Thames Valley Family Health Team

The Dose Spring/Summer 2023

In This Issue…

An introduction to providing inclusive primary care to trans patients

This article was contributed by Caitlin Wild, PharmD Candidate (2023) from the University of Waterloo

Source: Canadian Pharmacists Association

In Ontario, around half of trans people are uncomfortable discussing trans concerns with their primary care provider[1]. Many trans people have had negative experiences when accessing healthcare, including the refusal to provide gender-affirming care.

Gender affirming healthcare *refers to all healthcare which supports a patient's gender identity and expression. It may include counselling, prescribing of medications, or surgery.*

Suicidal ideation and suicide attempt rates are very high among trans people, with the highest rates in those planning for medical transition (surgery and/or hormone therapy) but have not begun[1]. Much of the suicidality risk stems from the persecution and stigma that trans people face in their day-to-day lives and can be reduced by providing compassionate gender-affirming care. Caring for trans and nonbinary patients includes transition-related therapies if this is aligned with the patient's goals, but also all their other primary care needs.

It is important to remove any barriers that may make it challenging for trans patients to access care and feel comfortable. Some strategies to creating a welcoming and comfortable environment for trans people in primary care recommended by Rainbow Health Ontario include:

- Provide intake forms that allow for patients to self-identify and include their chosen name, pronouns and gender identity.
- Ensure that ALL staff and healthcare providers use appropriate pronouns and names aligned with the patient's gender identity. Always ask if you are not sure and do not make assumptions.
- Use individual identifiers (e.g. pins, symbols on name badges, signs in individual offices) to distinguish LGBT2SQ+ supportive care providers
- Familiarize staff with basic terminology used by the trans community.
- Ensure patients have psychosocial supports. Some may benefit from therapy with a trans positive therapist, peer support groups, social work, discussing transitioning with family and friends etc.

Glossary of terminology used by the trans community (Rainbow Health)

Sex: A label we are given at birth to describe our physical bodies and reproductive capacity. Characteristics of the body used to determine biological sex may include genitals, gonads, hormones, chromosomes, and secondary sex characteristics.

Gender Identity: a person's internal self-awareness of being a certain gender

Gender role/expression: The social expression of gender. Often described as being on a spectrum between masculine to feminine. Often related to, but sometimes distinct from, gender identity. For example, some trans or cis women may identify as butch or have a masculine presentation, and some cis or trans men may be feminine or identify as femme.

Cis: Having a non-trans gender identity. In other words, having a gender identity which is the same as the sex assigned at birth.

Transfeminine: An umbrella term to describe all persons assigned male at birth who transition to live as girls/women (i.e. trans women) or somewhere on the feminine spectrum.

Transmasculine: An umbrella term to describe all persons assigned female at birth who transition to live as boys/men (i.e. trans men) or somewhere on the masculine spectrum.

Trans: Trans refers to a state of incongruence of one's gender identity with the gender assigned at birth. It is an umbrella term for people who are not cis, includes persons who are (or identify as) non-binary as well as transmasculine and transfeminine people.

Non-Binary: Umbrella term for anyone who does not identify with static, binary gender identities. Includes persons who may identify as having an intermediary gender (e.g. genderqueer), as being multiple genders (e.g. bigender, polygender, etc.), as having a shifting gender (gender fluid), or as not having a gender altogether (agender).

Two-Spirit: An umbrella term describing the diversity of gender expressions and sexual orientations present in traditional belief systems held by North American First Nations persons.

According to the World Professional Association for Transgender Health, ***primary care providers are well suited to provide care to the trans population*.** Referring to an endocrinologist may be necessary in medically complex patients and children, but it is typically not required for more uncomplicated adult patients. ***Referrals to other specialties may result in undue stress for the patient due to long wait times.***

Useful Trans Health Resources for Primary Care Providers:

Guidelines for gender affirming primary care with trans and non-binary patients

Quick Reference Guide by Sherbourne Health

Rainbow Health Ontario's resources for healthcare providers

Rainbow Health Ontario's online learning platform, LGBT2SQ Health Connect

In the fall issue of The Dose we will review the hormonal treatments used for masculinizing and feminizing therapy.

