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2023 UPDATE ON THE SCREENING AND TREATMENT OF LOCALIZED PROSTATE CANCER

Wee Loon Ong, MD
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2023 UPDATE ON THE SCREENING AND TREATMENT OF LOCALIZED PROSTATE CANCER

Introduction

Prostate cancer represents a major burden of disease in Canada. It represents the third leading cause of cancer mortality in men with more than 24,000 individuals diagnosed in 2021. The diagnosis and management of prostate cancer is a continuously evolving area, and the aim of this article is to provide current information on various aspects of prostate cancer care, as an aid for primary care physicians (PCPs) as they guide men through the prostate cancer journey.

Prostate Cancer Screening

The recommendations for prostate cancer screening with prostate specific antigen (PSA) testing have changed over the past decade. Recommendations for any type of screening are a balance between the benefit of early diagnosis (and improved oncologic outcomes) vs the harms associated with the screening and downstream tests.

The evidence supporting the benefit of PSA-based prostate cancer screening was based on two randomized clinical trials, with contradictory results. The European Randomized Study of Screening for Prostate Cancer (ERSPC) showed that PSA-based screening in a largely unscreened population reduced prostate cancer-specific mortality.¹

At a median follow-up of nine years, the relative risk reduction (RRR) of prostate cancer death was 20% by intention-to-treat (ITT) (i.e., how the patient was randomized) while the efficacy analysis (results according to whether or not patients were screened) was 27%. This translated to a number needed to screen (NNS) of 1410 and number needed to diagnose (NND) of 48 men to prevent one prostate cancer death. As the trial matured, the NNS and NND declined. At 13 years, the NNS and NND were 781 and 27 respectively, while at 21 years it was 246 and 14 respectively,² results similar or better than screening effectiveness for breast cancer (NNS 233-377) and cervical cancer (NNS 3497).⁴

The U.S. Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial confounded the screening guidelines as it showed no benefit in prostate cancer-specific mortality.⁵ However, the data that was not noted by the U.S. Preventative Services Task Force (USPSTF) or the Canadian Task Force on Preventive Health Care (CTFPHC) committees is that 85% of the men randomized to screening were compliant, whereas 90% of the men in the control arm received opportunistic screening but were recorded as if they had received no screening.⁶ The implication of this is that a greater number of men received screening in the “no-screening” control arm than the “screening” control arm, yet only ITT analyses were reported.⁵

More than one round of screening further reduces the risk of prostate cancer death (RRR 25% for one round vs 48% for more than one round of screening).⁷ In addition, the initial PSA level can be used to guide decisions regarding further PSA testing (or the timing of the next screening). Specifically, in men age 55 to 69, a PSA level of <1.0 ng/mL resulted in a < 3% likelihood of being diagnosed with prostate cancer 16 years later.⁸ If a second screening was conducted eight years after, the risk of prostate cancer death at 16 years was 0.03%.

Initial Work-up for Elevated PSA

There have been several changes in practice that have reduced the harm associated with screening. The first is to only refer men for work-up if they have a significant risk of having clinically significant prostate cancer (csPC: ISUP Grade Group 2 [i.e., Gleason 7] or higher disease). This can be calculated online (<https://riskcalc.org/PCPTRC/>); however, as a rule of thumb, for a 55-year-old Caucasian male with no family history, a normal digital rectal exam and no previous biopsy, the risk of csPC is equal to the PSA.

Generally, men with >5% risk of csPC should be investigated. Ideally, these men should be referred on to a multidisciplinary uro-oncology team. The establishment of multidisciplinary diagnostic programs, such as the Diagnostic Assessment Program (DAP) endorsed by Cancer Care Ontario, has enabled men with elevated PSA to have timely access to a multidisciplinary uro-oncology team for subsequent work-up (<https://www.cancercareontario.ca/en/find-cancer-services/diagnostic-assessment-program-locations>).

Multiparametric magnetic resonance imaging (mpMRI) is now a standard second screening test for men with elevated csPC risk (sometimes referred to as the “manogram”). It is primarily based on data from two Phase 3 randomized clinical trials.^{9,10} In both trials, men with elevated PSA were randomized to standard systematic prostate biopsy, or upfront mpMRI followed by targeted biopsy of the MRI-detected prostate lesions (biopsy was not done if the MRI was negative). In the Canadian PRECISE study, the MRI-guided approach reduced the risk of requiring a biopsy by 30%, increased the likelihood of detecting csPC by 5%, and decreased the risk of detecting ISUP Grade Group 1 (i.e., Gleason 6) disease by 50%.¹⁰ This is now the preferred approach endorsed by Cancer Care Ontario.¹¹

Once a decision is made to proceed with prostate biopsy, it is most often performed using the transrectal (TR) approach, whereby under ultrasound guidance, the biopsy trocar is passed through the rectal wall

into the prostate. However, the transperineal (TP) approach, whereby the biopsy trocar passes through the transperineal skin (rather than the rectal wall), is recognized as being superior for various reasons.¹² TR biopsy is associated with increased risk of infection and urosepsis, despite the use of antibiotic prophylaxis. While there are no randomized trials comparing the TR and TP approaches in terms of infection rate, the differences in infection rates were shown to be stark with virtually zero risk of infection or urosepsis with TP;¹³ even when prophylactic antibiotic was omitted.¹⁴ In addition, there is some evidence suggesting that the TP approach provides superior detection of anterior tumour.¹⁵ Currently, TP biopsy is available solely at Sunnybrook Hospital and North York General Hospital in Toronto.

Conservative Management: Active Surveillance vs Watchful Waiting

Screening tends to detect lower grade disease (77% in the PROTECT trial had ISUP Grade Group 1 disease)¹⁶ and in the 2000's virtually all of these men with low grade disease (Gleason 3+3 or ISUP Grade 1) were treated with surgery or radiotherapy and experienced the attendant side effects.

However, clinical data has shown that not all men with newly diagnosed prostate cancer require upfront treatment. At least three randomized clinical trials have investigated active treatment with observation in men with localized prostate cancer.¹⁶⁻¹⁸ With median follow-up of 15–20 years, all these studies have consistently shown no significant differences in prostate-cancer specific death with observation, especially in men with low-risk prostate cancer. This has prompted numerous guidelines to revise their recommendations to active surveillance (AS) for these men.^{19,20} Population-based studies in Ontario show that more than 85% of men with low-risk prostate cancer are initially managed with AS (Cancer Care Ontario data). This reduces the harm associated with treatment²¹ as more than 50% of men remain treatment-free 15 years following the initial diagnosis.²²

The disease management objectives of men on AS is distinct from those of men managed with a *watchful waiting* (WW) program, where the care objective is not to delay curative-intent treatment, but to forgo curative-intent treatment and reserve palliative-intent treatment (including androgen deprivation therapy or palliative radiotherapy) for when symptomatic disease progression occurs. This approach is generally recommended for men with favourable prostate cancer with a life expectancy of fewer than 10 years. In these cases, PSA monitoring, tests or physical examinations should not be done; otherwise it represents a form of AS.

Curative-intent Treatment Options for Localized Prostate Cancer

Men who opt for curative-intent treatment have various treatment options, including surgery and radiotherapy,

each with distinct side effect profiles.^{23,24} The rapid advancement in both surgical and radiotherapy techniques over the years has improved outcomes post-treatment. Evidence suggests that robotic-assisted radical prostatectomy (RARP) might have better urinary continence and potency results vs those of open radical prostatectomy with equivalent tumour control.^{25,26}

Advancements in radiotherapy technologies and an improved understanding of the radiobiology of prostate cancer have allowed us to deliver more precise and fewer doses of radiotherapy; this improves tumour control while reducing radiotherapy-related bowel and bladder toxicities. In addition, this has allowed us to shorten the course of prostate radiotherapy from 39 treatments over eight weeks to five treatments with stereotactic body radiotherapy (SBRT) over 1.5 weeks with favourable early toxicity and quality of life outcomes.²⁷ In the PACE-A randomized study of RARP vs SBRT, 0% vs 2% of men had significant bowel changes; 47% vs 5% of men reported incontinence pad use; and 40% vs 10% of men had loss of sexual function, respectively, at 2 years post-treatment.²⁸ These non-invasive, short-course treatments are extremely beneficial in terms of patient convenience and healthcare cost savings.

From a cancer outcome perspective, in the PROTECT trial, surgery and radiotherapy resulted in the same low risk of metastasis (5.4% at 15 years) and prostate cancer death (2.7% at 15 years) for men with intermediate-risk prostate cancer.¹⁶ In a large, propensity matched study among U.S. Centres of Excellence comparing men with high-risk prostate cancer treated with surgery, external beam radiotherapy plus hormones, and external beam radiotherapy plus brachytherapy and hormones, both the risk of metastatic spread (32.7% vs 18.4% vs 10.7%) and prostate cancer death (13.3% vs 10.3% vs 9.3%) at 10 years were reduced.²⁹ There is no randomized clinical trial comparing surgery and radiotherapy in this population. Therefore, it is important that men considering curative-intent treatment be seen by both urologists and radiation oncologists prior to finalizing their treatment decision-making. However, currently in Ontario, fewer than 50% of men undergoing surgery are seen in consultation with a radiation oncologist.³⁰

Conclusion

The diagnosis and management of localized prostate cancer is a continuously evolving area. PCPs play an important role in guiding men through their prostate cancer journey. It is important for PCPs to discuss the benefits and harm of PSA testing, ensure timely referral for further work-up in men with elevated PSA scores, and ensure that all men have the appropriate consultations within a multidisciplinary clinic prior to treatment decision-making.

