>3,5</sup> Overall, ASA should not be used for primary prevention (ie, patients without CVD).

**Methods:** Three randomized controlled trials (RCTs) of 100 mg of ASA daily versus placebo for primary prevention followed 12546 adults (mean age 64, 70% male) at moderate CVD risk (10% to 20%) for 5 years<sup>2</sup>; 15480 patients with type 2 diabetes (mean age 63, 63% male) for 7.4 years<sup>4</sup>; and 19114 older adults (mean age 74, 44% male) for 4.7 years.<sup>3,5</sup>

**Results:** Taking 100 mg of ASA daily did not improve cardiovascular outcomes for adults at moderate risk (4.29% vs 4.48%)<sup>2</sup> or older adults (3.5% vs 3.9%).<sup>3</sup> In adults with type 2 diabetes, CVD occurred in 8.5% of those taking ASA compared with 9.6% taking placebo (rate ratio of 0.88; 95% CI 0.79 to 0.97).<sup>4</sup> Gastrointestinal<sup>2</sup> and major<sup>3,4</sup> bleeds were 0.5% to 1% higher for ASA users in all studies, giving a number needed to harm (NNH) of 100 to 200 over 5 to 7 years. No study found improvement in cancers, and 1 found ASA increased mortality (5.9% vs 5.2%; NNH=143 over about 5 years).<sup>5</sup>

**Which diet, low carbohydrate or low fat, is superior for achieving weight loss?**

**Bottom line:** Diet type, regardless of genetic predisposition, does not lead to statistically significant differences in weight loss for obese adults at 1 year. The diet that a patient can sustain is likely more important.<sup>6</sup>

**Methods:** An RCT (N=609) compared low-fat (<20 g/d) and low-carbohydrate (<20 g/d) diets for weight loss in obese adults (mean age 40, mean body mass index 33 kg/m<sup>2</sup>, 43% male) over 1 year. Participants could slowly increase the fat or carbohydrate to reach the minimum sustainable in the long term. The study used genotyping to determine if genetically predisposed participants lost more weight on the matched diet. Participants met frequently with a dietitian and were not asked to reduce caloric intake; however, mean caloric intake decreased by 500 to 600 kcal daily. Eating well and activity were encouraged.

**Results:** At 1 year, no statistical difference in weight loss was found between the low-fat (mean loss of about 5.3 kg) and low-carbohydrate (mean loss of about 6 kg) diets. Results from genetic testing found no significant interaction between diet and genotype. Weight changed in both groups from a 10-kg gain to a 30-kg loss.

**What works best for improving vulvovaginal symptoms in menopausal women?**

**Bottom line:** For treating bothersome vulvovaginal symptoms in menopausal women, placebo gel has

comparative effectiveness to estradiol (10 µg) or commercial vaginal moisturizers.<sup>7</sup>

**Methods:** An RCT (N=302) compared estradiol 10 µg (Vagifem), vaginal moisturizer (Replens), and placebo gel for improvement in vulvovaginal “most bothersome symptom(s)” (vaginal penetration pain, dryness, itching, irritation, and pain) in menopausal women (mean age 61) over 12 weeks. Symptoms were scored from 0 to 3, with higher scores indicating more bothersome symptoms.

**Results:** No statistical differences between estradiol, vaginal moisturizer, or placebo gel were found. From a 2.5 baseline mean score, symptom scores improved to 1.2 to 1.4 in all groups. No differences in adverse events or almost any other outcomes were found.

**Do opioid or nonopioid medications work better for treating chronic back and osteoarthritis pain?**

**Bottom line:** In adults with chronic back or osteoarthritis pain, nonopioid management led to similar or slightly better (0.5 on a 10-point scale) pain control than opioid management at 1 year. Function and quality of life were not different. Opioids led to more medication-related adverse effects.<sup>8</sup>

**Methods:** An RCT (N=240) compared opioids with nonopioid agents (acetaminophen, nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, lidocaine, capsaicin, pregabalin, duloxetine) in adults with chronic back (65%) or osteoarthritis (35%) pain over 1 year. Participants (mean age 58, 87% male) started with a baseline pain score of 5.4 out of 10.

