Thames Valley Family Health Team

THE DOSE

Fall Updates

In this issue:

Practice Tool Spotlight: Osteoarthritis (OA) Treatments

The PEER group is an Evidence and CPD program run through the Alberta College of Family Physicians (https://peerevidence.ca/). They produce excellent evidence-based resources for primary care with the goals of minimizing bias and focusing on patient-oriented outcomes/shared decision making. You may be most familiar with their Tools for Practice summaries.

The PEER group recently published an umbrella systematic review about pharmacologic and non-pharmacologic treatments for OA. The review focuses on outcomes that are meaningful to patients: the **proportion of patients with meaningful improvement of 30%** (rather than average improvement in pain scores). The systematic review is available free here: https://www.cfp.ca/content/cfp/66/3/e89.full.pdf

Treatment Options for OA Pain:

Benefits vs Harms	Modality	Meaningful pain improvement (vs placebo)	NNT	Withdrawals due to adverse events (vs placebo)
Benefits likely to exceed harms:	Exercise (type of activity not important, usually led by a physiotherapist)	47% (vs. 21%)	4	Similar to control
	Intra-articular corticosteroids	50% (vs. 31%)	6	Similar to placebo
	Topical NSAIDs	61% (vs. 47%)	8	5% (vs. 4%)
Benefits may not exceed harms in some patients:	Oral NSAIDs – consider naproxen and ibuprofen (lowest CV risk)	57% (vs. 39%)	6	Similar to placebo
	SNRIs* (duloxetine)	64% (vs. 43%)	5	12% (vs. 6%)
No benefit:	Acetaminophen (similar to placebo)	Not statistically significant		Similar to placebo
Harms likely exceed benefits	Opioids**	47% (vs. 43%) Similar to placebo in trials >12 weeks	32	21% (vs 7%)
Benefits unclear***	Glucosamine	Efficacy similar to placebo in publically-funded trials		Similar to placebo
	Chondroitin			
	Viscosupplementation (hyaluronic acid)			Not reported

*no RCTs have evaluated venlafaxine for OA pain

** When trials > 4 weeks were analyzed, the benefits of opioids were not statistically significant

***Preplanned subgroup analysis demonstrated no effect with glucosamine, chondroitin, or viscosupplementation in studies that were only publicly funded

The authors could not identify any systematic reviews that included patient-oriented outcomes (e.g. meaningful pain improvements) for platelet-rich plasma injections, counselling, cannabinoids, or TCAs.

D. Angevine BSc. Pharm, K. Koroluk PharmD, T. Kontio BSc. Pharm, S. Yoeun PharmD, P. Patel PharmD October 2020

PRACTICE TIP: symptomatic treatment of OA is often well-suited to an "n-of-1 trial". If the potential benefits outweigh the harms, then a trial is worth a shot! Just remember to schedule reassessment and discontinue any treatments that are not benefiting the patient.

Useful Practice Tools:

- Interactive decision aid for comparing interventions for OA: https://pain-calculator.com/calculators/osteoarthritis-pain/
- Simplified 2-page PDF decision aid: https://www.cfp.ca/content/cfp/suppl/2020/03/09/66.3.191.DC1/PEER_Decision_Aid_Osteoarthritis.pdf
- Exercise prescription:
- https://www.exerciseismedicine.org/canada/assets/page_documents/EIM_PrescriptionPad_ENG_web_2017.pdf

Should we be using low dose ASA for primary prevention of cardiovascular disease?

Bottom line:

Older trials previously demonstrated a benefit for ASA primary prevention. However, newer trials that are more reflective of our current patient population have not shown the same benefit. The lack of benefit may be due to a more aggressive approach on reducing cardiovascular risk factors (increased statin use, blood pressure management and higher smoking cessation rates). The use of **ASA is not recommended for primary prevention** of first vascular event in most patients. Recent evidence from ARRIVE (low- mod risk of CVD), ASPREE (≥70 years old) have not found a reduction in CV death but an increase in major bleeding. The risk of bleeding outweighs potential benefits for treatment. ASA for primary prevention is **no longer recommended by Hypertension Canada or Canadian Stroke Best Practice guidelines.** There is **uncertainty** for patients that are at high risk for cardiovascular disease with low risk of bleeding. The decision to start or stop ASA should be an individualized with share decision making process. Click here for a flow sheet for a flow sheet of assessing indications for aspirin and the potential risk vs benefit.