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PRACTICAL IMPLEMENTATION OF LIPID LOWERING FOR CARDIOVASCULAR RISK REDUCTION IN PRIMARY CARE

Introduction

With the advent of safe lipid-lowering drugs, particularly statins and non-statin agents such as ezetimibe, and with the emergence of newer therapeutics such as monoclonal antibodies and RNA technologies, it has become apparent that major adverse cardiovascular (CV) events can be reduced both in primary and secondary prevention by 20–50% through lowering of low-density lipoprotein cholesterol (LDL-C) by 1–2 mmol/L. The purpose of this paper is to provide a pragmatic approach to the implementation of the 2021 Canadian Cardiovascular Society Guideline for managing dyslipidemia in adults.¹

A) Screening and Identification of an Atherogenic Lipid Profile

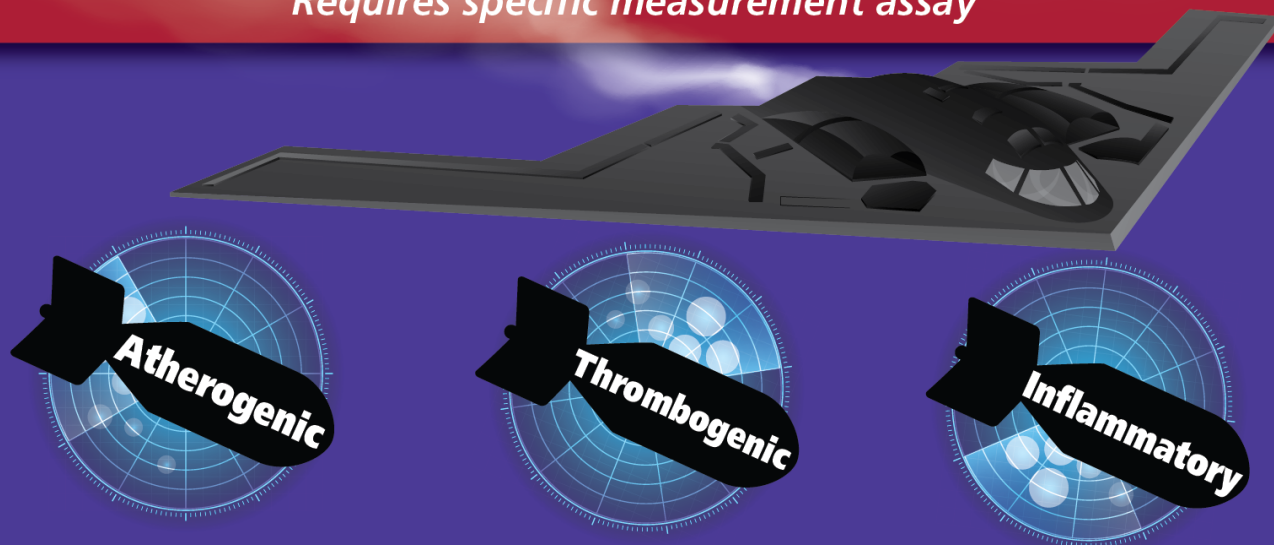
Adults ≥ 40 years of age should have a complete lipid screen which need not be fasting. However, screening should occur at younger ages in women who are postmenopausal or have a history of hypertensive disorders of pregnancy. Similarly, younger adults of South Asian or Indigenous heritage and of either sex should be screened. Regardless of age, a full lipid profile should also be measured in any individual with evidence of preclinical or clinical atherosclerosis (including abdominal aortic aneurysm or erectile dysfunction [ED] in males); a family history of either dyslipidemia or early CV events; the presence of non-lipid

CV risk factors such as diabetes, obesity, chronic kidney disease, hypertension or smoking; and the presence of inflammatory diseases (rheumatoid arthritis [RA]; systemic lupus erythematosus [SLE]; psoriatic arthritis [PsA]; ankylosing spondylitis [AS]; inflammatory bowel disease [IBD]; human immunodeficiency virus [HIV]; and chronic obstructive pulmonary disease [COPD]). A lipid profile is also warranted at any age in patients in whom corneal arcus, xanthelasma and tendinous xanthomas are evident as these may be manifestations of familial hypercholesterolemia.

Lipid screening should now routinely include not only a measure of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and LDL-C but also a one-time measurement of Lp (a), a particularly malignant, apolipoprotein B containing atherogenic particle with additional atherothrombotic and inflammatory properties that is almost entirely genetically determined and, therefore, imparts a lifelong risk that runs in families. Its elevation cannot be deduced from any other component of the lipid panel; therefore, it must be specifically measured to know if it is imparting additional vascular risk. Otherwise, it may cause damage “under the radar” and not be suspected as playing a critical role until events have occurred either prematurely or recurrently. Clinical trials are underway to determine if agents that can specifically and profoundly lower this atherogenic

Lipoprotein (a)

Requires specific measurement assay



When elevated consider treating all modifiable risk factors earlier and more aggressively.

Genetically determined; family screening warranted.

Figure 1. Lp (a). Lp (a) is an atherogenic lipoprotein that cannot be detected without ordering specific testing. The particle resembles LDL-C but has additional inflammatory and thrombotic properties that further enhance CV risk. It should be measured once with an initial standard lipid profile to ensure complete assessment of atherogenic dyslipidemia (AD); courtesy of G.B. John Mancini, MD, FRCPC, FACC.

particle will be associated with CV risk reduction. For now, detection of an elevation warrants “risk enhancement” i.e., the individual is at higher risk than implied by other risk factors; therefore earlier and more aggressive management of all modifiable CV risk factors should be considered. Repeated measurements are not warranted. However, because the levels are genetically determined, screening for high Lp (a) as part of a full lipid profile in first degree relatives should be considered (**Figure 1**).

Interpreting the Lipid Profile: Consider Triglycerides First

In patients found to have a TG ≥ 1.5 mmol/L, it is important to know that the LDL-C may be misleading when calculated in the usual fashion and that it is only one component of atherogenicity (**Figure 2**). Simple arithmetic indicates that as TG elevates, the calculated LDL-C must decline for any given measure of TC and HDL-C. Under these circumstances, the atherogenicity of the lipid profile is more accurately reflected by an apolipoprotein B

measurement, specifically apolipoprotein B100. The latter correlates somewhat with the non-HDL-C. **Figure 3** (cholesterol “triads”) summarizes the comparable levels of LDL-C, non-HDL-C and apolipoprotein B that warrant therapy and/or intensification of therapy when statins are insufficient. Note that when HDL-C, “the good cholesterol,” is subtracted from the total cholesterol, the result is non-HDL-C which reflects “the bad cholesterol”. Thus, non-HDL-C is a measure of the cholesterol in lipid particles containing an apolipoprotein B and which are atherogenic. Finally, if a patient is known or found to have TG >4.5 mmol/L, fasting lipid profiles are warranted during on-going care. However, even though the LDL-C is not calculated or reported by most laboratories when the TG is >4.5 mmol/L, non-HDL-C and apolipoprotein B can still guide risk assessment and therapy.

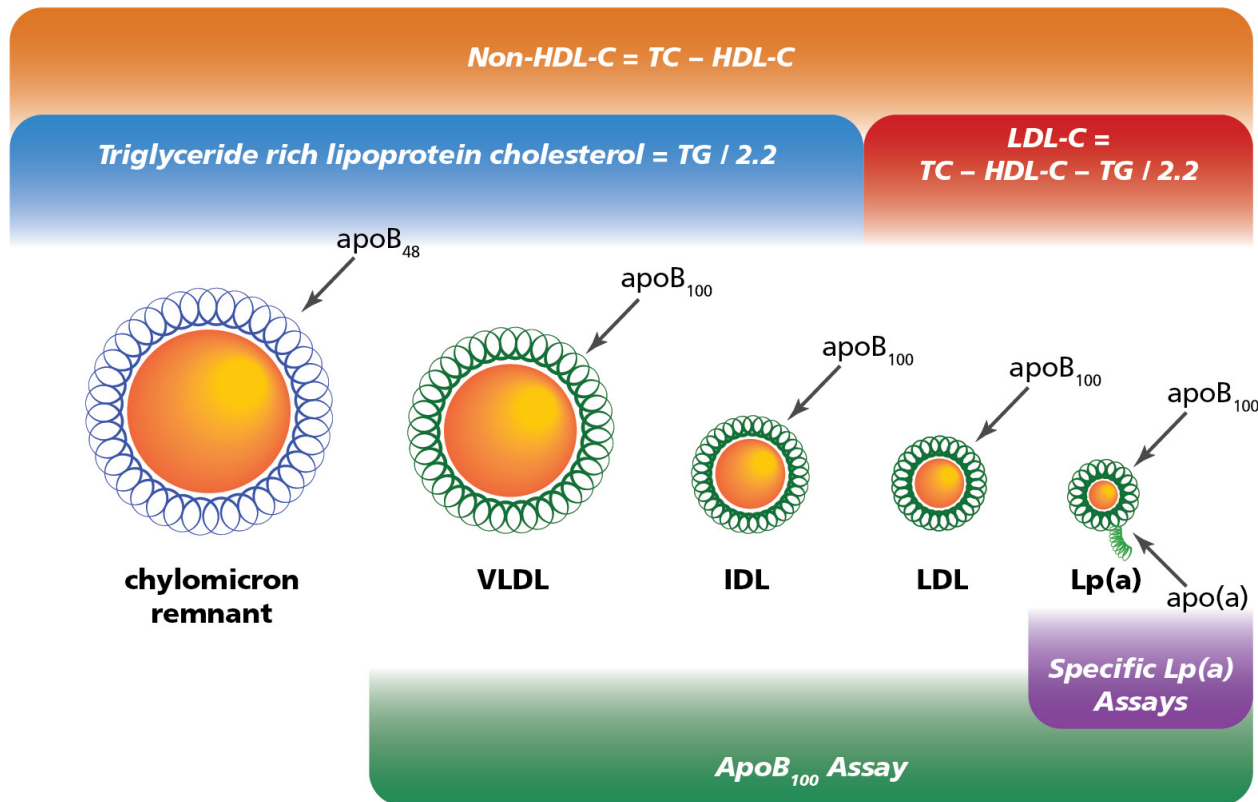


Figure 2. Atherogenic lipid particles and their relationship to cholesterol measurements and specific assays. Depicted are the largest (and generally the fewest) atherogenic particles, chylomicron remnants associated with an apolipoprotein B48 (derived from the intestine), followed by smaller and progressively more numerous atherogenic particles (particularly LDL) associated with apolipoprotein B100 (derived from the liver). The illustration shows how the commonly-employed Friedewald equation is used to calculate LDL-C from measures of total cholesterol, HDL-C and TG divided by 2.2. In addition, the figure emphasizes how LDL and LDL-C are not the sole determinants of atherogenicity. More specific assays for apolipoprotein B100 and for Lp (a) help to clarify the atherogenicity of any given lipid profile. Specialized laboratories and research laboratories may measure particles directly; however, such assays, beyond those for lipoprotein (a), are not used in clinical practice; courtesy of G.B. John Mancini, MD, FRCPC, FACC.

