Thames Valley Family Health Team

THE DOSE

In this issue:

To Everything, a Season: Summer Focus on Heart Failure

You may start seeing SGLT2 inhibitors (SGLT2i) prescribed for patients without diabetes, as several recent studies have resulted in updated recommendations on their use in patients with heart failure. The April 2021 update to the Canadian Cardiovascular Society Heart Failure guidelines now recommend an SGLT2i as a 4th drug in patients with heart failure with a reduced ejection fraction (HFrEF) in addition to ACEi/ARB or angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers, and mineralocorticoid receptor antagonists.[1]

Summary of the trials evaluating SGLT2i in HFrEF:

Trials	**DAPA-HF[2]**	**EMPEROR-Reduced[3]**
Drug intervention	Dapagliflozin 10 mg	Empagliflozin 10 mg
Comparator	Placebo	Placebo
Population		
Mean age	66.5 years +/- 11	67 +/- 11
Proportion male	77%	76%
Mean LVEF	31% (+/- 6.8%)	27.4% (+/- 6.1%)
NYHA Class Breakdown:		
Class II	68%	75%
Class III	32%	24.4%
% patients with diabetes	45%	50%
% of patients on:		
ACEi/ARB or ARNI	94.4%	94.7%
Beta-blocker	96%	80%
MRA	71%	71.3%
Primary endpoint:	CV death or worsening HF ARR 4.9% **NNT = 21** over 1.5 years	CV death or HD hospitalization ARR 5.3% **NNT = 19** over 1.3 years
Secondary endpoint: All-cause mortality	ARR 2.3% **NNT = 44** over 1.5 years	Not significant HR 0.92 (0.77-1.1)

ARR = absolute risk reduction, NNT = number needed to treat, HR = hazard ratio

Common Questions and Practical Tips:

Q: Are SGLT2i approved by Health Canada for use in patients with heart failure but without diabetes?

A: Only dapagliflozin carries an official Health Canada indication for use in patients with HFrEF without diabetes. However, both dapagliflozin and empagliflozin have been explicitly studied in this population.

Results for canagliflozin in heart failure have not yet been published. Secondary outcomes from the CANVAS trial suggest a potential benefit in reducing hospitalization or death due to heart failure (HR 0.69; 95% CI [0.48–1.00]), but these results have not yet been evaluated in trials evaluating patients with heart failure specifically.

Q: Do these drugs lower mortality like other triple therapy HFrEF medications?

A: Dapagliflozin has been shown to lower mortality in patients with HFrEF both with and without diabetes.

Q: Is this benefit a class effect?

A: There appears to be some benefit for patients with heart failure across SGLT2i, but the extent of their benefit may vary. Dapagliflozin is the only agent with a proven benefit for mortality as well as heart failure hospitalizations (HHF). Empagliflozin has been shown to reduce HHF. Canagliflozin has yet to have published results for its explicit use in patients with heart failure and cannot yet be recommended for HFrEF alone at this time.

Q: Should I titrate other drugs to target doses first or start an SGLT2i right away?

A: Start an SGLT2i even if patients are not at Heart Failure target doses of other medications. The benefits of an SGLT2i holds up even if patients are not yet at target doses for other medication classes.[4] The Kaplan-Meier curves for worsening heart failure separated soon after randomization in the DAPA-HF trial, indicating that starting an SGLT2i as soon as possible is beneficial.[2]

Q. What are the target doses for these drugs in HFrEF?

A. Only standard doses of SGLT2i were used in DAPA-HF and EMPEROR-reduced (10 mg of dapagliflozin and empagliflozin respectively). As such, there is no proven benefit in HRrEF to increasing doses to a higher target as you would with ACEi/ARBs or beta-blockers in HFrEF.

Q. Do I have to adjust a patient's furosemide dose when I start an SGLT2i?

A. This will depend on the patient's volume status. If the patient is euvolemic, consider reducing the furosemide dose empirically before starting an SGLT2i with close monitoring. If volume depletion occurs after initiating the SGLT2i, reduce the furosemide dose by 30-50%.[5]

Q. How do I adjust my patient's other medications for diabetes to avoid hypoglycemia when starting an SGLT2i for HFrEF benefits?

