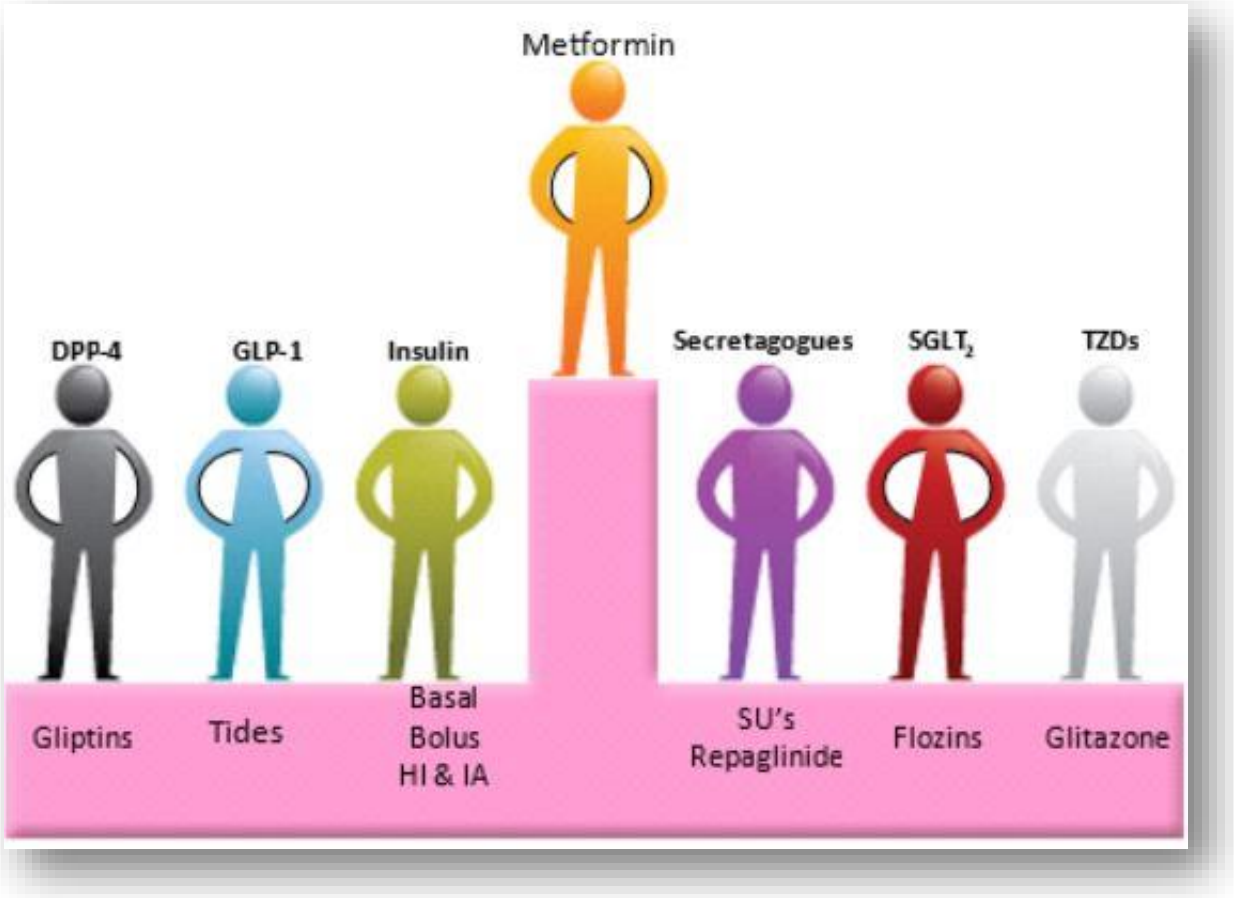
Type 2 Diabetes



What after Metformin?

Academic Detailing Service

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"Seek simplicity, and mistrust it."
Alfred North Whitehead

Table of Contents

Tables, Figures and Appendices

Definitions and Abbreviations

A1C	Glycated hemoglobin
ARR, ARI	Absolute risk reduction, absolute risk increase
BG	Blood glucose
CADTH	Canadian Agency for Drugs and Technologies in Health
CDA	Canadian Diabetes Association
CrCl	Creatinine clearance
CI	Confidence interval
CV	Cardiovascular
CVD	Cardiovascular disease – defined as an acute coronary syndrome, history of a myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral vascular disease
DM	Diabetes mellitus
DPP-4	Dipeptidyl peptidase-4 (inhibitors)
FPG	Fasting plasma glucose
GFR, eGFR	Glomerular filtration rate, estimated glomerular filtration rate
GLP-1	Glucagon like peptide-1 (receptor agonists)
HF	Heart failure
HHNS	Hyperosmolar hyperglycemic nonketotic syndrome
HR	Hazard ratio
LDL	Low density lipoprotein
MI	Myocardial infarction
NNT/NNH	Number needed to treat, number needed to harm
OR	Odds ratio
PG	Plasma glucose
PPG	Postprandial plasma glucose
RCT	Randomized controlled trial
RR	Relative risk
SGLT-2	Sodium glucose cotransporter 2 (inhibitor)
SrCr	Serum creatinine
SU	Sulfonylurea
T2DM	Type 2 diabetes mellitus
TZDs	Thiazolidinediones

Summary

- Diabetes mellitus (DM) comprises two major forms which are distinctly different in their pathophysiology.
  - Type 1 DM is an autoimmune disease in which the body destroys its pancreatic β cells, resulting in a lack of insulin production.
  - Type 2 DM is primarily related to insulin resistance.
- Short-term complications of type 2 diabetes include:
  - Hypoglycemia
  - Hyperosmolar hyperglycemic nonketotic syndrome (HHNS)
- Long-term complications of type 2 diabetes involve the vascular system and include:
  - Microvascular – nephropathy, neuropathy, retinopathy
  - Macrovascular – MI, stroke, peripheral vascular disease
- Insulin resistance and inadequate insulin secretion, referred to as T2DM, is associated with an increased risk of microvascular and macrovascular disease outcomes. The increased risk of CVD in T2DM persists even after discounting smoking, hypertension and dyslipidemia implicating dysglycemia as an independent, but not the sole contributor to risk.
- CVD risk increases exponentially when insulin resistance and inadequate insulin secretion are accompanied by other metabolic derangements which collectively constitute the metabolic syndrome.
- CVD is responsible for much of the associated morbidity and mortality of T2DM.
  - Care should be taken **to treat all concomitant risk factors** for the complications of T2DM, especially **hypertension and hyperlipidemia** where they have been **shown to reduce CVD related events.**

Question 1: Will interventions that lower blood glucose decrease clinically relevant events in people with type 2 diabetes? Page 15

- Observational epidemiological studies have established that the risk of vascular complications is progressively related to the level and duration of chronic hyperglycemia.
  - These studies show that hyperglycemia and vascular complications coexist but does hyperglycemia cause the vascular complications? **And if so, will interventions that lower blood glucose decrease clinically relevant events?**
- Therapeutic interventions for lowering blood glucose levels in T2DM include lifestyle modifications, non-insulin agents and insulin.
- Lifestyle modification is recommended as the **foundation** on which all additional diabetes therapies should rest.

- There is evidence that a reduction in glucose levels with glucose lowering agents reduces the risk of surrogate markers of microvascular complications but proof that glucose lowering agents cause a reduction in the risk of macrovascular complications is uncertain. **The precise ability of glucose lowering per se to reduce CVD risk has not been elucidated.**

Question 2: What are the recommended glycemic treatment targets? Page 19

According to the 2013 update of the Canadian Diabetes Association Guidelines[1]:

- Glycemic targets should be individualized based on age, duration of diabetes, risk of severe hypoglycemia, presence or absence of CVD, and life expectancy.
- Therapy in most individuals with T2DM should be targeted to achieve an A1C ≤ 7.0% in order to reduce the risk of microvascular and, if implemented early in the course of disease, macrovascular complications.
- An A1C ≤ 6.5% may be targeted in some patients to further lower the risk of nephropathy and retinopathy but this must be balanced against the risk of hypoglycemia.
- Less stringent A1C targets (7.1%-8.5% in most cases) may be appropriate in certain patients.

The Diabetes Care Program of Nova Scotia Guidelines for Frail Elderly Residents in Long-Term Care (LTC) Facilities recommend more liberalized targets to improve patient safety and reduce the risk of hypoglycemia and related sequelae resulting from over management**.**

Question 3: What non-insulin glucose lowering agents are currently available and where do they act? Page 23

- Please refer to the list of agents on page 23 and to Figure 2 on page 24.

Question 4: Is there a defined choice and order of intervention? Page 25

- There is insufficient clinical trial data to determine **optimal treatment sequence** and number of agents to use.
- Eventually most patients become truly insulin deficient and require insulin therapy for management. Insulin treatment in T2DM is generally instituted with basal insulin alone and intensified to basal plus bolus insulin regimens if glycemic goals are not achieved.
  - The addition of newer non-insulin drugs to previous insulin treatment may allow for partial or complete reduction in insulin dose.
    - This can result in fewer hypoglycemic episodes and less weight gain.
    - The effects on long term vascular outcomes are uncertain.

Question 5: Why is metformin the first line agent? Page 27

- Metformin is commonly accepted as the first-line oral therapy for T2DM in conjunction with lifestyle modification.
  - Metformin is not associated with hypoglycemia or weight gain, is low in cost and has many years of usage.
  - Whether metformin is started as monotherapy or in combination with another glucose lowering agent varies and often depends on the presenting A1C.
- Claims of metformin reducing **macrovascular outcomes** have been made since the publication of the UKPDS 34 trial in 1998. The trial, a sub study of the original UKPDS trial, showed a reduction in macrovascular risk in newly diagnosed obese patients treated with metformin.
- Since then trial results have been equivocal on the matter of whether metformin reduces CV events. Based on the currently available evidence, the specific effect of metformin on macrovascular outcomes and mortality cannot be firmly confirmed or rejected.
- The side effects of metformin are mainly gastrointestinal and are generally transient and resolve spontaneously during continued treatment. Occasionally, temporary dose reduction may be useful. During initiation, gradual dose titration is required.
- Metformin is renally excreted and requires dosing adjustment in renal impairment. It is capable of causing severe acidosis in overdose.

Question 6: What factors inform choices after metformin? Page 31

Choice of agent after metformin is primarily influenced by effects on vascular and surrogate outcomes, safety and cost.