Triglycerides			Clinical Implications	
< 1.5 mmol/L	≥ 1.5 mmol/L			
LDL-C mmol/L	non-HDL-C mmol/L (percentile equivalents)	Apolipoprotein B g/L (percentile equivalents)		
≥ 5.0	≥ 5.8	≥ 1.45	➡➡	Treat at any level of risk
≥ 3.5	≥ 4.2	≥ 1.05	➡➡	Treat if at moderate risk
≥ 2.0	≥ 2.6	≥ 0.80	➡➡	Intensify statin treatment of primary prevention patients
≥ 1.8	≥ 2.4	≥ 0.70	➡➡	Intensify statin treatment of secondary prevention patients

Figure 3. The Lipid Triads. When TG is <1.5 mmol/L, the LDL-C is adequate for diagnostic and therapeutic purposes. However, when TG is ≥1.5 mmol/L, the non-HDL-C and apolipoprotein B equivalents are important to consider. Therefore, the first step in interpreting the lipid profile is to determine if the TG is completely normal or even mildly elevated; courtesy of G.B. John Mancini, MD, FRCPC, FACC.

	Statin-indicated Conditions	Treatment Warranted Based on FRS Stratification
Secondary Prevention	ASCVD	N/A
Primary Prevention	DM > 40 yo, or > 30 yo with microvascular disease or > 15 y duration	FRS > 20%/10y
	CKD (non-dialysis, eGFR <60ml/min/1.73m ² , UACR ≥ 3 mg/mmol	FRS ≥ 10%/10y and LDL-C ≥ 3.5 mmol/L (or non- HDL-C ≥ 4.2 mmol/L or apolipoprotein B ≥ 1.05 mmol/L)
	LDL-C ≥ 5mmol/L (or non-HDL-C ≥ 5.8 mmol/L or apolipoprotein B ≥ 1.45 g/L) or patient with familial hypercholesterolemia	FRS ≥ 10%/10y and LDL-C < 3.5 mmol/L but in association with risk enhancers*
		FRS ≥ 5%-9.9%/10y and LDL-C ≥ 3.5 mmol/L (or non- HDL-C ≥ 4.2 mmol/L or apolipoprotein B ≥ 1.05g/L) and presence of risk enhancers*

*Risk Modifiers Not Reflected in Framingham Risk Scoring or Statin-indicated Conditions	
*Risk Enhancers From Randomized Clinical Trials:	• hs-CRP >2.0 mg/L • Elevated waist-to-hip ratio • Prediabetes, metabolic syndrome, IFG or IGT • LVH/other EKG abnormalities in hypertensive patients
*Risk Enhancers From Epidemiological Studies:	• Family history of premature CVD • Elevated Lp (a) • Preclinical ASCVD (e.g., CAC score >0) • Obesity • Inflammatory diseases • ED • Pregnancy-related complications • Indigenous and South Asian ethnicity
Risk De-enhancers:	CAC Score = 0 in moderate FRS patient

Table 1. Summary of patient profiles warranting lipid lowering for reduction of CV risk; courtesy of G.B. John Mancini, MD, FRCPC, FACC. ASCVD = atherosclerotic cardiovascular disease; DM = diabetes mellitus; FRS = Framingham risk score; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; hsCRP = High-Sensitivity C-Reactive Protein; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; LVH = left ventricular hypertrophy; EKG = electrocardiogram; CVD = cardiovascular disease; CAC = coronary artery calcium; ED = erectile dysfunction.

B) Who to Treat (Table 1)

Framingham Risk Score Considerations

Statin-indicated conditions are those that can be identified clinically, without the need for risk calculation. Clinical trials have proven the benefit of lipid-lowering therapy for secondary prevention i.e., those with clinical atherosclerotic cardiovascular disease (ASCVD). Similarly, for primary prevention, most patients with Type 2 diabetes mellitus (T2DM) (those >40 years of age; or with over 15 years' duration of T2DM or evidence of microvascular disease [MVD]) and those with chronic kidney disease (CKD) (eGFR <60 mL/min/1.73m² or urine albumin-creatinine ratio [ACR] ≥3.0 mg/mmol) have been shown to benefit. While this is not based on clinical trials, it is known that patients with very high LDL-C (≥5.0 mmol/L) and those with familial hypercholesterolemia have improved CV outcomes through long-term LDL-C lowering.

Subjects Identified with Framingham Risk Stratification

In patients who do not meet the obvious statin-indicated criteria, the current recommendation is to stratify risk based on the Framingham Risk Score (FRS) and to treat patients at high risk (≥20% risk of events/10 years). The clinician should also advocate therapy in patients with moderate risk (10%-19% risk of CV events/10 years) and LDL-C ≥3.5 mmol/L. Even in those with risk of 5%-9.9%, therapy is warranted if the LDL-C is ≥3.5 mmol/L if other risk enhancers are also present. Patients with LDL-C <3.5 mmol/L would warrant therapy if the risk is moderate and other risk enhancers studied in clinical trials but not part of the FRS or the statin-indicated conditions are also present (e.g., c-reactive protein [CRP] >2.0 mg/L, presence of end-organ damage such as left ventricular hypertrophy [LVH] in hypertensive patients, or presence of metabolic syndrome/prediabetes/impaired fasting glucose [IFG]/impaired glucose tolerance [IGT]/high waist-to-hip ratio). Other risk enhancers supported through epidemiologic evidence should also be factored in (e.g., family history of premature CVD; Lp(a) >50mg/dL or >100 nmol/L; pregnancy-related complications; Indigenous or South Asian ethnicity; evidence of preclinical atherosclerosis; concomitant HIV; or inflammatory diseases). Therapy is generally not advocated in adults if FRS is <5%/10 years and if none of these other risk enhancers are present.

Coronary Artery Calcium Scoring: Primary Value is in the Treatment-reluctant Patient

It must be emphasized that any disposition formulated by the physician will always be subject to patient-physician discussions prior to implementation or lack of implementation. When a patient conforms to a profile, as outlined above, of having a high likelihood of reaping benefit from lipid lowering, but remains reluctant to accept the rationale for therapy, the demonstration of already established atherosclerosis may facilitate acceptance of recommended therapy. This is important to consider

particularly if the risk has been estimated as moderate (≥10%-19.9% by the Framingham equation) wherein clinical studies have shown optimal utility. However, even above and below this level of risk, some patients may not accept treatment recommendations. Although not generally recommended in these circumstances, a coronary artery calcium scoring (CACS) may aid in patient counselling. This is especially the case when features such as a family history of premature ASCVD, high Lp(a), or high LDL-C (≥3.5%) are present and patients remain reluctant to accept therapy (**Figure 4**). For practical purposes, if the calcium score is above 100 Agatston units, it suggests that a moderate FRS is likely an underestimation and that the patient should be reclassified to high risk. A score of 1-99 suggests that the patient is still indeed at least at moderate risk. With the additional knowledge that atherosclerosis is already established, the patient may view the value of the indicated therapy more favourably. The finding of a zero score generally portends a good, short-term prognosis (the patient is re-classified to a low risk). Some patients may prefer to forego preventive therapy based on the zero calcium score when their perception of the negative impact of taking daily medications is high. Others, however, may accept preventive therapy as a way to try to maintain the low atherosclerotic burden status implied by the zero calcium score. It is imperative to re-evaluate the situation, at least within five years, if modifiable risk factors, particularly LDL-C, remain untreated. It is also essential that the decision to forego therapy is truly the patient's decision because clinicians are obliged to indicate that in the setting of a CACS of zero Agatston units the rate of events is low, but it is not in fact zero. Part of this may be due to the fact that non-calcified plaque may still be present when the CACS is zero and non-calcified plaque may progress in the presence of untreated risk factors. In general, physicians should be advocating therapy for modifiable risk factors as this is the safest long-term strategy. In addition, every effort should be made to treat all modifiable risk factors in patients with T2DM, on-going smoking and family history of premature CV disease wherein the reclassification role of CACS is less well-accepted.

A) Limited Therapeutic Options

At the time of writing, according to the 2021 guidelines and for most practical purposes, LDL-C-related CV risk can be addressed with statins, ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors although the armamentarium continues to be augmented with novel medications. Another therapeutic tool, icosapent ethyl, is discussed in the context of residually elevated TG levels while on statins. Fenofibrate, also in the setting of high TG, is discussed however, it is not used to lower CV risk (**Figure 5**).

