Review of the top 5 geriatrics studies of 2018-2019

Cheryl A. Sadowski, BSc(Pharm), PharmD, FCSHP, BCGP; Morgan Bharadia, BSc(Pharm), RPh; Susan K. Bowles, BSc(Pharm), PharmD, MSc, FCSHP; Jennifer E. Isenor, BSc(Pharm), PharmD, RPh; Tejal Patel, BSc(Pharm), PharmD

Introduction

The literature in any specialty is vast and challenging for practitioners to keep up with. There is a need for publications summarizing current geriatrics practice for pharmacists in Canada. The objective of this review was to identify and summarize the most relevant published articles on geriatrics practice that pertain to pharmacists in Canada.

Methods

This study took place over 4 phases, using methodology previously described.[1-3]

Phase I—Literature search

Two investigators (MB, CS) conducted a literature search in October 2019 (updated December 2019) to identify articles published in the past 12 months. Searches in MEDLINE, EMBASE and Cochrane Library were limited to English-language, full-text publications and included the following keywords: *dementia, major neurocognitive disorder, delirium, falls, urinary incontinence, fecal incontinence, polypharmacy* and *medications*. In addition, the McMaster EvidenceAlerts and tables of contents of the *Journal of the American Geriatrics Society*, *Age and Ageing* and the *Canadian Geriatrics Journal* were searched. The presentation of the geriatrics update from the American Geriatrics Society for 2019 was reviewed for relevant articles. Consensus between both investigators (MB, CS) was used to identify the most relevant and highest-impact articles, with a target of <50 articles.

Phase II—Expert selection

The list of articles identified in phase I were compiled into SurveyMonkey and distributed to experts in geriatric pharmacy practice in Canada. The experts were identified by contacting the 10 academic (Faculty) programs in Canada and asking for their primary geriatrics lead. The experts were then asked to identify their top 15 choices.

Phase III—Pharmacist selection

Pharmacists who were not part of this geriatric expert group were contacted to identify articles that would be of interest to frontline practitioners. The pharmacists who were members of the Canadian Society of Hospital Pharmacists (CSHP) and Canadian Pharmacists Association (CPhA) joint primary care specialty network, the CSHP geriatrics specialty network and the CPhA Knowledge to Practice Advisory Circle (KPAC) were contacted. Through SurveyMonkey, these pharmacists were shown the top 15 articles and selected their top 5.

Phase IV—Summarizing articles

The top 5 articles were summarized by the investigators.

DOI:10.1177/17151635211018725

Results

LIPID MANAGEMENT

Van der Ploeg MA, Floriani C, Achterberg WP, et al. Recommendations for (discontinuation of) statin treatment in older adults: review of guidelines.* J Am Geriatr Soc *2020;68(2):417-25. Originally published online October 30, 2019.

Background/purpose: Statins are the most commonly prescribed class of medications for Canadian seniors.[4] Among those aged 85 years and older, 42% are prescribed statins,[4] despite the lack of evidence supporting the use of these agents in this age group. Statin prescriptions have been increasing, even in those who are severely frail or over 80 years of age, and statins are typically prescribed until death.[5,6] Although statins are commonly considered benign, they have risk and do not improve outcomes in the short term. Currently, there is little guidance on the discontinuation of statins in older adults. The purpose of this systematic review was to describe guideline content related to statin prescribing in older adults.

Search strategy and selection criteria: The authors searched articles and online guidelines from 2009 to 2019, and the guideline had to focus on cardiovascular disease (CVD) prevention concerning the general population. The guidelines were subjected to a quality measure (AGREE-II) and information was extracted regarding medication safety, health-related outcomes factors (e.g., frailty, health status), preferences (e.g., shared decision making) and if a statin should be started or continued.

Results: From 9502 records, 33 relevant guidelines were identified from 11 countries, including Canada. Fifteen guidelines did not address statin discontinuation at all; the remaining 18 guidelines were the focus of the review. All 18 guidelines discussed statin intolerance, with 16 recommending discontinuation. None of the guidelines recommended discontinuation based on age, but 3 guidelines suggested discontinuation if a patient has poor health status or limited life expectancy, sometimes referencing frailty, multimorbidity or functional decline. There were vague references to shared decision making, patient preferences, considering health status and pharmacokinetic/pharmacodynamic differences in a minority of the guidelines.