Finerenone (Kerendia®) for secondary cardiorenal risk reduction in type 2 diabetes

New to the Canadian market, finerenone is a new non-steroidal, highly selective, mineralocorticoid receptor antagonist. Based on evidence of positive cardiorenal outcomes, finerenone may be a reasonable adjunct therapy to add for patients with T2DM and CKD (urine ACR >30 and eGFR 25-75) who are already on or have a contraindication to evidence-based therapy, though there is a lack of consensus between guidelines about its exact place in therapy. Finerenone is expensive and drug coverage is currently limited to private insurance. It has a high risk of causing hyperkalemia. Additional information about finerenone can be found later in the newsletter here.

Academic detailing update: Anxiety and depression

This spring we have started to offer academic detailing visits on Anxiety and Depression.

Did you know…

…evidence does not support universal screening for anxiety and depression?
→ *in a visit we might discuss who would be appropriate to screen*

…that online CBT is as effective as in-person CBT?
→ *in a visit we might discuss the many ways in which you can help your patient access psychotherapy*

…that generally all antidepressants have a similar level of efficacy for depression?
→ *in a visit we might discuss how to engage in patient-centred selection of an agent*

…when to switch someone's antidepressant, and when to consider adding on a drug for augmentation?
→ *in a visit we might discuss the patient characteristics which may help make this decision*

Over the coming months we will be offering a refresh on the Type 2 Diabetes topic, with EMR tools for diabetes from Evidence2Practice Ontario being launched.

If this newsletter has reached you and you are a prescriber outside of the Thames Valley FHT, you can request a 1:1 Mainpro+ accredited academic detailing visit directly from the Centre for Effective practice on their website.

Answers to common questions about treatments for allergic rhinitis

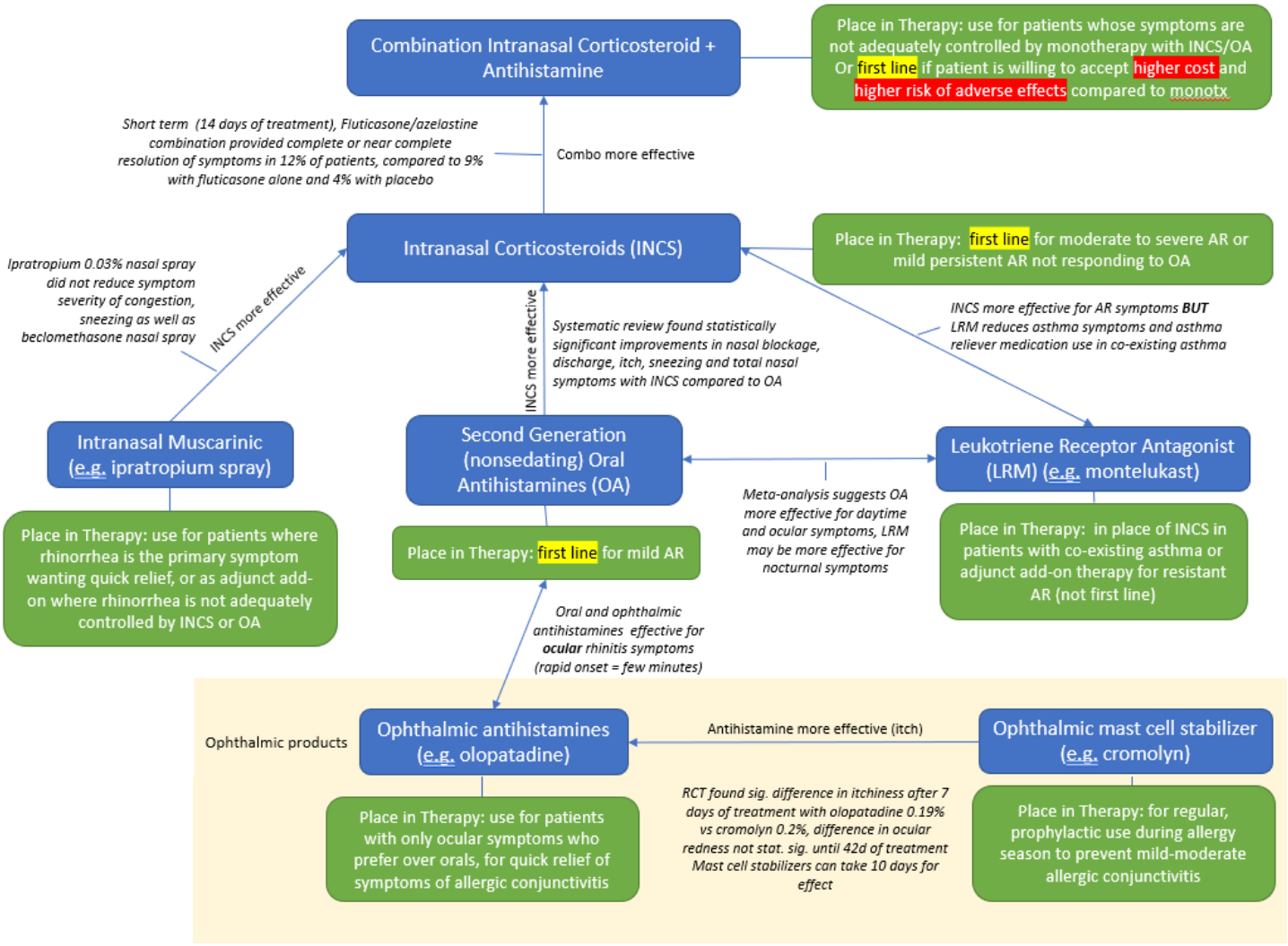
Allergic rhinitis (AR) season is in full swing, and our pharmacists often get questions about considerations for drug selection – which agents treat which symptoms, comparative effectiveness, coverage and cost. For more information about these considerations, see Figure 1 (symptoms treated, cost, coverage) and Figure 2 (comparative effectiveness, place in therapy of various agents).