The busy clinician should focus on being able to optimally use statins and ezetimibe initially. As there are many statins, another practical point is to become comfortable with the use of rosuvastatin and atorvastatin which are

Coronary Artery Calcium Scoring in Treatment-Reluctant Patients

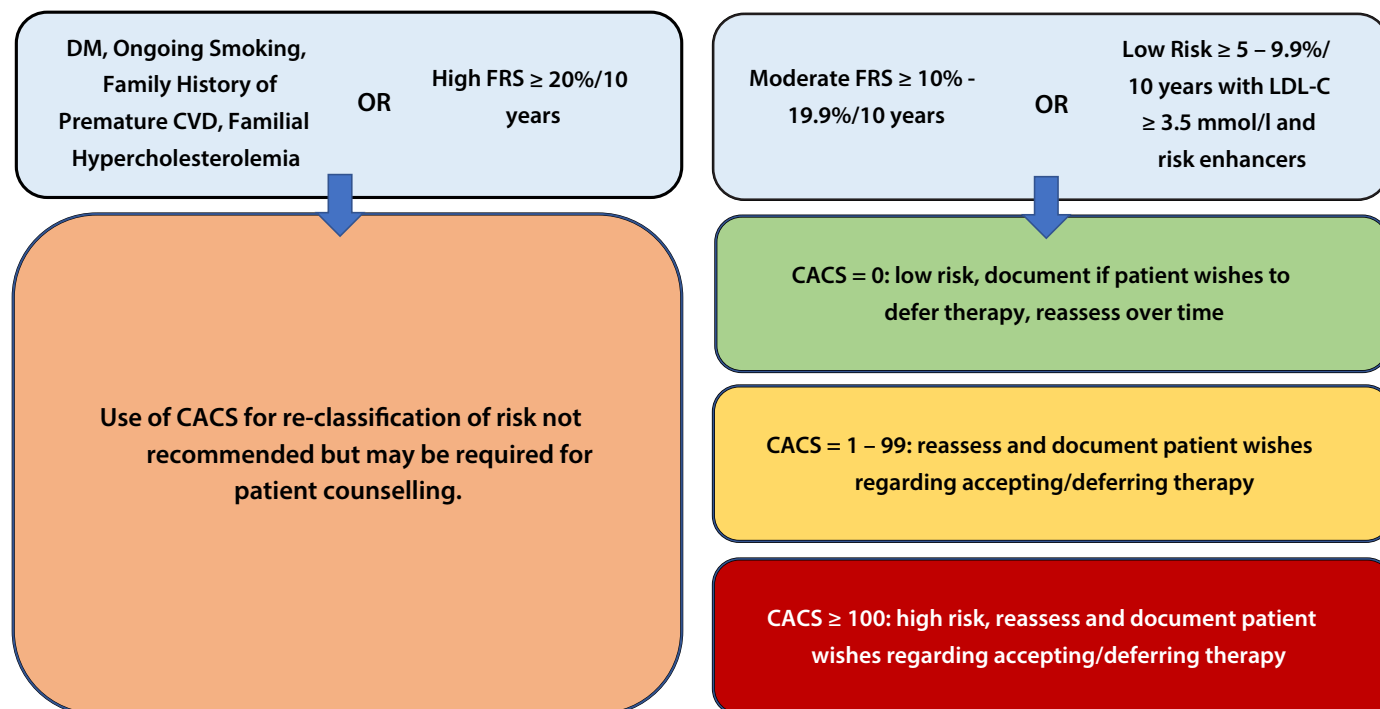


Figure 4. Practical use of CACS. The application of CACS is best-established in patients with a moderate risk but who are reluctant to accept risk reduction therapy. In such patients, the risk can be modified upwards or downwards. Applications outside this realm are less well accepted and are not generally recommended (i.e., in subjects with high Framingham risk, family history of premature CVD, ongoing smoking, T2DM, and familial hypercholesterolemia); courtesy of G.B. John Mancini, MD, FRCPC, FACC.

	Standard Therapy	Non-Statin Therapies			Other
	Statin	Ezetimibe	PCSK9 Inhibitor	IPE	Fenofibrate
Primary Prevention	✓	✓	Familial Hypercholesterolemia	T2D with additional risk factors, on statins and TG 1.5 – 5.6 mmol/L	Warranted to reduce risk of pancreatitis if TG ≥ 10 mmol/L; address secondary causes (e.g. alcohol, uncontrolled DM etc.)
Secondary Prevention	✓	✓	Familial Hypercholesterolemia with ASCVD*	ASCVD on statin and TG 1.5 – 5.6 mmol/L	

* Appropriate for patients with ASCVD alone, particularly those with high risk features such as recent acute coronary syndromes, recurrent events, prior bypass surgery, peripheral vascular disease, elevated lipoprotein (a), diabetes etc. Access will depend on province, private insurance or willingness to pay out of pocket. Inclisiran is an alternative to PCSK9 inhibitors but was not evaluated for the current lipid guideline

Figure 5. The cholesterol therapeutic armamentarium. Practitioners should be comfortable with use of these agents in patients found to warrant lipid-related CV risk reduction in primary and secondary prevention. Fenofibrate is not used for CV risk reduction; however, it is generally used to prevent pancreatitis in patients with TG >10 mmol/L, or at lower levels when there is a history of recurrent pancreatitis; courtesy of G.B. John Mancini, MD, FRCPC, FACC.

very effective at low, moderate or high doses, and even with intermittent dosing as might be required in patients with intolerance to daily doses of statins. Finally, although theoretically it may make sense to bypass the relatively modest LDL-C-lowering effect of ezetimibe and to proceed directly to PCSK9 inhibitors when patients remain substantially above threshold on statins, access to this class is often contingent upon proof of a trial of ezetimibe. Optimal utilization of these three agents can achieve a 50%, 20% and 60% lowering of LDL-C respectively. Used together, a net lowering from baseline of approximately 85% can be achieved.

Some clinicians may wish to expand their armamentarium with the use of resins (e.g., colestevlam which provides an anticipated 20% lowering of LDL-C if tolerated at full dose) or small interfering RNA (siRNA) medications such as inclisiran which yields a 50% lowering with injections every six months. However, currently it is quite reasonable to leave these agents to the purview of specialists.

Using a Threshold as an Objective

The adequacy of LDL-C-lowering therapies and the need for statin add-ons are evaluated with respect to achieving LDL-C levels past the threshold. For most primary prevention settings in adults, using a statin add-on is warranted if the LDL-C remains >2.0 mmol/L or in the secondary prevention setting when the LDL-C remains >1.8 mmol/L while on a maximally tolerated statin (**Figure 3**). If the TG level is ≥ 1.5 mmol/L, it is important to use the non-HDL-C or preferably the apolipoprotein B thresholds shown in **Figure 3** to determine if intensification of therapy is warranted.

Unique Considerations When Triglycerides are Elevated

As indicated above, triglyceride values ≥ 1.5 mmol/L require care in properly evaluating the atherogenicity of the lipid profile, at least warranting consideration of non-HDL-C (a simple approximation of cholesterol in the apolipoprotein B bearing, atherogenic lipid particles) or preferably by measuring apolipoprotein B directly. Beyond this diagnostic implication, there is also a therapeutic implication for patients with ASCVD or high-risk T2DM who are already receiving statins and with remaining TG levels between 1.5 mmol/L and 5.6 mmol/L. In these settings, a unique, pharmaceutical grade formulation of eicosapentanoic acid (isopent ethyl) has been demonstrated to reduce CV risk whereas over-the-counter (OTC) fish oils and other formulations containing both eicosapentanoic acid and docosahexanoic acid (known as omega-3s) have failed to confer this CV risk reduction. The only other tool to consider for the therapeutic armamentarium is fenofibrate, not for CV risk reduction but rather for reduction of the risk of pancreatitis if TG >10 mmol/L.

Conclusion

This brief overview attempts to provide a practical distillation of the 2021 Guidelines for the Management of Dyslipidemia in Adults. The discussion is designed to provide “clinical pearls” and to help navigate the more sophisticated concepts that extend well beyond a focus merely on LDL-C. The new emphasis on weighing the implications of genetically elevated Lp (a), as well as the impact of even modestly elevated TG levels, both for the interpretation of the lipid profile and for therapeutic implications, are demonstrated. The objective is to provide the clinician with a rationale for implementing statins, intensifying statins, using statin add-ons such as ezetimibe and PCSK9 inhibitors, and considering novel agents such as icosapent ethyl in appropriate patients. Additional resources are available to augment this overview: (The CCS Dyslipidemia Guideline Pocket Guide [<https://ccs.ca/pocket-guides/>], The CCS Dyslipidemia Guideline “At a Glance” [<https://ccs.ca/companion-resources/>] and the CardioRisk Calculator [<https://www.circl.ubc.ca/cardiorisk-calculator.html>]).

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Dr. Denise Black is a graduate of the University of Manitoba School of medicine and she completed residency training in OB/GYN in Manitoba as well. In a career that spans 4 decades, she has been involved in both academic and private practice. While in academia, Dr. Black served as the Director of the post graduate medical education program in Obstetrics and Gynecology and served as an examiner for the Royal College. She also was the OB/GYN consultant for the Manitoba HIV team during the early years when intrapartum AZT was first introduced as a way to reduce vertical transmission. Access to appropriate and timely contraceptive care is a professional passion, and advocacy, education, and removing barriers to access is a personal mission. Dr. Black has published in both the fields of contraception and menopause and worked as an author of the SOGC menopause guidelines.



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MENOPAUSE HORMONE THERAPY: 2023 UPDATE

Introduction

The publication of the Women's Health Initiative (WHI) study in 2002 caused a precipitous decline in use of menopause hormone therapy (MHT). Prior to publication, approximately 43% of women aged 45-74 used MHT; following publication, this number dropped to 11%.¹ Fear of breast cancer was the largest motivator behind this decline. Since the WHI study, menopause medical education has been inadequate; it is estimated that 41% of medical schools do not include menopause education in their undergraduate curriculum.² The same study highlighted significant knowledge gaps regarding menopause management among practicing physicians.

Menopausal women are asking questions and expecting answers. Advocacy groups such as the Menopause Foundation of Canada are empowering women to acknowledge the impact of menopausal symptoms on the workplace, personal relationships and personal health. As MHT is considered first-line therapy (in the absence of contraindications), it behooves healthcare providers to have a working knowledge of MHT.

Indications for MHT

The indications for MHT vary. In Canada, guidelines state that MHT is indicated for the management of vasomotor symptoms due to menopause, and MHT may be safely initiated in women without contraindications who are less than 60 years of age, or less than 10 years from

their final menstrual period.³ The indication from the North American Menopause Society is for treatment of bothersome vasomotor symptoms and prevention of bone loss.⁴ The International Menopause Society indications are much more permissive, advocating that MHT is indicated for management of menopause-related complaints, including vasomotor symptoms, muscle and joint aches and pains, and sleep disturbances.⁵

Contraindications to MHT

Contraindications to MHT are listed in **Table 1**.

Assessing Patients for MHT

Suitability for various types of MHT depends on individual assessment of patient risks. Cardiovascular disease (CVD) risk assessment, venous thromboembolic (VTE) risk assessment, breast risk assessment, and the presence or absence of a uterus will determine the most appropriate choice of MHT.

CVD assessment includes the presence or absence of significant hypertension; hyperlipidemia (especially elevated triglycerides [TG's]); Type 2 diabetes (T2DM) or impaired glucose tolerance; obesity (BMI >35); smoking; and age >65.