Implications for practice: This study highlights that individuals age 75 years and older are inadequately represented in statin studies and thereby underrepresented in clinical practice guidelines. Although the guidelines present the recommendations with very muted language, there appears to be general support for discontinuing statins for intolerance and in patients with poor health status, although this leaves the vague interpretation of "poor health status" and "intolerance" up to the clinician. Currently, a guide for statins is under development in Canada based on feedback from health care professionals.[7] Pharmacists can approach statin prescribing/deprescribing by integrating an assessment of frailty, medication burden and medication safety into decision-making with patients.

Bottom line for the front line: Frailty you diagnose? Then statin, adios.

POLYPHARMACY, FRAILTY, COGNITION

Porter B, Arthur A, Savva GM. How do potentially inappropriate medications and polypharmacy affect mortality in frail and non-frail cognitive impaired older adults? A cohort study.* BMJ Open *9(5):e026171.

Background/purpose: Frailty occurs when an individual's ability to recover from stressor events is limited due to the cumulative depletion of physiological reserves over time.[8] Frailty is a key driving factor in adverse health outcomes, hospitalizations and mortality.[8,9] Research is needed to explore the intersection of dementia, frailty and medication use, all of which increase with aging.[10-14] The objective of this study was to determine 1) the association between potentially inappropriate medications (PIMs) and survival among older adults with cognitive impairment and 2) the effect of frailty on this relationship.

Study population: Data were obtained from a sample of the cohort enrolled in the Cognitive Function and Aging Study II (CFAS II), which was designed to examine the epidemiology of dementia in primary care practices in England. Participants enrolled in this study provide data on socioeconomic characteristics, lifestyle, health, activities of daily living, cognition, health care and social-care contact and medications. The CFAS studies have recruited over 15,000 patients who have been followed for over 2 decades, representing one of the largest cohort studies relating to cognition. For the current analysis, data from participants ≥65 years, with a mini-mental status exam (MMSE) of ≤24 at baseline and reliable medication data, were included.

Outcomes: The primary outcome was survival at 8 years of follow-up. Univariate and multivariate analyses were conducted to investigate the impact of different classes of PIMs, polypharmacy (5-9 medications), hyperpolypharmacy (≥10 medications) and frailty on survival. PIMs were based on Screening Tool of Older Persons' Prescriptions (STOPP) criteria[15] with a specific focus on psychotropics, anticholinergics and proton

pump inhibitors (PPIs). Frailty status (not frail, prefrail and frail) was based on established criteria.[16]

Results: Of the 7762 CFAS II participants, 1154 met the eligibility criteria. The mean age of this sample was 79 years, 62% were female and 13% had a diagnosis of dementia. Participants had a mean (SD) of 2.4 (1.6) comorbidities and were taking 5.5 (3.6) medications. Forty-four percent were taking at least 1 PIM, and 42.7% and 9.5% were on polypharmacy and hyperpolypharmacy, respectively. At baseline, 36.4% were frail and 45.9% were prefrail.

Although polypharmacy, hyperpolypharmacy and use of antipsychotics were found to increase mortality significantly in univariate analysis, multivariate analysis that adjusted for frailty indicated that mortality was significantly different only among participants who were prescribed hyperpolypharmacy (hazard ratio [HR], 1.60; 95% confidence interval [CI], 1.16-2.22) and antipsychotics (HR, 3.28; 95% CI, 1.85-5.80). The other classes of PIMs (anticholinergics, antidepressants, benzodiazepines, PPIs) were not found to be significantly associated with mortality. Both prefrail and frail participants were at higher risk of mortality compared to individuals who were not frail in the adjusted model (prefrail HR, 1.56 [95% CI, 1.11-2.20]; frail HR, 1.90 [95% CI, 1.32-2.71]).

When stratifying by frailty status, the relative risk of mortality was not statistically significantly different among antipsychotic users at the different levels of frailty ($p = 0.995$). The results were similar for the other variables except for benzodiazepines, in which mortality was found to be significantly lower in frail individuals than not frail or prefrail individuals (frail HR, 0.43 [95% CI, 0.21-0.86]; not frail HR, 0.92 [95% CI, 0.11-7.78]; prefrail HR, 1.40 [95% CI, 0.66-2.97]).