A. SGLT2i rarely cause hypoglycemia unless patients are also taking an insulin secretagogue (e.g. sulfonylurea) or insulin. If a patient's blood sugar is well-controlled on an insulin secretagogue, reduce their dose by 25-50% before starting an SGLT2i. If a patient is on basal insulin, consider the following protocol:[6]

- Fasting blood glucose frequently <6.0 mmol/L: reduce basal insulin dose by 20%
- Fasting blood glucose frequently 6.0-8.0 mmol/L: reduce basal insulin dose by 10%
- Fasting blood glucose frequently >8.0 mmol/L: basal insulin adjustment likely not required

Q. What about patients with heart failure with preserved ejection fraction (HFpEF)?

A. Post-hoc subgroup analyses in original SGLT2i trials suggest a potential benefit in HFpEF, but studies specifically looking at this population have yet to be published. The EMPEROR-preserved (empagliflozin) and DELIVER (dapagliflozin) trials evaluate CV outcomes in patients with HFpEF and results will likely be published in 2021/2022. The EMPERIAL-Preserved study did not find a significant difference between epagliflozin and placebo on a 6-minute walk test or symptom scores in patients with HFpEF after 12 weeks. A similar study of dapagliflozin (DETERMINE-preserved) has yet to be published.

Q. My patients with heart failure often have comorbid chronic kidney disease (CKD). What should I do if my patient's creatinine clearance is less than 30 ml/min?

A. Although the HFrEF trials for SGLT2i have included more patients with renal dysfunction than prior diabetes trials, DAPA-HF and EMPEROR-reduced trials excluded patients with an eGFR of less than 30 and 20 ml/min respectively. Data regarding their use in these populations is very limited. However, ~50% of patients in EMPEROR-reduced had stage 3 CKD (eGFR 30-59 ml/min).

Note that SGLT2i can increase serum creatinine levels, often temporarily. Initially, increases occur within 7 days of starting the medication, and changes tend to stabilize after 1-3 months. Note an early drop in eGFR of 15-20% is acceptable, but consider monitoring more closely in those at high risk of acute kidney injury.[1]

Looking for more?

This excellent webinar recently produced by the CFPC entitled "The Art and Science of medication optimization for heart failure with reduced ejection fraction" may be what you're looking for: .youtube.com/watch?v=EfIP-Nu7t14

Is denosumab better than bisphosphonates for preventing osteoporotic fractures?

Bisphosphonates and denosumab, in systematic review[1], meta-anylysis[2,3,4] and a real-world case cohort review[5], have demonstrated **similar fracture protection**. When compared to placebo, they **reduce the risk of fracture by a relative 40-50%**.

Approximate absolute difference over 1-4 years when compared to placebo in post-menopausal women (CPJ May 2021)[6]

	Denosumab and bisphosphonates
Hip	~0.5-1%
Non vertebral	~1.5-3%
Vertebral	~3-6%

Is there an increased vertebral fracture risk when stopping denosumab or if a dose is missed?

- Denosumab's effect on bone turn over markers return to baseline levels 9 months after the last dose unlike in patients treated with bisphosphonates who remain below baseline levels for greater than 48 months.
- Delayed dosing (**greater than 8 months between doses**) or stopping of denosumab has been associated with an increased vertebral fracture risk.[7]
- The risk of fracture on denosumab therapy was 1.2 per 100 patient years but increased to 7.1 per 100 patient years (similar to placebo) when denosumab was stopped in the FREEDOM extension trial.[8]
- The **risk of multiple vertebral fractures** was higher in the denosumab group: 4.2 vs 3.2 per 100 patient years in the placebo group.[8]

Can the increased vertebral fracture when stopping therapy be prevented?