Medication no longer available in Canada

- Meperidine (Demerol) tablets have been discontinued
- Ertugliflozin (Steglatro)- discontinued due to "business decisions"
- Ulipristal acetate (Fibristal)- withdrawn from market **due to risk of liver injury**. It is recommended to repeat liver enzymes 2-4 weeks after stopping therapy and have patients monitor for signs of liver injury.

Medications now covered under ODB

- **Toujeo Doublestar (**Insulin glargine 300u/ml**):** It contains 900u (3ml) per pen vs 450u (1.5ml) in Toujeo. **Patients requiring at least 20 units per day**. It delivers doses in 2-unit increments and can deliver up to 160 units in a single injection.

Drug Focus: Allopurinol

The 2020 ACR guidelines for management of gout recommends allopurinol for first line therapy for gout prophylaxis including those with CKD stage ≥3. Febuxostat (Uloric) should be avoided in patients with previous cardiovascular disease as it may increase the risk of death. (Health Canada warning: https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2019/71511a-eng.php)

Who to treat with Urate lowering therapy?

Strongly Recommended	Conditionally Recommended	Do NOT treat
Patients with ≥1 subcutaneous tophi Evidence of radiographic damage attributed to gout ≥2 gout flares per year	Infrequent gout flares <2 gout flares per year First gout flare plus one of the following: • Co-morbid moderate to severe CKD (Stage ≥3) • Serum urate levels >535 umol/L (9mg/dL) • Urolithiasis (calcium oxalate stones)	In patients experiencing their first gout flare Asymptomatic hyperuricemia with no gout flares or tophi

Monitoring:

- **Patients of South East Asian or African descent are at higher risk for allopurinol hypersensitivity reactions. They should be ideally screened for HLA-B*5801 allele prior to initiating therapy but this cannot be done in London.**
- Baseline monitoring of: Liver enzymes, renal function, CBC and serum urate
- CBC and serum urate to be checked every 2-5 weeks after dose increases then every 6 -12months or as indicated
- Renal function should be checked q3 months then yearly or as indicated
- Liver enzymes should be monitored periodically
- **Patients should discontinue allopurinol if rash develops after starting.**

Starting dose:

- In normal renal function starting doses should be **≤100mg po daily** with food
- Initiate at doses <100mg/day in patients with CKD Stage ≥3
  - Consider dosing allopurinol at doses less than 1.5mg per ml/min of renal function
    - Example: A patient with a CrCL 50mL/min should start at less than 75mg per day

eGFR mL/minute/1.73 m^2	Suggested initial dose
>30 to 60	50 mg daily
>15 to 30	50 mg every other day
5 to 15	50 mg twice **weekly**
<5	50 mg once **weekly**

[a]ACR (FitzGerald 2020); Becker 2019; Stamp 2012; Vargas-Santos 2017

- **Requires concomitant anti-inflammatory (colchicine, naproxen, prednisone) for 3-6 months to reduce gout glares**

PRACTICE TIP: Starting with lower doses reduces the risk of a gout flare and hypersensitivity reactions. The highest risk is during the first 1-2 months after initiation of therapy. Consider keeping initial dose for the first 2 months to reduce the hypersensitivity risk.

Dose titration:

- Increase the dose by 25-100mg every 2-8 weeks until target is reached
  - Note >50% of patients with need a dose higher than 300mg po daily to achieve target

D. Angevine BSc. Pharm, K. Koroluk PharmD, T. Kontio BSc. Pharm, S. Yoeun PharmD, P. Patel PharmD October 2020

When to initiate?

- Consider initiation of low dose allopurinol during a gout flare while the patient is motivated to start
  - In small trials, patients started on allopurinol during a gout flare did not extend flare duration or severity.

Treat to target approach:

- ACR guidelines recommend a uric acid target of <360umol/L
- However, a review of the evidence by Tools of Practice did not find a reduction in gout flares, pain or function when compared to standard allopurinol dosing (https://gomainpro.ca/wp-content/uploads/tools-for-practice/1589571963_tfp262allopurinolfv.pdf)

Duration of therapy:

- 2020 ACR guidelines recommend continuing indefinitely if well tolerated and not burdensome to the patient
  - Stopping urate lowering therapy has been associated with increased urate levels and more frequent flares. 13% of patients in clinical remission who stopped prophylaxis therapy had no flares during a 5yr follow up period
  - This would mean ~1 out of 10 patients may not need long term therapy
    - https://www.primaryhealthtas.com.au/wp-content/uploads/2018/09/A-Guide-to-Deprescribing-Allopurinol-2019.pdf

Drug Interactions- Note not a complete list of drug interactions

- Diuretics **increase the risk of hypersensitivity** reactions as they can increase the levels of allopurinol. Diuretics can also increase urate levels by fluid depletion and decreasing urate excretion
- ACE inhibitors: **increase the risk of hypersensitivity** reactions
- Warfarin- allopurinol can increase the INR. Consider repeating the INR with starting or stopping allopurinol
- AzaTHIOprine- consider alternative therapy. There is increased risk of bone marrow suppression due to increased levels of azathioprine
- Amoxicillin or ampicillin: Increased risk of rash or hypersensitivity reactions.