Figure 1: Symptoms treated with pharmacotherapy for allergic rhinitis

	Rhinorrhea	Sneezing	Nasal Congestion	Sinusitis	Nasal Polyps	Allergic Conjunctivitis	Urticaria	ODB Coverage	Cost
Oral Nonsedating Antihistamines			Possibly w/ ?desloratadine/ cetirizine					X	$7-15+ (varies by pack size) $40/month for Rx drugs
Oral and Topical Decongestants			Short Term Use Only					X	$5-10 /bottle
Leukotriene Receptor Antagonists								**	$25/30d
Intranasal Corticosteroids						Variable effects		✓ (some†)	$23-45 /bottle (Beclomethasone and budesonide are the cheapest)
Intranasal Antihistamines*								X	$115/bottle
Intranasal Muscarinics								X	$30/bottle
Ophthalmic Mast Cell Stabilizers						10d to onset of effect		✓	$5-12 /bottle
Ophthalmic Antihistamines								X	$32-38 /bottle
Saline irrigation				Small benefit				X	$15+ (varies by product)

*In Canada, intranasal antihistamines are only available in combination with corticosteroid in Dymista (fluticasone/azelastine)
**montelukast is not covered for AR, covered for children aged 2-5 for asthma with LU code 382, may apply for EAP for asthma if adult patient has a disability precluding use of inhalers or for children aged 5-18 whose asthma is not adequately controlled with inhaled corticosteroids
†beclomethasone 50mcg spray, budesonide 100mcg aqueous spray, ciclesonide 50mcg spray
Chart adapted from similar charts in RxTx and RxFiles (see references)

Figure 2: Comparative efficacy and place in therapy of agents used to treat allergic rhinitis



*Sedating antihistamines, oral and nasal decongestants are not included in this graphic as they are generally not widely used due to their adverse effects. Sedating antihistamines are not more efficacious than nonsedating. There may be a role for short-term use of these agents in individual patients on a case-by-case basis

Pharmacy practice update: administration of substances by inhalation and injection

New regulations have been approved allowing pharmacists in Ontario with appropriate training to administer substances by inhalation or injection to patients for reasons other than for demonstration and education. This includes a number of drugs e.g. biologics, antidiabetic agents, osteoporosis treatments, blood thinners, inhalers (full list here). These changes come into effect July 1, 2023.