- There is conflicting evidence whether the use of a bisphosphonate after denosumab reduces fracture risk.
- Alendronate (70mg q weekly), when given after denosumab, maintained BMD when initiated when the next denosumab dose was due. The change in BMD was a secondary outcome of the study, which did not examine fracture rate.[9]
- Zoledronic acid IV 5mg yearly for 1-2 years, starting when the next dose of denosumab is due, may prevent the loss of bone mineral density gained from denosumab.[10]
- Further research is needed to confirm if bisphosphonates prevent the increased vertebral fracture risk with stopping denosumab.

Did you know? The yearly cost of: Denosumab is $975 Alendonrate 70mg weekly is $175, Zoledronic Acid 5mg IV q yearly is $415

Bottom line: Bisphosphonates provide similar prevention of fractures compared to denosumab. Denosumab dosing should not be delayed more than 1 month due to potentially increasing the risk of vertebral fractures.

Practice tools

Helping your patient decided on therapy: https://osteoporosisdecisionaid.mayoclinic.org/index.php/osteo/index

Dietary sources of calcium: https://www.unlockfood.ca/en/Articles/Bone-Health/Food-sources-of-calcium.aspx

Calcium calculator: https://osteoporosis.ca/bone-health-osteoporosis/calcium-calculator/#page-1

New drug

Lemborexant (Dayvigo) – A new sleep aid for the longest days of the year?

Indication: sleep onset and sleep maintenance insomnia

How it works Orexin receptor antagonist: Orexins are responsible for wakefulness by stimulating other neurons. The blockade of the receptor would promote sleep. Note: Orexin's may also play a role in feeding behavior, energy homeostasis, reward systems, cognition and mood.[1,2]

Efficacy compared to placebo: time to fall asleep was ~4-8mins faster[2], difference in wake after sleep onset was ~12-25mins[2], total sleep time was improved by 18-22mins[3] for up to 12 months[4]

Dosing: 5mg or 10mg qhs with a minimum of 7 hrs anticipated of sleep time available (Note there is not a consistent dose response effect but higher risk of adverse drug reactions with higher doses[1,2,3]

Contraindications: Narcolepsy

Precautions: Patients should be cautioned against driving and other tasks that required mental alertness if Lemborexant was taken less than 7 hrs prior (especially the 10mg dose), worsening of mood, not studied in mod-severe COPD/ sleep apnea

Common ADR: Somnolence, headache

Cataplexy-like symptoms (sudden leg weakness): lasting seconds to minutes, either at night or during the day,

Sleep paralysis 1.3% (5mg) and 1.6% (10mg)-can last up to several minutes during sleep-wake transitions

Complex sleep behaviours (eg, sleep walking, driving, other dangerous activities),

Hypnagogic hallucinations 0.1% (5mg) 0.7% (10mg)

Increased risk of falls

Drug interactions: Avoid moderate/strong 3A4 inhibitors (AUC↑ ~300%), avoid alcohol (AUC ↑ 70%), other CNS depressants

Cost: ~$1.60 per tablet plus pharmacy fees

Bottom line: CBTi considered first line therapy for insomnia. Lemborexant has demonstrated similar improvements to z-drugs in sleep latency, wake after sleep onset and total sleep time. Lemborexant benefits have been demonstrated for up to 12 months. Patients should be caution about next day sedation/impairment, avoidance of alcohol and cataplexy-like symptoms that can occurred both during the day and at night.

Drug recalls:

Certain brands and lots of Irbesartan, losartan and valsartan including their combination products have been recalled due to an azide impurity. Azides are used in the manufacturing process of medications but are typically removed during the process. The FDA, Health Canada and the EU have established an acceptable reference range that if ingested daily for 70 years would not increase the risk of cancer. The cancer risk of above the reference range is unknown.

Bottom line: Not all brands of irbesartan, losartan and valsartan have been recalled. Patients should be directed to contact their home pharmacy to see if their medication was recalled. If needing to convert to another ARB or ACEI, an approximate equivalent doses can be found here (https://thamesvalleyfht.ca/wp-content/uploads/2020/05/TheDoseACEIsARBs-drina.pdf)

Recall notice: https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2021/75715a-eng.php

Linessa 21 only 1 lot (lot 200049, expiry 03/2023) has been recalled due to missing or mispackaged pills. Patients should be directed back to their community pharmacy for a replacement.