VTE risk assessment includes obesity (BMI>35); past history of VTE; the presence of a prothrombotic mutation; and age >65.⁶

Contraindications to estrogen	Contraindications to progestogen
• Undiagnosed abnormal vaginal bleeding • Known, suspected, or history of breast cancer • Known or suspected estrogen-dependent cancers (i.e., endometrial, ovarian) • Coronary heart disease • Active or history of venous thromboembolism • Active or history of stroke • Known thromboembolism • Active liver disease • Known or suspected pregnancy	• Undiagnosed abnormal vaginal bleeding • Current or history of breast cancer

Table 1. Contraindications to systemic menopausal hormone therapy; adapted from Yuksel N et al, 2021.³

Breast risk assessment includes family history, presence of a genetic mutation and breast density.

The presence or absence of a uterus will determine the need for endometrial protection.

Selecting a therapy

For patients with an indication and no contraindications, the data support that for those with increased CVD or venous thromboembolic risk, transdermal estrogens at the lowest dose to relieve symptoms have the safety advantage. For those in this higher risk group who have a uterus, the use of micronized progesterone for endometrial protection is recommended, as it does not further increase thromboembolic risk and is viewed to be metabolically favourable for CVD risk.⁷ The use of the levonorgestrel IUS 52 mg in this group is also endorsed, although it is off-label in Canada.

Observational data suggests that for women who have undergone a benign breast biopsy, have a family history of breast cancer, or for those with a BRCA 1 or 2 genetic variant who have undergone oophorectomy, hormone therapy use is not contraindicated and does not further increase their risk of breast cancer.⁴ Increased breast density is a recognized risk factor for breast cancer. A recent meta-analysis, using data from digital mammography, estimates that women with BI-RADS category D breasts (highest density) have a 3.89 fold increase (2.47-6.13) in breast cancer risk vs those with BI-RADS category A breasts.⁸ Estrogen-progestogen therapies further increase breast density, in a dose-dependent fashion, irrespective of the choice of progestogen.⁹ For those with dense breasts, an agent that does not increase breast density (tissue selective estrogen complex [TSEC] or tibolone) may be beneficial.¹⁰ For women using systemic estrogen who have a uterus, adequate endometrial protection is indicated.

Products Available in Canada

In Canada, there are a variety of products, dosages and routes of administration available. Oral estrogens are available as stand-alone therapy, or can be used in combination with endometrial protective agents. Transdermal estrogens are available as patches (changed

once or twice weekly) or daily use gels. Progestogens are available as natural micronized progesterone or synthetic progestins, and are available as part of a combination or as stand-alone therapy. The use of the progestin IUS for endometrial protection as part of an MHT regimen is off-label in Canada; however, there is evidence of endometrial protection with the levonorgestrel-releasing intrauterine system (LNG-IUS) 52 mg for up to 5 years for MHT use, even with higher doses of estrogen administration (Table 2).¹¹

Innovative Therapies

Two novel non-estrogen progesterone/progestin hormone therapy (EPT) therapies are available in Canada. Both of these are fixed-dose, single oral tablet combination therapies.

Tibolone is a synthetic steroid. The parent compound has no metabolic effect; however, once ingested, it performs different actions in various tissues due to tissue selective metabolism. Some metabolites have estrogenic effects on the bone, vagina and brain (for vasomotor symptoms), while one isomer has progestogenic (endometrial protective) activities and mild androgenic properties. The breast is not stimulated due to local enzyme activity which inhibits formation of active estrogens at the breast.¹² In a clinical study, the use of tibolone over a six-month period did not increase breast density.¹³ During the first six months of use, approximately 20% of users with a uterus will experience unscheduled bleeding or spotting; by twelve months this declines to approximately 10%.¹⁴ These are results similar to those seen with estrogen/progestogen therapy.

Conjugated estrogens with bazedoxifene (CE/BZA) is the first product to provide relief of hot flushes and endometrial protection without a progestogen. It is considered a tissue selective estrogen complex (TSEC) and uses a selective estrogen receptor modulator (SERM) to provide endometrial protection. The bazedoxifene (SERM component) provides potent antagonistic activity at the endometrium. The unique combination of this estrogen and this SERM provides relief of vasomotor symptoms, with reported unscheduled bleeding rates of 10% during the first six months, and 1.8% thereafter; this incidence is very similar to that of placebo.¹⁵

Generic	Trade name	Strengths available	Starting dosage
Estrogens			
Oral			
Conjugated estrogens	Premarin	0.3, 0.625, 1.25 mg tablets	0.3–0.625 mg once daily
17 β -estradiol (micronized)	Estrace Lupin-estradiol	0.5, 1, 2 mg tablets 0.5, 1, 2 mg tablets	0.5–1 mg once daily
Transdermal patch			
Twice weekly 17 β -estradiol patches	Estradiol Derm Estradol Oesclim	50, 75, 100 μ g patches 25, 37.5, 50, 75, 100 μ g patches 25, 50 μ g patches	25–50 μ g twice weekly
Once weekly 17 β -estradiol patches	Climara	25, 50, 75, 100 μ g patches	25–50 μ g once weekly
Transdermal gel			
17 β -estradiol gel	EstroGel	0.06% gel 0.75 mg estradiol per 1.25 g metered dose(= 1 actuation)	1–2 metered doses/actuation once daily
	Divigel	0.1% gel Sachets contain 0.25, 0.5, 1 mg	0.5–1 mg sachets once daily
Progestogens			
Oral			
Medroxyprogesterone	Provera Apo-medroxy Pro Doc Limitee Teva-medroxyproges- terone	2.5, 5, 10 mg tablets 2.5, 5, 10 mg tablets 2.5, 5, 10 mg tablets 2.5, 5, 10 mg tablets	2.5 mg daily for continuous regimen 5mg daily for 12–14 days/month for cycle regimen
Progesterone (micronized)	Prometrium PMS-progesterone Reddy-progesterone Teva-progesterone	100 mg capsules 100 mg capsules 100 mg capsules 100 mg capsules	100 mg daily for continuous regimen 200 mg daily for 12–14 days/ month for cyclic regimen
Norethindrone acetate	Norlutate	5 mg tablets	5 mg once daily
Intrauterine			
Levonorgestrel IUS	Mirena	52 mg per IUS	For 5 years
	Kyleena	19.5 mg per IUS	For 5 years
Combination hormone therapy preparations			
Oral			
17 β -estradiol (E2) and NETA	Activelle Activelle LD	1mg E2 and 0.5 mg NETA tablet 0.5 mg E2 and 1 mg DRSP tablet	1 tablet daily
17 β -estradiol (E2) and DRSP	Angeliq	1 mg E2 and 1 mg DRSP tablet	1 tablet daily
Transdermal patch			
17 β -estradiol (E2) and NETA	Estalis 140/50 Estalis 250/50	50 μ gE2 and 140 mg NETA patch 50 μ gE2 and 250 mg NETA patch	For 140/50 patch, twice weekly application
TSEC			
CE and bazedoxifene	Duavive	0.45 mg CE and 20 mg bazedoxifene tablet	1 tablet daily
Synthetic steroid			
Tibolone	Tibella	2.5 mg oral tablet	1 tablet daily

Table 2. Systemic menopausal hormone therapy products in Canada; adapted from Yuksel N et al, 2021.³

* Not approved for menopausal hormone therapy by Health Canada.

* Mirena is the only LNG-IUS marketed in Canada that has evidence for endometrial protection.

CE: conjugated estrogen; DRSP: drospirenone; IUS: intrauterine system; INETA: inorethindrone acetate; SERM: selective estrogen receptor modulator; TSEC: tissue selective estrogen complex.

Following 24 months of use, there was a small **decrease** in breast density, similar to that of placebo.¹⁶

Managing Side Effects

The most commonly-reported side effects are mastalgia and unscheduled bleeding. Rates vary between MHT preparations.

With continuous estrogen/progestogen therapy and tibolone, unscheduled bleeding in the first six months of use is reported at approximately 20-25%. In the absence of increased risk of endometrial cancer, no investigations are mandated during this period. Any bleeding following the first six months of therapy needs to be adequately investigated.¹⁷ If thorough investigations are negative and bleeding persists, switching to CE/BZA (in patients not considered at increased VTE or CVD risk) may alleviate the bleeding issues.¹⁸

Mastalgia is a common side effect during the initial three months of EPT use, with rates approaching 25%. With tibolone or CE/BZA, mastalgia rates are similar to those of placebo.

Initial Fears

When the original WHI publication first appeared, the headlines sensationalized the increased cardiovascular (CV) and breast cancer risks.

Since that publication, numerous scientific works have provided clarity concerning CV risks. A Cochrane Review which stratified CV risk according to age at the initiation of MHT showed a statistically significant 48% reduction in coronary heart disease (CHD) among individuals who initiated MHT prior to age 60 or less than 10 years from their final menstrual period.¹⁹ This data has played a significant role in allaying the fears of CV risk.

The breast cancer fears are difficult to undo, and breast cancer risk due to MHT is difficult to quantify. Guidelines recognize that the relationship between MHT and breast cancer is complex. Attention to lifestyle modification is emphasized. Certain regimens may be considered more “breast friendly” than others, specifically, micronized progesterone rather than synthetic progestins, and perhaps CE/BZA.¹⁰

Duration of Use

Following the publication of the WHI study, it became entrenched in popular culture that duration of MHT use should be limited to five years or less. Current guidelines reflect that the average duration of hot flushing is 7.4 years. Extended use is permissible, provided that initiation of MHT occurred prior to age 60 or less than 10 years from the final menstrual period. In women > 65 who have opted to continue MHT, it is recommended that oral estrogen users switch to a transdermal estrogen at the lowest effective dose. The current thinking is that MHT should be used in the appropriate patient, at the appropriate dose, for the appropriate length of time.⁴

Annual follow up is recommended to discuss the patient's desire to either continue or discontinue MHT, and to assess for new co-morbidities.