Common drugs that can increase urate levels:

- Loop or thiazide diuretics
- Alcohol
- Levodopa
- Niacin or Nicotinic acid
- Salicylates (low dose)

PRACTICE TIP: If treating hypertension with a thiazide diuretic it may be reasonable to switch to an alternative agent. If starting allopurinol, but unable to use an alternative agent, consider reducing allopurinol's starting dose by 50% and extending the titration interval.

Frequently asked question:

Is there additional benefit of using a DPP-4 inhibitor (sitagliptin, linagliptin) with a GLP-1 agonist?

Bottom line: Considering the mechanism of action of DPP-4 inhibitors (increase endogenous GLP-1 levels) and synthetic GLP-1 agonists the combination is unlikely to be beneficial. At present, this combination would not be recommended due to lack of benefit in significantly improving A1C, MACE outcome and the financial cost of this combination (Avg DPP-4 inhibitor $100/month).

Endogenous GLP-1 is broken down by the enzyme DPP-4. Synthetic GLP-1 agonists have been modified to impair metabolism by DPP-4 that has increased their half-life from 5mins for endogenous to up to 7 days for the injectable once weekly GLP-1 agonists (semaglutide/dulaglutide). There have been 2 studies looking at the combination therapy of GLP-1 agonists and DPP-4 inhibitors. In a 20-week trial, patients on exenatide 10mcg sc bid had the addition of either placebo or sitagliptin 100mg daily to their regimen. This studied demonstrated a small 0.3% decrease in A1C in the sitagliptin group compared to placebo. This benefit may be due to the use of exenatide due to its short half-life and twice daily administration of 30-60mins before a meal. There has been a case series of 18 patients that failed to demonstrate a synergistic response with the combination therapy of longer acting GLP-1 agonists (Exenatide ER 2mg/ Albiglutide 30mg) and sitagliptin 100mg daily.

Animal studies have shown no difference in pharmacokinetic profile of liraglutide when sitaglipin was added.

Academic Detailing update

We are offering one-on-one virtual visits to discuss balanced, evidence-based information on type 2 diabetes: non-insulin pharmacotherapy and providing diabetes care during COVID-19.