Drug discontinuations:

Brand name Macrobid has been discontinued. However, an interchangeable generic is still available and scripts written for Macrobid will be substituted with the generic version.

ODB Seniors Drug Coverage Starting Aug 1, 2021

There is new threshold for determining low-income seniors:

- $22,200 (for single seniors)
- $37,100 (for senior couples)

Seniors who qualify will have their annual deductible ($100) waived and have a lower co-pay of $2 or less.

All qualifying Seniors must complete the application form found here:
http://www.forms.ssb.gov.on.ca/mbs/ssb/forms/ssbforms.nsf/FormDetail?openform&ENV=WWE&NO=014-3233-87

In case your patient asks:

Aducanumab: A drug worth remembering?

Bottom line: The FDA advisory panel[1] had voted against approval of aducanumab for the treatment of Alzheimer's disease with the current data that is available. Hopefully, the required phase 4 trial of aducanumab will give clarity on the benefit of removal of amyloid plaque on the more important endpoint of improved cognition and function.

Additional information:

- Not currently approved in Canada but was granted accelerated approval by the FDA for the treatment of Alzheimer's disease.[1]
- Mechanism of action is the binding and removal of beta amyloid, leading to the removal of plaques.
- Original trials (EMERGE and ENGAGE) were terminated by the manufacturer due to futility.[1]
- Post- Hoc analysis of EMERGE trial demonstrated an absolute difference in MMSE score of 0.6 in the high dose group (clinical significant change difference is considered 1-3 points) and a change in CDR-SB score of 0.39 (clinical significant change is considered 1-2 points)[2]
    - Meta-analysis of therapies targeting amyloid plaque did not demonstrate a significant change in cognitive function in MCI patients during the study period of clinical trials[3]
- Safety: Amyloid-related imaging abnormalities- edema (ARIA-E) was seen in 25% in the low dose group, 35% in the high dose groups, compared to 3% in the placebo group.
    - ARIA-E symptoms can include confusion, disorientation, gait disturbance, ataxia, visual disturbance, headache, nausea, falls and blurred vision. [1]
- Cost is $56,000 USD per year plus the cost of monthly infusions and of PET scans for monitoring for ARIA-E

My first dose of COVID-19 vaccine was Astra Zeneca. What should I take for my second dose?

https://uwaterloo.ca/pharmacy/sites/ca.pharmacy/files/uploads/files/i_got_astrazeneca_for_my_first_dose_what_should_i_do_for_my_second_-_long_version.pdf

Patient handout
https://uwaterloo.ca/pharmacy/sites/ca.pharmacy/files/uploads/files/i_got_astrazeneca_for_my_first_dose._which_vaccine_is_best_for_my_second_1_pager.pdf

Is it okay to mix and match mRNA vaccines?

https://uwaterloo.ca/pharmacy/sites/ca.pharmacy/files/uploads/files/is_it_okay_to_mix_moderna_and_pfizer.pdf

Did you know?

Potential risk factors for genital infections in patients with diabetes treated with SGLT-2 inhibitors:

- Females
- History of genital infections in the year prior to starting therapy
- Smoking status (Infection risk in Current smokers 18.3% vs 9.3% in non smokers)[1]
- Uncircumcised males

Prevention

- adequate personal hygiene including rinsing with water after urination and before bed
- wearing cotton underwear
- staying hydrated

Frequently asked question: What topical acne creams are covered by ODB?

There are currently only 3 topical acne creams covered by ODB:

1. Clindoxyl (clindamycin/ benzoyl peroxide) 1%/5% - stable for 2 months at room temperature
2. BenzaClin (clindamycin/benzoyl peroxide) 1%/ 5% - stable for 3 months in the fridge
3. Stieva-A (tretinoin) available as 0.01%, 0.025%, or 0.05%

Note: Benzoyl peroxide products and tretinoin (Stieva) should be spaced away from each other (i.e benzyl peroxide in AM and tretinoin at HS) as benzoyl peroxide can inactivate tretinoin.