Implications for practice: This study confirmed the highly prevalent use of polypharmacy, hyperpolypharmacy and PIMs in older adults with cognitive impairment. The use of 10 or more medications had a statistically significant impact on mortality, as did the use of antipsychotics, which aligns with current practices to encourage careful prescribing, deprescribing and avoiding PIMs. Most surprisingly, the study found a significantly lower risk of mortality among frail individuals on benzodiazepines compared to prefrail and not frail individuals. This result is interpreted as an outlier within the body of evidence of benzodiazepines and safety. This particular result should be used with caution because of small sample size, confounding based on the types of patients prescribed benzodiazepines, multiple analyses or chance.

Bottom line for the front line: A wise woman once said: Don't use antipsychotics.

ANTICOAGULATION

Deitelzweig S, Keshishian A, Li X, et al. Comparisons between oral anticoagulants among older nonvalvular atrial fibrillation patients.* J Am Geriatr Soc *2019;67(8):1662-71.

Background/purpose: Older adults receiving anticoagulation for atrial fibrillation (AF) receive the greatest benefit for stroke prevention but also have the greatest risk for serious bleeding events.[17] More than 50% of nonvalvular AF (NVAF) patients are over 80 years of age but represent only a fraction of study participants.[18] Because of a lack of evidence in this age group, consensus regarding the preferred anticoagulant for AF has not been achieved. The purpose of this retrospective observational study was to compare the risk of stroke, embolism and bleeding in patients 80 years and older with NVAF and who are prescribed non–vitamin K antagonist oral anticoagulants (NOACs) or warfarin.

Study population: This analysis was of the subset of patients age ≥80 years with NVAF who were part of the ARISTOPHANES (Anticoagulants for reduction in stroke: observational pooled analysis on health outcomes and experience in patients) study. Included seniors were covered by government programs in the United States and had started apixaban (A), dabigatran (D), rivaroxaban (R) or warfarin (W) between January 2013 and September 2015. Seniors were identified through databases with claims data.

Exposure and comparator: Comparative analyses for effectiveness and safety were done using propensity score matching of baseline characteristics to compare 6 pairs (A vs W, D vs W, R vs W, A vs D, A vs R and D vs R).

Outcomes: The primary outcomes were stroke or systemic embolism (S/SE) and major bleeding (MB). These outcomes were identified through hospital diagnoses on claims data. A secondary outcome was mortality.

Results: A total of 103,511 patients were included, with 49,801 (48%) being on W. In every comparison of NOACs to W, the NOACs were associated with lower risk of S/SE: A (HR, 0.58; 95% CI, 0.49-0.69), D (HR, 0.77; 95% CI, 0.60-0.99) and R (HR, 0.74; 95% CI, 0.65-0.85). Only A had a lower rate of MB (HR, 0.60; 95% CI, 0.54-0.67). D was similar to W (HR, 0.92; 95% CI, 0.78-1.07) and R had more MB (HR, 1.16; 95% CI, 1.07-1.24). Patients on A had a lower risk of S/SE and MB compared to D or R. D had similar risk of S/SE as R but lower risk of MB. The all-cause mortality was lower for all NOACs vs W, while A was superior to D and R and D was similar when compared to R.

Implications for practice: The increased use of NOACs has been supported by a systematic review that showed lower risk of bleeding complications and generally superior outcomes,[19] as well as guidelines that have recommended NOACs over warfarin.[20] This has led to increased use of NOACs as a choice over W for younger patients, but there was still hesitancy about safety in older adults, particularly those age 80 years and older,

leading to many being untreated. This study demonstrated that in adults over 80 years with NVAF, NOACs have superior effectiveness compared to W. Bleeding remains a risk, but in some cases, NOACs were safer than W. Although some research in this area is promising in terms of effectiveness and safety, we still require additional information on older adults who are frail, those who reside in long-term care facilities and patients with dementia or multimorbidity, while considering medication and monitoring burden, as well as pharmacoeconomics.[21]

Bottom line for the front line: Warfarin, we've met another anticoagulant, and we're leaving you.

BONE HEALTH

***Zullo AR, Zhang T, Lee Y, et al. Effect of bisphosphonates on fracture outcomes among frail older adults.* J Am Geriatr Soc 2019;67:768-76.**

Background/purpose: Bisphosphonates (Bp) are frequently underused in frail, older adults due to limited evidence supporting benefits and concerns about potential harms. The Minimum Data Set (MDS) in the United States includes data from individuals residing in nursing homes, and this data set provided a cohort of 24,571 individuals who were using the medications of interest. This population-based retrospective cohort study examined the effects of Bp on hip fractures, nonvertebral fractures and severe esophagitis among frail, older nursing home residents.