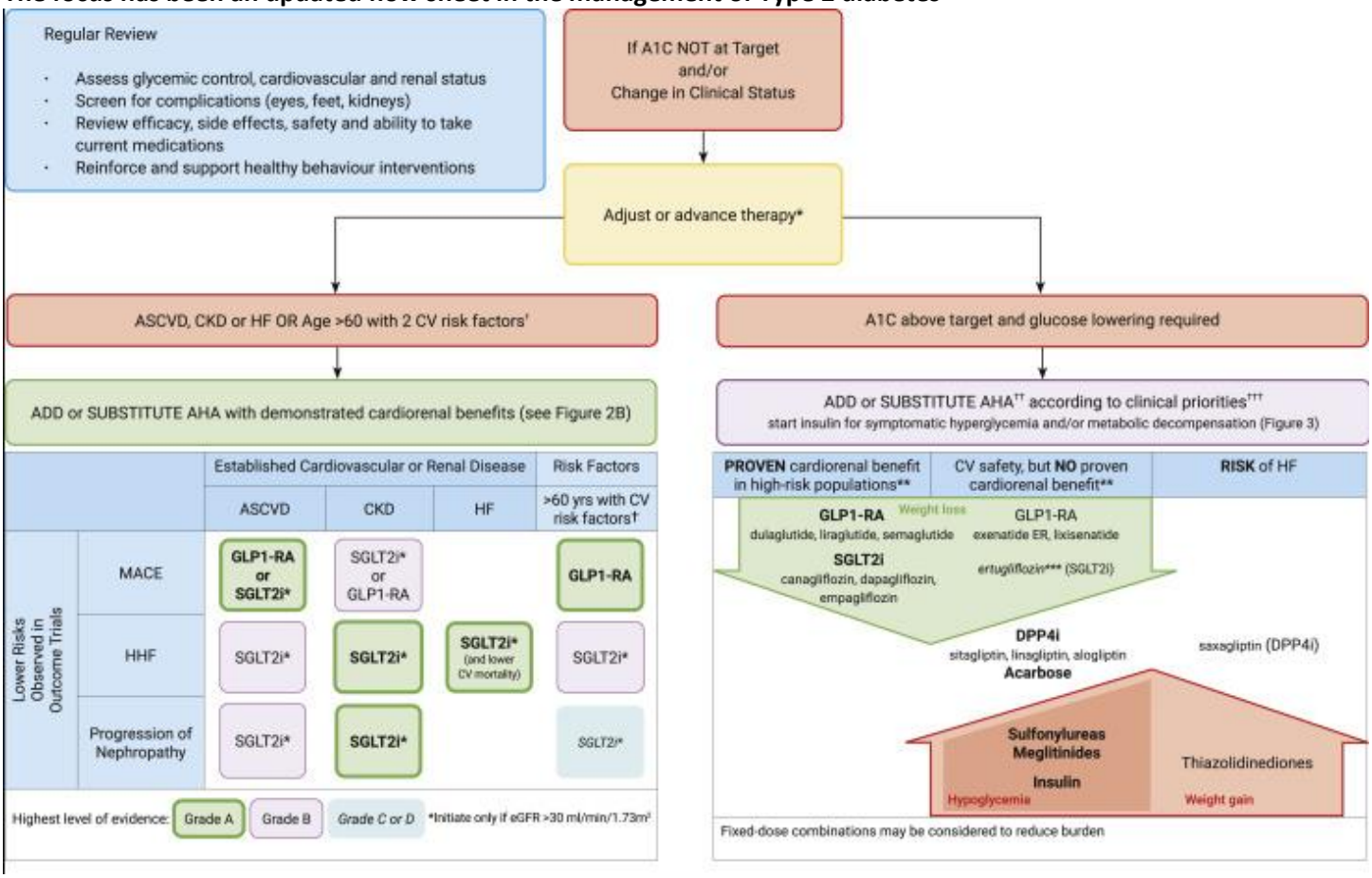
During your visit, your academic detailer can discuss:

- Individualizing choice of antihyperglycemic treatment according to risk vs benefit as well as patient factors and preferences.
- Individualizing and reassessing A1c targets according to patient factors and preferences
- Individualizing approach to routine diabetes care, with considerations for patients with type-2 diabetes during the COVID-19 pandemic.

This Mainpro+ accredited service is offered free of charge by the Centre for Effective Practice, a not-for-profit organization that is free of commercial interest. **TVFHT physicians and NPs can sign up by contacting their team pharmacist**. For **non-TVFHT physicians** contact Nicole Seymour (nicole.seymour@cep.health) OR by completing the form at cep.health/academic-detailing

Diabetes Canada has released a pharmacotherapy update for 2020

The focus has been an updated flow sheet in the management of Type 2 diabetes



They have created a user guide with frequently asked questions around the changes

- https://www.canadianjournalofdiabetes.com/article/S1499-2671(20)30229-X/pdf

Product Safety Updates

Amlodipine (Norvasc) is now contraindicated in patients with:

- obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis)
- haemodynamically unstable heart failure after acute myocardial infarction

In an amlodipine long-term, placebo-controlled study in patients with severe heart failure (NYHA class III and IV), the reported incidence of pulmonary edema was higher in the amlodipine treated group than in the placebo group.

Ticagrelor (Brilinta) has been associated with bradyarrhythmia including second-and third-degree atrioventricular block based on case reports.

Montelukast (Singulair) has had serious neuropsychiatric events reported in patients with and without a previous history of psychiatric disorder

- Symptoms may include agitation, aggression, depression, sleep disturbances, suicidal thoughts and behavior including suicide
- Neuropsychiatric symptoms **can persist after stopping** montelukast in some cases.
- In allergic rhinitis, consider reserving montelukast for patients who have trialed alternative therapies such as intranasal steroids and/or antihistamines that experience lack of efficacy or issues with tolerability.
    - Montelukast has a modest benefit similar to oral antihistamines but is less effective than intranasal steroids in treatment of allergic rhinitis

Ingenol mebutate (Picato) may increase the risk of skin cancer in some patients. In a 3-year study involving 484 patients the incidence of skin malignancy with Ingenol mebutate was 3.3% compared to 0.4% in the imiquimod. Health Canada is currently reviewing the data. Patient should be advised to monitor their skin for unusual skin changes or growths and seek medical advice if any occur.