Other topical therapies available but **not covered by ODB:**

Combinations
Tactu (benzyl peroxide + adapalene)
Biacna (tretinon /clindamycin)

Antibiotics:
Clindamycin (Dalacin T)
Aczone (dapsone)

Vitamin A derivatives
Differin (adapalene)
Tazorac (tazarotene)

Podcast on topical combo therapies for acne
https://gomainpro.ca/tools-for-practice/articles/details/?id=721&page-title=Clearing+up+the+evidence+for+topical+acne+combination+products

Did you know that beta blockers may mask symptoms of hypoglycemia?

Beta blockers mask the neurogenic/autonomic symptoms (tremor, tachycardia etc.) of hypoglycemia except for sweating.

Summer sun safety

Health Canada has recently issued a warning about the potential increase in skin cancers with the use of thiazide diuretics. The mechanism of this increased risk maybe due their photosensitizing effect.[1,2] There are over 300 medications that can increase the risk of photosensitivity including:

- antibiotics (septra, tretacyclines, metronidazole, quinolones etc.)
- cardiac medications (thiazide diuretics, furosemide, diltiazem, nifedipine)
- topical medications (benzoyl peroxide, tretinoin, coal tar)
- NSAIDs

Patient handout on sun safety
https://dermatology.ca/wp-content/uploads/2018/06/Sun-Safety-for-Everday-8-5-x-11-April-2018-2page-EN.pdf

Practice tip: Consider adding a comment to wear sunscreen on the prescription directions for all diuretics

The Dark Side of Summer: Lyme disease

Parts of London-Middlesex, Elgin and Oxford counties are deemed an estimate risk area. [1]

Prevention of Lyme disease is key!

Reducing risk around the house

- Keep grass cut short
- Remove debris and leaves from around walls
- Put barriers around property to keep deer away
- Place outdoor sitting or play sets in sunny locations away from trees

Clothing

- Wear pants and long-sleeved shirts that are light in color
    - Pull socks over pant legs and tuck in your shirt
- Put clothes into dryer
    - high heat for 10-15mins, low heat 90mins
- check clothes and gear prior to entering your home
- use permethrin spray (available in USA) on clothing or clothing with permethrin applied (can be found at Mark's, MEC, SAIL etc.)
- Use DEET or Icaridin on clothing and skin

Showering within 2 hours helps to remove ticks[2]

Checking for ticks when coming in from outside (Patient handout found here https://www.canada.ca/en/public-health/services/publications/diseases-conditions/top-10-tick-hiding-spots-body-poster.html)

Prompt removing of ticks if found with tweezers (Video on removal https://www.canada.ca/en/public-health/services/video/lyme-disease-properly-remove-tick.html)

Indications for prophylaxis

Prophylaxis can be considered if **all** of the following criteria are met:

1. blacklegged tick
2. has been attached for greater than 24hr-36hrs with signs of engorgement (see images)
3. treatment starts within 72 hrs of tick removal [3,4]

Different stages of engorgement

Adult Female

Nymphs

The risk of contracting Lyme disease in high-risk areas following a black legged tick bite is ~ 2.2%. Doxycycline prophylaxis reduces the risk to ~0.2% (NNT would range from 40-125 due to the wide confidence interval). The relative benefit of prophylaxis would be less in lower risk areas or if the tick is not engorged.[5]

Can doxycycline be used for Lyme disease prophylaxis in children less than 8 years old?