EFFECTS ON VASCULAR OUTCOMES

- Determination of the **effects on vascular outcomes** between agents requires direct comparative RCTs adequately powered to demonstrate these clinical effects.
- There are a number of comparative trials between the agents, new and old, that have been conducted; however, they are of short duration and report on surrogate outcomes only.
- Empagliflozin (Jardiance®) has been shown to decrease CV death in a very high risk T2DM population; it was compared to placebo and therefore the trial does not inform how it compares to other agents in a similar population.
- Revealing the clinical relevance of the extra-glycemic effects of each agent and how they compare to each other is needed to optimally define treatment sequence.
- The evidence available to date regarding macrovascular and microvascular outcomes is judged to be low in strength and insufficient. Table 6 summarizes the known effects of the second line glucose lowering agents (non-insulin and insulin) on diabetes related morbidity and mortality.

EFFECTS ON SURROGATE OUTCOMES

- **A1C reduction**
  - The A1C lowering ability of most of the non-insulin agents is generally similar.
    - Monotherapy reduces A1C **approximately 1% on average** (e.g. A1C 8.5% to 7.5%).
    - Most dual non-insulin therapy combinations have similar efficacies and reduce A1C about 1% more than monotherapies (range 0.64% to 0.96% when added to metformin).
    - Compared with continued treatment with metformin and a SU, addition of DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors, TZDs, and insulins produced statistically significant reductions in A1C (range -0.89% to -1.17%); whereas, meglitinides and alpha-glucosidase inhibitors did not.
  - Insulin lowers A1C the most.

- **Durability (duration of A1C reduction)**
  - When selecting an agent, it is desirable to choose one that is going to have an extended A1C lowering ability in order to delay adding on another therapy.
  - Unfortunately, the concept of durability of non-insulin agents is a difficult one to define. To add to the uncertainty, there are few studies on glucose lowering agents that have been done to date looking at durability as their primary outcome.

- **Changes in body weight**
  - The clinical significance of body weight changes associated with glucose lowering medications is unclear. The available data are from short term RCTs typically less than one year. It is uncertain whether these weight changes persist.

- **Changes in blood pressure and lipid levels**
  - The SGLT-2 inhibitors have been associated with a reduction in blood pressure and an increase in LDL. The clinical relevance of these changes is uncertain.

SAFETY

- Risk of hypoglycemia attributable to each agent is not possible to precisely quantify or compare.
- Table 9 provides the current safety data for the drug classes.

COST

- Tables 10, 11 and 12 provide the wholesale daily costs for single non-insulin agents, non-insulin combination products and cost per 100 Units of bolus and basal insulin.
- Daily costs of single non-insulin therapies can range from $0.15 to $9.00 wholesale.

Introduction

What is type 2 Diabetes Mellitus?

Diabetes mellitus (DM) comprises two major forms which are distinctly different in their pathophysiology.[2]

- Type 1 DM is an autoimmune disease in which the body destroys its pancreatic β cells, resulting in a lack of insulin production.
- Type 2 DM is primarily related to insulin resistance.

Insulin resistance is a metabolic disorder occurring when the body's cells cannot properly utilize insulin. Insulin assists in the transport of glucose and amino acids into the cells.

- One of the primary causes of insulin resistance is excess body fat. The majority of overweight people are insulin resistant.[3]
- There are some people with insulin resistance who are not overweight but they are in the minority, approximately 12%. The proposed underlying cause in these individuals is genetic predisposition.[4]
- Aging and environmental factors also play a role.[5]

If an individual cannot increase pancreatic insulin secretion efficiently to compensate for insulin resistance, blood glucose rises and a diagnosis of T2DM is made. The resulting hyperglycemia can impair pancreatic β cell function and exacerbate insulin resistance, leading to a cycle of hyperglycemia causing a worsening metabolic state.

Short-term complications of T2DM include:

- Hypoglycemia
- Hyperosmolar hyperglycemic nonketotic syndrome (HHNS)

Long-term complications of T2DM include:

- Microvascular
  - Nephropathy and neuropathy
    - Usually manifest initially subclinically, with microalbuminuria and abnormal electrophysiologic findings, respectively. They advance over time to albuminuria and physical findings of neuropathy including diminished thresholds for vibration and light touch sensation.[6]
    - These subclinical and early clinical findings are by themselves not clinically significant; however, with time they can progress to further injury and loss of function with severe clinical consequences.[6]
    - The development of end stage kidney disease requiring dialysis or a transplant usually takes years of diabetes duration.[6] The lifetime risk of dialysis ranges from 0.1% to 5.0% depending on A1C and age of T2DM onset (Table 1).[7]

Table 1: Lifetime Risk for Endstage Renal Disease in T2DM*[7]

A1C levels	Lifetime Risk for Endstage Renal Disease¥			
	Age of Onset			
	45yr	55yr	65yr	75yr
	%			
7	2.0	0.9	0.3	0.1
8	2.7	1.3	0.5	0.1
9	3.5	1.6	0.6	0.1
10	4.3	2.1	0.8	0.2
11	5.0	2.5	0.9	0.2

*For patients who develop end-stage renal disease, the average amount of time spent in this disease state was 5.2 years for those who were 45 years of age at diabetes onset, 4.6 years for those who were 55 years of age at onset, 4.0 years for those who were 65 years of age at onset, and 2.7 years for those who were 75 years of age at onset.
¥ Base-case results

- More advanced stages of retinopathy require at least 10 years. Macular edema and proliferative retinopathy do not usually occur until 15 to 20 years of diabetes duration. The latter two can lead to loss of vision. The lifetime risk of blindness ranges from 0% to 4.2% depending on A1C and age of T2DM onset (Table 2).[7]

Table 2: Lifetime risk of blindness due to diabetic retinopathy in T2DM*[7]

A1C levels	Lifetime Risk for Blindness¥			
	Age of Onset			
	45yr	55yr	65yr	75yr
	%			
7	0.3	0.1	<0.1	<0.1
8	1.1	0.5	0.2	<0.1
9	2.6	1.2	0.5	0.1
10	5.0	2.5	1.0	0.3
11	7.9	4.4	1.9	0.5

* For patients who become blind, the average amount of time spent blind was 11.0 years for those who were 45 years of age at diabetes onset, 8.3 years for those who were 55 years of age at onset, 5.2 years for those who were 65 years of age at onset, and 3.2 years for those who were 75 years of age at onset.
¥ Base-case results

- Macrovascular – Myocardial infarction (MI), stroke, peripheral vascular disease
  - Insulin resistance and inadequate insulin secretion, referred to as T2DM, is associated with an increased risk of macrovascular disease outcomes. The increased risk of CVD in T2DM persists even after discounting smoking, hypertension and dyslipidemia implicating dysglycemia as an independent contributor to risk but not the only contributor.[8]
- Estimating the absolute CVD risk in an individual is dependent on the presence of other contributing risk factors.
- CVD risk increases exponentially when insulin resistance and inadequate insulin secretion are accompanied by other metabolic derangements which collectively constitute the metabolic syndrome.[9]
  - These include:
    - Abdominal obesity
    - Dyslipidemia
    - Hypertension
    - Impaired fibrinolysis
    - Increased risk of thrombosis
    - Chronic Systemic Inflammation[10]
  - Several inflammatory markers are highly correlated with the degree of obesity and insulin resistance, and, in turn, these same inflammatory markers are predictive of CVD.[11,12]
- When these risk factors are examined along with traditional risk factors such as age, sex, smoking behavior, and family history of premature CVD, the outcome is the global cardiometabolic risk profile that predicts CVD. Cardiometabolic risk refers to the sum of risk factors that increase an individual's risk of having a CV event (Figure 1).[13]

Figure 1: Traditional and emerging CVD risk markers that contribute to global cardiometabolic risk[14]

(From the Canadian Cardiometabolic Risk Working Group)

- Predicting an individual's absolute CVD risk in clinical practice requires the use of a validated algorithm that adequately captures all relevant risk predictors and their respective weighted contributions in people with T2DM.
  - As there is no ideal CVD risk calculator, use the validated calculator that is familiar to you in clinical practice.
- CVD is responsible for much of the associated morbidity and mortality of T2DM. Therefore, it is important to focus treatment to what will have the greatest clinical impact on improving CV outcomes.
  - Hyperglycemia is not the only predictor of untoward clinical outcomes; it is one of numerous mechanisms linking T2DM to CVD.
  - Care should be taken **to treat all concomitant risk factors** for the complications of T2DM, especially **hypertension and hyperlipidemia** where they have been **shown to reduce CVD related events.**
- The remainder of this document will focus on the therapeutic interventions for lowering blood glucose levels.

We have addressed six clinical questions:

1. Will interventions that lower blood glucose decrease clinically relevant events in people with T2DM?
2. What are the CDA recommended glycemic treatment targets?
3. What non-insulin glucose lowering agents are currently available and where do they act?
4. Is there a defined choice and order of intervention?
5. Why is metformin the first line agent?
6. What are the factors informing choices after metformin?

In preparing this document, we reviewed

- Primary publications
- CADTH reports
- Review articles and meta-analyses
- Cochrane reviews
- Guidelines from Canada, United States and United Kingdom
- British Columbia Provincial Academic Detailing Service "Glucose Lowering Medications for Type 2 Diabetes", October 2015

Question 1: Will interventions that lower blood glucose decrease clinically relevant events in people with type 2 diabetes?

- Observational epidemiological studies[15–18] have established that the risk of vascular complications is progressively related to the level of and duration of exposure to chronic hyperglycemia.
  - These studies show that hyperglycemia and vascular complications coexist but does hyperglycemia cause the vascular complications? **And if so, will interventions that lower blood glucose decrease clinically relevant events?**[18]

- Therapeutic interventions for lowering blood glucose levels in T2DM include lifestyle modifications, non-insulin agents and insulin.

LIFESTYLE MODIFICATIONS

- Lifestyle modification is recommended as the **foundation** on which all additional diabetes therapies should rest.
- These recommendations are supported by physiological studies, clinical experience, observational studies, and randomized controlled trials(RCTs) showing reduced levels of glucose, blood pressure, and some lipids, as well as improvements in general well-being and other indexes of health.[13,19,20]
- The **Look AHEAD** (Action for Health in Diabetes) study, conducted from 2001 to 2012, tested the hypothesis that an intensive lifestyle intervention for weight loss (involving caloric restriction and exercise) would achieve significantly greater reductions in CVD morbidity and mortality than a control condition of diabetes support and education among participants with T2DM.
  - A total of 5,145 people were enrolled, with 2,575 randomized to the intensive group and 2,570 to the control group.[21–29]
  - At baseline, characteristics were as follows:
    - Mean age 58.7 years (range 45-74 years, 60% women, 37% minorities)
    - BMI 36 kg/m^2
    - Mean disease duration 5 years
    - Mean A1C 7.3%
    - 86.5% on any glucose lowering agent; < 30% of people were on insulin
    - 14% had a history of CVD
  - Results
    - Intensive lifestyle intervention **did not significantly** reduce the primary outcome, CVD-related morbidity/mortality (i.e., CVD death, non-fatal MI, non-fatal stroke, hospitalized angina), after nearly 10 years of follow-up.

