Practice points to consider when managing Type 2 Diabetes Mellitus in patients with cardiovascular disease

The Atlantic Cardiovascular Society (ACS) represents cardiologists and internists who provide cardiac care throughout Atlantic Canada. The ACS received a mandate from its membership to provide guidance regarding the treatment of diabetes in patients with cardiovascular disease. While there are excellent national guidelines addressing the prevention and treatment of cardiovascular disease in persons with diabetes (CDA 2013), there is a need for enhanced and current guidelines for glycemic management specific to patients with Coronary Artery Disease (CAD) and Heart Failure (HF). It is also hoped that a simplified framework will be useful to clinicians primarily focused on cardiac care, since generally, all approved classes of drugs are included in existing treatment algorithms regardless of whether such classes are frequently or only rarely prescribed in clinical practice. In addition, the proliferation of new drug classes currently available and the implications of positive results from recent cardiovascular outcomes trials has led to a degree of therapeutic confusion, particularly for clinicians who do not primarily treat hyperglycemia.

The ideal treatment of diabetes would provide effective, durable glycemic control with minimal adverse effects, particularly hypoglycemia and weight gain, while respecting the increasingly constrained fiscal budgets of Atlantic Canada. However, in reality, substantial improvements in longevity in people with longstanding diabetes have increased requirements for more complex regimes to control progressive hyperglycemia. While newer agents have demonstrated less adverse events there are also unprecedented results from new trials demonstrating decreased CV outcomes thus enhancing cost effectiveness. The aim of this management guide is to provide practical, candid advice to the membership, focusing on agents that are in common use in our communities and those that provide documented improvements in cardiovascular outcomes. Note that our articulated position is in keeping with guidelines of multiple national and international groups.

PRACTICE POINTS

METFORMIN: Recommended as the first line agent. **Discontinue at the time of angiography if eGFR < 60 mls/min or if receiving large volume contrast** (>100cc i.e. CT abdomen/pelvis, CT angiography of aorta or lower extemities) and may resume 48 hours after if renal function stable i.e. <25% increase above baseline. (Baerlocher M. CMAJ Oct 2012). Approximately 5% of patients limited by ongoing and significant GI side effects but anecdotally may be better tolerated in brand name products (Glumetza once daily or fixed dose combinations with other oral agents such as DPP-4 inhibitors or SGLT-2 inhibitors). Up to 85% of the effective dose seen at doses of 1500 mg/d so 850 mg pill BID is one option to minimize pill volume and GI side effects. (Sherifali *et. al.* Diabetes Care, 2010).

DPP-4 INHIBITORS: "Gliptins' are easy to prescribe due to the virtual absence of side effects (with the exception of saxaglitin which has been associated with increased HF admission). **Targets post prandial hyperglycemia and most effective for A1C < 8% if used as monotherapy**. Can expect A1C reductions of ~ 0.7%. Renal doses available but no dose change required for linagliptin. Can add on to insulin but **do not use with injectable GLP-1 agonists as they are from the same class**. All agents in this class have fixed dose combination pills with metformin.

SGLT-2 INHIBITORS: Empagliflozin is one of the agents recommended in patients with A1C >7% and cardiovascular disease (CDA guideline update 2016). This class is well tolerated but requires adequate renal function for glucose-lowering effect and high responders are those with high GFR. **Generally better glucose lowering effect if A1C > 8% due to more glucose undergoing renal filtration and see less effect if only mildly elevated A1C**. May be very useful added to insulin in patients with insulin resistance, high A1C and normal eGFR. Weight loss and decreased BP an added benefit. Likely renal protective (EMPA-RENAL) and renal trials ongoing for other agents in this class but expect improved proteinuria. Generally better glucose lowering effect if A1C >8%. Relatively easy to prescribe but ~3% of males and ~9% females develop lower UTI or genital candidal infection – responds to usual treatment and generally no recurrence with continued therapy. **Postural symptoms an issue in patients on loop diuretics so may need dose reduction of diuretic and caution if frail elderly**. Note: empagliflozin 10 mg was as effective as 25 mg for glucose control and CVD outcomes in EMPA-REG. **Avoid this class in T1DM due to risk of DKA, also hold in T2DM if prolonged fasting/surgery or if dehydrated due to rare case reports of peri-operative DKA**. Although a rare occurence, DKA is possible in patients with T2D. Trial data suggests that canagliflozin use is associated with an increased risk of leg and foot amputations. Consider factors that may predispose patients to the need for amputations prior to initiating canagliflozin. (FDA, 2017) The association with dapaglifozin and empaglifozin is currently unknown.