Bottom Line: The use of doxycycline (4.4mg/kg or 200mg >45kg as a single dose) in children could be consider with informed consent. The American Academy of Pediatrics, Infectious Disease Society of American and Children's Hospital of Eastern Ontario would consider it a treatment option as the risk of dental staining is considered to be low.[3,4,6] The Canadian Paediatric Society states that some experts would recommend treatment with doxycycline prophylaxis as "data on the safety of short courses of doxycycline for children <8 years old, coupled with its proven efficacy for treating LD, including meningitis, has prompted more permissive use of this antimicrobial"[7]. This is based off 3 cohort studies[8,9,10] examining children's teeth who have been exposed to doxycycline vs non- exposed controls for the treatment of Rocky Mountain Spotted Fever and atypical asthma with treatment durations of up to 10 days. There was no significant difference in tooth discoloration between the two groups when examined by trained dentists. Doxycycline, compared to other tetracyclines, has a lower affinity of calcium binding and thus would be less likely to bind to calcifying teeth causing dental staining. The risk of tooth discoloration is dose dependent as well as duration dependent. The alternative would be watchful waiting for 30 days and treating with amoxicillin 50mg/kg (max 500mg per dose) tid for 14 days if symptoms developed. The benefit of using amoxicillin at treatment doses for prophylaxis is unknown as previous trials were under-dosed and under-powered to detect a difference.

Practice Resources

Doxycycline compounding formula: https://www.sickkids.ca/en/care-services/for-health-care-providers/compounding-service/

CHEO: assessment algorithm https://www.ottawapublichealth.ca/en/professionals-and-partners/resources/Documents/Ottawa-Algorithm-for-Lyme-Disease_July2019.pdf

Map can be found here https://www.publichealthontario.ca/-/media/documents/o/2021/ontario-lyme-disease-risk-area-map-2021.pdf?la=en

eTick is a free tick identification service available online or by downloading the mobile eTick app. An expert will identify the photo of your tick within 48 hours

Patient handouts

https://www.cdc.gov/lyme/resources/toolkit/factsheets/Hooks_Ticks-and-Lyme-Disease-508.pdf
https://www.cps.ca/en/documents/position/preventing-mosquito-and-tick-bites

Academic detailing: Type 2 Diabetes and insulin therapy

Wondering what are the differences between all the new insulins? How do you convert between the basal insulins? Book an appointment with your FHT pharmacist for an accredited one on one discussion to have your questions answered.

A small sample of the information that will be discussed:

When issues with insulin arise...

1. be sure to review injection technique with the patient and ensure they are injecting correctly
2. ensure that prandial insulin is being injected at the correct time with regards to meals
3. assess patients regularly for lipohypertrophy when they are in the office

What is a biosimilar?

A biosimilar is a highly similar version of an existing biological drug. Since biological drugs are complex, large and made by living organisms, it is impossible for them to be identical to the original drug. It may help to think of them as a generic version, thinking of how we talk about these drugs currently. Biosimilars are not interchangeable and would need a prescription to switch between the agents.

Basaglar is a biosimilar to Lantus insulin (glargine insulin 100u/ml). It costs 25% less than Lanus. Switching a patient on Lantus to Basaglar would save them about $277/year (depending on their dose).

EAP is going digital

Ontario Drug Benefit Exceptional Access Program will **no longer accept faxes** to review applications **starting Jan 1, 2022**. EAP requests will need to be submitted to the SADIE portal. A Go Secure login is required to access SADIE. The benefits of using SADIE are: faster response times and specific criteria required for coverage will be available.

SADIE login can be found here (https://www.health.gov.on.ca/en/pro/programs/sadie/)

Adverse drug reporting

Medication side effects are not fully captured during randomized trials due to study populations and trial duration limitations. It is important to report suspected adverse drug reactions, even if not certain, to Health Canada.

Reporting of an ADR requires only 4 things:

1. **patient information** - for reasons of confidentiality the patient name should not be used
2. **description of the adverse reaction**
3. **name of the health product** you suspect caused the adverse reaction
4. **contact information** in case Health Canada requires additional information

The online form can be found here: https://hpr-rps.hres.ca/side-effects-reporting-form.php?form=voluntary&lang=en

Your patient had a reaction to a vaccination?

The vaccine specific reporting form can be found here:
https://www.publichealthontario.ca/-/media/documents/a/2020/aefi-reporting-form.pdf?la=en

The completed form should be **faxed** to your local health unit:
MLHU: 519-663-9581
SWPH: 519-539-6202

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