- 403 versus 418 persons with events in the intervention and control group respectively (1.83 versus 1.92 events per 100 person years; HR 0.95, 95% CI 0.83-1.09, p=0.51)
- There was a suggestion of heterogeneity of response for the primary outcome based on the history of prior CVD at baseline.
- Although not significant, intensive lifestyle intervention
  - Reduced the primary outcome in those **without CVD** at baseline (HR 0.86; 95%CI 0.72-1.02)
  - Increased the primary outcome in those **with CVD** at baseline (HR 1.13, 95%CI 0.90-1.42)

- Intensive lifestyle intervention **did reduce** a number of significant and long-term improvements in a number of other outcomes, including
  - Significant and sustained weight loss
  - Glucose control
  - Greater likelihood of partial remission during the 1st 4 years*
  - Blood pressure
  - Lipid profile except LDL
  - Physical fitness and physical function
  - Renal outcomes
  - Urinary incontinence in men and women
  - Erectile dysfunction
  - Sleep apnea
  - Quality-of-life
  - Fewer hospitalizations, fewer medications and healthcare costs

  *Partial remission of diabetes was defined as a transition from meeting diabetes criteria to a prediabetes level of glycemia (ie, fasting plasma glucose level of 6.7-7 mmo/L and A1C of 5.7%-6.5%) with no glucose lowering medication.

- Conclusions
  - Despite the overall **lack of CVD risk reduction** in this trial, intensive lifestyle intervention remains important for care of patients with T2DM, particularly when accompanied by medication management. Less medication was required to achieve respective recommended treatment targets in the intervention group.
  - Intensive lifestyle intervention resulted in **other potential benefits** important to patients such as improvements in physical functioning and quality of life.
  - Future research is needed to determine if results observed in this trial would be replicated **among younger** patients, those without established T2DM, and/or those with no pre-existing CVD.

➢ The **Da Quig Diabetes Prevention study**[30] showed a **significant reduction** in CVD mortality with lifestyle intervention in **younger** people with impaired glucose tolerance (FPG 5.6 mmol/L).

- Patients were enrolled in 1986 and the intervention phase lasted for 6 years. In 2009, participants were followed up and the primary outcomes of cardiovascular mortality, all-cause mortality, and incidence of diabetes in the intention-to-treat population were assessed.
- Thirty three clinics (n=577) were involved. Patients were randomized to
  - Diet only (9 clinics, n=148)
  - Exercise only (9 clinics, n=155)
  - Diet and exercise (7 clinics, n=136)
  - Control (8 clinics, n=138)
- Results
  - 542 (94%) of 576 participants (one refused baseline examination) had complete data for mortality and 568 (99%) contributed data to the analysis. 174 participants died during the 23 years of follow-up (121/430 in the intervention group versus 53/138 in the control group).
  - There was a significant reduction in
    - Total mortality (28.1% vs 38.4%; HR 0.71, 95% CI 0.51-0.99, p=0.049)
    - CV disease mortality (11.9% vs 19.6%; HR 0.59, 95% CI 0.36-0.96;p=0.033)
  - The incidence of diabetes was 72.6% (68.4–76.8) versus 89.9% (84.9–94.9); HR 0.55, 95% CI 0.40–0.76; p=0·001).[30]

- **Health behaviour modifications** are often difficult to achieve and sustain long-term. Thus, glucose lowering agents as well as antihypertensives and lipid lowering agents are often added as an adjunct to health behaviour intervention in hopes of optimally reducing the clinically relevant complications of T2DM.

INSULIN AND NON-INSULIN AGENTS

- In Canada, glucose lowering agents can be approved without direct evidence that they reduce the risk of diabetes related morbidity and mortality.[31]
- There is evidence that a reduction in glucose levels with glucose lowering agents reduces the risk of surrogate markers of microvascular complications but proof that glucose lowering agents cause a reduction in the risk of macrovascular complications is uncertain. **The precise ability of glucose lowering per se to reduce CVD risk has not been elucidated.**
- The initial prospective RCTs were conducted in patients with **recently diagnosed T2DM**. These trials, the **UKPDS 33 and 34**, showed that improved glycemic control significantly reduced the risk of early indicators of microvascular complications (UKPDS 33)[32] and had some benefit in reducing macrovascular outcomes (UKPDS 34).[33]
  - Subsequent observational data from long-term follow-up of the UKPDS cohorts 33 & 34, the UKPDS 80,[34] showed the following in patients who had previously been in the intensively treated groups:

- A persistence of significant microvascular benefits from UKPDS 33
- Beneficial effects on CVD outcomes
- During the 10 years of the UKPDS 80, mean A1C levels became similar in all groups within 1 year and remained similar for the following 9 years;
  - Median A1C was approximately 8% (Interquartile range 6.9-9.6).

- The beneficial effects on CV outcomes in patients who had previously been in the intensively treated groups have been interpreted to indicate that achieving optimal glucose control **early** in the course of T2DM could have long-term benefits irrespective of the treatment modality (metabolic memory or legacy effect).
- The UKPDS trials 33[32], 34[33] and 80[34] have several design challenges that cause the results to be questioned. Unfortunately, subsequent trials have neither supported nor refuted the UKPDS data.
- Properly designed trials powered to show a reduction in **clinically relevant vascular outcomes** are lacking in general but particularly in people with recently diagnosed T2DM.

➢ Three major studies, ACCORD[35], ADVANCE[36] and VADT[37], have been conducted in patients with **long standing T2DM** evaluating the vascular effects of **intensive versus less intensive** glycemic control**.**

- The mean disease duration at baseline in these trials was 10, 8 and 11.5 years, respectively.
- These trials showed the benefit of intensive glycemic control on **early indicators** of microvascular outcomes.
- None of them independently confirmed a significant benefit of tight glycemic control on macrovascular outcomes.
- The **less intensive** strategy was shown to have a **lower risk of severe hypoglycemia** compared to the intensive strategy. **The evidence is less certain for other clinical outcomes.**

➢ The CDA guidelines interpret the available evidence to suggest that microvascular and macrovascular events may be reduced by

- Intensifying therapy targeting an A1C < 7.0% in **younger** patients with **recently diagnosed** diabetes and a lower initial A1C value; however, may be associated with an increased risk of hypoglycemia.
- Individualized and higher A1C targets in **older** type 2 patients with longer duration of diabetes, established CV risk factors, severe hypoglycemia episodes and/or without A1C reduction despite treatment intensification.(1)

Question 2: What are the recommended glycemic treatment targets?

According to the 2013 update of the Canadian Diabetes Association Guidelines:[1]

- Glycemic targets should be individualized based on age, duration of diabetes, risk of severe hypoglycemia, presence or absence of cardiovascular disease, and life expectancy [Grade D, Consensus].
- Therapy in most individuals with T2DM should be targeted to achieve an A1C ≤ 7.0% in order to reduce the risk of microvascular [Grade A, Level 1A (**UKPDS 33**)] and, if implemented early in the course of disease, macrovascular complications [Grade B, Level 3 (**UKPDS 80**)].

Academic detailing comments:

In the **UKPDS 33** trial[32] a significant reduction in any diabetes related endpoint was achieved with intensive therapy that lowered A1C levels to a median of 7.0% over 10 years when compared with conventional treatment that achieved a median A1C of 7.9%.

- Most of the risk reduction in the "any diabetes-related aggregate endpoint" was due to a 22% relative risk reduction in microvascular endpoints, largely the result of fewer cases of retinal photocoagulation.
  - Total microvascular events:
    Event rates 8.2 vs 10.6%, RRR 22%, ARR 2.4%, NNT 42 (95% CI 22 to 312) for 10 yrs
  - Retinal photocoagulation:
    Event rates 7.6 vs 10.3%, RRR 29%, ARR 2.7%, NNT 37 (95% CI 21 to 149) for 10 yrs
  - No survival benefit was noted and the trial did not conclusively inform the impact of intensive glucose lowering on the risk of blindness, end stage renal disease, amputation or CV events.
- The **UKPDS 80** trial[34] results have been interpreted to indicate that achieving "optimal glucose control" early in the course of T2DM could have long-term benefits.
  - The guidelines are defining "optimal glucose control" to be an A1C target of ≤ 7.0%.
  - However during the 10 years of the UKPDS 33 and 34 trials, the median A1C in the intensive groups were 7% and 7.4%, respectively and in the conventional therapy groups 7.9% and 8%, respectively.
  - Therefore a target between 7% and 7.4% would more accurately reflect the trial data on which the recommendation is based.

- An A1C ≤ 6.5% may be targeted in some patients with type 2 diabetes to further lower the risk of nephropathy [Grade A, Level 1 (**ADVANCE**[36])] and retinopathy [Grade A, Level 1], but this must be balanced against the risk of hypoglycemia [Grade A, Level 1 (**ACCORD**[35])].

Academic detailing comments:

- In the **ADVANCE** trial[36] a significant reduction in major microvascular events (a primary composite outcome of nephropathy and retinopathy) was achieved with intensive therapy that lowered mean A1C levels to 6.5% over 5 years versus 7.3% in the standard group.
  - Most of the risk reduction in incidence of major microvascular events was due to a reduction in surrogate outcomes of nephropathy (development of macroalbuminuria or doubling of the SrCr level).
    - For major microvascular events over 5 years
      Event rates 9.4 vs 10.9%, ARR 1.5%, NNT 67 (95% CI 38 to 264)
    - Nephropathy over 5 years
      Event rates 4.1 vs 5.2%, RRR 21%, ARR 1.1%, NNT 91 (95% CI 53-314)
    - Retinopathy over 5 years resulted in no significant difference
      Event rates 6 vs 6.3%, ARR 0.3%
  - Severe hypoglycemia*and hospitalizations due to severe hypoglycemia occurred more frequently in the intensive therapy group versus the standard therapy group.
    - Severe hypoglycemia:
      Event rates 2.7 vs 1.5%, ARI 1.2%, NNH 83
    - Increased rate of hospitalizations due to severe hypoglycemia:
      Event rate 1.1% vs 0.7%, p=0.04

  * Defined as episodes requiring the assistance of another person and documentation of either a plasma glucose < 2.8 mmol/l or symptoms that promptly resolved with oral carbohydrate, intravenous glucose, or glucagon.

- In the **ACCORD** trial[35] a significant reduction in macroalbuminuria and a surrogate measure of diabetic retinopathy were achieved with intensive therapy that maintained an A1C level of 6.4% over 3.5 years versus 7.5% in the standard therapy group.
  - However, intensive therapy was also associated with an increased risk of
    - All cause mortality:
      Event rate: 5% vs 4%; ARI 1.05% NNH=96 (95% CI 54 to 403) and
    - Hypoglycemia requiring medical assistance:
      Event rate 10.5 vs 3.5%, ARI 7%, NNH=14 (95% CI 13 to 17)
  - The benefit of reducing the early markers of nephropathy and retinopathy with the achievement an A1C target of ≤ 6.5 must be weighed against the increased risk of severe hypoglycemia and death.