There are no long-term, randomized, controlled trials to assess the impact of long-term hormone therapy use on rates of breast cancer. One study showed progressively increasing risk with extended use; however, the overall applicability of this data is difficult, as the preparations used in the study are not the regimens currently in use, with very few study patients using micronized progesterone, and none using CE/BZA.²⁰ It is important to counsel patients about the lack of robust data to predict the impact of prolonged MHT use on breast cancer risk.

Summary

Significant advances have been made in our scientific understanding concerning the risks and benefits of MHT since the WHI study. The lessons learned have been these:

1. **Initiation less than 10 years from the patient's final menstrual period, or prior to age 60, confers the greatest advantages with the least amount of risk.**
2. **In the absence of contraindications, women with increased CV or VTE risk should use a transdermal estrogen at the lowest dose to effectively relieve symptoms. If endometrial protection is necessary, micronized progesterone or LNG-IUS 52 mg should be used (off-label in Canada).**
3. **Dense breasts are a risk factor for breast cancer. Women with dense breasts should use an agent that doesn't further increase density, such as CE/BZA or tibolone.**
4. **There is no “five-year rule” for duration of MHT use. Use of the appropriate therapy, at the appropriate dose, for the appropriate duration is the new rule.**
5. **Although short-term use of MHT (especially “breast-friendlier” options) does not appear to increase breast cancer risk, there is a lack of quality evidence concerning the risks of long-term therapy. Patients are capable of making their own decisions about uncertain outcomes.**
6. **The most common nuisance side effects are unscheduled bleeding and mastalgia. Lowering the medication dose or switching to an agent with a different bleeding or tenderness profile may be beneficial.**

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CASE REPORT: ALLERGIC RHINITIS

CASE #1

A 32-year-old female presents to her primary healthcare professional (HCP) with a long history of intermittent nasal congestion, sneezing, rhinorrhea, and itchy eyes. She recalls experiencing these symptoms in high school, but notes that her condition has worsened over the years. Her symptoms were previously present only in the summer; however, they now extend year-round. She reports that her symptoms affect her sleep when she has complete nasal blockage, that she is forced to blow her nose throughout the night, and that the constant waking leaves her feeling fatigued. She notes that she has “tried everything” in terms of over-the-counter (OTC) medications and that she finds the side effects bothersome. She is requesting allergy testing and has heard that there is “a shot” available.

Rhinitis and Allergic Rhinitis

Rhinitis affects up to 40% of the population¹ in the United States, and allergic rhinitis is the most common etiology.² As we learned during the COVID-19 pandemic, differentiating allergic rhinitis from acute infectious rhinitis is important in helping to determine patients' risk of infecting others, as well as proper management of the condition. Approximately 10%-30% of adults and 40% of children in the United States have allergic rhinitis.² The estimated Canadian prevalence is 20%.³

Allergic rhinitis is known to cause varying degrees of impact on patients' quality of life (QOL), with potential impact on sleep, resulting in fatigue, headaches, poor concentration, and irritability.² Severe symptoms can

lead to absenteeism from school or work, and decreased productivity. In allergic rhinitis, symptom overlap exists with chronic sinusitis, asthma, dental problems, and sleep apnea. Asthma, in particular, is closely associated with rhinitis, with a combined airway inflammatory response; this aids in guiding diagnosis and treatment.²

CLINICAL PEARL: Rhinitis is common in all age groups and can have a significant effect on individuals' QOL.

Signs and Symptoms of Allergic Rhinitis

Symptoms of allergic rhinitis include sneezing, itchy nasal passages, rhinorrhea, congestion, post-nasal drip, and cough, along with associated with conjunctival symptoms of itchy, red, watery eyes.⁴

Physical examination findings include infraorbital discolouration, nasal creasing, and pale and congested turbinates.⁴ An older classification would have been based on seasonal or perennial patterns; however, it is now deemed more useful to classify allergic rhinitis according to intermittent or persistent symptoms, and to base severity on QOL impact (**Figure 1**).⁴

Allergenic triggers include indoor (animals, dust mites) and outdoor allergens (pollen, molds), along with occupational considerations. Cannabis is a newly recognized allergen in light of recent legalization.⁵ Of note, allergic rhinitis often co-exists with non-allergic rhinitis, specifically, irritant rhinitis or vasomotor rhinitis.

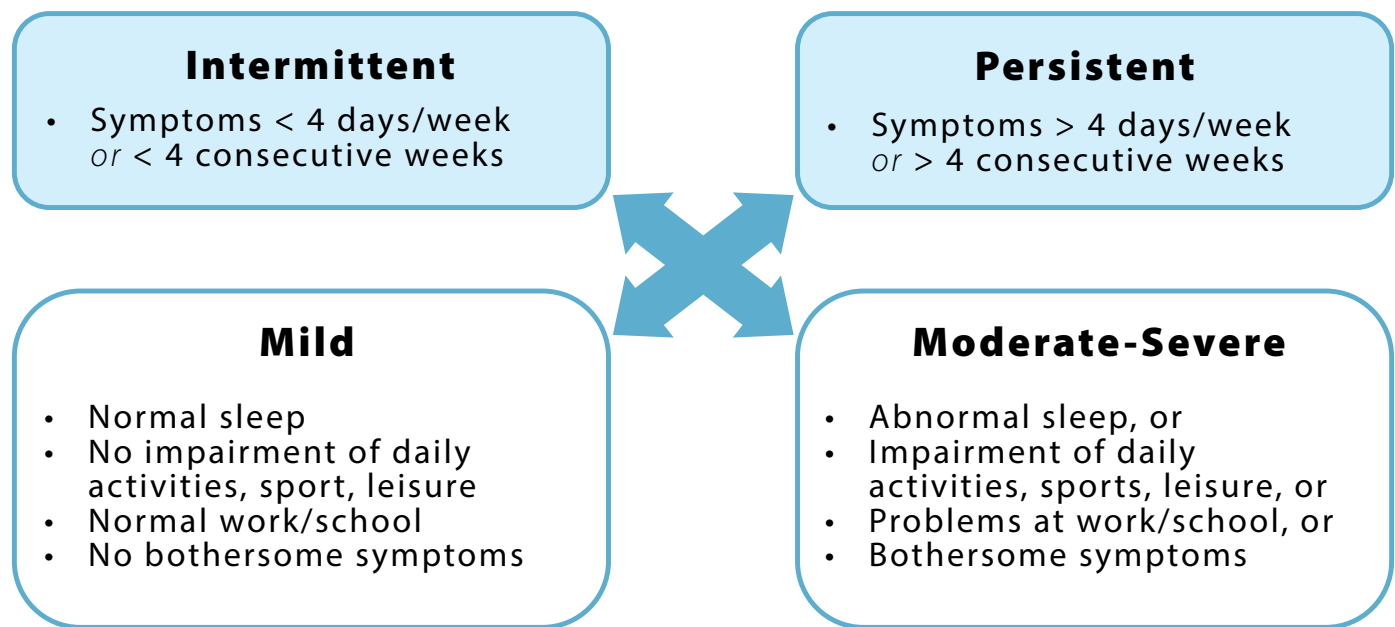


Figure 1. Classification of allergic rhinitis symptoms.⁴



Figure 2. Allergen-specific serum IgE testing entails a blood test and is used when allergy skin prick testing is not viable; photo courtesy of Dr. Gina Lacuesta.

CLINICAL PEARL: As part of the patient work-up, consider seasonal patterns and home environment (e.g., animals, carpet, cannabis exposure) vs irritants (e.g., smoke, fragrances, household cleaners.)

Allergy Testing

Identification of allergy triggers can be sought from the patient history; however, objective demonstration of IgE sensitization should be conducted. This entails referral to an allergist for either allergy skin prick testing or allergen-specific serum IgE testing. Allergy skin prick testing is practical, quick, cost-effective and accurate when performed properly; its reported sensitivity and specificity are 80%-97% and 70%-95% respectively.⁶ There are no absolute contraindications for skin prick testing; however, the results can be difficult to interpret in patients who are very young or of advanced age, or in those with skin conditions such as severe eczema or dermatographism. Medications that can interfere with skin prick testing include antihistamines, tricyclic antidepressants (TCA's), neuroleptics, histamine H2-receptor antagonists (H2-blockers), and omalizumab; these should be held prior to allergy skin prick testing. Allergen-specific serum IgE testing entails a blood test and is used when allergy skin prick testing is not viable (**Figure 2**).⁶

CLINICAL PEARL: All patients with rhinitis symptoms should be considered for allergy testing.

It is important to bear in mind, however, that the severity of allergic rhinitis is not determined by either of the above-mentioned allergy testing methods. Determination of the severity of rhinitis is based on its effect on a patient's QOL and the frequency of their symptoms.

Treatment

The management of allergic rhinitis may initially appear simple, particularly with ready patient access to OTC medications. However, patient education and counselling in avoidance strategies, medication choices and treatment techniques are essential to treatment success.

Non-pharmacologic

Non-pharmacologic management is the initial phase of treatment for allergic and non-allergic rhinitis. Strategies for the avoidance of relevant allergens and irritants may not be practical or desired by the patient; however, they should still be discussed.