**Results:** At 1 year, pain score was significantly ( $P=.03$ ) lower in the nonopioid group (3.5 out of 10) versus the opioid group (4 out of 10). Other outcomes, including function, quality of life, and emergency department use, were not significantly different. Side effects occurred more frequently in those taking opioids compared with those taking nonopioid agents (2 symptoms reported vs 1 from a 19-item checklist;  $P=.03$ ). Tramadol was used by 11% of the nonopioid group for additional pain relief, and 85% of the opioid group used less than 50 mg of morphine equivalent per day.

**Does increasing daily water intake improve recurrent urinary tract infections in women?**

**Bottom line:** Encouraging premenopausal women with recurrent cystitis to increase daily water consumption by 1.5 L per day can help reduce cystitis episodes.<sup>9</sup>

**Methods:** An RCT (N=140) compared increasing water consumption (1.5 L extra per day) with regular daily water consumption for prevention of cystitis in premenopausal women (mean age 36, mean of 3 episodes of cystitis in the past year) over 1 year.

**Results:** At 1 year, mean occurrence of cystitis was significantly less ( $P<.001$ ) in those randomized to additional water consumption (mean 1.7 episodes) compared with unchanged water consumption (mean 3.2 episodes). Most (93%) women drinking extra water had

fewer than 3 cystitis episodes a year (compared with 12% in the unchanged water consumption group), giving a number needed to treat (NNT) of 2 at 1 year.

#### ***Do omega-3 fatty acids reduce CVD in patients with diabetes or improve symptoms of dry eye disease?***

**Bottom line:** Omega-3 fatty acids do not reduce CVD, cancer, or death<sup>10,11</sup> and do not improve dry eye disease better than placebo.<sup>12</sup>

**Methods:** Two large primary prevention RCTs compared 1000 mg daily of omega-3 fatty acids with placebo in 15480 patients with diabetes (mean age 63, 63% male) over 7.4 years<sup>10</sup> and 25871 patients (mean age 67, 49% male) over 5.3 years.<sup>11</sup> Another RCT (N=535) compared 3000 mg of omega-3 fatty acids (oral) with placebo for dry eye symptoms over 1 year (mean age 58, 19% male, baseline symptom score of 44 out of 100).<sup>12</sup>

**Results:** No difference was found in CVD, cancer, or death from any cause between patients taking omega-3 fatty acids and those taking placebo.<sup>10,11</sup> Improvement in dry eye symptoms was similar with omega-3 fatty acids and placebo (symptom score reduced by 14 vs 13 out of 100;  $P = .40$ ).<sup>12</sup>

#### ***Does icosapent improve cardiovascular outcomes in patients with a history of diabetes or CVD?***

**Bottom line:** In patients with a history of diabetes or CVD, icosapent reduced CVD for 1 in 21 patients over placebo after 5 years. Compared with placebo, icosapent caused 1 more patient in 72 to develop atrial fibrillation at 5 years.<sup>13</sup>

**Methods:** An RCT (N=8179) compared icosapent ethyl (2 g) twice daily with placebo for prevention of CVD in adults with established CVD or diabetes (median age 64, 71% male, 58% with diabetes, 71% with existing CVD, all taking statins) over 5 years. Icosapent is derived from eicosapentaenoic acid, one of the components of omega-3 fatty acids.

**Results:** At 5 years, CVD occurred less frequently in those taking icosapent (17.2%) compared with placebo (22.0%; hazard ratio of 0.75; 95% CI 0.68 to 0.83; NNT=21). Specifically, stroke, myocardial infarction, and CVD death occurred less often in the icosapent group (11.2%) compared with placebo (14.8%; hazard ratio of 0.74; 95% CI 0.65 to 0.83; NNT=28). Atrial fibrillation was more common in those taking icosapent (5.3%) compared with placebo (3.9%; NNH=72). Icosapent reduced triglyceride levels by approximately 20% compared with placebo.