In case your patient asks: COVID-19 testing in the community

Pharmacy based COVID-19 screening for asymptomatic patients that meet the following criteria:

- Residents or workers in long-term care home
- Visitors to a long-term care home
- Residents or workers in homeless shelter
- International students that have passed their 14-day quarantine period
- Farm workers
- Individuals who require a COVID-19 test for international travel clearance
- Self-Identified Indigenous

Screening will be available **by appointment only** at the following Shoppers Drug marts:

London

- 395 Southdale Rd. E (Whiteoaks)
- 603 Fanshawe Park Rd. W (Wonderland and Fanshawe)
- 3090 Colonel Talbot Rd. (Lambeth- Colonel Talbot/Southdale)
- 1155 Commissioners Rd E (Pondmills)

St. Thomas
107 Edward St.

Woodstock:
333 Dundas St., Woodstock

Discussing ASA for primary prevention with your patient

Older trials had previously demonstrated a benefit for ASA primary prevention. However, newer trials that are more reflective of our current patient population have not shown the same benefit. The lack of benefit may be due to a more aggressive approach on reducing cardiovascular risk factors such as increased statin use, blood pressure management and higher smoking cessation rates.

When reassessing a patient on ASA consider the following 3 step approach:

The potential benefit

Please note the relative risk for **mortality and stroke crosses 1** and the benefit would be considered **not significant**

Reference: Patel J et al. Aspirin for primary prevention of CVD. ACSAP 2020 Book 1 Cardiology Care.

Table 3. ASA (75–100 mg) vs. Placebo in the Primary Prevention of CVD

Outcomes	No. of Patients	Certainty of Evidence	Relative Effect (RR - 95% CI)	Absolute Anticipated Risks over 10 Yr (P) Risk with placebo (A) Risk with ASA[a]	
Total mortality	161,660	Moderate	0.97 (0.93–1.02)	P - 83 per 1000[b] A - 2 fewer per 1000	
MI (nonfatal)	142,566	High	0.83 (0.76–0.90)	Low risk[c]	P - 27 per 1000[d] A - 5 fewer per 1000
				Moderate risk	P - 83 per 1000 A - 14 fewer per 1000
				High risk	P - 136 per 1000 A - 23 fewer per 1000
Stroke (nonfatal ischemic and hemorrhagic strokes)	127,433	Moderate	0.95 (0.85–1.06)	Low risk[c]	P - 23 per 1000[d] A - 1 fewer per 1000
				Moderate risk	P - 65 per 1000 A - 3 fewer per 1000
				High risk	P - 108 per 1000 A - 5 fewer per 1000

[a]The risk difference in the aspirin group (and its 95% CI) is based on the estimated risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Control group risk estimate for 10-yr mortality applies to a 60-yr-old person (male or female) and comes from population-based data from Statistics Norway. Mortality increases with age (e.g., 50-yr-old man; 40 deaths per 1000 in 10 yr) and is lower in females than in males (e.g., 2.5% in women age 50 yr vs. 4% in men age 50 yr).

[c]Risk groups correspond to low (5%), medium (15%), and high risk (25%) according to the Framingham score (or other risk tool) to estimate 10-yr risk.

[d]Control group risk estimates in low, moderate, and high CV risk groups are based on the Framingham score. We have used data from an individual patient data meta-analysis to provide estimated risks for patient-important outcomes not covered by the Framingham Risk Score. We have also adjusted for 20% overestimation associated with the Framingham Risk Score.

Information from: Guirguis-Blake JM, Evans CV, Senger CA, et al. Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review for the US Preventive Services Task Force: Evidence Synthesis No. 131. AHRQ Publication No. 13-05195-EF-1. Agency for Healthcare Research and Quality, 2015; ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018;379:1529; McNeil JJ, Nelson MR, Woods RL, et al. Effect of aspirin on all-cause mortality in the healthy elderly. N Engl J Med 2018;379:1519; Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet 2018;392:1036.