- Less stringent A1C targets (7.1% - 8.5% in most cases) may be appropriate in patients with any of the following [Grade D, Consensus]:[1]

  a) Limited life expectancy
  b) High level of functional dependency
  c) Extensive coronary artery disease at high risk of ischemic events
  d) Multiple comorbidities
  e) History of recurrent severe hypoglycemia
  f) Hypoglycemia unawareness
  g) Longstanding diabetes for whom it is difficult to achieve an A1C ≤ 7.0% despite effective doses of multiple glucose lowering agents, including intensified basal-bolus insulin therapy.

Academic detailing comments:

- Results of the ACCORD[35] trial influence these target recommendations.
  - The increased rate of all cause mortality in the ACCORD intensive group suggests that aggressive treatment to reach a low A1C may not be safe in all patients especially those with a high A1C and significant CV risk.
  - Subgroup analysis of the ACCORD intensive population suggests that those with a low CV risk and lower baseline A1C have a better benefit to risk ratio.
- People in the ACCORD intensive group were on considerably more agents and had more frequent changes in therapy compared to people in the ADVANCE intensive group.
  - 52% of ACCORD intensive therapy patients were on 3 oral hypoglycemics + insulin vs the majority of the ADVANCE intensive therapy patients who were on metformin and gliclazide.
  - The ADVANCE[36] and ACCORD[35] intensive therapy groups reached **similar A1C values** but the ADVANCE intensive therapy group was not associated with an increase in death and had fewer episodes of hypoglycemia causing medical intervention compared to ACCORD.

- A recent review article highlighted the substantial uncertainty about optimal glycemic control in **older adults** with T2DM.[38] They recommend that
  - Benefits and harms, patient preferences about treatment and treatment burden be considered.
  - For the majority of older adults, an A1C target between 7.5% and 9% will maximize benefits and minimize harms.

- Liberalized targets for the frail elderly are also recommended in Nova Scotia.
  - The Diabetes Care Program of Nova Scotia Guidelines for **Frail Elderly** Residents in Long-Term Care Facilities recommend more liberalized targets to improve patient safety and reduce the risk of hypoglycemia and related sequelae resulting from over management**.**
  - Guidelines can be found at http://diabetescare.nshealth.ca/sites/default/files/files/DCPNSLTCPhase2.pdf

Question 3: What non-insulin glucose lowering agents are currently available and where do they act?

Here is a list of the currently available products.

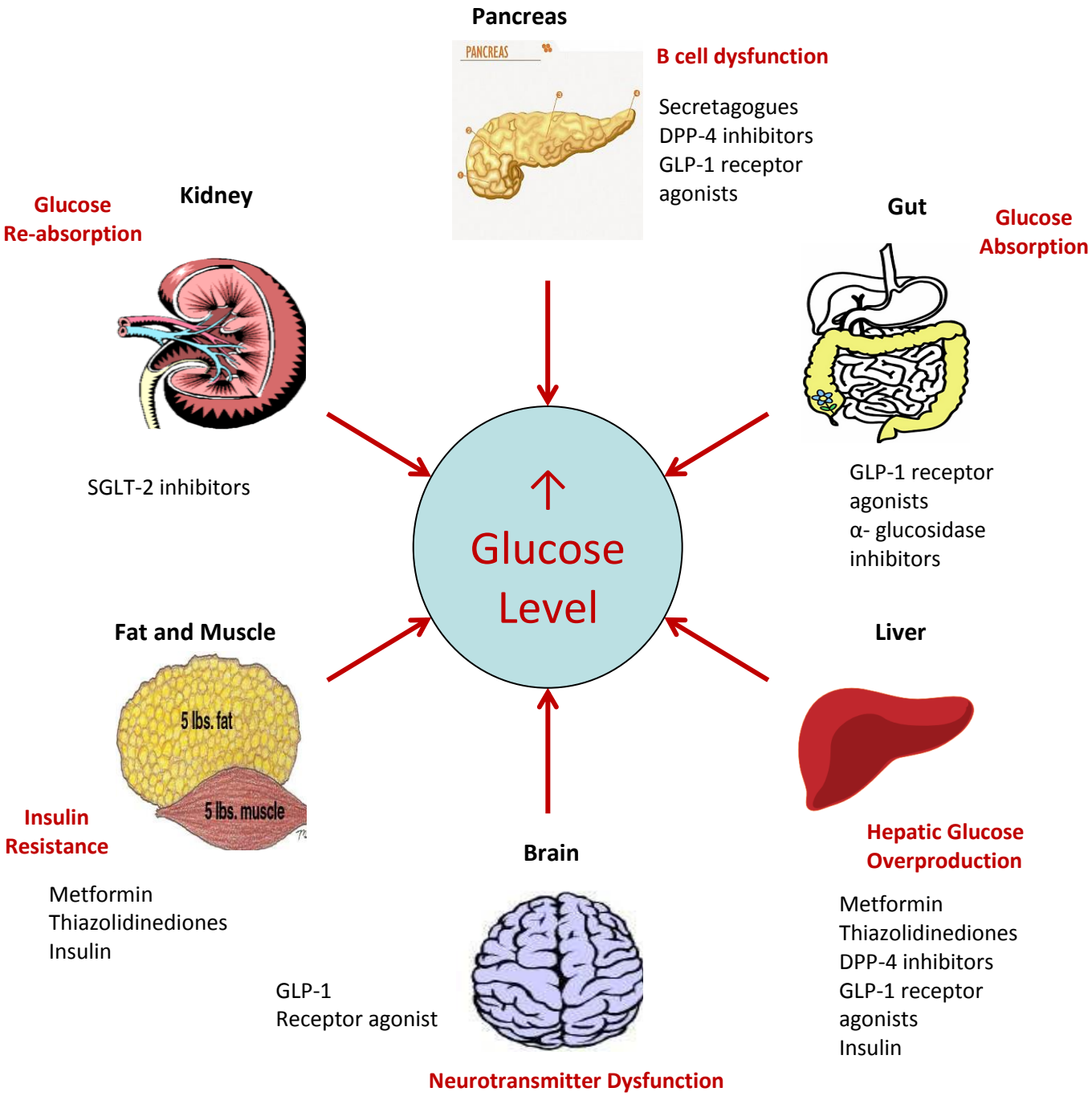
- **Metformin** (Generics, Glucophage®, Glumetza®)
- **Secretagogues**
  - Sulfonylureas
    - Gliclazide (Generics, Diamicron®, Diamicron MR®)
    - Glimepiride (Amaryl®)
    - Glyburide (Generics, Diabeta®)
    - Chlorpropamide (Generics)
    - Tolbutamide (Generics)
  - Meglitinides
    - Repaglinide (Gluconorm®)
- **Alpha-glycosidase Inhibitor**
  - Acarbase (Glucobay®)
- **Thiazolidinediones**
  - Pioglitazone (Actos®)
  - Rosiglitazone (Avandia®)
- **Dipeptidyl Peptidase 4 (DPP-4) Inhibitors**
  - Sitagliptin (Januvia®)
  - Saxagliptin (Onglyza®)
  - Linagliptin (Trajenta®)
  - Alogliptin (Nesina®)
- **Glucagon Like Peptide 1 (GLP-1) Receptor Agonists**
  - Exenatide (Byetta®)
  - Exenatide extended release (Bydureon®)
  - Liraglutide (Victoza®)
  - Dulaglutide (Trulicity®)
- **Sodium Glucose co-transporter (SGLT-2) Inhibitors**
  - Canagliflozin (Invokana®)
  - Dabagliflozin (Forxiga®)
  - Empagliflozin (Jardiance®)

MECHANISMS OF ACTION

Mechanistic approaches include insulin replacement, drugs that stimulate the pancreas to release insulin, sensitization of tissues to the action of insulin, inhibition of glucose production

or the breakdown of glycogen, increased peripheral utilization of glucose and decreased renal glucose reabsorption.

Figure 2: Mechanism of action of the currently available non-insulin and insulin agents.



Graphics from http://www.clipartpanda.com/categories/

Question 4: Is there a defined choice and order of intervention?

- There is insufficient clinical trial data to determine **optimal treatment sequence** and approach as in number of combined agents. Therefore, prescribers are left to rationalize various patterns of practice based on theoretical and practical issues in the absence of the ideal dataset to drive clinical decision-making. See Figure 3.
- As T2DM is characterized by insulin resistance and continued decline in beta cell function, glucose levels will likely worsen over time requiring ongoing treatment changes.
  - It is recommended that timely adjustments are made to try to attain target A1C within 3 to 6 months.
- While endogenous insulin secretion is still present, recent practice has been to use combinations of non-insulin agents to counteract the pathophysiologic defects of T2DM at multiple points.
- Although insulin can be used as stand-alone therapy, there is substantial patient and physician preference not to use insulin as first- or second-line therapy. Insulin is now more commonly used as add-on to other non-insulin agents. However, it is recommended to use insulin as initial therapy when individuals have symptomatic hyperglycemia and metabolic decomposition.
- Eventually most patients become truly insulin deficient and require insulin therapy for management. Insulin treatment in T2DM is generally instituted with basal insulin alone and intensified to basal plus bolus insulin regimens if glycemic goals are not achieved.
  - The addition of newer non-insulin drugs to previous insulin treatment **may allow** for partial or complete reduction in insulin dose.
    - This can result in fewer hypoglycemic episodes and less weight gain.
    - The effects on long term vascular outcomes are uncertain.[39]

Figure 3: Treatment considerations for T2DM

METFORMIN FIRST LINE AGENT

THEN WHAT?

- ❖ SU[a] or GlucoNorm[a]
- ❖ Glucobay[b]
- ❖ TZDs: Actos, Avandia[c]
- ❖ DPP-4 inhibitors: Onglyza, Trajenta[d], Januvia, Nesina
- ❖ GLP-1 receptor agonists: Victoza, Byetta, Trulicity
- ❖ SGLT-2 inhibitors: Invokana, Forxiga, Jardiance
- ❖ Insulin

Jardiance[62] was shown to ↓ CV death vs placebo but direct comparative trials between glucose lowering agents powered to measure diabetes related vascular outcomes are lacking. Data are insufficient to inform the choice of one agent over another at this time.

Effects on vascular outcomes

Safety

Effects on surrogate outcomes

Cost

Risk of hypoglycemia attributable to each agent is not possible to precisely quantify or compare.
All the agents have adverse effects.
The significance of these effects is dependent on the individual.
See Table 9 for complete list.