What does this mean for primary care?

Patients who are fearful or who have difficulty self administering their home injections will have access to support from their community pharmacist to inject their medication for them. Some patients may choose to have routine injections they have historically had administered in office (e.g. denosumab - Prolia®, vitamin B12) given to them at their community pharmacy, without the pharmacy needing to pursue a direct order or medical directive to inject. Some pharmacies may charge the patient a fee (usually around $20) for this service.

Rethinking menopausal hormonal therapy

This article was contributed by Caitlin Wild, PharmD Candidate (2023) from the University of Waterloo

The Womens Health Initiative (WHI) studies were prematurely stopped in 2002 and 2004, due to increased risks of coronary events, breast cancer, stroke and venous thromboembolism and subsequently menopausal hormone therapy (MHT) became highly controversial.[1] Interestingly, the WHI studies were NOT designed to assess the risks and benefits of hormone therapy in treating **menopausal symptoms**. Rather, they were designed to assess the risks and benefits of hormone therapy in ***older, post-menopausal*** women.[4]

Other limitations of the WHI:

- Women were older, average age of 63 (50 –79) and an average 12 years since initiation of menopause.[4]
- Absence of vasomotor symptoms, multiple comorbidities
- Study of only one route of administration (oral), one type of estrogen (conjugated equine estrogen) and one type of progesterone (MPA). [4]

What were the actual risks from the WHI? [2]

Outcome	**Results observed in the WHI[2,3,4]**
Breast cancer	8 more cases per 10,000 patients yearly (p=0.04) This risk is comparable to the increased breast cancer risk associated with obesity or low physical activity and is less risk than two glasses of wine daily. [2,3,4]
Coronary heart disease (CHD)	7 more events per 10,000 patients yearly (p=0.13) on estrogen and progesterone therapy (EPT) No increased risk of CHD in those women just taking estrogen
Gallbladder disease	47 more self-reported cases per 10,000 patients yearly (p =<0.001) on EPT 58 more self-reported cases per 10,000 patients yearly (p=<0.001) on estrogen monotherapy
Stroke*	8 more events per 10,000 patients yearly (p=0.01) on EPT 12 more events per 10,000 patients yearly (p=0.01) on estrogen monotherapy
VTE*	18 more events per 10,000 patients yearly (p=<0.001) on EPT 7 more events per 10,000 patients yearly (P=<0.001) on estrogen monotherapy

*In patients with moderate risk for CVD (smoking, hypertension, etc.) transdermal or low dose estrogen may be a better option. Transdermal route along with lower doses of therapy may decrease the risk of VTE and stroke.[2,3,4]

Impact of Hormone Discontinuation

The premature release in combination with the misinterpretation of the initial findings of the WHI impacted society as a whole! Not only were the results discussed through regular scientific channels – but EVERYONE was talking about it, including numerous talk show hosts! Millions of women decided to discontinue MRT almost overnight – which not only left women to experience bothersome menopause related symptoms and reduced quality of life, but they also lost protection from osteoporosis and fractures. The controversy from the studies rippled for many years and resulted in a sustained reduction of 80% MRT prescription use over the next 10 years. This translated into a 55% increase in hip fractures and countless premature deaths.[5]

What to do in 2023?

MRT remains the most effective treatment for vasomotor symptoms and the genitourinary syndrome of menopause and has been shown to prevent bone loss and fractures. Current Health Canada approved indications for MRT include vasomotor symptoms, prevention of bone loss, and genitourinary/vulvovaginal symptoms.[6] Approximately 80% of menopausal women will experience vasomotor symptoms at some point in their life.[1] Vasomotor symptoms (VMS) can have a significant impact on one's quality of life. Various effects include insomnia, sleep apnea, mood swings, impaired concentration, and memory along with social and work impairments. This is why it is very important to consider treatment options for women experiencing these bothersome symptoms. MHT remains the gold standard, most effective treatment option for vasomotor symptoms and genitourinary syndrome of menopause with an approximate 75% reduction in symptom severity and frequency. [3]