For animal dander, removal of the animal from the home is preferred; strategies such as keeping the animal out of the bedroom, and the use of HEPA air filters can help. For dust mites, recommended practices include the use of mattress and pillow dust mite protective covers; weekly washing of bedding in hot water; use of a mechanical dryer, and the avoidance of carpeting. Pollen avoidance is difficult; however, keeping windows closed and minimizing outdoor exposure during peak pollen periods

is ideal. Avoidance of irritants such as cigarette smoke, harsh cleaners and fragrances will help in both allergic and non-allergic rhinitis.⁴

Pharmacologic

In the pharmacologic management of rhinitis, several first-line OTC agents are available. Shared decision-making plays a major role in determining if the patient prefers oral medications or corticosteroid nasal sprays, as well as in assessing their expectations for rapidity of relief (**Figure 3**).⁶

In the majority of patients, it is recommended to initiate treatment with non-sedating, second-generation antihistamines. These are preferred over first-generation antihistamines due to the side effects profile of first-generation antihistamines, which are reported to cause sedation; cardiac arrhythmias; and hyperreactivity, and have a short duration of action. The second-generation antihistamines have demonstrated an excellent safety profile; some of these agents have favourable pregnancy

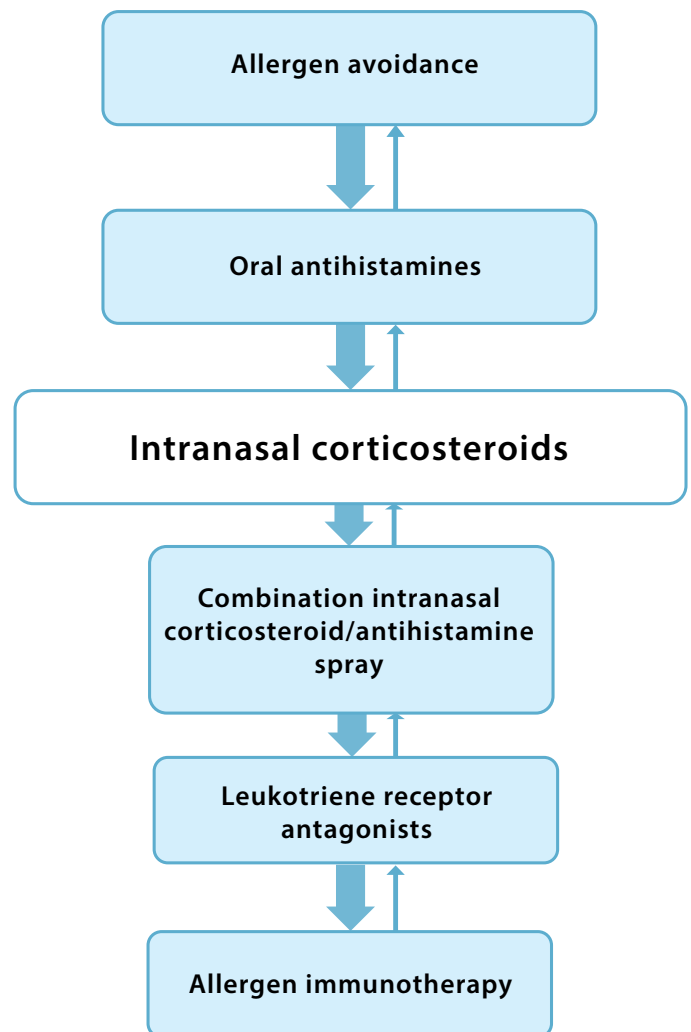


Figure 3. A simplified, stepwise algorithm for the treatment of allergic rhinitis. Treatments can be used individually or in any combination; courtesy of Dr. Gina Lacuesta.

	Usual adult dose	Usual pediatric dose
Oral antihistamines (second generation)		
Bilastine (Blexten)	1 tablet (20 mg) once daily	For children ≥ 4 years of age: 1 tablet (20 mg) once daily
Cetirizine (Reactine)	1-2 tablets (5 mg) once daily	5–10 mL (1-2 teaspoons) once daily (children's formulation)
Desloratadine (Aerius)	1 tablet (5 mg) once daily	2.5–5 mL (0.5–1.0 teaspoon) once daily (children's formulation)
Fexofenadine (Allegra)	1 tablet (60 mg) every 12 h (12-h formulation)	Not currently indicated for children <12 years of age
Loratadine (Claritin)	1 tablet (10 mg) once daily	5–10 mL (1-2 teaspoons) once daily (children's formulation)
Rupatadine (Rupall)	1 tablet (10 mg) once daily	For children ≥ 12 years: 1 tablet (10 mg) once daily For children 2–11 years and body weight 10–25 kg: 2.5 mL (0.5 teaspoon) once daily For children 2–11 years and body weight > 25 kg: 5 mL (1 teaspoon) once daily

Table 1. Overview of second generation oral antihistamine options for allergic rhinitis.⁴

EN = each nostril

Intranasal corticosteroids		
Beclomethasone (Beconase)	1–2 sprays ($\mu\text{g}/\text{spray}$) EN, twice daily	1 spray (50 $\mu\text{g}/\text{spray}$) EN, twice daily
Budesonide (Rhinocort)	2 sprays (64 $\mu\text{g}/\text{spray}$) EN, once daily or 1 spray EN, twice daily	2 sprays (64 $\mu\text{g}/\text{spray}$) EN, once daily or 1 spray EN, twice daily (do not exceed 256 μg)
Ciclesonide (Omnaris)	2 sprays (50 $\mu\text{g}/\text{spray}$) EN, once daily	Not indicated for children < 12 years of age
Fluticasone furoate (Avamys)	2 sprays (27.5 $\mu\text{g}/\text{spray}$) EN, once daily	1 spray (27.5 $\mu\text{g}/\text{spray}$) EN, once daily
Fluticasone propionate (Flonase)	2 sprays (50 $\mu\text{g}/\text{spray}$) EN, once daily or every 12 h (for severe rhinitis)	1–2 sprays (50 $\mu\text{g}/\text{spray}$) EN, once daily
Mometasone furoate (Nasonex)	2 sprays (50 $\mu\text{g}/\text{spray}$) EN, once daily	1 spray (50 $\mu\text{g}/\text{spray}$) EN, once daily
Triamcinolone acetonide (Nasacort)	2 sprays (55 $\mu\text{g}/\text{spray}$) EN, once daily	1 spray (55 $\mu\text{g}/\text{spray}$) EN, once daily
Combination intranasal corticosteroid/antihistamine nasal spray		
Fluticasone propionate/azelastine hydrochloride (Dymista)	1 spray EN, twice daily	For children ≥ 12 years of age: 1 spray EN, twice daily Not recommended for children < 12 years of age

Table 2. Overview of intranasal and combination intranasal corticosteroid/antihistamine nasal spray options for allergic rhinitis.⁴

EN = each nostril

safety data and pediatric safety data.⁷ These medications can be used PRN or daily, with usage guided by patterns based on patient history and skin test results (**Table 1**).⁴

CLINICAL PEARL: Patients should be educated on selecting plain non-sedating antihistamines vs antihistamines in combination with decongestants. The chronic use of decongestants can lead to hypertension, palpitations, difficulty sleeping, and rebound symptoms.

If patients continue to be symptomatic following a medical trial of at least a few weeks, adding a nasal corticosteroid will be successful in most cases: robust clinical data has shown the efficacy of a combination regimen over antihistamines alone (**Table 2**).^{4,6} Proper education in nasal spray technique, and discussion concerning the importance of long-term compliance and the safety of nasal corticosteroids, are imperative for patients to achieve treatment success. Newer combination nasal steroids and nasal antihistamines have shown benefit over nasal corticosteroids alone.⁸ Certain nasal corticosteroids are available OTC. Frequently, these agents have coverage with private or provincial drug plans.

CLINICAL PEARL: Instruct patients on proper technique in the administration of corticosteroid nasal sprays i.e., aim towards the turbinates, rather than the septum; gently sniff the spray to prevent it running down the back of the throat; use daily for 3-4 weeks before assessing efficacy.

The majority of patients implementing the above treatments will be successful in managing their allergic rhinitis. If they continue to experience symptoms, the addition of anti-leukotrienes will be beneficial in a select few patients; however, it is difficult to predict which patients will benefit from this regimen.⁹ Sinus rinses may be beneficial, particularly with chronic sinusitis complications. Note, though, that sinus rinses can be cumbersome and uncomfortable for some patients.

Despite the treatment successes noted above, certain patients will remain symptomatic; may experience treatment side effects; have difficulty with daily compliance; or may simply want to focus on long-term management and the potential for alteration of their allergy status altogether. Desensitization may be indicated in such cases and referral to an allergist should be considered.¹⁰

Allergen immunotherapy: SCIT

Allergen immunotherapy has been utilized for decades; it had been practiced long before the currently-available antihistamines and nasal corticosteroids came to market.

Desensitization is the process of introducing increasing amounts of an allergen to induce tolerance. Traditional subcutaneous immunotherapy (SCIT) has evolved over the years. Standardized extracts and protocols have improved its efficacy and a significant number of patients can now expect improved symptom control, a decreased

need for allergy medications, or complete cessation of medication use.¹⁰

Depending on the allergens affected, pre-seasonal SCIT for pollen allergy or perennial SCIT for perennial allergens are treatment options. SCIT administration protocols can be challenging; they entail weekly injections over several months in pre-seasonal SCIT, or monthly injections spanning a number of years in perennial SCIT. Side effects can include local injection site reactions; large local allergic reactions; mild systemic reactions; or, very rarely, even fatal anaphylaxis. In light of this, SCIT must be administered in a setting prepared to treat anaphylaxis; SCIT is not a home-based treatment. Despite its difficult regimen, many patients select this option and experience treatment success. Treatment for 3–5 years with perennial immunotherapy can often lead to prolonged improvement even following cessation of treatment.¹⁰

Allergen immunotherapy: SLIT

Various options for sublingual immunotherapy (SLIT) have been available in Canada since 2016. Rapidly dissolving tablets are placed under the tongue and are locally absorbed. Currently, only tree, grass, ragweed pollen and dust mite allergens are available; allergen combination tablets are not available at this time. For multi-sensitized patients, multiple separate dosings during the day are necessary, which can be cumbersome for the patient. The initial dose should be administered in an observed setting; however, the advantage to the patient is that subsequently these are home-based, albeit daily, treatments. Side effects include minor local oral itching, swelling and irritation, and itchy ears and throat, although these are often transient. Rare cases of dysphagia and eosinophilic esophagitis have occurred.^{11,12} After three years of SLIT treatment, patients have continued to show improvement following cessation of therapy.¹³

CLINICAL PEARL: Home-based desensitization therapy is now available for some allergens. Several options for inhalant allergy immunotherapy are available: SCIT for pre-seasonal and perennial allergies; and SLIT. Refer to an allergist if a patient fails medical treatment, experiences side effects, finds compliance difficult, or wishes to consider desensitization.

Conclusion

Allergic rhinitis is a common condition affecting all age groups. Patients have ready access to first-line OTC medications. However, in the presence of uncontrolled symptoms, the identification of allergens, and patient education about treatment options and techniques, will improve management of the condition. The effectiveness of desensitization has improved, along with the patient accessibility afforded by new, home-based sublingual treatments. Offering patients with allergic rhinitis more recently-developed treatment options will help to improve the severity of symptoms as well as their QOL.