GLP-1 AGONISTS: Injectable non-insulin agents (pre-loaded pens) that promote glycemic control and weight loss but expensive ($140 - $150 per month). **Avoid if gastroparesis since slows gastric emptying to improve satiety**. **Liraglutide is favorable for renal outcomes and safe for use in renal failure due to lack of renal excretion**. LEADER trial demonstrated reduced death from CV causes and death from any cause. Note that Grade A evidence exists for patient's age ≥ 50 years (Age < 50, Grade D evidence). Semaglutide also demonstrated favorable CV outcomes (SUSTAIN 6). Once weekly injections in this class (exenatide and dulaglutide) are currently available and combinations with basal insulin analogues soon to be available (Liraglutide/degludec and lixisenatide/Lantus). **Do not combine with DPP-4 inhibitors as both are from the incretin class**.

TZD'S: This class is infrequently used due to adverse effects of weight gain and fluid retention (sometimes leading to heart failure in susceptible individuals) as well as fractures in postmenopausal women. Rosiglitazone has been absolved of risk for coronary events (FDA 2013 and FDA 2016). TZD's can occasionally be useful in young patients with marked insulin resistance and are noted for delayed onset of glycemic effect but very durable control of A1C when used early in the course of diabetes.

SULFONYLUREAS: No CV outcomes trial data available and glimepiride is the only member of this class in a current trial (CAROLINA, 2019). **Avoid use, if possible, in patients with coronary disease, renal insufficiency and in frail elderly due to risks of hypoglycemia**. Glyburide has active metabolites that potentiate hypoglycemic action for many hours so should be avoided in favor of newer generation SU's such as gliclazide. Expect rapid effect on glycemia but limited durability of response beyond 6 - 12 months. **Discontinue SU once prandial insulin initiated**.

BASAL INSULIN: Best used when highest glucose of the day is fasting as basal targets nocturnal hepatic glucose output. Outpatient - start at 10 units HS and increase by 1 unit nightly until AM glucose 5-6 mmol/L expecting target dose will be 40 - 50 units. Inpatient can start at 0.20 – 0.30 units/kg, favoring lower doses in elderly and in renal insufficiency. Unlikely to be effective as monotherapy if HS glucose is already very high due to marked post prandial hyperglycemia; such patients often end up on huge doses of basal insulin with risk of hypoglycemia during increased activity or change in nutrition i.e. hospital admission. Better to add 1-3 prandial doses (start 4-6 units per meal and titrate up) for significant hyperglycemia. If already on large dose of basal alone (usually Lantus) and in poor control, can decrease dose by 25% - 40% and use this amount for divided prandial insulin doses i.e. 80 units Lantus → 50 units Lantus + 10 units rapid insulin at each meal. (McCall A., Endocrinolol Metab Clin North Am, 2012)

BASAL NPH: Intermediate acting (cloudy) insulin often started as basal in combination with oral agents – average required dose in trials ~40 – 50 units HS. Requires adequate mixing of preservatives prior to injection (rotate pen 20 x) or risk of hypoglycemia within a few hours of injection.

BASAL LANTUS: Long acting basal insulin often started as basal in combination with oral agents - average dose in trials ~ 47 units. More expensive (~ 2.5 x) and no improvement in A1C vs. NPH but less nocturnal hypoglycemia which is a relevant safety issue in patients with coronary artery disease. Outpatient starting dose 10 units OD and increase by 1 unit daily until AM glucose 5 - 6 mmol/L. Biosimilar 'Basaglar' now available and is 15% less expensive; may see automatic substitution on public and private plans. Cannot assume bioequivalence with Lantus if switching. Lantus insulin is also available in a concentrated form (300 units/ml) called TOUJEO which may offer improved ease of injection for large doses due to smaller volume. However, the dose in units may need to increase 10 - 15% when switching from Lantus.