Insulin ↓ A1C the most.
Non-insulin agents ↓A1C less but each to a similar extent.

Clinical relevance of agents effects on BP, lipids & body weight unclear.

Glucophage, Diamicron, Diabeta least costly ($0.15-0.40 per day)
GLP-1 receptor agonists most costly ($5.20-9.00 per day)
See Table 10

Footnotes:

[a] Glucose lowering mechanism similar between sulfonylureas (SUs) and GlucoNorm; concomitant use not recommended. Current evidence does not confidently differentiate between SU agents or between SU agents and repaglinide in terms of their efficacy and safety due to insufficient comparative data; repaglinide use not recommended in ages > 75 yrs; diamicron & diabeta least costly

[b] Poorly tolerated, rarely used

[c] Canadian prescribing restrictions: Use only if all other oral glucose lowering medications are inadequate, contraindicated or not tolerated and obtain patients written informed consent

[d] Not indicated for use with insulin due to possible increase in CV risk with combination

Graphics from http://www.clipartpanda.com/categories/doctor-patient-clipart

Question 5: Why is metformin the first line agent?

BENEFITS OF METFORMIN

- Metformin is commonly accepted as the first-line therapy for T2DM in conjunction with lifestyle modification.
  - Metformin monotherapy causes A1C reductions of 1.1% to 1.5% depending on the dosage.[40]
  - It is not associated with hypoglycemia or weight gain, is low in cost and has many years of usage.
  - It has been widely used in Europe since the 1950s and available in the United States since 1994.
  - Whether metformin is started as monotherapy or in combination with another glucose lowering agent varies and often depends on the presenting A1C.[41]
- Claims of metformin reducing **macrovascular outcomes** have been made since the publication of the UKPDS 34 trial in 1998. This trial, a substudy of the original UKPDS trial, showed a reduction in macrovascular risk in newly diagnosed obese patients treated with metformin.
- Since then trial results have been equivocal on the matter of whether metformin reduces CV events. Based on the currently available evidence, the specific effect of metformin on macrovascular outcomes and mortality cannot be firmly confirmed or rejected.[42]

EVIDENCE FOR METFORMIN

- **UKPDS-34**[33]
  - Table 3 presents the primary and secondary outcomes after 10.7 years follow-up for the 753 overweight patients randomized to metformin or prescribed diet. The median dose of metformin was 2550 mg/day (Interquartile range 1700–2550).

Table 3: Results of UKPDS-34 Metformin (n=342) versus diet (n=411)

Efficacy outcomes	Event rate %		RRR %	ARR %	NNT for 10.7 yrs	
	Met	Diet			NNT	95%CI
Any diabetes related endpoint¥	28.6	38.9	26	10.3	10	6-28
Diabetes related death¥	8.2	13.4	39	5.2	19	10-124
All cause death¥	14.6	21.7	32	7.1	14	8-64
MI§	11.4	17.8	36	6.4	16	9-73
Stroke§	3.5	5.6	37	2.1	NS	
Microvascular complications§	7	9.2	29	2.2	NS	

¥ *Primary outcomes*

- Any diabetes related endpoints - Defined as sudden death, hyper- or hypoglycemia-related death, MI, angina, HF, stroke, renal failure, amputation, vitreous hemorrhage, retinopathy requiring photocoagulation, and blindness
- Diabetes related death - Defined as death from MI, stroke, PVD, kidney disease, hypo- or hyperglycemia, or sudden death

§ *Secondary Outcomes*
MI (Fatal, non-fatal) and sudden death
Stroke (Fatal and non-fatal)
Microvascular complications - Defined as retinopathy requiring photocoagulation, vitreous haemorrhage, and fatal or non-fatal renal failure

- It is important to note that...
  - These results were drawn from a small population of patients allocated to metformin (n = 342), which is < 10% of all patients randomized in the UKPDS study.
  - The UKPDS 34 was not strictly a metformin monotherapy versus placebo trial. It tested a strategy of intensive glucose lowering versus less intensive glucose lowering in a small subgroup of overweight people whose initial therapy was metformin.

➢ **SPREAD-DIMCAD**[43]

- Hong et al conducted a multicenter, randomized, double-blind, placebo-controlled clinical trial. A total of 304 T2DM patients with coronary artery disease were randomly assigned to receive either glipizide (30 mg daily) or metformin (1.5 g daily) for 3 years, with insulin added as needed to achieve an A1C < 7%.
- Baseline characteristics:
  - Mean age 63 years
  - Mean weight 69 kg
  - Duration of diabetes 5.6 years
  - Duration of CVD 3 years
  - Mean A1C 7.6%
  - Hypertension 67-71%
  - Prior MI 53-63%
  - Prior stroke 13-18%
  - Prior arterial revascularization 62-64%

- The primary end points were times to the composite of recurrent cardiovascular events, including
  - Death from a cardiovascular cause,
  - Death from any cause,
  - Nonfatal MI,
  - Nonfatal stroke, or
  - Arterial revascularization.

- At the end of study drug administration, both groups achieved a significant decrease in the level of A1C (7.1% in the glipizide group and 7.0% in the metformin group).
- At a median follow-up of 5.0 years, 91 participants had developed 103 primary end points. Metformin was associated with a 10% absolute risk reduction (Intension to treat analysis) in the primary composite outcome.
  - Event rates 35% vs 25%; HR 0.54 (95%CI 0.3-0.9); RRR 29%, ARR 10%, NNT 10
- SPREAD-DIMCAD is the first double-blind RCT to compare different effects of glipizide and metformin in major CV events among patients with CVD and T2DM. It extends the generalizability of UKPDS-34 to high risk patients with existing diabetes.
- SPREAD-DIMCAD has been criticized for the following reasons:
  - Lack of washout period before randomization
  - Uncertain whether observations can be extended to people without CVD or other SU's. The trial used glipizide but **various SUs may differ in their effects on CV risk**.
  - It is difficult to discern whether metformin was beneficial or glipizide detrimental or both.

➢ **Meta-analysis by Boussageon et al.**[42]

- A 2012 meta-analysis concluded that there was no proof that metformin could prevent CV deaths and events; it could increase or decrease the death rate.
  - A 25% reduction or a 31% increase in all-cause mortality cannot be excluded.
  - A 33% reduction or a 64% increase in CV mortality cannot be excluded (Table 4).
- 13 RCTs (n=13,110) were retrieved; 9,560 patients were given metformin, and 3,550 patients were given conventional treatment or placebo. Duration ≥ 5 years.
- The authors noted that
  - The UKPDS study results need confirmation.
  - Compared with other glucose lowering agents metformin might have the fewest disadvantages.
  - **[In 2012], none** of the other available glucose lowering agents were **shown to be superior to metformin** in terms of vascular outcomes in direct comparative trials.

Table 4: Results of meta-analysis by Boussageon[42]

Outcomes	RR	95% CI
All cause mortality	0.99	0.75 to 1.31
CV mortality	1.05	0.67 to 1.64
MI	0.90	0.74 to 1.09
Stroke	0.76	0.51 to 1.14
Heart failure	1.03	0.67 to 1.59
Peripheral vascular disease	0.90	0.46 to 1.78
Leg amputations	1.04	0.44 to 2.44
Microvascular complications	0.83	0.59 to 1.17

LIMITATIONS OF METFORMIN

- **Lactic Acidosis**
  - Historically, metformin therapy has been associated with **rarely** causing lactic acidosis.
  - The reported incidence estimates are very low and range from 1-10 per 100,000 patient-years; however, when it does occur it is associated with high mortality at 30-50%.
  - For this reason the Compendium of Pharmaceuticals and Specialties lists the following as contraindications to metformin use:[44]
    - Renal insufficiency (GFR ≤ 30 ml/min)
    - Congestive heart failure requiring pharmacologic treatment
    - Advanced age (≥ 80 years old), unless CrCl indicates renal function not reduced
  - A 2014 systematic review[45] assessed the risk of lactic acidosis associated with metformin use in individuals with impaired kidney function.
    - They concluded that "The risk of lactic acidosis is essentially nil in the context of clinical trials including those that did not specify kidney disease as an exclusion criterion."
    - "Data from observational clinical practice data sets are conflicting with most appearing to confirm the drugs overall safety profile, finding lactic acidosis rates not different from those in the general populations of patients treated with other agents."
  - Assuming that the real incidence estimate of lactic acidosis with metformin was 10 per 100,000 patient years, the benefit of metformin therapy would outweigh risk.[46]
- Metformin is renally excreted and is capable of causing severe acidosis in **overdose**.[44]
  - There is limited guidance on how to modify the metformin dose specifically in the **presence of renal disease**; however, the following general **anecdotal** dosage adjustments have been recommended.
    - eGFR > 60 mls/min - no change in metformin dosage
    - eGFR 30-60 mls/min - ↓ dose 50% (2000 mg to 1000 mg daily)
    - eGFR 15-30 mls/min - ↓ dose 75% (2000 mg to 500 mg daily)

- **Gastrointestinal side effects**
  - The side effects of metformin are mainly gastrointestinal and include epigastric discomfort, diarrhea, nausea and vomiting.
  - These side effects are observed in approximately 30% of patients, and have led to treatment discontinuation in 5% of patients.[47–49]
  - These symptoms are generally transient and resolve spontaneously during continued treatment. Occasionally, temporary dose reduction may be useful.[50]
    - During initiation, **gradual dose titration** is required.
    - Patients should take metformin with a meal.

- **Should Metformin be temporarily held in the setting of diagnostic and interventional procedures using contrast media?**
  - In patients with GFR < 45mL/min:
    - Metformin should be stopped at the time of contrast injection and should not be restarted for at least 48 hours and only then if renal function remains stable (less than 25% increase compared to baseline creatinine). It is generally unnecessary to stop metformin 48 hours prior to contrast injection but special care should be taken in patients with severe or acute renal dysfunction.
  - In patients with GFR > 60mL/min receiving larger volumes of contrast (>100mL):
    - Metformin should be withheld for 48 hours after the procedure.

Reference: Canadian Association of Radiologists: Consensus Guidelines for the Prevention of Contrast Induced Nephropathy 2011[51]

Question 6: What factors inform choices after metformin?

Choice of agent after metformin is primarily influenced by effects on vascular and surrogate outcomes, safety and cost.

EFFECTS ON VASCULAR OUTCOMES

- Determination of the **effects on vascular outcomes** between agents requires direct comparative RCTs adequately powered to demonstrate these clinically relevant effects.
  - Since the risk of vascular complications has been **associated** with the A1C level, differences in levels between groups **could be credited** for causing the differences in outcomes.
  - As a result, the A1C between groups needs to be similar to reveal whether the effects between agents are clinically relevant. The A1C lowering ability of most of the oral glucose lowering agents is generally similar; therefore it is the extra-glycemic effects that will distinguish their place in therapy.