In the case described above, following referral to an allergist, allergy skin prick testing was performed; the patient was positive for tree and grass pollen, as well as dust mites. Avoidance measures were discussed and the treatment advanced to nasal corticosteroids and daily antihistamines. The patient follow-up reveals that her symptoms are improved with this treatment; however, she continues to experience significant symptoms in the spring/summer season from May to June. Desensitization options are discussed, and, for ease of treatment, she elects to try sublingual desensitization to tree and grass pollen as a home-based treatment along with the antihistamines and nasal corticosteroids used year-round.

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REDEFINING DIABETES STRATEGIES IN PRIMARY CARE: FOUR NEW PILLARS OF MANAGEMENT

Introduction

The management of Type 2 diabetes mellitus (T2DM) is possibly becoming one of the most challenging aspects of primary care. With millions of individuals worldwide living with T2DM, who are at a higher risk of developing multiple additional chronic conditions including cardiovascular disease (CVD) and renal disease, it is imperative that primary care practitioners (PCPs) around the world are comfortable with the management of T2DM. However, with dozens of T2DM medications available, many of which have associated risks of side effects such as hypoglycemia, the management of T2DM can be quite time-consuming for the busy family physician.

In light of the above, it is important that we look at T2DM through a new lens. It is imperative that clinicians view the management of T2DM not just as "blood glucose management" but rather, that they adopt a person-centric, holistic management approach that takes into account the mitigation of microvascular and macrovascular complications, in order to reduce the morbidity and mortality associated with the condition. When it comes to the management of this condition, one needs to be less of a "glucologist" and more of a "diabetologist". In order to develop this approach, with the busy PCP in mind, I suggest four pillars on which to focus during a T2DM appointment, that are beyond the laboratory HbA1c measurement (**Figure 1**).

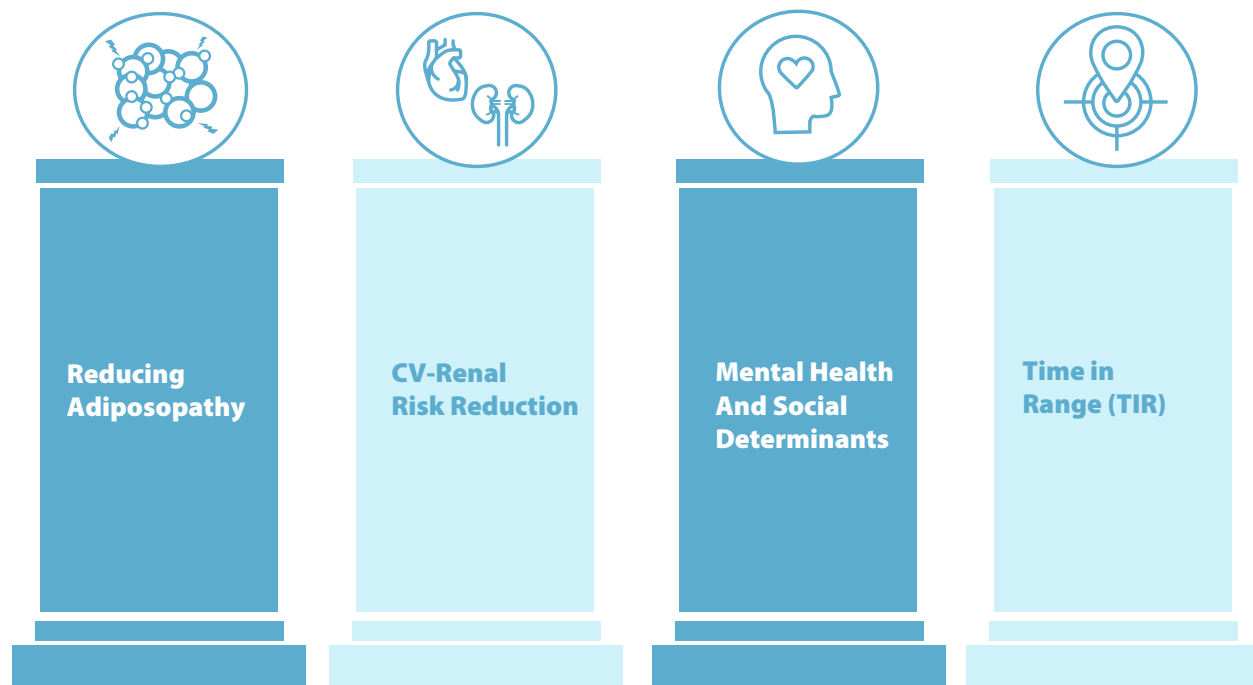
1. Reducing the burden of adiposopathy

Obesity is known to increase insulin resistance. However, current obesity definitions are restrictive as they only take into account the height and weight of the individual. It is actually the excessive adipose tissue (particularly that which is deposited in and around the viscera) that leads to chronic comorbidities; this concept of the "sick fat tissue" is known as adiposopathy. We know that sustained weight loss of >5% can lead to improvement in glycemic control, as well as cardiovascular (CV) outcomes.¹ At the same time, the likelihood of achieving diabetes remission is directly proportionate to the degree of weight loss. It is imperative that weight loss strategies include medical nutrition therapy (ideally under the supervision of qualified personnel such as a registered dietitian) and physical activity, in combination with behavioural therapy, pharmacotherapy and/or bariatric surgery.^{2,3} Therefore, for the appropriate patient with T2DM, ideally a clinician would favour utilization of diabetes pharmacotherapy that does not lead to weight gain but, instead, promotes loss of excess adiposopathy. This would imply the use of agents such as glucagon-like peptide-1 receptor agonists (GLP-1 RA) followed by sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors); they perform markedly better than other classes of T2DM therapy in this regard.^{4,5}

2. Reducing cardiovascular and renal event risks

Duration of exposure to hyperglycemia and poor control of T2DM are known to be directly proportional to increased

Diabetes Management



Person-centered approach

Figure 1. The four pillars on which to focus during a T2DM appointment, that are beyond the laboratory HbA1c measurement; courtesy of Akshay Jain, MD, FRCPC, FACE, CCD, ECNU, DABIM, DABOM.

risk of CV and renal events. We now have robust evidence demonstrating that utilization of SGLT-2 inhibitor therapy can reduce the risk of hospitalization for heart failure (HF), as well as progression of nephropathy in patients at greater risk of experiencing these events. At the same time, both GLP-1RA and SGLT-2i therapy with appropriate agents have been shown to reduce the risk of heart attacks, strokes and CV events in patients with known atherosclerotic cardiovascular disease (ASCVD). Finally, GLP-1RA therapy using appropriate pharmacotherapy is effective in primary prevention of CV events in individuals >60 years old living with T2DM with additional risk factors. In addition, the established guidelines suggest the use of a CV risk reduction strategy with appropriate control of hypertension and dyslipidemia, smoking cessation, and use of agents such as renin-angiotensin-aldosterone system (RAAS) inhibitors and statins, among others.

In light of this, we are now encouraged to consider agents such as GLP-1RA's and SGLT-2i's as disease-modifying agents when addressing high-risk individuals with T2DM as a result of their ability to reduce the risk of developing CV and renal events.⁶

3. Mental health and social determinants of health

Often, while managing conditions such as T2DM, excessive importance is placed on laboratory parameters/objective targets and clinicians may forget the overall

mental health of the individual living with that condition. T2DM is associated with metabolic, mechanical, monetary and mental health consequences that often affect the overall well-being and glycemic control of the individual. The financial burden arising from direct costs (e.g., cost of medications, devices, travel to medical appointments) as well as indirect costs (e.g. absenteeism, diminished productivity, diabetes-related disability causing unemployment) frequently lead to an individual being unable to use medications as directed. This contributes to inadequate glycemic control, thereby leading to a greater risk of T2DM-related complications. It is therefore imperative that we evaluate for T2DM distress as well as the financial burden of T2DM when performing a patient assessment. Access to medication is an extremely important consideration when selecting appropriate pharmacotherapy; if access is restricted, alternatives should be discussed.⁷

4. Time in range

Glycemic control continues to be a major pillar in the management of T2DM. In individuals who continue to have suboptimal glycemic control despite addressing the three aforementioned pillars, reiteration of diabetes education with lifestyle modifications, as well as escalation of pharmacotherapy should be considered. Current guidelines promote preferentially using agents that are

able to lower elevated blood sugars without the risk of hypoglycemia and/or weight gain. Following metformin monotherapy, these would constitute GIP/GLP-1 RA, GLP-1RA's, SGLT-2i's and dipeptidyl peptidase 4 inhibitors (DPP-4i's), in order of degree of glucose lowering capability. Medication selection should be influenced by the three pillars cited above, as well as consideration of contraindications, tolerability, and patient access and preference. Clinicians have long regarded HbA1c as the gold standard for the assessment of glycemic control. However, HbA1c is merely an estimate of the average of blood sugars and therefore may not provide an accurate reflection of an individual's glycemic excursions. With the availability of continuous glucose monitoring (CGM) devices, we are now able to obtain an accurate representation of the total time an individual has achieved glucose readings in a predefined target range (time in range [TIR]). Worsening TIR is associated with worsening microvascular complications.⁸ More importantly, TIR also provides a very good understanding of an individual's risk for hypoglycemia. When combined with an ambulatory glucose profile, clinicians can develop a targeted approach toward the adjustment of pharmacotherapy and patient counseling regarding lifestyle changes. Importantly, in addition, the individual with T2DM can view these glycemic excursions on an ongoing basis, thereby leading to ongoing modifications that will support them in improving their glycemic control. Therefore, CGM devices are not only helpful for glucose measurement but also for behavioural modification. Improving access to these devices in the future can lead to being able to focus on more than just a HbA1c laboratory measurement in order to understand glycemic control.

Conclusion

Focusing on each of the above-mentioned four pillars will assist the busy PCP in delivering a holistic, person-centered management approach for T2DM that extends beyond merely playing the role of a "glucologist".

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