MRT is safe in the appropriate patient population

In general, the data suggests there is no increased risk of death with MRT for healthy women (with no contraindications) **younger than 60 or within 10 years of the start of menopause** who are experiencing bothersome symptoms of menopause.[2] Contraindications to hormone therapy are included in the table below.[2,3]

Contraindications to Oral and Transdermal Hormone Therapy	
Unexplained vaginal bleeding	Prior CHD: stroke, MI or VTE
Liver disease	Personal history or genetic high risk of thromboembolic disease
History of estrogen-sensitive cancer	Pregnancy

In women with gallbladder disease, diabetes, high risk of breast cancer, high risk of heart disease or migraine with aura, the use of MHT should be done cautiously.

The risks of hormone therapy are dependent on the type of hormone used, dose, duration, route of administration, timing of initiation and whether a progestogen is used in combination with an estrogen. There are increased risks associated with hormone therapy when used for extended duration and with increasing age. The North American Menopause Society (NAMS) states: *"For women who initiate hormone therapy more than 10 years from the start of menopause or when aged 60 years or older, the benefit-risk ratio is less favourable than younger women due to the increased risks of CHD, stroke, VTE and dementia."*[2]

Engage in shared decision making

Shared decision making with the patient is essential, and periodic follow ups should be done to evaluate the risk-benefit profile of continuing with hormone therapy. Since a lot of women may experience vasomotor symptoms that effect their quality of life for multiple years, the duration of therapy should be individualized and take into consideration symptoms, benefits, and the individual's risk. An age-based stopping rule is not clinically appropriate according to NAMS. The WHI studies which were limited to 5-7 years of therapy are the longest RCT currently completed, so the question of appropriate duration is not sufficiently answered by our current data.[2] A tool that may be helpful in shared decision making can be found at this link: An efficient tool for the primary care management of menopause (cfp.ca). Part of this tool includes the MQ6, which can be found below.

Figure 1. The Menopause Quick 6 questionnaire: *If a patient answers yes to any of questions 1 to 4, she might be a candidate for treatment, and further exploration and assessment is warranted. The Society of Obstetricians and Gynaecologists of Canada and International Menopause Society guidelines recommend that questions 2 to 6 be asked of all perimenopausal women.*[4,6]

Consider all treatment options

Non hormonal medications for vasomotor symptoms are available that may offer some relief. These include antidepressants, gabapentin, clonidine, and oxybutynin. These medications come with their own risks and adverse effects as well. These can be considered if the patient has a contraindication to hormone therapy or would prefer another option. [3]

Bottom Line: The risk to benefit ratio of menopausal hormone therapy in healthy women aged younger than 60 years or within 10 years of menopause onset is acceptable (assuming no contraindications).[2] For all patients, the risks of hormone therapy should be weighed against the various risks of not treating, including poor quality of life.

Hormone Therapy Used in Menopause: Treatment Options[3,8]

ORAL ESTROGENS	DOSE	ODB COVERAGE
CONJUGATED ESTROGENS (PREMARIN)	0.3-0.625 mg daily	★ (LU CODE)
17- BETA ESTRADIOL (ESTRACE)	0.5-1 mg daily	✓ (GENERIC)
TRANSDERMAL ESTROGENS		
17-BETA ESTRADIOL PATCH (ESTRADOT, ESTRADIOL DERM, CLIMARA)	ESTRADOT, ESTRADIOL DERM: 25-50 mcg twice weekly CLIMARA: 25-50mcg once weekly	✗
17- BETA ESTRADIOL GEL (ESTROGEL)	0.75-1.5mg (1-2 actuations) applied daily	✗
ORAL ESTROGEN AND PROGESTIN COMBINATIONS		
17 BETA ESTRADIOL/DROSPIRENONE (ANGELIQ)	1 tablet (1mg/1mg) daily	✗
ESTRADIOL HEMIHYDRATE/NORETHINDRONE ACETATE (ACTIVELLE)	1 tablet (1mg/0.5mg) daily	✗
TRANSDERMAL ESTROGEN AND PROGESTIN COMBINATIONS		
17 BETA ESTRADIOL/NORETHINDRONE ACETATE PATCH (ESTALIS)	1 patch applied twice weekly	✗
ORAL PROGESTINS		
MEDROXYPROGESTERONE ACETATE (PROVERA)	2.5mg daily or 5mg daily first 12 days of every month	✓ (GENERIC)
NORETHINDRONE ACETATE (NORLUTATE)	5mg daily	✗
MICRONIZED PROGESTERONE (PROMETRIUM)	100mg daily or 200mg for 12-14 days of every month	✓ (GENERIC)
TISSUE SELECTIVE ESTROGEN COMPLEX		
CONJUGATED ESTROGEN/BAZEDOXIFENE (DUAVIVE)	1 tablet (0.45mg/20mg) daily	✗