- There are a number of comparative trials between the agents, new and old, that have been conducted; however, they are of short duration and report on surrogate outcomes only.
- **Available data do not clearly guide the use of glucose lowering agent choices in terms of their effect on vascular outcomes.** Revealing the clinical relevance of the extra-glycemic effects of each agent and how they compare to each other are needed to optimally define treatment sequence.
  - Two of the agent choices after metformin have been studied in **direct comparative** trials adequately powered to demonstrate vascular outcomes, the SU glipizide and rosiglitazone.
    - The **SPREAD-DIMCAD**[43] **trial** studied glipizide versus metformin.
      - Metformin was associated with a 10% ARR in the primary composite outcome of CV death, any death, nonfatal MI, nonfatal stroke, or arterial revascularization compared to glipizide.
      - It is difficult to discern whether metformin is beneficial or glipizide is detrimental or both. Glipizide, which is not marketed in Canada, is similar to glyburide. Gliclazide and glimepiride may differ in their effects on vascular risk in T2DM.
    - The **RECORD trial**[52] studied a SU plus metformin versus rosiglitazone plus a SU or metformin. SUs included glyburide, glimepiride or gliclazide.
      - Adding rosiglitazone to patients on either metformin or a SU seems to be no more detrimental on CVD endpoints than combining metformin and a SU.
      - Rosiglitazone did however cause an increase in heart failure (2.7% vs 1.3%; HR 2.10, 95% CI 1.35 to 3.27).
  - The **UKPDS 33**[32] is often referenced as providing evidence of a microvascular benefit for the SUs and insulin combined; however, this was not strictly a SU monotherapy or an insulin monotherapy versus placebo clinical trial. The trial was designed to test a strategy of intensive glucose lowering versus less intensive glucose lowering in which some of the participants' initial therapy was a SU.
  - There are 2 direct comparative RCTs sufficiently powered to measure **CVD outcomes** in people with T2DM currently ongoing, the TOSCA.IT[53] and CAROLINA[54] trials.
    - In the **TOSCA.IT** trial, people with type 2 diabetes inadequately controlled with metformin monotherapy (n=3,371) were randomized to add-on therapy with a SU or pioglitazone. Participants will be followed for up to 48 months in an open-blinded fashion to assess a composite of all-cause mortality and non-fatal cardiovascular endpoints.
    - The **CAROLINA** trial, by contrast, is a double-blinded, randomized study, in people with type 2 diabetes without optimum glycemic control and who are at high risk of CVD. Participants (n=6,000) were randomized to receive treatment with linagliptin, glimepiride or placebo and will be followed for 400 weeks to CVD mortality or morbidity endpoints.

- Both trials will help determine whether SUs, as a group, increase the risk of adverse CV events compared with other glucose lowering agents.
  - SUs remain a popular second-line option.
  - There has been an ongoing, almost permanent, debate over whether or not the SUs increase mortality and CVD death.
  - The UKPDS study was the first to suggest a potential mortality risk among patients treated with metformin plus a SU. Since then, there have been a number of systematic reviews and meta-analyses **showing conflicting results**.

- There are **placebo controlled** trials evaluating the effects of non-insulin agents on vascular outcomes but they **do not inform relative benefit and risk between agents**.
  - Pioglitazone was shown to decrease CVD events versus placebo on a secondary endpoint in the PROACTIVE trial.[55]
    - However, these results are viewed by many as hypothesis generating at best.
  - Three of the DPP-4 inhibitors, sitagliptin (TECOS trial[56]), saxagliptin (SAVOR-TIMI 53 trial[57]) and alogliptin (EXAMINE[58]), failed to show a CVD benefit versus placebo after ~ 4 years on a background of standard therapy.
    - It has been suggested that a longer follow-up period may be necessary to further confirm these results. The median follow-up period for SAVORTIMI 53, EXAMINE AND TECOS was 2.1 years, 1.5 years and 3 years respectively.
    - A similarly designed trial is currently ongoing comparing linagliptin to placebo (CARMELINA[59]) expected to be published in 2018.
  - GLP-1 receptor agonists, liraglutide and exenatide are currently being studied to determine their effects on CVD outcomes compared to placebo.
    - Publication of the liraglutide (LEADER[60]) trial is expected in early 2016.
    - Publication of the exenatide (EXSCEL[61]) trial is expected in early 2018.
  - The SGLT-2 inhibitor empagliflozin has been shown to **reduce CV death** in a single randomized, double-blind, placebo-controlled trial. Since this is the **only agent** among the choices after metformin to show this outcome, further discussion regarding the interpretation of this evidence is warranted.
    - The **EMPA-REG OUTCOME trial**[62] enrolled 7,020 people with T2DM at **high risk for CVD** events.
      - At baseline, all had established CVD and 10% had heart failure.
    - Patients were randomized to either 10 or 25 mg empagliflozin or to placebo in addition to their standard care.
      - At baseline 30% were on 1 agent, 50% on 2 agents and 20% on > 2 agents.

- Follow up was for a median period of 3.1 years.
  - At 3.1 years, A1C was 7.81% in the pooled empagliflozin groups and 8.16% in the placebo group, a 0.35% difference.
- The empagliflozin groups did **statistically significantly reduce** the primary outcome (p = 0.04) relative to placebo. See Table 5 for further details.

Table 5: Results of the EMPA-REG OUTCOME trial[62]

Efficacy outcomes	Event rate %		RRR	ARR	NNT for 3.1 yrs	
	Empagliflozin n=4,687	Placebo n=2,333			NNT	95%CI
CV death, MI, stroke*	10.5	12.1	13 %	1.6 %	63	31-8300
1° + hospitalization for unstable angina§	12.8	14.3	11%	1.5 %	NS	
All cause death	5.7	8.3	32 %	2.6 %	39	26-77
CV death	3.7	5.9	38 %	2.2 %	46	30-91
Hospitalization for heart failure	2.7	4.1	34 %	1.4 %	72	43-212
MI (non fatal)	4.5	5.2	13 %	0.7 %	NS	
			RRI	**ARI**		
Stroke (non fatal)	3.2	2.6	23 %	0.6 %	NS	

ARR, absolute risk reduction; ARI, absolute risk increase; RRR, relative risk reduction; RRI, relative risk increase; NNT, number needed to treat; CI confidence interval; NS , not significant

* **Primary outcome: driven by CV death, no significant difference between groups in rates of MI or stroke**

§ Key secondary outcome

- All cause death and CV death were reduced to the same extent in patients with heart failure at baseline, who had high use of medications used to treat heart failure, as in patients without heart failure at baseline. Thus, outcomes were not predominantly driven by patients with heart failure at baseline.[63]
- The authors note that the mechanisms behind the observed empagliflozin benefits are uncertain. It is not known whether benefits are unique to empagliflozin or a class effect.
  - Similarly designed trials for canagliflozin and dapagliflozin are currently ongoing but are not yet published.
    - The CANagliflozin cardioVascular Assessment Study (CANVAS)[64] started in December 2009 and is scheduled to be completed in April 2017. Included patients have a diagnosis of T2DM and a history of, or a high risk for, CV disease.

    - The DECLARE-TIMI58[65] dapagliflozin trial started in April 2013 and is scheduled to be completed in April 2019. It included patients with T2DM and at high risk for CV disease.

- Only **genital infections** were significantly increased in the empagliflozin groups relative to placebo.
    - As experience with the SGLT-2 inhibitors increases, further adverse effects are being reported. Case reports of diabetic ketoacidosis, dehydration and urinary tract infections have recently been reported by various drug safety organizations.
- It remains unclear how empagliflozin would compare with another glucose lowering agent given on a background of standard therapy since the EMPA-REG OUTCOME trial was compared to placebo.
- It is also uncertain if the trial results can be extrapolated to a population **without existing CVD or more recent onset T2DM.**
    - In the EMPA-REG OUTCOME[62] trial, only 15% of the population had disease duration under 5 years. Fifty seven percent had disease duration > 10 years.
    - The entire population had established CVD (history of MI, stroke, PVD and/or unstable angina).
- **Content Reviewer Comment:** Trial data do not suggest better glucose control was responsible for the beneficial outcomes. At study termination, the A1C difference was minimal (0.35%). The mechanism of benefit is unclear but the outcome is impressive.

BOTTOM LINE: Effects on vascular outcomes*:* More carefully designed trials are needed to determine the relative vascular effects of the glucose lowering agents, old and new. The evidence available to date regarding macrovascular and microvascular outcomes is judged to be low in strength and insufficient. Table 6 summarizes the known effects of the second line glucose lowering agents on diabetes related morbidity and mortality.

Table 6: Effect of the second line glucose lowering agents on diabetes related morbidity and mortality

Glucose lowering agent	Outcomes		
	Retinopathy, nephropathy, neuropathy	CVD death, MI, stroke	Mortality
SUs			
Gliclazide, glimepiride & glyburide	Effect uncertain	Effect uncertain	Effect uncertain
Repaglinide	Effect uncertain	Effect uncertain	Effect uncertain
TZDs			
Pioglitazone	Effect uncertain	**↑ risk HF**	Effect uncertain
Rosiglitazone	Effect uncertain	**↑ risk HF & MI**	Effect uncertain
DPP-4 Inhibitors			
Sita-, saxa- & alogliptin	Effect uncertain	**No benefit vs Pl**	**No benefit vs Pl**
linagliptin	Effect uncertain	Effect uncertain	Effect uncertain
GLP-1 receptor agonists	Effect uncertain	Effect uncertain	Effect uncertain
SGLT-2 Inhibitors			
Canagliflozin, dapagliflozin	Effect uncertain	Effect uncertain	Effect uncertain
Empagliflozin	Effect uncertain	**↓ risk CV death vs Pl**	**↓ risk vs Pl**
Insulin	Effect uncertain*	Effect uncertain*	Effect uncertain*

* Effect uncertain while endogenous insulin secretion is present.

Adapted from information in PAD Glucose Lowering Medications for Type 2 Diabetes Oct 2015 with permission[66]

EFFECTS ON SURROGATE OUTCOMES

- **A1C reduction**
  - The A1C lowering ability of most of the non-insulin agents is **generally similar**.
    - Monotherapy reduces A1C approximately 1% on average (e.g. A1C 8.5% to 7.5%).
    - The maximum A1C lowering effect is seen at 3 to 6 months.[67–69]
    - Like metformin, standard or starting doses for most agents generally result in similar A1C reductions compared to higher or maximum doses. See Appendix 1 for examples of dose response relationships of the various oral agents.
  - Most dual non-insulin therapy combinations have similar efficacies and reduce A1C about 1% more than monotherapies (range 0.64% to 0.96% when added to metformin).[40,67,68,70]

- Compared with continued treatment with metformin and a SU, addition of DPP-4 inhibitors, GLP-1 receptor agonists, TZDs, and insulins produced statistically significant reductions in A1C (range -0.89% to -1.17%); whereas, meglitinides and alpha-glucosidase inhibitors did not.[71]
  - SGLT-2 inhibitors have also been shown to significantly reduce A1C, in a similar range, when added to metformin and an SU.[72]
- Insulin lowers A1C the most.