#### ***Can acetaminophen prevent recurrent febrile seizures in children?***

**Bottom line:** Treating fever in children with acetaminophen reduces recurrent seizures for that fever. Ability to prevent initial seizure or future seizures with new fever is unclear.<sup>14</sup>

**Methods:** An RCT (N=438) compared using acetaminophen (10 mg/kg) suppository every 6 hours with

no antipyretics for prevention of recurrent febrile seizures in children at 24 hours (aged 6 months to 5 years, 54% male, with 1 seizure and fever  $\geq 38^\circ\text{C}$ ).

**Results:** At 24 hours, recurrent seizure occurred less frequently in children taking acetaminophen (9%) versus no therapy (24%; NNT=7). Note that this study was done in Japan, where recurrent febrile seizure is more common, making successful intervention more likely.

#### ***Can bath additives improve symptoms of eczema in children?***

**Bottom line:** Bath additives did not statistically or clinically significantly improve eczema scores. Other outcomes important to patients remained unchanged.<sup>15</sup>

**Methods:** An RCT (N=483) compared emollient bath additives to no additives and assessed the patient-oriented eczema measure (POEM; scored 0 to 28; higher scores indicate more severe symptoms) at 16 weeks and 1 year in children (mean age 5, 49% male, mean POEM score of 10 [or moderate severity]).

**Results:** At 16 weeks, children in the bath additives group had improved 0.41 POEM points more, compared with those not using additives. The difference was not statistically or clinically significant, as POEM's minimally clinically important difference is 3. No difference was found in eczema exacerbations, quality of life, or steroid use.

#### ***American College of Physicians: guidance statement on hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) targets for nonpregnant adults with diabetes***

**Bottom line:** Recommendations for HbA<sub>1c</sub> targets vary considerably among practice guidelines. Recommendations for lower targets are often based on weaker evidence.<sup>16</sup>

**Methods:** Authors reviewed and assessed the quality of 6 diabetes guidelines specifically addressing HbA<sub>1c</sub> targets in nonpregnant adults.

**Results:** The 4 key recommendations were as follows:

- implement a personalized approach to glycemic control, considering cost, treatment burden, benefits and harms, and the patient's health, life expectancy, and preferences;
- target HbA<sub>1c</sub> levels between 7% and 8% for most patients;
- consider reducing pharmacotherapy for patients with HbA<sub>1c</sub> levels less than 6.5%; and
- treat to minimize symptoms of hyperglycemia and avoid HbA<sub>1c</sub> targets in patients with a life expectancy of less than 10 years.

Lower HbA<sub>1c</sub> targets in some guidelines appear to be linked to poorer use or assessment of evidence.

#### ***Runners-up***

**Increasing inhaled steroids for pediatric asthma:** In children taking daily low-dose steroids who had had at least 1 asthma exacerbation in the previous year, giving 5 times the dose of inhaled steroids at early signs of loss

of control does not improve symptoms or the number of exacerbations but might lead to small reductions (2 mm) in growth at 1 year.<sup>17</sup>

**Increasing inhaled steroids for adult asthma:** In adults taking daily low-dose steroids who had at least 1 asthma exacerbation in the past year, giving 4 times the dose of inhaled steroids when asthma deteriorated prevented exacerbations for 1 in 15 but caused thrush or dysphonia for 1 in 36 patients at 1 year.<sup>18</sup>

**Human papillomavirus testing versus cytology for Papanicolaou tests:** In women with no history of cervical cancer or cervical intraepithelial neoplasia grade 2 or worse, human papillomavirus testing every 4 years leads to less cervical intraepithelial neoplasia grade 3 or worse lesions (2 in 1000 women) compared with cytology screening every 2 years (5 in 1000 women).<sup>19</sup>