Study population: Included were long-stay (≥100 days) nursing home residents ≥65 years in the United States, with new use of a Bp or calcitonin (CT). The index date was the first eligible dispensing of a Bp or CT. Those who received osteoporosis treatment in the year prior to the index date were excluded. Data were linked with nursing home data sets and claims data.

Exposure and comparator: New use of a Bp was the exposure of interest. Bp users were 1:1 propensity score matched to new users of CT as the active comparator. An active comparator was used to minimize residual confounding.

Outcomes: The outcomes were 1) hip fractures, 2) nonvertebral fractures and 3) esophagitis requiring hospitalization, detected using ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) diagnostic codes.

Results: The propensity score–matched cohort included 5209 new Bp and CT users in each group, with a mean (SD) follow-up of 2.4 (1.7) years. Mean (SD) age was 85 (8) years, 87.1% were women, 52% had moderate to severe cognitive impairment and the groups were similarly matched with a mean of 10.8 comorbidities and an average of 12.9 and 13 medications in the Bp and CT groups, respectively. The rate of hip fracture was 0.83 (HR, 0.83; 95% CI, 0.71-0.98) times lower in those on Bp compared to those on CT, with an absolute difference in restricted mean survival time without hip fracture of 28.4 days (95% CI, 6.0-50.8) over a 6-year follow-up period. The number needed to treat was 239 and 154 over 3- and 6-year follow-up, respectively. No statistically significant differences were identified in hospitalized nonvertebral fractures (HR, 0.91; 95% CI, 0.80-1.03) or hospitalized esophagitis (HR, 1.11; 95% CI, 0.84-1.47).

Implications for practice: The reduced risk of hospitalized hip fracture with the use of Bp was small; however, given their association with high rates of health care utilization, functional decline, impaired quality of life and increased mortality, it may be considered on an individual basis.[22,23] Consistent with other studies, a lag in time of 6 months to benefit was noted, and as such, life expectancy should be considered prior to initiation.[24,25] A life expectancy of at least 1 year is likely required to warrant consideration. Although reassuring to see no statistically significant increase in hospitalized esophagitis, a potential clinically significant difference is not ruled out with the upper bound of the 95% CI for the HR at 1.47. Unfortunately, other safety concerns were not considered, such as atypical femur fracture. The results are not sufficient to warrant recommendation of Bp use in all older adults in nursing homes. Individual risks for adverse effects not evaluated must be considered, as well as life expectancy to determine if the modest decrease in hip fracture risk may outweigh potential risks.

Bottom line for the front line: Breaking with deprescribing—bisphosphonates work.

CV PROTECTION

***McNeil JJ, Woods RL, Nelson MR, et al. Effect of Aspirin on Disability-free Survival in the Healthy Elderly.* N Engl J Med 2018;379(16):1499-1508.**

Background/purpose: The Aspirin in Reducing Events in the Elderly (ASPREE) study was recently summarized by Barry et al.[26] with a focus on cardiovascular secondary endpoints. As this study was ranked as high priority by geriatric pharmacy experts and Canadian frontline pharmacists, we identified the value in summarizing these publications through a geriatrics lens. Until recently, older adults have been nearly absent from acetylsalicylic acid (ASA) primary prevention studies.[27] This double-blind randomized controlled trial, published as 3 companion papers,[28-30] set out to investigate whether ASA use in healthy, community-dwelling older adults would prolong healthy life span and if this outweighs the risks associated with its use.

Study population: Inclusion criteria were men and women from Australia and the United States who were ≥70 years, or ≥65 years for African American or Hispanic individuals in the United States. Those with CVD, atrial fibrillation, conditions with a high risk of bleeding, anemia, uncontrolled hypertension or those taking continuous antiplatelets or anticoagulants were excluded; nonsteroidal anti-inflammatory drug (NSAID) use was allowed. Patients were also excluded if they had dementia, physical disability (e.g., inability to transfer) or limited life expectancy (<5 years).

Exposure and comparator: Patients were randomized to 100 mg of enteric-coated ASA daily (n = 9525) or matching placebo (n = 9589).

Outcomes: The primary outcome was disability-free survival, a composite of the first occurrences of death, dementia and physical disability. Secondary endpoints included individual components of the primary composite endpoint, fatal and nonfatal cancer, mild cognitive impairment and depression. The secondary endpoints of death and fatal and nonfatal CVD, including stroke and major bleeding, were published in companion articles.