BASAL LEVEMIR: More weight favorable than NPH and Lantus but somewhat more expensive and lack of 24 hour action particularly in lower doses in presence of normal renal function. Insulin degludec will also be available in combination pen with the GLP-1 agonist liraglutide (iDeglira).

SICK DAY MEDICATION LIST: Proactively provide patients diagnosed with diabetes and cardiovascular disease with a completed SAD MANS card in the event they develop an illness where they are unable to maintain adequate fluid intake or have an acute decline in renal function.

COMBINATION THERAPY FOR TYPE 2 DIABETES

According to national guidelines, Metformin remains the recommended initial therapy for T2DM and Figure 1 provides a template for the addition of a second agent in patients with cardiovascular disease. Choice of agent is influenced by impact on underlying heart disease, presence of renal dysfunction, degree of hyperglycemia, risk of hypoglycemia, obesity, access and patient preference.

The addition of a third oral agent for glucose control often does not yield the same degree of A1C lowering as when used earlier in the course of diabetes. Combination pills with Metformin are available for all the available DPP-4 and SGLT 2 inhibitors. Fixed dose combination pills of DPP-4 inhibitors and SGLT 2 inhibitors are now being released in Canada.

COMMONLY USED COMBINATION THERAPIES ARE:

1. Metformin plus SU and/or DPP-4 inhibitors.
2. Metformin plus SU and/or SGLT2 inhibitors.
3. Metformin plus SGLT2 inhibitor and/or DPP-4 inhibitor (A SGLT2 with positive CV outcome data is preferred)
4. Metformin is most commonly continued when insulin is initiated in order to minimize weight gain but all of the agents above may be used with insulin, however, sulfonylureas should be discontinued when prandial insulin is initiated.
5. GLP-1 agonists (non-insulin injectables that result in glucose control and weight loss) may be used in combination with Metformin and with insulin (A GLP-1 receptor agonist with positive CV outcome data is preferred), but have not yet been studied in combination with SGLT 2 inhibitors and are not effective when combined with DPP-4 inhibitors as they are both from the incretin class.

FIGURE 1 - Management of T2DM in patients diagnosed with Cardiovascular Disease

METFORMIN*

INITIAL THERAPY FOR PATIENTS WITH T2D

Avoid if decompensated Heart Failure or eGFR < 30

Reduce dose if eGFR 30 - 59

CHOICE OF AGENT AFTER METFORMIN THERAPY IS BASED ON CV OUTCOME TRIAL EVIDENCE

POSITIVE CV Outcome Data

Canagliflozin *(Invokana)*
Decreased CV events with no change in CV death

Empagliflozin *(Jardiance)*
Decreased Death From CV Causes, Death From Any Cause & Hospitalization For Heart Failure

Liraglutide *(Victoza)*
Decreased death from CV causes, & Death from any cause

NEUTRAL CV Outcome Data

Exenatide *(Bydureon & Byetta)*

Sitagliptin *(Januvia)*

Saxagliptin *(Onglyza)*
Avoid if risk of Heart Failure

Insulin Degludec *(Tresiba)*

Insulin Glargine *(Lantus & Toujeo)*

Pioglitazone *(Actos)*
Occasionally used if severe insulin resistance, avoid if risk of Heart Failure

PENDING CV Outcome Data

Dulaglutide *(Trulicity)*
REWIND reports in 2018

Dapagliflozin *(Forxiga)*
DECLARE reports in 2019

Glimiperide *(Amaryl)*
CAROLINA reports in 2019

Linagliptin *(Trajenta)*
CARMELINA reports in 2019

**Metformin should be the initial therapy in patients with T2DM as per the panel recommendations. When selecting an agent to add, consider the clinical cardiovascular evidence or outcome data.*

Note: There are no CV outcomes data pending for SU's other than glimepiride.