**Effects of remeasuring blood pressure (BP):** A study using an automated electronic medical record prompt to repeat BP measurement in all patients with BP greater than 140/90 mm Hg found an average decrease of 8 mm Hg, with 36% of these patients having a normal reading on repeat measure.<sup>20</sup>

**Antibiotics versus appendectomy for appendicitis:** In a 5-year follow-up to an RCT, adults treated with antibiotics for acute appendicitis had a cumulative recurrence of 39% but had fewer complications (7%) compared with those who had had an immediate appendectomy (24%).<sup>21</sup>

**Steroids versus night splints for carpal tunnel syndrome:** Adults with mild to moderate carpal tunnel syndrome randomized to methylprednisolone injections had improved pain (1.1 out of 10 more improvement) and symptoms at 6 weeks compared with those wearing night splints; however, this improvement was not sustained at 6 months.<sup>22</sup>

## Conclusion

Research from 2018 produced several high-quality studies in CVD but also spanned the breadth of primary care, including pediatrics, women's health, and pain management, among other areas.

**Ms Perry** is Knowledge Translation Expert with the Alberta College of Family Physicians in Edmonton. **Dr Moe** is Clinical Evidence Expert for the College of Family Physicians of Canada in Mississauga, Ont. **Dr Korownyk** is Associate Professor in the Department of Family Medicine at the University of Alberta in Edmonton. **Dr Lindblad** is Knowledge Translation and Evidence Coordinator for the Alberta College of Family Physicians and Associate Clinical Professor in the Department of Family Medicine at the University of Alberta. **Dr Kolber** is Professor in the Department of Family Medicine at the University of Alberta. **Ms Thomas** is Project Manager, Education and Knowledge Translation, for the Alberta College of Family Physicians. **Dr Ton** is Clinical Evidence Expert for the College of Family Physicians of Canada. **Dr Garrison** is Associate Professor in the Department of Family Medicine at the University of Alberta. **Dr Allan** is Director of Programs and Practice Support for the College of Family Physicians of Canada and Professor in the Department of Family Medicine at the University of Alberta.