➢ **Durability (duration of A1C reduction)**[70]

- When selecting an agent it is desirable to choose one with extended A1C lowering ability to delay the need for further therapy.
- Unfortunately, the concept of durability of non-insulin agents is a difficult one to define. Also there are few studies done to date with durability as their primary outcome.
- There is speculation that agents such as the incretins (i.e. DPP-4 inhibitors and GLP-1 receptor agonists) and TZDs offer prolonged glycemic control by slowing the decline of beta-cell function; however, the evidence is limited, inconclusive, and of uncertain clinical relevance.

➢ **Changes in body weight**

- A 2013 CADTH review[40] reported weight changes occurring when the following agents, with the exception of the SGLT-2 inhibitors, were added to metformin compared to metformin alone. (See Table 7)
- Weight change for the SGLT-2 inhibitors compared with placebo was reported in another systematic review.[73]

Table 7: Weight changes with glucose lowering agents[40, 73]

Agent	Weight change (kg)	95% credible interval
SUs	**2.1 ↑**	1.3 – 2.9 kg
Meglitinides	**1.8 ↑**	0.5 – 3.1 kg
TZD	**2.7 ↑**	1.9 – 3.5 kg
Basal insulin	**1.7 ↑**	0.3 – 3.1 kg
Biphasic insulin	**3.1 ↑**	1.5 – 4.7 kg
Acarbose	**No effect**	-
DPP-4 inhibitors	**No effect**	-
GLP-1 receptor agonists	**1.8 ↓**	0.8 – 2.9 kg
SGLT-2 inhibitors	**1.74 ↓**	1.45 – 2.03 kg

- The clinical significance of body weight changes associated with glucose lowering medications is unclear. The above data is taken from short term RCTs typically less than one year, therefore whether these weight changes persist is uncertain.[40,70,71,73]

- **Changes in blood pressure and lipid levels**
  - The SGLT-2 inhibitors have been associated with a reduction in blood pressure and an increase in LDL. The clinical relevance of these changes is uncertain.[73]

SAFETY

- Please refer to the official Product Monographs for any dosing adjustments needed in the presence of **impaired renal function**.[39]
- Risk of **hypoglycemia** attributable to each agent is not possible to precisely quantify or compare.
  - There are short term trials reporting on the comparative rate of hypoglycemia but they
    - Have variable definitions of hypoglycemia
      - Most report mild episodes (defined as those that are self-treated) making clinical relevance difficult to determine

- Rarely report severe hypoglycemic events (defined as needing help from a 3rd party)
  - The reported rates of severe hypoglycemia with the SUs and metformin were compared in a systematic review.[74] The review did find a significant increase in severe hypoglycemic episodes with the SUs (RR 5.64) but this was based on only 13 events reported in 3,801 participants (only 5 of the 14 trials included reported this outcome).
  - There is less data available for the other glucose lowering agents.

- Do not give consideration to the intensity of the glucose lowering strategy (i.e A1C targeted) or the doses of the comparators.

- Systematic reviews[40,71] have reported data (see Table 8 below) for overall hypoglycemia but the evidence was too limited to evaluate severe events. **Clinical interpretation** of **overall hypoglycemia** is **challenging**. SGLT-2 inhibitors were not included. A separate systematic review[73] noted the risk of hypoglycemia for the SGLT-2 inhibitors was OR 1.28 (95%CI 1.0-6.6) compared with placebo.

Table 8: Increased overall hypoglycemic risk when adding glucose lowering agents

Added agent	↑ risk of overall hypoglycemia	
	Added to metformin[40]	Added to metformin + SU[71]
SUs	OR 7.5 (95% CI 4.4 - 13.7)	-
Meglitinides	OR 8.3 (95% CI 3.3 - 23.4)	-
Basal insulin	OR 4.1 (95% CI 1.7 - 10.7)	OR 2.0 (95% CI 1.2 – 3.6)
Biphasic insulin	OR 7.0 (95% CI 2.8 - 18.1)	-
Acarbose	No significant ↑	-
TZDs	No significant ↑	OR 5.6 (95% CI 2.8 -11.3)
DPP-4 inhibitors	No significant ↑	OR 2.5 (95% CI 1.0 – 6.6)
GLP-1 agonists	No significant ↑	OR 2.1 (95% CI 1.5 – 2.8)

- Table 9 provides the current safety data for the drug classes.

Table 9: Current safety data[75]

Drug	Adverse effects			Not recommended or Contraindicated
	Confirmed	Cannot confirm or reject	Case reports	
SUs	Dose related GI effects Skin hypersensitivity reactions		Various blood dyscrasias	Sulfa allergy G6PD deficiency
TZDs	edema, weight gain, macular edema ↑ fracture risk ↑ risk of pneumonia			Heart failure IHD Bladder cancer
DPP-4 Inhibitors	Skin hypersensitivity reactions ↓ lymphocyte count	Acute and chronic, fatal and nonfatal pancreatitis, pancreatic cancer[#]	Joint pain Possible renal events noted for saxa, sita & alo Thrombocytopenia with sita	Heart Failure • lina & sita not recommended • saxa & alo use cautiously Lina + insulin not recommended
GLP-1 receptor agonists	Dose related GI effects Skin hypersensitivity reactions, anaphylaxis ↑ HR, PR interval prolongation Injection site reactions	Acute and chronic, fatal and nonfatal pancreatitis, pancreatic cancer[#]	Possible renal events	Inflammatory bowel disease, diabetic gastroparesis Hx of medullary thyroid cancer or in Multiple Endocrine Neoplasia syndrome type 2
SGLT-2 inhibitors	Dose related - dehydration, hypovolemia, orthostatic hypotension, hypotension, osmotic diuresis, LDL ↑ ↑ SrCr, ↓ eGFR Acute kidney injury* ↑ fracture risk (canagliflozin) UTIs and genital infections ↑potassium, ↑hemoglobin, hematocrit		Ketoacidosis Serious UTIs	Volume depletion Bladder cancer

GI- gastrointestinal; G6PD - glucose 6 phosphate dehydrogenase deficiency; IHD – Ischemic heart disease; HR- heart rate; saxa-saxagliptin; sita- sitagliptin; alo- alogliptin; lina- linagliptin; UTI- urinary tract infection; SrCr – serum creatinine; eGFR (estimated glomerular filtration rate)

* Summary Safety Review, Health Canada Oct 16,2015 (www.hc-sc.gc.ca) [76]

Table adapted from PAD information

[#] A CNODES population cohort study of ~ 1 million people found no increased risk of pancreatic cancer associated with the use of incretin based drugs compared with SUs after a median follow up of 1.2 – 2.8 years. This potential adverse drug reaction will need to be monitored long term owing to the latency of the cancer. [77]

COST

- Tables 10, 11 and 12 present the average daily cost of single non-insulin agents, combination non-insulin products and insulin, respectively. (McKESSON costs Feb 2016)

Table 10: Average daily cost of single non-insulin agents

Non-insulin agents	Strengths	Usual daily maintenance dose	Cost* / day
Alpha Glucosidase Inhibitor			
Acarbose (Glucobay)	50, 100mg	50-100mg three times a day	0.88 - 1.22
Biguanides			
Metformin (Glucophage, generic)	500, 800mg	500-2550 mg daily divided doses	0.04 - 0.18
Metformin ER (Glumetza)	500, 1000mg	500-2000 mg per day	0.64 - 2.55
Insulin Secretagogues - Sulfonylureas			
Gliclazide (Diamicron, generic)	80 mg	80-320 mg per day (doses>160mg should be BID)	0.09 - 0.37
Gliclazide MR (Diamicron MR)	30, 60 mg	30-120 mg once daily	0.09 - 0.43
Glimepiride (Amaryl, generic)	1, 2, 4mg	1-4 mg once daily (may ↑ to 8 mg/day)	0.39 - 0.77
Glyburide (Diabeta, generic)	2.5, 5 mg	1.25-20 mg once daily	0.02 - 0.23
Insulin Secretagogues-Meglitindes			
Repaglinide (Gluconorm, generic)	0.5, 1, 2 mg	0.5 - 4 mg (max daily dose:16 mg/day)	1.05 - 3.03
Thiazolidinediones			
Pioglitazone (Actos, generic)	15,30 ,45 mg	15-30 mg once daily. Max 45mg/day	0.58 – 1.22
Rosiglitazone (Avandia)	2, 4 mg	4-8 mg daily (single or divided dose)	2.34 – 3.35
Incretin Agents – DPP-4 inhibitors			
Linagliptin (Trajenta)	5 mg	5 mg once daily	2.44
Saxagliptin (Onglyza)	2.5, 5 mg	2.5-5 mg once daily	2.60 – 3.11
Sitagliptin (Januvia)	25, 50, 100mg	100 once daily (25-50mg renal dosing)	2.84
Alogliptin (Nesina)	6.25, 12.5, 25mg	25 mg once daily (6.25-12.5 mg renal)	2.84
Incretin Agents - GLP-1 receptor agonists			
Exenatide (Byetta)	5, 10 mcg	10 mcg BID	5.18
Exenatide extended release (Bydureon)	2 mg	2 mg once **WEEKLY**	7.43
Liraglutide (Victoza)	6 mg/ml	1.2-1.8 mg once daily	5.97 – 8.95
Dulaglutide (Trulicity)	0.75, 1.5 mg	0.75 - 1.5 mg once **WEEKLY**	7.43
SGLT-2 Inhibitors			
Canagliflozin (Invokana)	100, 300 mg	Usual dose one tablet once daily	2.84
Dabagliflozin (Forxiga)	5, 10 mg	Usual dose one tablet once daily	2.84
Empagliflozin (Jardiance®)	10, 25 mg	Usual dose one tablet once daily	2.84