Finerenone (Kerendia®) Information

Drug name	Finerenone (Kerendia®)
Approved Indication	As adjunct to standard of care therapy in adults with chronic kidney disease (CKD) and type 2 diabetes (T2D) to reduce the risk of: • End-stage kidney disease and a sustained decrease in estimated glomerular filtration rate, • Cardiovascular death, non-fatal myocardial infarction and hospitalization for heart failure
Mechanism of Action	Nonsteroidal highly selective mineralocorticoid receptor antagonist (MRA) Proposed mechanism: reduction of inflammation and fibrosis in kidney, heart and blood vessels
Dosing	Starting Dose: • 10 mg once daily if eGFR ≥ 25 to < 60 mL/min/1.73m2 • 20 mg once daily if eGFR ≥ 60 mL/min/1.73m2 N.B. It is recommended to start finerenone if serum potassium ≤ 4.8 mmol/L. If serum K+ > 4.8 to 5.0 mmol/L, initiation of finerenone treatment may be considered with additional serum K+ monitoring within the first 4 weeks based on patient characteristics and serum K+ levels

<table>
<tr><td>Dose adjustment</td><td>It is recommended to re-check serum potassium and eGFR after 4 weeks of treatment to determine maintenance dose of finerenone, based on the chart below
<table>
<tr><th>Serum potassium (mmol/L)</th><th>KERENDIA dose (after 4 weeks and thereafter)</th></tr>
<tr><td>≤ 4.8</td><td>Maintain 20 mg once daily.
For patients on 10 mg once daily, increase the dose to 20 mg once daily if eGFR has not decreased > 30% compared to the prior measurement.</td></tr>
<tr><td>> 4.8 – 5.5</td><td>Maintain dose.</td></tr>
<tr><td>> 5.5</td><td>Withhold KERENDIA.
Restart at 10 mg once daily if serum potassium ≤ 5.0 mmol/L.</td></tr>
</table></td></tr>
<tr><td>Contraindications</td><td>Hypersensitivity to finerenone
Addison’s Disease
Concomitant treatment with strong CYP 3A4 inhibitor (e.g. ketoconazole, clarithromycin, ritonavir)</td></tr>
<tr><td>Precautions</td><td>Weak/moderate CYP 3A4 inhibitors (increased exposure to finerenone, consider increased lab monitoring) and moderate/strong CYP 3A4 inducers (reduced exposure to finerenone, possible decreased effect)
Severe hepatic impairment (Child Pugh C) – avoid use due to potential significant increase in exposure to finerenone, excluded from phase III trials
Hyperkalemia – consider more frequent K+ monitoring in patients at risk of hyperkalemia; risk factors include low eGFR, higher serum potassium and previous episodes of hyperkalemia.</td></tr>
<tr><td>Pregnancy/ Breastfeeding/ Special populations</td><td>Pregnancy – no human studies available, excluded from trials; finerenone should not be used during pregnancy unless there has been careful consideration of the benefit for the mother and the risk to the fetus (animal models showed fetal harm at 4 times the usual exposure of the drug)
Breastfeeding – risk to nursing infant cannot be excluded based on animal data. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from finerenone therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman
Pediatrics – use has not been studied or authorized in children
Geriatrics - of the 6510 patients who received KERENDIA in the FIDELIO-DKD and FIGARO-DKD studies, 40.4% were between 65 and 74 years, and 14.2% were 75 years and older, no significant differences demonstrated in efficacy between older and younger adults in the trials</td></tr>
<tr><td>Adverse Drug Reactions</td><td>Hyperkalemia (14%, see trial information below for incidence of hyperkalemia leading to permanent discontinuation, less frequent), anemia (6.5%, similar incidence 6.1% in placebo arms) hypouricemia (5.1%), hypotension (4.6% - mean reduction of 3mmHg systolic 1-2mmHg diastolic), pruritis (2.9%, similar to placebo 2.2%), hyponatremia (1.3%)</td></tr>
<tr><td>Drug interactions</td><td>CYP 3A4 inhibitors, inducers as described above in contraindications/precautions
Grapefruit (increase plasma concentration)
Avoid concomitant use of medications which can increase potassium (e.g, other MRAs, potassium-sparing diuretics)
Use with caution and monitor potassium more closely when taken concomitantly with potassium supplements, trimethoprim or trimethoprim-sulfamethoxazole (consider holding finerenone temporarily)*
*note: all patients in the FIDELIO-DKD and FIGARO-DKD were on background ACEi/ARB treatment, so while they can also increase serum potassium the combination was studied in the Phase III trials</td></tr>
<tr><td>Summary of pivotal trials</td><td>FIGARO-DKD (Cardiovascular trial)[2]
Population: 7437 patients with type 2 diabetes and either:
eGFR 25-90 mL/min + urine albumin-to-creatinine ratio 30 to 300 mg/g
eGFR ≥60 mL/min + urine albumin-to-creatinine ratio 30 to 5000 mg/g
treated with optimized RAAS blockade pharmacotherapy</td></tr>
</table>