### Contributors

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

### Competing interests

None declared

### Correspondence

**Dr G. Michael Allan;** e-mail [mallan@cfpc.ca](mailto:mallan@cfpc.ca)

## References

- Evidence Alerts [website]. Hamilton, ON: Health Information Research Unit, McMaster University. Available from: <https://plus.mcmaster.ca/EvidenceAlerts>. Accessed 2019 Jan 31.
- Gaziano J, Brotons C, Coppolecchia R, Cricelli C, Darius H, Gorelick P, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomized, double-blind, placebo-controlled trial. *Lancet* 2018;392(10152):1036-46.
- McNeil JJ, Wolfe R, Woods RL, Tonkin AM, Donnan GA, Nelson MR, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med* 2018;379(16):1509-18. Epub 2018 Sep 16.
- ASCEND Study Collaborative Group; Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, et al. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med* 2018;379(16):1529-39. Epub 2018 Aug 26.
- McNeil JJ, Nelson MR, Woods RL, Lockery JE, Wolfe R, Reid CM, et al. Effect of aspirin on all-cause mortality in the healthy elderly. *N Engl J Med* 2018;379(16):1519-28. Epub 2018 Sep 16.
- Gardner CD, Trepanowski JF, Del Gobbo LC, Hauser ME, Rigdon J, Ioannidis JPA, et al. Effect of low-fat versus low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: the DIETFITS randomized clinical trial. *JAMA* 2018;319(7):667-79.
- Mitchell CM, Reed SD, Diem S, Larson JC, Newton KM, Ensrud KE, et al. Efficacy of vaginal estradiol or vaginal moisturizer versus placebo for treating postmenopausal vulvovaginal symptoms: a randomized clinical trial. *JAMA Intern Med* 2018;178(5):681-90.
- Krebs EE, Gravelly A, Nugent S, Jensen AC, DeRonne B, Goldsmith ES, et al. Effect of opioid versus nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: the SPACE randomized clinical trial. *JAMA* 2018;319(9):872-82.
- Hooton TM, Vecchio M, Iroz A, Tack I, Dornic Q, Seksek I, et al. Effect of increased daily water intake in premenopausal women with recurrent urinary tract infections: a randomized clinical trial. *JAMA Intern Med* 2018;178(11):1509-15.
- The ASCEND Study Group Collaborative. Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med* 2018;379(16):1540-50. Epub 2018 Aug 26.
- Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, et al. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med* 2019;380(1):23-32. Epub 2018 Nov 10.
- The Dry Eye Assessment and Management Study Research Group. n-3 Fatty acid supplementation for the treatment of dry eye disease. *N Engl J Med* 2018;378(18):1681-90. Epub 2018 Apr 13.
- Bhatt D, Steg G, Miller M, Brinton E, Jacobson T, Ketchum S. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med* 2019;380(1):11-22. Epub 2018 Nov 10.
- Murata S, Okasora K, Tanabe T, Ogino M, Yamazaki S, Oba C, et al. Acetaminophen and febrile seizure recurrences during the same fever episode. *Pediatrics* 2018;142(5):e20181009. Epub 2018 Oct 8.
- Santer M, Ridd MJ, Francis NA, Stuart B, Rumsby K, Chorozoglou M. Emollient bath additives for the treatment of childhood eczema (BATH): multicentre pragmatic parallel group randomized controlled trial of clinical and cost effectiveness. *BMJ* 2018;3(361):k1332.
- Qaseem A, Wilt TJ, Kansagara D, Horwitch C, Barry MJ, Forciea MA, et al. Hemoglobin A<sub>1c</sub> targets for glycemic control with pharmacologic therapy for nonpregnant adults with type 2 diabetes mellitus: a guidance statement update from the American College of Physicians. *Ann Intern Med* 2018;168(8):569-76. Epub 2018 Mar 6.
- Jackson DJ, Bacharier LB, Mauger DT, Boehmer S, Beigelman A, Chmiel JF, et al. Quin-tupling inhaled glucocorticoids to prevent childhood asthma exacerbations. *N Engl J Med* 2018;378(10):891-901.
- McKeever T, Mortimer K, Wilson A, Walker S, Brightling C, Skeggs A, et al. Quadrupling inhaled glucocorticoid dose to abort asthma exacerbations. *N Engl J Med* 2018;378(10):902-10.
- Ogilvie GS, van Neikerk D, Kraiden M, Smith LW, Cook D, Gondara L, et al. Effect of screening with primary cervical HPV testing versus cytology testing on high-grade cervical intraepithelial neoplasia at 48 months: the HPV FOCAL randomized clinical trial. *JAMA* 2018;320(1):43-52.
- Einstadter D, Bolen SD, Misak JE, Bar-Shain DS, Cebul RD. Association of repeated measurements with blood pressure control in primary care. *JAMA Intern Med* 2018;178(6):858-60.
- Salminen P, Tuominen R, Paajanen H, Rautio T, Nordstrom P, Aarnio M, et al. Five-year follow-up of antibiotic therapy for uncomplicated acute appendicitis in the APPAC randomized clinical trial. *JAMA* 2018;320(12):1259-65.
- Chesterton LS, Blagojevic-Bucknall M, Burton C, Dziedzic KS, Davenport G, Jowett SM, et al. The clinical and cost-effectiveness of corticosteroid injection versus night splints for carpal tunnel syndrome (INSTINCTS trial): an open-label, parallel group, randomized controlled trial. *Lancet* 2018;392(10156):1423-33.

This article is eligible for Mainpro+ certified Self-Learning credits. To earn credits, go to [www.cfp.ca](http://www.cfp.ca) and click on the Mainpro+ link.

La traduction en français de cet article se trouve à [www.cfp.ca](http://www.cfp.ca) dans la table des matières du numéro d'avril 2019 à la page e140.