The side effects

Reference: Uptodate ASA Primary Prevention

Major extracranial bleed risk over 10 years per 1000 patients treated			
Relative risk	**CVD risk category**	**Placebo**	**ASA**
1.46 (1.32 to 1.62)	**Low risk**	**8**	**12 (4 more compared to placebo)**
	Moderate risk	**24**	**35 (11 more compared to placebo)**
	High risk	**40**	**58 per 1000 (18 more compared to placebo**

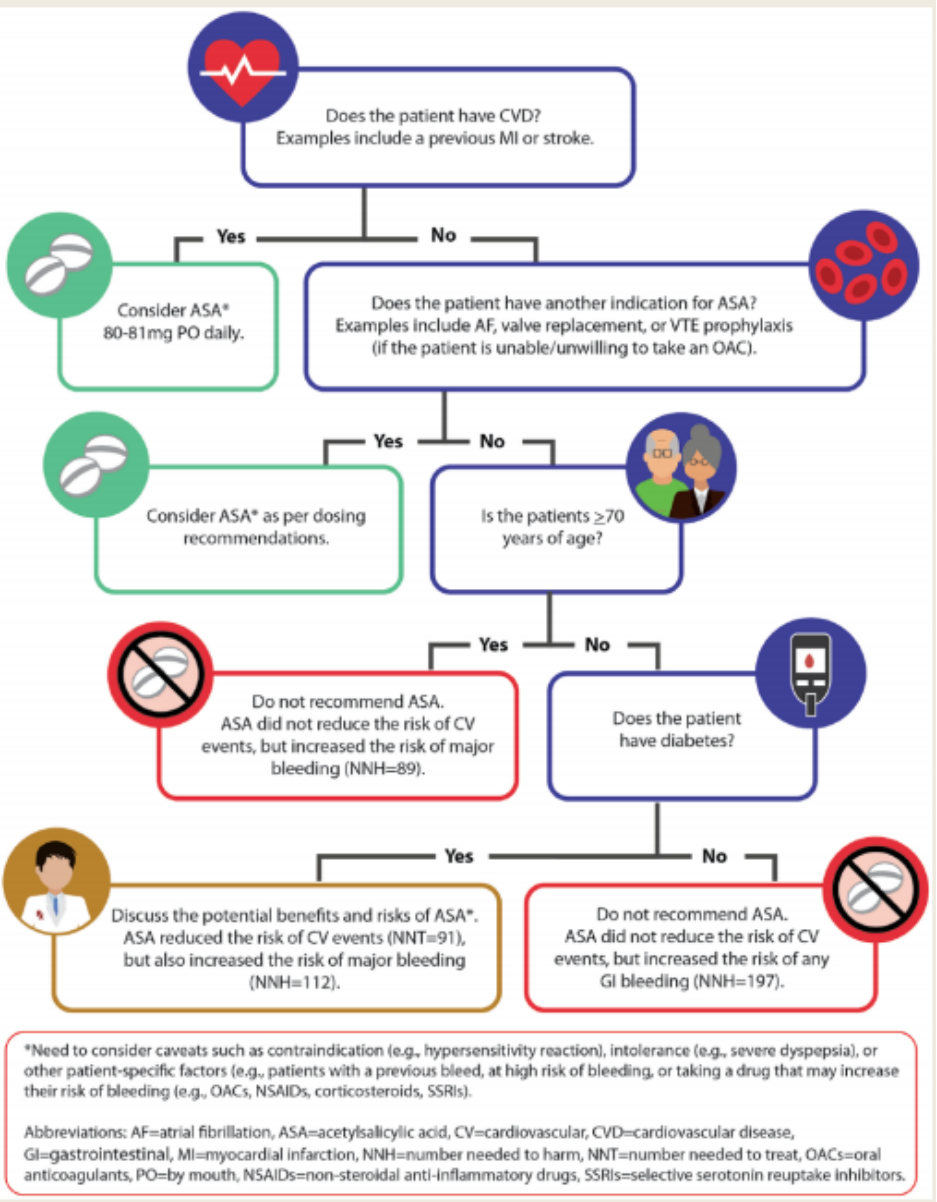
Note: SSRIs, SNRIs, NSAIDs and steroids may increase the risk of bleeding

Patient Preferences

Patient preferences such as number of pills, cost, patient values on preventing MI or bleeding risk etc. should be considered

D. Angevine BSc. Pharm, K. Koroluk PharmD, T. Kontio BSc. Pharm, S. Yoeun PharmD, P. Patel PharmD October 2020

Flowsheet for assessing aspirin for cardiovascular disease



Note: CVD included asymptomatic CVD such as carotid stenosis

Reference: Barry AR, Semchuk WM, Thompson A, LeBras MH, Koshman SL. Use of low-dose acetylsalicylic acid for cardiovascular disease prevention: A practical, stepwise approach for pharmacists. *Can Pharm J (Ott)*. 2020;153(3):153-160. Published 2020 Mar 19. doi:10.1177/1715163520909137

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