Results: The study included 9114 older adults (median age 74 years); they were primarily nonracialized (91%) women (56%) from Australia (87%); 4% of patients were aged 65 to 69, 55% aged 70 to 74, 26% aged 75 to 79, 11% aged 80 to 84 and 4% aged 85 and older.[31] Investigators described the majority (59%) of patients as not frail, 39% as prefrail and only 2% of patients as frail using the adapted Fried frailty criteria.[16] After a median of 4.7 years, stopped early for lack of efficacy, there was no difference in disability-free survival with ASA use (HR, 1.01; 95% CI, 0.92-1.11; p = 0.79). There was also no difference in fatal and nonfatal CVD (HR, 0.95; 95% CI, 0.83-1.08). Major hemorrhagic events increased (HR, 1.38; 95% CI, 1.18-1.62; p < 0.001); this included an increase in intracranial and upper gastrointestinal bleeds. Although there was an increase in death from any cause (HR, 1.14; 95% CI, 1.01-1.29), of which cancer was a major contributor, this may have been a chance finding due to multiplicity.

Implications for practice: Unique from other large ASA trials, the ASPREE trial incorporated prevalent diseases in the older adult population and emphasized the importance of healthy aging in a preventative therapy.[27] However, this study did not show a benefit of ASA use in older adults without a history of CVD in either healthy aging or cardiovascular events, and there was a clear increased risk of bleeding (NNH 98).[28-30,32] This study does not directly apply to severely frail, institutionalized patients or patients with dementia, but we could hypothesize that the benefits would be further diminished and risks amplified. Lacking also is clear guidance on deprescribing in those already using ASA for primary prevention. The 2019 AGS Beers Criteria, updated prior to the publication of ASPREE, recommends that ASA for primary prevention be used with caution in adults ≥70 years of age, based on a 2016 systematic review.[33,34] The ASPREE trial suggests the use of ASA for primary prevention in healthy older adults should be avoided.

Bottom line for the front line: Of primary importance—no ASA. ■

From the Faculty of Pharmacy & Pharmaceutical Sciences (Sadowski, Bharadia), University of Alberta, Edmonton, Alberta; the College of Pharmacy (Bowles, Isenor), Dalhousie University, Halifax, Nova Scotia; and the School of Pharmacy (Patel), University of Waterloo, Waterloo, Ontario. Contact cherylas@ualberta.ca.

Conflicts of Interest: *The authors have no conflicts of interest to declare.*

Funding: *This research was unfunded.*

ORCID iDs: *Cheryl A. Sadowski https://orcid.org/0000-0002-4526-7054*

Morgan Bharadia https://orcid.org/0000-0003-3244-1946

Susan K. Bowles https://orcid.org/0000-0003-0821-3222

Jennifer E. Isenor https://orcid.org/0000-0003-1648-7362

Tejal Patel https://orcid.org/0000-0003-3002-8306

References

1. Barry AR, Babadagli HE, Chen JW, et al. Review of the top 5 cardiology studies of 2017-18. *Can Pharm J (Ott)* 2020;153(1):32-6.

2. Gonzalez-Reyes A, Pluye P, Power B, et al. Top 5 primary care topics for pharmacists in 2016. *Can Pharm J (Ott)* 2018;151(3):176-8.

3. Mysak T, Sadowski CA, Foley HL, George-Phillips K. Recent trials in neurology that should influence your practice. *Can Pharm J (Ott)* 2015;148(1):41-7.

4. Canadian Institute for Health Information. *Drug use among seniors in Canada, 2016*. Ottawa (ON): CIHI; 2018.

5. Gulliford M, Ravindrarajah R, Hamada S, Jackson S, Charlton J. Inception and deprescribing of statins in people aged over 80 years: cohort study. *Age Ageing* 2017;46(6):1001-5.

6. Morin L, Vetrano DL, Rizzuto D, Calderon-Larranaga A, Fastbom J, Johnell K. Choosing wisely? Measuring the burden of medications in older

adults near the end of life: nationwide, longitudinal cohort study. *Am J Med* 2017;130(8):927-36.

7. Farrell B, Tsang C, Raman-Wilms L, Irving H, Conklin J, Pottie K. What are priorities for deprescribing for elderly patients? Capturing the voice of practitioners: a modified delphi process. *PLoS ONE* 2015;10(4):e0122246.

8. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. *Lancet* 2013;381:752-62.

9. Rockwood K, Song X, Mitnitski A. Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey. *CMAJ* 2011;183:E487-94.

10. Prince M, Wilmo A, Guerchet M, et al. *World Alzheimer Report 2015: the global impact of dementia; an analysis of prevalence, incidence, cost and trends*. Available: https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf (accessed Apr. 28, 2020).

11. Herr M, Sirven N, Grondin H, et al. Frailty, polypharmacy and potentially inappropriate medications in old people: findings in a representative sample of the French population. *Eur J Clin Pharmacol* 2017;73:1165-72.

12. Martinot P, Landre B, Zins M, et al. Association between potentially inappropriate medications and frailty in the early old age: a longitudinal study in the GAZEL cohort. *JAMDA* 2018;19:967-73.

13. Eshetie TC, Nguyen TA, Gillam MH, et al. A narrative review of problems with medicine use in people with dementia. *Exp Opin Drug Saf* 2018;17:825-36.

14. Redston MR, Himer SN, McLachlan AJ, et al. Prevalence of potentially inappropriate medication use in older in patients with and without cognitive impairment: a systematic review. *J Alzheimers Dis* 2018;61:1639-52.

15. O'Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2015;44:213-8.

16. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146-57.

17. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. *Chest* 2018;154(5):1121-201.

18. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. *Circulation* 2017;135(10):e146-e603.

19. Sommerauer C, Schlender L, Krause M, et al. Effectiveness and safety of vitamin K antagonists and new anticoagulants in the prevention of thromboembolism in atrial fibrillation in older adults—a systematic review of reviews and the development of recommendations to reduce inappropriate prescribing. *BMC Geriatr* 2017;17(Suppl 1):223.

20. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association practical guide on the use of non–vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018;39(16):1330-93.

21. De Simone V, Mugnolo A, Zanotto G, Morando G. Direct oral anticoagulants for patients aged over 80 years in nonvalvular atrial fibrillation: the impact of frailty. *J Cardiovasc Med (Hagerstown)* 2020;21(8):562-9.

22. Schousboe JT, Paudel ML, Taylor BC, et al. Pre-fracture individual characteristics associated with high total health care costs after hip fracture. *Osteoporos Int* 2017;28(3):889-99.

23. Alexiou KI, Roushias A, Varitimidis SE, Malizos KN. Quality of life and psychological consequences in elderly patients after a hip fracture: a review. *Clin Interv Aging* 2018;13:143-50.

24. Inderjeeth CA, Chan K, Kwan K, Lai M. Time to onset of efficacy in fracture reduction with current anti-osteoporosis treatments. *J Bone Miner Metab* 2012;30(5):493-503.

25. Black DM, Delmas PD, Eastell R, et al.; HORIZON Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356(18):1809-22.

26. Barry AR, Babadagli HE, Chen JW, et al. Review of the top 5 cardiology studies of 2017-18. *Can Pharm J* 2020;153(1):32-6.

27. Grimm R, McNeil JJ, Applegate W, et al. Study design of ASPirin in Reducing Events in the Elderly (ASPREE): a randomized, controlled trial. *Contemp Clin Trials* 2013;36(2):555-64.

28. McNeil JJ, Woods RL, Nelson MR, et al. Effect of aspirin on disability-free survival in the healthy elderly. *N Engl J Med* 2018;379(16):1499-508.

29. McNeil JJ, Wolfe R, Woods RL, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med* 2018;379(16):1509-18.

30. McNeil JJ, Nelson MR, Woods RL, et al. Effect of aspirin on all-cause mortality in the healthy elderly. *N Engl J Med* 2018;379(16):1519-28.

31. McNeil JJ, Woods RL, Nelson MR, et al. Baseline characteristics of participants in the ASPREE (ASPirin in Reducing Events in the Elderly) study. *J Gerontol Ser A Biol Sci Med Sci* 2017;72(11):1586-93.

32. Fritsch P, Kolber M. *Does an ASA a day really keep the doctor away?* Available: https://gomainpro.ca/tools-for-practice/ (accessed Apr. 28, 2020).

33. Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans CV. Bleeding risks with aspirin use for primary prevention in adults: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2016;164(12):826-35.

34. Fick DM, Semla TP, Steinman M, et al. American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2019;67(4):674-94.