	○ Mean eGFR ml/min, mean urine ACR mg/g Intervention: finerenone 10 or 20 mg daily vs placebo • Dosing: 10 mg daily if eGFR 25-59 ml/min, 20 mg daily if eGFR >60 Median follow up 3.4 years Primary outcome: **Composite CV outcome** of time to cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure • Event rate 12.4% in the finerenone group and 14.2% in the placebo group (hazard ratio, 0.87; 95% confidence interval [CI], 0.76 to 0.98; P=0.03) ○ Benefit driven primarily by hospitalization for heart failure • **NNT 56 over 3.4 years** to avoid 1 event in the composite CV outcome AE: incidence of hyperkalemia-related discontinuation of the trial regimen was higher with finerenone (1.2%) than with placebo (0.4%) **FIDELIO-DKD (Renal trial)[3]** Population: type 2 diabetes and urine albumin-to-creatinine ratio 30 to 5000 mg/g and an estimated glomerular filtration rate ≥25 to <75 mL per min per 1.73 m^2 treated with optimized RAAS blockade • Mean eGFR 44 ml/min, mean urine ACR 850 mg/g Intervention: finerenone 10 or 20 mg daily vs placebo • Dosing: 10 mg daily if eGFR 25-59 ml/min, 20 mg daily if eGFR >60 Median follow-up 2.6 years Primary outcome: Composite renal outcome: kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes • 17.8% in the finerenone group and 21.1% in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.93; P=0.001) • **NNT 30 over 2.6 years** to avoid 1 event in the composite renal outcome AE: hyperkalemia causing permanent drug discontinuation ~2.3% in finerenone arm, 1.0% in placebo arm
Areas of Controversy	Guidelines are inconsistent with respect to recommended background therapy; some (AACE) recommend patients are on the highest tolerated dose of a RAAS blocker only, others (NICE) recommend background treatment with both maximally tolerated RAAS and SGLT2i. Only 4.6% of participants in the FIDELIO-DKD and 8.4% of patients in FIGARO-DKD were being treated with a SGLT2i at baseline. A sub group analysis of FIDELIO-DKD (n=254) showed no significant difference in efficacy or safety outcomes in patients taking SGLT-2 inhibitors versus those that did not.[4] It is unclear if other MRAs such as spironolactone offer benefits similar to finerenone. There are no head-to head trials comparing finerenone to spironolactone or eplerenone.
Cost/coverage	~$350 for 90 days supply CADTH recommendation: Reimburse with clinical criteria/conditions Not currently covered by ODB or NIHB

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