Table 11: Average daily cost of non-insulin combination products

Non-insulin combinations	Strengths	Usual daily maintenance dose[39]	Cost* / day
Metformin + Rosiglitazone (AvandaMet)	500mg/2mg 1000mg/2mg 500mg/4mg 1000mg/4mg	Starting dose 2mg/500mg may increase to a maximum dose of 8mg/2000mg per day	1.26-3.76
Metformin + Sitagliptin (Janumet)	500 mg/50mg 850mg/50mg 1000mg/50mg	Usual dose one tablet twice per day	2.97
Metformin + Sitagliptin (Janumet XR)	500mg/50mg 1000mg/100mg 1000mg/50mg	Usual dose two tablets once daily	2.97
Metformin + Linagliptin (Jentadueto)	500mg/2.5mg 850mg/2.5mg 1000mg/2.5mg	Usual dose 1 tablet twice per day	2.57
Metformin + Saxagliptin (Komboglyze)	500mg/ 2.5mg 850mg/ 2.5mg 1000mg/ 2.5mg	Usual dose 1 tablet twice per day	2.76
Metformin + alogliptin (Kazano)	500mg/12.5mg 850mg/12.5mg 1000mg12.5mg	Usual dose 1 tablet twice per day	2.97
Metformin + dapagliflozin (Xigduo XR)	850mg/ 5mg 1000mg/ 5mg	Usual dose 1 tablet twice per day	2.84

*McKESSON costs Feb 2016

Table 12: Cost per 100 Units of bolus and basal Insulin

Insulin	Cost*/100 U
Bolus Insulins	
Novolin ge Toronto	
• **vial**	**2.35**
• penfill	3.07
Humulin R	
• **vial**	**2.50**
• cartridge/ kwikpen	3.26
Insulin Aspart (Novorapid)	
• **vial**	**3.15**
• penfill	4.25
• flextouch	4.43
Insulin Glulisine (Apidra)	
• **vial**	**2.74**
• cartridge	3.62
• solostar	3.64
Insulin Lispro 100U/ml (Humalog)	
• **vial**	**3.04**
• cartridge	4.08
• kwikpen	4.00
Insulin Lispro 200U/ml (Humalog)	
• kwikpen	3.72
Basal insulin	
NPH (Humulin N)	
• **vial**	**2.50**
• cartridge/ kwikpen	3.26
NPH (Novolin GE)	
• **vial**	**2.40**
• penfill	3.15
Insulin glargine 100U/ml (Lantus)	
• **vial**	**6.70**
• cartridge/ soloSTAR	6.72
Insulin glargine 300U/ml (Toujeo)	
• soloSTAR	6.37
Insulin detemir (Levemir)	
• **vial**	**7.50**
• flextouch	7.76

*McKESSON costs Feb 2016

WHEN IS INSULIN NEEDED

- Due to the progressive nature of T2DM, most people will eventually require insulin therapy to compensate for the diminishing supply of endogenous insulin. Until that time non-insulin agents appear to be most commonly used, sometimes up to 4 agents at once.
- More recently, the initiation of insulin is delayed until oral agents are deemed unlikely to be sufficient to reach the A1C goal. According to the 2013 Canadian Diabetes Guidelines,[41] it is recommended to start an initial glucose lowering regimen containing insulin only when individuals have **symptomatic hyperglycemia and metabolic decomposition** [Grade D, Consensus].
- A study by Brown et al. published in 2003, showed that a hypothetical patient progressing from lifestyle interventions to SU or metformin monotherapy, then to oral combination therapy, before initiation of insulin could potentially accumulate nearly 5 years of a A1C > 8.0% from diagnosis until starting insulin. Unfortunately the clinical relevance of the excess A1C burden was not evaluated.[78]
- As stated in the 2013 Canadian Diabetes guidelines:[41]
  - "Ideally, consideration would be made towards the selection of agents [insulin and non-insulin] with evidence demonstrating ability to not only lower glucose levels, but also reduce the risk of diabetic vascular complications. Unfortunately, the majority of evidence remains equivocal in this regard as most clinical trials compared varying levels of glycemic lowering as opposed to direct comparison between agents used to achieve such glycemic control."
- Effects on vascular outcomes between agents are not available except for metformin versus glipazide and rosiglitazone plus metformin or a SU versus metformin plus a SU.
- In the **absence of clinical trial data** to direct optimal treatment sequence, management strategies are completely based on achieving recommended A1C targets. The addition of a 3rd non-insulin agent typically results in an incremental A1C reduction of ~ 1%.[71]
- A 2013 CADTH review update concluded that adding insulin NPH to metformin plus SU remained the most cost-effective third-line therapy in patients inadequately controlled on metformin and a SU. DPP-4 inhibitors were the most cost-effective treatment option if insulin as a treatment option is removed.[71]
  - The SGLT-2 inhibitors were not included in this review. There is interest in updating this review yet again to incorporate these agents.
- The 2013 Canadian guidelines comment that adding insulin to existing non-insulin agent(s) may result in better glycemic control with a smaller dose of insulin and may induce less weight gain and fewer hypoglycemic episodes than when oral agents are stopped and insulin is used alone.[37]

- Since basal insulins do not control postprandial (after meal) glucose levels, ongoing non-insulin therapies are not discontinued. Although there is some controversy whether secretagogues, especially SUs should be continued when insulin is started, a common approach is to stop these medications only when bolus insulin is introduced.
- If daytime hypoglycemia occurs, the non-insulin agents (secretagogues) may need to be reduced or discontinued or the insulin dose reduced.
- The addition of non-insulin agents to insulin for people not at target may result in improved glycemic control. Insulin needs may decrease.
- Sometimes SUs, DPP-4 inhibitors and GLP-1 receptor agonists may be stopped when insulin needs change to a basal/bolus regimen.[79]
- Combining insulin with TZDs is not approved in Canada; therefore TZDs should be stopped when insulin is started. The combination of linagliptin and insulin is not recommended by the manufacturer of linagliptin.

ARE SULFONYLUREAS ASSOCIATED WITH ADVERSE CARDIOVASCULAR EVENTS? IS THERE A DIFFERENCE BETWEEN SU AGENTS?

- There are several hypotheses linking SUs as a group to adverse CV events but none provide conclusive evidence.
- Observational evidence suggests an increased CV risk but these data may be subject to residual confounding and bias.
    - For example, metformin is often used as the comparator in the observational studies of SUs. Since metformin is often the first agent prescribed, the patient population is typically younger, with less severe hyperglycemia and a shorter duration of diabetes relative to the people prescribed a SU. Therefore the metformin group will have better CV health outcomes for reasons outside of what drug they are taking.
- RCT evidence suggests a neutral effect but most of these studies were not specifically designed to assess the effects of SUs on adverse CV event risk.
- The previously mentioned studies, TOSCA.IT and CAROLINA, may help answer whether SUs, as a group, increase the risk of adverse CV events compared with other glucose lowering agents, but their results are not expected for a few years.[80]

The next question is whether there are differences **within the SU group** with respect to adverse CV effects.

- The TOSCA.IT[53] and CAROLINA[54] trials will not answer this question.
- A clinical trial, powered to measure CV outcomes, that randomizes people to individual SU agents as well as placebo is needed to conclusively answer this question. In the meantime a recently published systematic review network meta-analysis provides the best available data.
- Simpson et al. included 7 RCTs that randomly allocated participants to different SUs in order to focus on assessing the CV safety of SUs individually rather than as a class.[81]

  The results obtained showed a lower risk of all-cause mortality associated with gliclazide (pooled RR 0.65) and glimepiride (pooled RR 0.83) compared with glyburide.

  - This finding is not surprising since it has been observed that SUs show different tissue-specific binding affinities to ATP-sensitive potassium channels (K_{ATP}).
    - The K_{ATP} channels on pancreatic β-cells and SU receptors (SUR1) are known to be the targets for SUs in order to exert their mechanism of action.
    - The inhibition of extra-pancreatic K_{ATP} channels and SU receptors in cardiac myocytes (SUR2A) and smooth muscle cells (SUR2B) is hypothesized to be the reason the SUs cause detrimental effects on the CV system.
    - Gliclazide is more selective for pancreatic SUR1 compared with glyburide, which binds non-selectively to both pancreatic SUR1 and cardiovascular SUR2A/B. Hence, it is speculated that gliclazide and glimepiride are associated with less CV risk than glyburide.
    - Unfortunately, there is insufficient evidence to state definitively that gliclazide and glimepiride are safer. The majority of studies examining receptor specificity of SUs were conducted in animals.

APPENDIX 1: DOSE RESPONSE RELATIONSHIPS (Copied from PAD B.C Provincial Academic Detailing Service with permission)[66]

Dose response relationships are often not characterized in a systematic manner. The literature does however provide the following examples:

- Metformin: doses ≥ 2000 mg per day reduced A1C by an additional 0.26% compared to lower doses (1000 to 1500 mg per day)[82]
- Metformin plus Glyburide: a combination of glyburide 5 mg plus metformin 500 mg (mean dose glyburide 17 mg/metformin 1740 mg per day) did not reduce A1C more than a combination of glyburide 2.5 mg plus metformin 500 mg (mean dose 8.8 mg glyburide/metformin 1760 mg per day)[83]
- Glimepiride: higher doses of glimepiride (e.g., 4 or 8 mg per day) did not reduce A1C significantly more than lower doses (e.g., 1 mg per day)[84]
- Acarbose: no evidence of an additional A1C reduction with doses greater than acarbose 150 mg per day[85]
- Saxagliptin: differences in A1C lowering between saxagliptin 5 mg per day and 2.5 mg per day ranged from 0.02% to 0.27% across RCTs reviewed by the U.S. FDA; there was no evidence of an additional A1C reduction with 10 mg per day (note, 10 mg is not an approved dose)[86]
- Linagliptin: there was no evidence of an additional A1C reduction with linagliptin 10 mg per day compared to 5 mg per day in RCTs reviewed by the U.S. FDA (note, 10 mg is not an approved dose)[87]
- Sitagliptin: sitagliptin 200 mg per day did not consistently reduce A1C compared to 100 mg per day in RCTs reviewed by the U.S. FDA (note, 200 mg is not an approved dose)[88]
- Alogliptin: alogliptin 25mg per day and 12.5 mg per day were generally similar in reducing A1C across RCTs reviewed by the U.S. FDA[89]
- Canagliflozin: differences in A1C lowering between canagliflozin 300mg per day and 100mg per day ranged from 0.09% to 0.25% across RCTs reviewed by the U.S. FDA[90]
- Dapagliflozin: differences in A1C lowering between dapagliflozin 10mg per day and 5mg per day ranged from 0.08% to 0.19% across RCTs reviewed by the U.S. FDA[91]
- Empagliflozin: differences in A1C lowering between empagliflozin 25 mg per day and 10 mg per day ranged from 0.06% to 0.13% across RCTs reviewed by the U.S. FDA[92]
- Liraglutide: liraglutide 1.8 mg per day and 1.2 mg per day were generally similar in reducing A1C across studies reviewed by the U.S. FDA; 18 systematic review found no significant difference between liraglutide 1.8 mg per day and 1.2 mg per day in reducing A1C[93]
- Exenatide: differences in A1C lowering between exenatide 10mcg BID and 5 mcg BID ranged from 0.22% to 0.40% across RCTs reviewed by the U.S. FDA[94]

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